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Handbook of Dialysis

Sixth Edition

John T. Daugirdas
Peter G. Blake
Todd S. Ing



Wolters Kluwer

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SIXTH EDITION

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This edition of the *Handbook* is dedicated to one of its founding editors, Dr Todd S. Ing, who unfortunately is no longer with us to provide his valuable guidance and support.

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*Deceased.

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PREFACE

We are very honored and pleased to present this sixth edition of the *Handbook of Dialysis* to professionals providing care for patients undergoing dialysis. While not completely "settled science," advances in dialysis therapy over the past 10 years have been modest. One meaningful advance has been a focus on the patient and on outcomes that are important to patients and their caregivers. Accordingly, the one new chapter that has been added, by Dr Mark Unruh, targets this new area of knowledge. Several chapters were removed from this edition. A chapter on sorbent-based dialysis is no longer included, as one major dialysis equipment manufacturer that was previously enthusiastic decided to abandon development of sorbent-based machines. We no longer include a chapter on reuse of hemodialyzers, although reuse continues to be practiced in some countries and regions. What was written about reuse in the fifth edition remains useful and valid. There is little new regarding hemodialysis or peritoneal dialysis adequacy. More frequent hemodialysis treatment schedules are perhaps increasing in popularity, but only slightly. There is less enthusiasm for use of kinetic modeling methods for both hemodialysis and peritoneal dialysis. For peritoneal dialysis, the emphasis now is on patient tolerability and convenience. With regard to hemodialysis, a small number of randomized trials have suggested increased survival when hemodiafiltration is added, as reviewed in an updated chapter. The exact mechanism of benefit remains a mystery, as predialysis and time-averaged levels of those middle molecules that are removed more efficiently by hemodiafiltration are only slightly reduced and remain far above levels in nonuremic individuals.

Much of the excitement around chronic kidney disease (CKD) has focused on the predialysis stages, and on use of new drugs that have been shown to improve survival in patients with predialysis CKD and may also retard progression. These advances are briefly described in the introductory chapter dealing with predialysis CKD, but of course, this is not the focus of this *Handbook*.

One of the founding editors of the *Handbook*, Dr Todd S. Ing, passed away while this sixth edition was in preparation. Dr Ing was a valued mentor to one of us (JTD) as well as to numerous other nephrologists. Readers can find a tribute to Dr Ing in the April 2024 issue of *Hemodialysis International*, 28(2):133-138, journal of the International Society of Hemodialysis, which Dr Ing was instrumental in founding. We miss him greatly.

In the final scene of the movie "Apocalypto" (released in 2006 by director Mel Gibson) indigenous inhabitants of Mexico (circa 1517 AD) peer through a coastal forest and see the approach of Spanish sailing ships. The message is that very soon for these cultures, everything will change. There have now been a handful of short-term successes with xenotransplantation, and it is quite possible that, at the time that a seventh edition of the *Handbook* is being contemplated, dialysis treatment will be reserved for those for whom xenotransplantation is not practicable.

Once again, we would like to thank the many chapter authors who agreed to write for the *Handbook*. The time demands on clinical nephrologists continue to increase, and we greatly

appreciate their willingness to allocate some of their precious time to share their insights and expertise.

John T. Daugirdas
Peter G. Blake

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PART I

Chronic Kidney Disease Management

1 Approach to Patients With Chronic Kidney Disease, Stages 1 to 4

Ajay K. Singh

Chronic kidney disease (CKD) can be defined in a variety of ways. The US Preventive Health Service defines it as decreased kidney function, with size-adjusted estimated glomerular filtration rate (eGFR/1.73 m^2) less than 60 mL/min, or as kidney damage that persists for at least 3 months.

Management involves the following considerations: screening, etiologic diagnosis, and staging of CKD severity; identifying patients at high risk of progression of renal and cardiovascular disease and attempting to slow progression; prevention and treatment of complications; and preparing the patient for transplantation or renal replacement therapy.

I. SCREENING, DIAGNOSIS, AND STAGING OF CKD SEVERITY.

Screening should focus on patients with CKD risk factors. These include diabetes, hypertension, cardiovascular disease, history of smoking, obesity, age greater than 60 years, indigenous racial origin, and a family history of CKD. Screening should include monitoring for the presence of proteinuria (because the degree of proteinuria affects the risk of progression) and measurement of kidney function.

A. Urinary protein measurement.

The US Preventive Health Service recommends urinary protein measurement as a screening test in all high-risk individuals. The American Diabetes Association (ADA) recommends that an evaluation for microalbuminuria be performed in all patients with type 2 diabetes at the time of diagnosis and in all patients with type 1 diabetes 5 years after initial evaluation. Screening can be done by urine dipstick, but this generally only detects those who are already macroalbuminuric. A urine dipstick test measures concentration only and can give false-negative results in dilute urine. A recommended and more reliable method is an early morning measurement of the albumin-to-creatinine ratio in a spot urine sample. The **urine albumin-to-creatinine ratio (UACR)** overcomes the problem of urine dilution because it measures the ratio of albumin to creatinine in the urine; as both will be affected by dilution, the effects of dilution will tend to cancel out. In terms of milligrams of albumin per gram or millimole of creatinine, **normoalbuminuria is defined as less than 30 mg/g (<3 mg/mmol); microalbuminuria as 30 to 300 mg/g (3-30 mg/mmol); and macroalbuminuria as greater than 300 mg/g (>30 mg/mmol)**. The risk of increased urine albumin excretion is continuous, and the risk is increased even when the albumin excretion is less than 30 mg/d. The UACR can be done at any time, but a morning test may increase sensitivity and will tend to exclude the relatively benign condition of **orthostatic proteinuria**, where proteinuria is present during the day but ceases while the subject is sleeping supine. A positive UACR test should be repeated at least twice over 3 months to exclude acute kidney injury (AKI) and to

confirm a positive test (Table 1.1).

TABLE 1.1 Staging of Chronic Kidney Disease

		Degree of Albuminuria (A) Category		
		A1	A2	A3
		<3 mg/mmol	3-30 mg/mmol	>30 mg/mmol
eGFR (G) Stage	eGFR/1.73 m^2	<30 mg/g	30-300 mg/g	>300 mg/g
		Risk, Intervention, and Referral		
G1	≥90	Green[a]	Yellow	Orange
G2	60-89	Green[a]	Yellow	Orange
G3a	45-49	Yellow	Orange	Red
G3b	30-44	Orange	Red	Red
G4	15-29	Red	Red	Red
G5	<15 on	Red	Red	Red

eGFR, estimated glomerular filtration rate; Green, low risk, screen only; yellow, moderately increased risk, treat to slow progression; orange, high risk, treat and refer; red, very high risk, treat and refer.

[a]Stages G1A1 and G2A1 are considered very low risk, and nothing other than monitoring of renal function is required.
Modified from various CKD and diabetes guidelines.

All patients with type 2 diabetes should have an annual spot measurement of UACR and eGFR. Patients with type 2 diabetes and a UACR ≥300 mg/g and/or an eGFR of 30 to 60 mL/min/1.73 m^2 should be monitored twice annually.

B. Measurement of kidney function

1. **Glomerular filtration rate (GFR).** The GFR, usually expressed in terms of milliliters per minute, is the volume of serum cleared by the kidneys per unit of time. The GFR depends on body size and age, and so an isolated value of GFR needs to be evaluated in context. One usually normalizes GFR to body surface area, specifically, per 1.73 m^2. In healthy subjects, GFR/1.73 m^2 is similar in men and women, but GFR/1.73 m^2 declines with age, averaging about 115 mL/min in young adults, 100 mL/min in the middle-aged, and then dwindling to 90, 80, and 70 mL/min as patient age increases to 60, 70, and 80 years, respectively.
2. **Serum creatinine.** Creatinine is produced at a relatively constant rate from creatine in muscle and is excreted by the kidneys by both glomerular filtration and tubular secretion. Normal creatinine concentrations range from 0.6 to 1.0 mg/dL (53-88 mcmol/L) in women and from 0.8 to 1.3 mg/dL (70-115 mcmol/L) in men. Measurement of the serum creatinine concentration is one way to obtain a rough estimate of the level of renal function, because as renal function falls, creatinine will continue to be produced, and the serum levels will rise. A doubling of the serum

creatinine will reflect a decline in GFR of approximately 50%. Doubling of serum creatinine from an initially low value can result in a serum creatinine still in the "normal range" despite a substantial loss of kidney function.

Serum creatinine levels are influenced by muscle mass, recent dietary intake, especially of cooked meat, and concomitant drug therapy (eg, treatment with cimetidine, a drug that blocks tubular secretion of creatinine and which will slightly increase the serum creatinine without any effect on GFR). In patients with cirrhosis and ascites, estimation of renal function from serum creatinine is particularly difficult. There can be a very low creatinine production rate due to extremely low muscle mass; plus, it is often difficult to determine ascites-free body weight for normalization. In such patients, serum creatinine levels in the 0.5- to 1.0-mg/dL range (44-88 mcmol/L), nominally "normal," may reflect moderately to markedly impaired levels of renal function. Even in patients without cachexia, the serum creatinine level must always be interpreted in the context of a patient's muscle mass. For example, a serum creatinine of 1.3 mg/dL (115 mcmol/L) can represent a creatinine clearance (C_{Cr}) of 94 mL/min in a young 80-kg male, but a creatinine clearance of only 28 mL/min in an older adult, 50-kg female.

Until recently, the serum creatinine was measured by a variety of methods, some of which, due to interfering substances in the blood, deviated substantially from "true" values of creatinine concentration as determined by isotope dilution mass spectrometry (IDMS). In the United States and many other countries, laboratories are now normalizing their measurement methods to IDMS, and the normalized values tend to be lower than those obtained using other methods.

3. **Creatinine clearance.** A timed (usually 24 hours) urine collection of creatinine excretion can be used to calculate the creatinine clearance (C_{Cr}), which is defined as the volume of serum cleared of creatinine per minute. Normal C_{Cr} is approximately 95 ± 20 mL/min in average-size adult women and 125 ± 25 mL/min in average-size adult men. To avoid the inaccuracies and inconvenience of timed urine collections, C_{Cr} can be estimated by using equations that estimate the per-minute creatinine excretion rate based on age, body size, gender, and in some equations, race. One equation that has been used for this is the **Cockcroft-Gault equation:**

$$\text{Estimated } C_{Cr} = (140 - \text{age}) \times (0.85 \text{ if female}) \times (W \text{ in kg})/(72 \times S_{Cr} \text{ in mg/dL})$$

or

$$\text{Estimated } C_{Cr} = (140 - \text{age}) \times (0.85 \text{ if female}) \times (W \text{ in kg})/(0.814 \times S_{Cr} \text{ in mcmol/L})$$

where W is body weight and S_{Cr} is the serum creatinine. This equation provides a quick and reasonably accurate estimate of renal function at the bedside.

4. **Estimated GFR (eGFR).** Creatinine clearance measurements have now been largely replaced by the calculation of an eGFR using any of a variety of prediction equations. These GFR prediction equations differ from the Cockcroft-Gault creatinine clearance in several ways. First, they were developed from data that measured GFR by iothalamate or other markers that are not secreted by the renal tubules, and so they predict GFR rather than creatinine clearance. All else being equal, the modification of diet in renal disease (MDRD) equation will give a lower

value for renal function (GFR) than creatinine clearance, which includes the tubular secretion component of renal function. Second, the eGFR prediction equations are normalized to body size and are expressed as eGFR/1.73 m^2 of body surface area. In contrast, creatinine clearance, whether obtained from a timed urine sample or from the Cockcroft-Gault equation, is a raw clearance that has not been adjusted for body size.

The original eGFR prediction equations were based on the serum level of creatinine. A second set of equations was based on serum levels of cystatin. Cystatin C is a 13-kilodalton protein produced by all cells that is filtered by the glomerulus and not reabsorbed. The production rate of cystatin C is not related to muscle mass or dietary meat intake, and cystatin C–based estimates of GFR correlate better with CKD-related outcomes than creatinine-based equations in some studies. Also, the relationship between serum creatinine and GFR is somewhat different in GLP subjects who self-identify as being of African American race versus those who identify as White. The cystatin-GFR relationship is not affected by race. Some of the newest efforts to predict GFR combine both serum creatinine and cystatin C levels. Laboratory methods of measuring cystatin C are not commonly standardized, and for the moment, cystatin C–based eGFR equations are not in wide use. Pending better and more widespread standardization of cystatin C measurements, one (US National Kidney Foundation Task Force) recommendation is to use a creatinine-based eGFR estimating equation that has been shown to be the least affected by race (Delgado, 2022). This so-called Chronic Kidney Disease Epidemiology Collaboration Equation—Revised (CKD-EPI-R; Inker, 2021) is somewhat complex and is discussed further in Appendix A.

5. **Problems with estimated clearances in AKI.** The estimating equations based on either creatinine or cystatin are based on steady-state assumptions. If one were to surgically remove both kidneys, the serum creatinine or cystatin C levels would begin to rise, but this increase would take place over several days as opposed to immediately. For this reason, none of the eGFR estimating equations described earlier are useful in situations where the level of kidney function is rapidly changing.

C. Kidney ultrasound. In patients found to have CKD, one should image the kidneys, commonly by ultrasound, to evaluate kidney size and to look for structural abnormalities, including evidence of cortical thinning to evaluate chronicity of kidney disease and signs of possible obstruction.

D. Laboratory values. Measurement of serum electrolytes (Na, K, Cl, HCO_3) should be performed to screen for metabolic acidosis and electrolyte disorders. A complete blood count screens for the presence of anemia. Serum calcium, phosphate, parathyroid hormone (PTH), and alkaline phosphatase levels can indicate metabolic bone disease, and serum iron, total iron-binding capacity, transferrin saturation, and ferritin are measured to check for iron deficiency.

E. Etiologic diagnosis. Identifying the underlying cause of CKD is important. CKD may be reversible, for example, in a patient with bilateral renovascular disease or chronic bladder neck obstruction from prostatic hypertrophy. The cause of CKD may provide insights into the tempo of disease progression. Since some etiologies of kidney disease are very likely to recur in a future kidney allograft, identifying the underlying cause of CKD at the outset may help in later management decisions.

II. SLOWING PROGRESSION OF CKD AND CARDIOVASCULAR DISEASE.

In patients with CKD with or without diabetes, risk factors for progression of renal disease are very similar to those associated with increased cardiovascular disease risk. One purpose of identifying patients with CKD early on is to attempt to correct and/or mitigate such risk factors, in the hopes of both maintaining GFR and minimizing cardiovascular risk. The main risk factors include smoking, high blood pressure, and hyperglycemia in patients with diabetes (and perhaps in nondiabetic persons as well). Elevated blood lipid levels, anemia, and elevated serum phosphate levels may contribute. Urinary protein excretion and even microalbuminuria markedly increase both the risk of progression and cardiovascular complications.

A. Cessation of smoking.

Smoking is a traditional cardiovascular disease risk factor, and cessation of smoking is important in terms of limiting cardiovascular risk. Evidence suggests that smoking accelerates the rate of progression of renal disease, emphasizing the importance of stopping smoking in patients with CKD.

B. Control of blood pressure (and proteinuria).

The target blood pressure recommended by Kidney Disease: Improving Global Outcomes (KDIGO) is less than 130/80 mm Hg for all patients with kidney disease, whether or not they have diabetes and regardless of degree of proteinuria. The Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated that a more aggressive systolic blood pressure target of less than 120 mm Hg was associated with marked cardiovascular protection in patients with hypertension without diabetes. This cardiovascular protection was observed in patients with CKD as well.

Whether or not hypertension is present, the use of renin-angiotensin system inhibition with either an angiotensin converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB) is recommended to slow the rate of CKD progression in all patients with diabetic kidney disease as well as in nondiabetic patients with CKD with proteinuria (spot urine protein-to-creatinine ratio of ≥200 mg/g). These drugs are used not only to lower blood pressure but to lower the amount of proteinuria when present. The 2024 American Diabetes Association guidelines recommend aiming for a greater than or equal to 30% reduction in urinary albumin in patients with CKD who have greater than or equal to 300 mg/g proteinuria.

Doses of ACEis or ARBs can be titrated upward to minimize the amount of proteinuria. Blood pressure, serum potassium, and serum creatinine should be monitored after initiation of therapy and after each dose change. Recent guidelines do not recommend the concurrent use of an ACEi and an ARB, or either of these drugs with a direct renin inhibitor. ACEis or ARBs are contraindicated in patients who are pregnant, particularly beyond the first trimester, and in patients with a history of angioedema. For patients with an eGFR/1.73 m^2 of greater than 15 mL/min, one rarely needs to adjust the dose of antihypertensive drugs downward due to impaired renal excretion, although the plasma half-life of some classes of antihypertensives will be increased (see Chapter 31).

Sodium restriction and the use of diuretics increase the antiproteinuric effects of ACEi/ARB therapy. Thiazide diuretics are the diuretic of choice for mild CKD, when S_{Cr} is less than 1.8 mg/dL (<160 mcmol/L). When S_{Cr} is greater than 1.8 mg/dL (>160 mcmol/L), a loop diuretic (twice-a-day dosing regimen) is recommended, due to presumed reduced efficacy of thiazides under those circumstances. A recent randomized trial demonstrated that chlorthalidone is effective in reducing blood pressure in patients

with CKD, including those with advanced CKD (Agarwal, 2021).

β-Blockers provide cardioprotection in heart failure and after myocardial infarction. They are no longer recommended by JNC 8 (Eighth Joint National Committee; James, 2014) as a first-line drug in treating hypertension. β-Blockers did show outcome benefit in treating patients with end-stage kidney disease (ESKD) receiving dialysis (Sinha and Agarwal, 2019), and their role in preventing sympathetic overload might be particularly useful in treating patients with CKD with hypertension. However, there are no large, randomized trials comparing the use of β-blockers with other classes of antihypertensive drugs in CKD.

C. Hyperglycemia, Sodium/glucose cotransporter 2 (SGLT-2) inhibitors, and continuous glucose monitoring sensors. In patients with CKD with diabetes, control of blood sugar has been shown to both retard progression of kidney disease and to mitigate cardiovascular disease risk. The 2022 KDIGO guidelines summarize the treatment/prevention strategy in such patients (Rossing, 2022).

SGLT-2 inhibitors are drugs that modulate sodium-glucose transport in the kidney, increasing urinary glucose losses and reducing glycemia. These drugs also have been shown to have unrelated renoprotective and cardioprotective effects, not only in patients with diabetes and CKD but also in nondiabetic patients with CKD (Wheeler, 2021). For this reason, their use can be considered to prevent progression in both groups of patients. The latest KDIGO CKD guidelines (2024) recommend giving SGLT-2 inhibitors to all patients with CKD and type 2 diabetes with an eGFR ≥ 20 mL/min/1.73 m^2. SGLT-2 inhibitors are also recommended for CKD patients without diabetes at this level of eGFR, if the UACR is greater than 200 mg/g (20 mg/mmol), or if heart failure is present (Levin, 2024).

The first line of drug treatment for patients with diabetes and CKD is moving toward using an SGLT-2 inhibitor, even when eGFR is as low as 20 mL/min/1.73 m^2. Metformin can be added as needed as long as eGFR is greater than 30 mL/min/1.73 m^2. Glucagon-like peptide-1 (GLP-1) receptor agonists are preferred glucose-lowering drugs for people with type 2 diabetes if SGLT-2 inhibitors and metformin are insufficient to meet glycemic targets or if they are unable to use one of those drugs (Rossing, 2022). GLP-1 receptor agonists appear to lower both urinary albumin excretion rate and to slow the decline in renal function in patients with type 2 diabetes and CKD (Mohamed, 2024).

One important recent advance in the control of glycemia has been the availability of glucose sensors applied to the upper arm with an attached microfiber that is inserted through the skin into the subcutaneous tissue, enabling monitoring of interstitial fluid glucose, which (with a slight delay) broadly reflects the blood glucose concentration. Continuous glucose monitoring may be especially useful in patients requiring insulin therapy, as it provides advance warning of impending hypoglycemia. Also, analysis of continuous glucose curves gives an alternative measure not only of average glucose but “time within range” and “time out of range,” either on the high or low glucose side. Although the outcomes and benefits of using such monitoring in patients with CKD with diabetes are yet to be determined, such devices should be considered in patients with diabetes and CKD to help optimize glycemia management. One study has suggested that the incidence of hypoglycemia is markedly increased in CKD, regardless of whether a patient has been diagnosed as having diabetes or not (Ushiogi, 2023).

D. Mineralocorticoid receptor antagonists (MRAs). Finerenone and MRAs have emerged as promising treatments for patients with CKD. These medications work by blocking the effects of aldosterone, a hormone that plays a role in salt and fluid balance; inflammation; and fibrosis in the kidneys, heart, and vasculature. Clinical trials have shown that finerenone and MRAs can reduce albuminuria, slow the decline in kidney function, and lower the risk of cardiovascular events in patients with CKD and high cardiovascular disease risk (Pandey, 2022). However, these drugs should be used with caution in patients with low blood pressure or hyperkalemia, and close monitoring is necessary to prevent potential adverse effects. The availability of potassium-binding drugs such as patiromer and sodium zirconium cyclosilicate can mitigate the risks of hyperkalemia with MRAs. Combined use of an MRA with an SGLT-2 inhibitor may be of added benefit in reducing UACR in patients with type 2 diabetes and CKD. (Ferreira, 2024). The most recent KDIGO CKD guidelines (2024) recommend use of a nonsteroidal MRA for CKD patients with type 2 diabetes mellitus "an eGFR >25 ml/min/1.73 m^2, normal serum potassium concentration, and albuminuria (>30 mg/g [>3 mg/mmol]) despite maximum tolerated dose of a renin-angiotensin system inhibitor" (2A) (Levin, 2024).

E. Aspirin. Aspirin (and also β-blocker therapy) cardioprotection after myocardial infarction should be similar in patients with CKD to that in patients with normal renal function. However, aspirin has been associated with gastrointestinal (GI) bleeding in patients with ESKD. Whether an increased risk is present in patients with stages 1 to 4 CKD is not well known. One systematic review study found little benefit of aspirin in terms of primary prevention of cardiovascular disease and a substantially increased bleeding risk (Pallikadavath, 2022).

F. Lipid-lowering therapy. Elevated levels of low-density lipoprotein (LDL) cholesterol and other lipid marker molecules are a traditional risk factor for cardiovascular disease. The cardioprotective effects of statins in non-CKD patients, even when cholesterol levels are in the normal range, have been described in several studies. Data in animals suggest that high lipid levels and cholesterol loading may augment glomerular injury. Thus, treatment of patients with CKD with statins to reduce lipids may both slow the rate of CKD progression and lower cardiovascular disease risk.

The 2013 KDIGO lipid guidelines (Wanner et al, 2013) recommend that all patients with CKD (eGFR/1.73 m^2 <60) not on dialysis and those aged 50 years and older be treated with either a statin or a statin/ezetimibe combination. Patients aged 50 years and older who have CKD by virtue of some evidence of renal damage but with eGFR/1.73 m^2 greater than or equal to 60, namely stage 1 or 2 CKD, should be offered statin treatment only, as evidence for the benefits of a statin/ezetimibe combination in this group is not strong. Finally, younger CKD (age 18-49) not on dialysis should be treated with statins if they have known coronary disease, diabetes, prior ischemic stroke, or a 10-year cardiovascular disease risk greater than 10%. The 2013 KDIGO lipid guidelines recommend that statins or the statin/ezetimibe combination should not be initiated routinely in patients undergoing dialysis, but if the patients are already on these drugs when dialysis is initiated, then these drugs should be continued.

In nondialysis patients with CKD, the benefits of these "lipid-lowering" drugs seem to be present regardless of the level of LDL cholesterol, and the current trend is to use overall cardiovascular disease risk and the presence of comorbidity rather than LDL

cholesterol levels as an indication for treatment. One meta-analysis supported the use of statins for the primary prevention of cardiovascular disease (Major, 2015). In the Study of Heart and Renal Protection (SHARP) trial, where both nondialysis patients and patients undergoing dialysis were studied, those given a combination of simvastatin and ezetimibe, experienced a reduction in cardiovascular outcomes (Baigent, 2011). However, it is not clear to what extent the benefits found were due to the statin (simvastatin) used or the addition of ezetimibe. Ezetimibe is an inhibitor of cholesterol absorption, and it decreases plasma levels of LDL cholesterol, triglycerides, and apolipoprotein B, and increases plasma levels of HDL cholesterol. As do statins, ezetimibe exerts significant antiatherogenic, anti-inflammatory, and antioxidant actions (Katsiki, 2013**)**.

Statins as a class have been associated with rhabdomyolysis, and dose reduction in severe renal impairment is recommended for some statins (eg, rosuvastatin) or when statins are used in combination with fibrates.

G. Dietary protein restriction. Dietary protein restriction as a treatment to slow CKD progression remains controversial. Evidence from animal studies demonstrates that diets high in protein lead to histologic abnormalities in the kidney and to proteinuria, and restricting protein intake slows progression. However, randomized clinical trials suggest that the effects of protein restriction are likely to be small and difficult to achieve. Meta-analyses suggest that protein restriction is moderately beneficial in reducing CKD progression. Recommendations differ from various guideline groups regarding the benefits of any further restriction of protein intake. The 2020 Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines (Ikizler et al, 2020) suggested that a restriction to 0.6 g/kg/d in metabolically stable patients without diabetes with an eGFR/1.73 m^2 less than 25 mL/min might be beneficial. A less severe protein restriction, 0.6 to 0.8 g/kg/d, was suggested for patients with diabetes. Canadian, many European, and the most recent KDIGO guidelines do not recommend protein restriction below 0.8 g/kg/d at any level of renal function. Restricting protein intake needs to be individualized to prevent malnutrition. Patients who are malnourished at the start of dialysis have a poorer survival than their well-nourished counterparts, and restricting food choices always carries the risk of a worsening nutritional status. Close follow-up for any evidence of malnutrition, either by clinical parameters or by serum albumin, is essential. A dietitian should be monitoring such patients carefully. In stage 4 and 5 patients, evidence of failing nutritional status is one key determinant in the decision to begin dialysis therapy.

H. Dietary sodium restriction. In patients with CKD who are hypertensive, KDIGO blood pressure guidelines recommend limiting dietary sodium intake to 2 g/d. Sodium restriction also has been shown to lower the degree of albuminuria in patients with CKD and diabetes (Chen, 2022).

I. Acidosis. Acidosis in CKD is generally mild and usually with a normal anion gap until kidney function is severely impaired. Chronic metabolic acidosis results in increased resorption of bone and has also been associated with an increased rate of progression of CKD. Studies in animals and humans have suggested that chronic metabolic acidosis and potentially increased tissue acidity have a pro-inflammatory and profibrotic effect that increases the rate of CKD progression. Although relatively small, randomized trials in humans have suggested the benefit of bicarbonate therapy in slowing CKD progression (Di Iorio, 2019), a systematic review in 2020 has pointed out that more

definitive evidence is still required (Hultin, 2020). Alkali can be provided as $NaHCO_3$, sodium citrate, or base in fruits and vegetables. A serum [HCO_3] of greater than 22 mEq/L has been recommended as a clinical goal.

J. Hyperkalemia. Treatment of acute hyperkalemia is discussed elsewhere. In the chronic setting, hyperkalemia usually is the result of relatively high dietary potassium intake, and especially, binge intake of high-potassium foods such as fruits. Hyperkalemia is also more commonly found in patients taking ACEis, ARBs, or MRAs such as aldosterone. It is also more common in patients taking nonsteroidal anti-inflammatory drugs as well as trimethoprim. The recent development of novel GI sorbents (patiromer, zirconium cyclosilicate) to prevent absorption of ingested potassium may allow more widespread use of renin-angiotensin-aldosterone system (RAAS) inhibitors and MRAs. Discontinuation of RAAS inhibitors after an episode of hyperkalemia versus continuing treatment has been associated with a higher mortality rate (Leon, 2022).

K. Hypomagnesemia. Low serum magnesium levels in patients with CKD have been associated with a poor prognosis. Magnesium levels may be low for many reasons and there is the potential for confounding, as hypomagnesemia is more common in patients with poor nutritional status. Magnesium is an anticalcification factor, and magnesium supplementation has been suggested to reduce vascular calcification and otherwise benefit patients with CKD. However, a systematic review of magnesium supplementation effects in CKD was inconclusive (Zhan, 2023).

L. KDIGO 2024 CKD clinical practice guidelines. These guidelines contain detailed information about diagnosing and monitoring CKD, as well as slowing the rate of progression. For an executive summary, see Levin, 2024.

III. MANAGEMENT OF COMPLICATIONS OF CKD

A. Anemia. Anemia is common in patients with CKD. As kidney disease advances, the incidence and prevalence of anemia increase. Anemia of CKD is multifactorial in etiology. The most common causes are erythropoietin deficiency, iron deficiency, and inflammation. Observational studies have suggested an increased risk of cardiovascular and renal complications, lower quality of life, and higher mortality with a lower Hb level. However, large randomized clinical trials have demonstrated that correction of anemia to an Hb level of 13 g/dL (130 g/L) and above with an erythropoiesis stimulating agent (ESA) is associated with either no benefit or an increased risk of cardiovascular complications, stroke, and/or death. Also, correction of anemia is associated with either no effect on kidney progression or an increased rate of ESKD. Studies have found an association between exposure to high doses of ESA and a heightened risk of adverse events. It is unclear whether this is causal, or a reflection of the relatively high Hb targets used, and the known association of ESA resistance with poor outcome. Contemporary approaches to anemia management emphasize only partial correction of anemia, with treatment of iron deficiency and inflammation and using the lowest possible dose of ESA.

1. **Iron status.** Iron deficiency is present in over 40% of patients with CKD not on dialysis. The causes of iron deficiency are multifactorial but include reduced absorption of iron; blood loss from either frequent blood draws or occult GI blood loss, and reduced nutritional intake. Iron status (iron stores and bioavailable iron

levels) should be evaluated regularly in patients with CKD. Ferritin is an iron storage protein, and its serum levels reflect iron storage. Serum ferritin is also an acute phase reactant, however, and patients with CKD often exhibit chronic inflammation; therefore, the ferritin level should be interpreted cautiously in inflamed patients. Serum ferritin values are of greatest predictive value for iron deficiency when low (<100 ng/mL), but are of limited value when elevated. The transferrin saturation (TSAT; serum iron × 100/total iron-binding capacity) is the most common method of measuring iron bioavailability. A TSAT less than 20% is indicative of low iron availability in CKD. Iron deficiency can lead to decreased effectiveness of ESA therapy. Therefore, before initiating ESA therapy, iron status must be addressed.

a. **Treatment of iron deficiency anemia.** Options for therapy depend on the stage of CKD and include oral and intravenous therapies. Oral iron therapy is the preferred method of treating nondialysis patients with CKD and is recommended by KDIGO as an initial approach to treating iron deficiency. Strategies to improve oral iron absorption include only taking pills on an empty stomach, avoiding enteric-coated formulations, and avoiding ingestion of iron with phosphate binders. Intravenous iron may be needed in some patients who either do not respond to oral iron or have large ongoing losses of iron (eg, chronic bleeding from the GI tract). The use of low-molecular-weight iron therapy is recommended—low-molecular-weight dextrans, ferrous gluconate, iron sucrose, or ferumoxytol. The use of high-molecular-weight iron dextran has been associated with an increased risk of severe anaphylaxis.

   Dosing strategies for oral iron aim at providing approximately 200 mg of elemental iron daily, which is equivalent to ferrous sulfate 325 mg 3 times daily, with each pill providing 65 mg of elemental iron. If iron repletion goals are not met after a 1- to 3-month trial, it is appropriate to consider intravenous iron supplementation. Intravenous iron can be administered as a single large dose or as repeated smaller doses, depending on the preparation used. The initial course of intravenous iron treatment is usually structured to supply approximately 1,000 mg of iron.

2. **ESAs**

   a. **Initiation of ESA therapy and hemoglobin thresholds.** Diagnosis and management of anemia in nondialysis patients with CKD is similar to that in ESKD and is discussed in detail in Chapter 32. The KDIGO guidelines recommend that erythropoietin therapy should not be started until the hemoglobin falls below 10 g/dL (100 g/L). KDIGO guidelines recommend maintaining the hemoglobin level between 9 and 11.5 g/dL (90 and 115 g/L), although the US Food and Drug Administration (FDA) now recommends that ESA dosing should be reduced or interrupted if the Hb level exceeds 11 g/dL (110 g/L). Treatment of anemia in CKD with ESA therapy should be individualized, and one of the main goals should be to reduce the need for blood transfusion. The KDIGO guidelines counsel caution when treating patients with CKD with a history of prior stroke or cancer. Thus, the effective Hb goal, in the United States at least, is 10 to 11 g/dL (100-110 g/L). In Europe and other parts of the world, the Hb goal is 10 to 12 g/dL. Allowing the Hb level to be less than

10 g/dL (10 g/L) might increase use of blood transfusions and thereby expose patients eligible for kidney transplantation to the allosensitizing effects of transfused blood.

b. **Types of ESA therapy.** There are short-acting and long-acting ESAs. Epoetin alfa, approved in 1989 and available worldwide, is a short-acting ESA with a half-life when given intravenously of about 8 hours and 16 to 24 hours when given subcutaneously. Several different short-acting ESAs and their biosimilars are available. A typical dose in a patient with CKD might be 4,000 to 6,000 units subcutaneously once a week. The most widely used long-acting ESA is darbepoetin alfa, with a half-life of about 25 to 50 hours when given IV or subcutaneously, respectively. The optimal administration dosing schedule for darbepoetin alfa is once weekly (a typical dose might be 20-30 mcg) or every 2 weeks (40-60 mcg) in a stable patient with CKD. The dose does not differ if given by the intravenous route or subcutaneous route. Methoxy polyethylene glycol-epoetin β is another long-acting ESA (approved by the FDA in 2007 for monthly dosing): Extended dosing is possible because a water-soluble polyethylene glycol moiety has been added to the epoetin β molecule. The half-life is approximately 136 hours. In the United States, the typical methoxy polyethylene glycol-epoetin β dose is 150 mcg/mo. In 2018, the FDA approved epoetin alfa-epbx a biosimilar to epoetin alfa.

c. **Frequency of administration and route of administration of ESAs.** The frequency of ESA administration is usually influenced by patient convenience and efficacy considerations. In nondialysis patients with CKD, longer-acting ESAs are preferred because their use is associated with fewer injections and/or visits to a doctor's office unless the patient can self-administer. The shorter-acting ESAs can be dosed once a week, or even once every 2 weeks.

d. **Iron deficiency with ESA treatment.** ESA treatment will increase iron utilization as iron is incorporated into red blood cells. Iron status should be monitored every 3 months with TSAT and ferritin while a patient is receiving ESA therapy and more frequently when initiating or increasing ESA dose, in the setting of ongoing blood loss, or in circumstances where iron stores are likely to become depleted.

e. **ESA hyporesponsiveness.** The prevalence of ESA hyporesponsiveness in nondialysis patients with CKD is poorly described, and there is tremendous geographic variation (in contrast, ~12% of patients undergoing hemodialysis are ESA hyporesponsive). There are several definitions of ESA hyporesponsiveness. Popular definitions include (1) erythropoiesis resistance index (ERI) defined as the average weekly erythropoietin (EPO) dose per kg body weight (wt) divided by the average hemoglobin (Hgb), calculated over a 3-month period (ERI = [EPO/wt]/Hgb). An index of greater than 2 is consistent with ESA hyporesponsiveness. (2) Dose based: intravenous ESA equivalent dose greater than or equal to 450 U/kg/wk. ESA hyporesponsiveness varies geographically. Causes of ESA hyporesponsiveness include iron deficiency, the presence of an inflammatory focus (diabetic ulcer, failed allograft), hyperparathyroidism, and nutrient deficiencies (eg, vitamin B_{12}, folate, carnitine, vitamin C).

3. **Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHI).** These

are oral agents that inhibit prolyl hydroxylase and thereby stabilize hypoxia-inducible factors that stimulate endogenous erythropoietin production. HIF-PHIs stimulate erythropoietin production both from the kidneys and the liver. HIF-PHIs may decrease hepcidin levels and modulate iron metabolism, thereby increasing iron-binding capacity and reducing the need for iron supplementation. For this reason, they may be particularly effective in patients with ESA resistance. There are at least five agents in this category that have been approved in various countries. These include roxadustat, vadadustat, daprodustat, molidustat, enarodustat, and desidustat. As of early 2025, in the United States, vadadustat and daprodustat have been approved by the Food and Drug Administration for treating anemia in CKD patients on dialysis. Concerns have been raised regarding potential adverse cardiovascular and liver effects of some of these candidate drugs, but initial safety results have been encouraging (Zheng, 2023).

B. Chronic kidney disease mineral and bone disorder (CKD-MBD). The pathogenesis of CKD-MBD is depicted in Figure 1.1. The management of serum phosphate, vitamin D, and PTH levels in patients undergoing dialysis is more fully discussed in Chapter 34 and only issues pertinent to CKD will be discussed here.

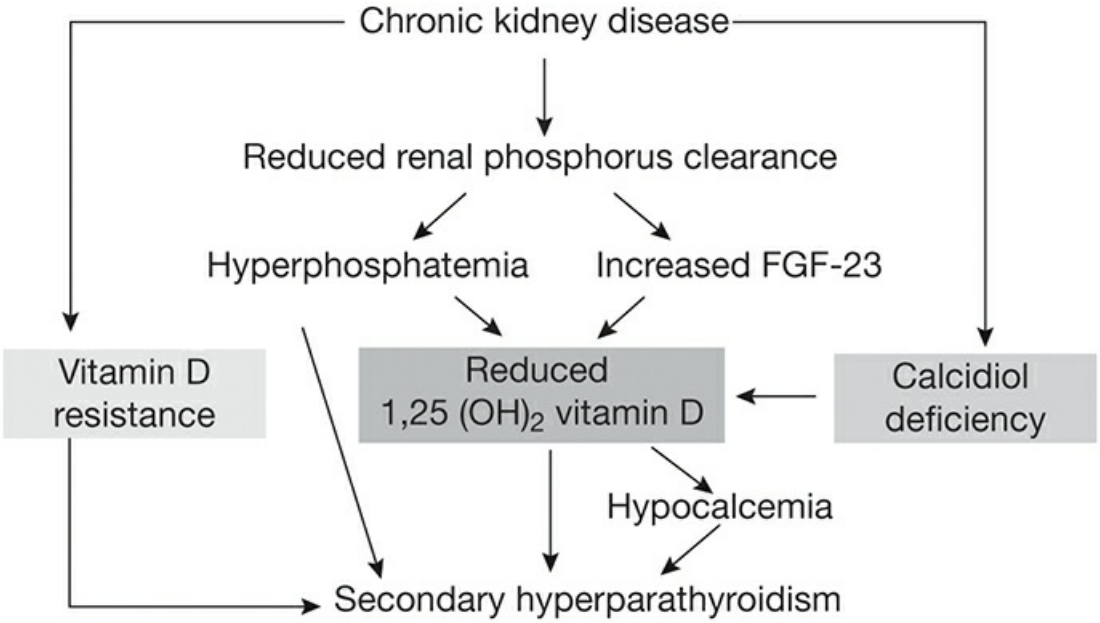


FIGURE 1.1: Pathogenesis of MBD. MBD, mineral bone disease. FGF, fibroblast growth factor. (Reprinted with permission from Macmillan Publishers Ltd: Nigwekar SU, Tamez H, Thadhani RI. Vitamin D and chronic kidney disease-mineral bone disease (CKD-MBD). *Bonekey Rep*. 2014;3:498. eCollection 2014.)

1. **Hyperphosphatemia.** A high serum phosphate level is a risk factor for mortality and adverse cardiovascular outcomes in both CKD and patients with ESKD. Hyperphosphatemia is associated with an increased risk of vascular calcification and left ventricular hypertrophy in ESKD. In a number of experimental renal failure models, hyperphosphatemia accelerates the progression of renal failure. In such models, hyperphosphatemia stimulates parathyroid gland growth and PTH secretion.
   a. **Target serum calcium and phosphate levels.** Previous recommendations to maintain serum calcium at the high end of the normal range to ensure PTH

suppression have been replaced by a strategy of keeping serum calcium toward the middle or low range of normal, to minimize the risk of vascular calcification. Similarly, serum phosphate levels should be maintained within the normal range.

b. **Dietary management.** Management includes a careful dietary review to look for abnormally high consumption of foods rich in phosphate, with a focus on processed foods containing high amounts of phosphate additives, and certain colas. One suggestion is to encourage the amount of plant-based foods as opposed to foods of animal origin, as the degree of phosphate absorption from plant-based foods may be reduced. One caveat is that nominally healthy foods, such as whole-grain cereals that contain relatively high amounts of fiber and desirable minerals such as magnesium, also contain higher amounts of phosphate, and reducing consumption of such "healthy" foods with the goal of reducing phosphate may be counterproductive. Phosphate intake should be restricted to 800 to 1,000 mg/d (26-32 mmol/d), though the amount of phosphate present in diets typically consumed is not clear due to incomplete information in nutritionist food databases. There are no large, randomized trials that show reduction of dietary phosphate improves outcomes in CKD.

c. **Phosphate binders.** Phosphate binders may be used to control undesirably high serum phosphate levels. The choices are described in Chapter 34. It is prudent to restrict total calcium intake in patients with CKD to about 1,500 mg/d (37 mmol/d) or less to minimize the risk of vascular calcification. This means that if calcium salts are used as phosphate binders, they may need to be combined with sevelamer, lanthanum, or, possibly, magnesium or one of the newer iron-containing phosphate binders described in Chapter 34. Aluminum-containing phosphate binders generally should not be used. The few placebo-controlled randomized trials that have been done of phosphate binder treatment in CKD demonstrated lower serum and urinary phosphate, but increased constipation and vascular calcification were suggested with some binders, and there was scant evidence for benefits in terms of reducing cardiovascular risk or CKD progression (Lioufas, 2022).

2. **Serum PTH levels.** Control of serum PTH levels is important to minimize the degree of parathyroid gland hypertrophy and the risk of developing large, nonsuppressible glands. Hyperparathyroidism is associated with bone disease, and PTH may also act as a uremic toxin with adverse effects on many different organ systems. The control of PTH secretion is detailed in Chapter 34.

   a. **Frequency of measurement.** The 2017 KDIGO update to the 2009 KDIGO guidelines for bone metabolism and disease in CKD (KDIGO, 2017) recommends monitoring serum levels of calcium, phosphate, PTH, and alkaline phosphatase activity beginning in CKD stage G3a. The recommended frequency of these measurements is now based on the severity of kidney disease. In CKD stage G3a or G3b: for serum calcium and phosphate, every 6 to 12 months; and for PTH, based on baseline level and CKD progression. In CKD stage G4: for serum calcium and phosphate, every 3 to 6 months; and for PTH, every 6 to 12 months.

   b. **Target range of PTH.** The intact PTH assay has been available since 1990 and identifies both 1-84 and 7-84 PTH, and most bone biopsy studies on which target

levels are based have employed this assay. Bio-intact PTH, also known as biPTH or whole PTH, is a newer assay that responds only to the complete 1-84 PTH molecule, resulting in PTH values that are about half as high as those measured by the previous "intact" PTH assay. Either assay can be employed for diagnosis and treatment of hyperparathyroidism in CKD, but the target PTH range will depend on the specific assay employed. As CKD progresses, the bone becomes resistant to the actions of PTH, and so the target PTH range increases. The initial KDOQI recommendations proposed various targets for PTH at different levels of renal impairment, but given the wide variation among assays and uncertainty of benefit, the 2017 KDIGO update states that for nondialysis CKD the optimal PTH level is not known, and to assess patients for modifiable risk factors, including hyperphosphatemia, hypocalcemia, high phosphate intake, and vitamin D deficiency (Grade 2C recommendation).

In adult patients with CKD stage G3a to G5 not on dialysis, the 2017 KDIGO update suggests that calcitriol and vitamin D analogs not be routinely used (Grade 2C recommendation). KDIGO recommends that one should "reserve the use of calcitriol and vitamin D analogs for patients with CKD stage G4 to G5 with severe and progressive hyperparathyroidism."

c. Serum alkaline phosphatase. Alkaline phosphatase is present in bone and is an indicator of bone turnover rate. When high, particularly in combination with an elevated serum PTH, serum alkaline phosphatase can be a reasonably good indicator of a hyperactive parathyroid gland that needs to be suppressed. The current KDIGO CKD-MBD guidelines recommend at least yearly monitoring of serum alkaline phosphatase levels for patients with stage 4 CKD and higher.

3. Vitamin D. In patients with CKD, serum 25-D levels are quite low, probably because of lack of sunlight exposure and low ingestion of vitamin D–containing foods. As CKD progresses, the rate of conversion of 25-D to 1,25-D by the 1-α-hydroxylase enzyme diminishes, and even with adequate 25-D levels, serum 1,25-D levels may be reduced and PTH suppression may be inadequate. Vitamin D affects multiple organ systems; most of these effects are beneficial, although excess vitamin D has been associated with vascular calcification and even accelerated renal failure. The 1-α-hydroxylase enzyme exists in various tissues, suggesting that it may be important to ensure proper levels of both 25-D and 1,25-D in the circulation for optimum health.

One problem with analyzing the effects of vitamin D on outcomes is that while low serum 25-D levels have been linked to several disease conditions and poor outcomes, interventional trials of supplementation with cholecalciferol or ergocalciferol have often shown no or borderline benefit, suggesting that a low serum 25-D level may be a marker of poor health. On the other hand, some of the negative results may be explained by the provision of inadequate doses of cholecalciferol to substantially raise serum 25-D levels. Effects of cholecalciferol supplementation on vascular endothelial function or stiffness and on left ventricular hypertrophy have been either negative or discordant. There have been no large, randomized trials done that would suggest that cholecalciferol supplementation reduces proteinuria in CKD, reduces cardiovascular events, or slows progression.

a. Target serum levels of 25-D in CKD. Serum levels of 25-D should be at

least 30 ng/mL (75 nmol/L). Low serum levels of 25-D have been linked to severe muscle weakness in older nonuremic patients. Because patients with CKD typically have very low levels of 25-D in the serum, for primary prevention, patients with CKD should be supplemented with at least 1,000 to 2,000 IU of cholecalciferol per day, and higher doses may be needed. Cholecalciferol is available in the United States only as an over-the-counter vitamin supplement. This level of cholecalciferol supplementation does not affect GI absorption of calcium or phosphate. To treat a low serum 25-D level, the 2003 KDOQI bone disease guidelines recommended using ergocalciferol, which is slightly less effective than cholecalciferol and is available only in relatively large dosage forms designed to be prescribed weekly or monthly. Ergocalciferol does have the advantage in the United States of being available as a formulary drug.

b. When to use active vitamin D preparations. In the more severe stages of CKD, conversion of 25-D to 1,25-D in the kidney becomes suboptimal, and even with adequate stores of 25-D, the serum levels of 1,25-D may remain low. In such situations, PTH often is not adequately suppressed. In patients with stage 3 and 4 CKD in whom serum PTH remains above the target range despite adequate serum levels of 25-D, the use of an active vitamin D preparation is indicated. Choices and doses of active vitamin D preparations (eg, calcitriol, paricalcitol, and doxercalciferol) are outlined in Chapter 34. As in patients with ESKD, when active vitamin D sterols are being given, the dose should be held or reduced in the presence of hypercalcemia or hyperphosphatemia.

c. Cinacalcet. Cinacalcet is a calcimimetic drug that increases the sensitivity of calcium receptors on the parathyroid gland to calcium, resulting in a decrease in PTH secretion. One main advantage of cinacalcet is its use in patients with hyperparathyroidism and high serum calcium and/or phosphate levels, where the use of active vitamin D sterols to suppress PTH would be contraindicated (active vitamin D sterols increase GI absorption of phosphate and may worsen hyperphosphatemia). Cinacalcet has been shown to lower PTH levels in patients with stage 3 and 4 CKD (Chonchol, 2009). The relative roles of cinacalcet versus active vitamin D sterols for PTH suppression in CKD patients not needing dialysis are not well defined. In the United States, product labeling of cinacalcet states that the drug is not indicated for use in nondialysis patients, and the 2009 KDIGO CKD-MBD guidelines do not recommend its use in the nondialysis CKD population.

IV. PREPARING A PATIENT FOR DIALYSIS. Tasks here include preparation for dialysis or preemptive kidney transplantation; placement of vascular or peritoneal access; choosing the most appropriate mode and location of dialysis (ie, peritoneal dialysis, outpatient hemodialysis center, home hemodialysis); vaccinations; continued nutritional management, particularly in terms of phosphate control; and prevention of fluid overload and hypertension. These are discussed in more detail in the next chapter.

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2 Management of Chronic Kidney Disease Stages 4 and 5: Preparation for Transplantation, Dialysis, or Conservative Care

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Once a patient has reached stage 4 chronic kidney disease (CKD), with a size-adjusted estimated glomerular filtration rate (eGFR/1.73 m^2) of less than 30 mL/min, they should be under a nephrologist's care. Ideally, the patient should also be a part of a multidisciplinary predialysis program that includes patient and family education, early choice of appropriate renal replacement modality, and, if dialysis is being considered, elective creation of dialysis access. The advantage of a programmatic approach to care is a planned outpatient initiation of dialysis in a patient who is both mentally and physically prepared. The importance of shared decision-making between the patient and the health care team has been emphasized in several high-quality clinical practice guidelines (Salas-Gama, 2022). It is likely that this approach results in fewer hospital days in the first month after beginning dialysis and substantial cost savings.

I. CHOICE OF MODALITY

A. Patient education. Of key importance is patient education about the various treatment options available when renal replacement therapy becomes necessary. Important questions to ask at this stage: would the patient best benefit from some form of dialysis, from preemptive transplantation, or from continued conservative management? In some cases, due to extreme patient debility or other reasons, dialysis may not be an appropriate option, and conservative management may be the best choice. Palliative care is an important option to be considered, particularly in older frail patients with comorbidities; however, decision-making needs to be individualized (Combs and Davison, 2015). These discussions are best initiated once a patient is still in stage 4 CKD and well before stage 5 has been reached.

B. Options for renal replacement therapy (Table 2.1)

TABLE 2.1 Treatment Options in Patients Who Need Renal Replacement Therapy

Modality	Description	Advantages	Disadvantages
Preemptive transplantation	Live or cadaver donor transplant before ever needing dialysis	Improved patient survival relative to conventional dialysis; lower long-term costs	Logistics of finding a suitable donor; need for compliance with immunosuppressive drugs
Home hemodialysis	3-6 times per week, either during the day or at night. Usually	When given more than 3 times per week, or when given as 8- to 10-h treatments, 3-3.5 nights per week, evidence suggests	Home is changed into a hospital; partner burnout; with some home

	assisted by a relative or caregiver; uncommonly, by a paid health care professional	better quality of life and better control of phosphate and blood pressure; may also reduce left ventricular hypertrophy	therapies, modification to home water systems is required; waste disposal; expense
Home peritoneal dialysis (PD)	Automated cycler, with most exchanges done during the night	Independence, relative simplicity	Need for delivery of large volumes of PD fluid; exposure to high amounts of glucose
In-center nocturnal hemodialysis	Three 7- to 9-h nocturnal treatments per week (or uncommonly, every other night) given in-center (either staff assisted or self-care)	Marked increase in weekly dialysis time with better control of phosphate, blood pressure, and anemia. Home does not need to be converted into a clinic. Dialysis time is spent sleeping.	Leaving home unattended on dialysis nights; travel to unit; relatively inflexible schedule
In-center conventional hemodialysis	Either staff assisted (the norm) or self-care	Short amount of time spent on dialysis; staff does all the work.	Travel to unit; relatively inflexible schedule. May be inadequate amount of dialysis
Postponing dialysis	Very-low-protein diet plus ketoanalogues, careful fluid management	May work to postpone dialysis for about 1 y in older patients with few comorbidities (no heart failure, diabetes)	Expense of ketoanalogues
Palliative care	Conservative management without dialysis	Good for those patients for whom dialysis is not expected to prolong life to a significant extent or in whom overwhelming comorbidities are present	Potentially reduced life expectancy

Modified from Tattersall JE, Daugirdas JT. Preparing for dialysis. In: Daugirdas JT, ed. *Handbook of Chronic Kidney Disease Management*. Wolters Kluwer Health, Lippincott Williams & Wilkins; 2011:511-523.

1. **Preemptive transplantation.** Transplantation offers survival superior to the standard forms of dialysis being offered today. Transplantation may not be indicated, however, for a patient who has severe problems with compliance in terms of medications. Preemptive transplantation has a higher success rate than when transplantation is initiated after hemodialysis, and for this reason, discussions about the feasibility of transplantation and transplantation workup should begin well in advance of any need for dialysis, usually when eGFR is well above 15 mL/min/1.73 m^2 (Kim, 2023; King, 2022).
2. **Dialysis: Home versus in-center therapy.** Among the end-stage kidney disease (ESKD) therapies, the choices made will depend on what is available in the local community. One of the main decisions to be made is whether the patient will be coming to a clinic for regular dialysis (hemodialysis in this case) or whether they would prefer the independence of dialyzing at home, using either a home hemodialysis system or peritoneal dialysis (PD). Logistical issues that are important to consider include transportation, the status of a patient's home, the amount of support available through interested family members who might assist as caregivers, and technical issues such as available water quality and electricity. A National Kidney Foundation's Kidney Disease Outcome Quality Initiative (NKF-KDOQI) Conference Report (Chan, 2020) recommends the pairing of smaller and/or newer home dialysis programs with larger more sophisticated programs that offer education and mentoring (hub and spoke model) and also support to patients and their care partners by their peers.

   In observational studies, mortality rates are lower in patients undergoing home

hemodialysis than in patients undergoing in-center hemodialysis, sometimes dramatically so, even after adjustments for common comorbidities and at similar total weekly dialysis times. Some of the home dialysis advantages may be due to unaccounted-for patient selection bias, as patients undertaking the responsibility to dialyze at home usually have a strong positive attitude, good compliance, and strong caregiver and/or family support structure, factors that are associated in their own right with increased survival. Mortality rates for in-center hemodialysis are similar to those for home PD, so the selection of home versus in-center dialysis should be based more on patient preferences than on any anticipated survival benefit.

3. **"Daily" hemodialysis.** Normally, whether done at home or in-center, hemodialysis therapy is offered 3 times per week, usually 3 to 5 hours per session. When the same amount of dialysis time is broken up into five or six sessions per week (usually 2-3 hours per session), some observational studies have shown better control of blood pressure, better nutrition (weight gain, increased appetite, and albumin), and better control of anemia. In the only moderate-sized randomized trial that has been done, the Frequent Hemodialysis Network (FHN) trial, where patients were randomized to get six treatments per week but in fact averaged only five, those assigned to more frequent dialysis for 1 year were found to have a reduction in left ventricular hypertrophy, improved physical functioning (those were the two primary outcomes), a reduced severity of hypertension, and marginally improved control of serum phosphate. There was no improvement in serum albumin, nutritional measurements, or control of anemia (FHN Trial Group, 2010). The details of various "daily" hemodialysis regimens are discussed in Chapter 15. Usually, frequent hemodialysis is done at home and is only rarely offered in-center or in self-care units. Such "daily" hemodialysis is gaining in popularity, especially with the availability of easy-to-use machines dedicated to delivering such therapy in the home setting.
4. **Long nocturnal hemodialysis.** With "daily" hemodialysis, the number of hours spent per week on dialysis is usually similar to, or only slightly greater than, the weekly time spent on conventional 3-per-week in-center dialysis. With nocturnal dialysis, substantially longer weekly dialysis times are the norm, because each session typically lasts for 7 to 9 hours. When nocturnal dialysis is given in-center, the usual frequency is 3 times per week, and the weekly dialysis time will be 24 hours per week compared to the usual 12 hours per week with conventional schedules. When applied at home, nocturnal dialysis can be given 3 times per week, every other night, or even 5 to 6 times per week, resulting in markedly more hours per week of treatment than conventional therapy. Long nocturnal dialysis is discussed in more detail in Chapter 15.
5. **Incremental hemodialysis.** Several studies have shown that initiation of a 3-per-week hemodialysis schedule in all patients who start dialysis may not be necessary, as many patients do equally well for one or more years dialyzed on a twice-per-week schedule (Caton, 2023). One approach, based on solute modeling and on one relatively large observational study (Obi, 2016), suggests that twice-a-week dialysis has similar mortality to 3-per-week dialysis as long as residual urine output is greater than 600 mL/d and residual kidney urea clearance is greater than 3.0 mL/min/1.73 m^2. However, studies from China and Korea have found similar initial

mortality with 2-per-week and 3-per-week dialysis regardless of the level of residual kidney function. Some studies have suggested that initiating dialysis using a 2-per-week schedule may help preserve residual kidney function compared to starting out with a conventional 3-per-week schedule, but not all studies have found this.

6. **Peritoneal dialysis (PD).** Due to its relative simplicity, PD offers patients a home-based therapy with very little requirement for special water systems and simple equipment setup time. The percentage of patients choosing PD over hemodialysis is about 12% in the United States and 20% to 30% in Canada. There are two types of PD for a patient to consider: continuous ambulatory peritoneal dialysis (CAPD), where a patient performs manual exchanges 4 or 5 times per day, and automated peritoneal dialysis (APD), where a patient hooks up to a machine at night and exchanges are carried out automatically while the patient sleeps. The relative benefits of each type of PD are discussed more fully in the PD chapters of this handbook.

   Patients for whom PD is often favored include:

   1. Infants or very young children
   2. Patients with severe cardiovascular disease
   3. Patients with difficult vascular access
   4. Patients who desire greater freedom to travel
   5. Patients who wish to perform home dialysis but do not have a suitable partner to assist them

   Contraindications include an unsuitable peritoneum due to the presence of adhesions, fibrosis, or malignancy. Also, a substantial number of patients experience an increase in their peritoneal membrane transport rate over time, resulting in inadequate ultrafiltration. Patients with diabetes tend to have a higher mortality when placed on PD versus hemodialysis, although in recent years this trend appears to have attenuated. A major cause of abandonment of PD is the occurrence of frequent episodes of peritonitis. Patient burnout is also a factor.

   PD is less expensive than hemodialysis, particularly in developing countries. PD allows patients independence and freedom to travel and does not constrain patients to a fixed in-center hemodialysis schedule, although a more flexible schedule is also possible with home hemodialysis. PD may not be the best option for patients who do not have a "do-it-yourself" mentality or who do not have the stability or social and family support at home to carry out a PD program. Some patients simply prefer a hemodialysis schedule of three or more well-defined periods per week during which they can get their dialysis "over with," leaving them free of any other dialysis responsibility. Some patients also enjoy the socialization that occurs in many hemodialysis units, including regular personal interaction with staff and other patients.

   There have been several improvements in PD over the past several years, including better disconnect systems, resulting in decreased peritonitis rates. Also, with the use of APD, there can be improved clearances. New PD solutions have become available, including glucose-based solutions with decreased amounts of glucose degradation products, as well as solutions using amino acids or icodextrin as the osmotic agent.

7. **Postponing dialysis.** In some patients, particularly older adults, who do not have

marked problems with fluid overload, it may be possible to postpone the need for dialysis by prescribing a low- and/or very-low-protein diet (± supplemented with ketoanalogues). Indeed, low-protein diets and very-low-protein diets may mitigate uremic complications and symptoms, including neurologic manifestations, metabolic acidosis, hyperkalemia, and hyperphosphatemia (KDIGO 2024 Clinical Practice Guideline). In carefully selected older patients assigned to this strategy, the need for dialysis was postponed on average by 1 year.

8. **The option not to dialyze: Palliative care.** There are no absolute contraindications to dialysis therapy. In some states, legal precedent exists guaranteeing dialysis to anyone who desires it despite the severity of other medical problems. When a patient is unable to voice their own thoughts and when the family has divided opinions about the desirability of initiation of life support by dialysis, the hospital ethics committee may be of assistance.

   The US Renal Physicians Association has issued clinical practice guidelines for stopping or never beginning dialysis in certain patients (Moss, 2001; Renal Physicians Association, 2010), which provide 10 recommendations for adult patients and 9 for pediatric patients. The guidelines emphasize shared decision-making, informed consent or refusal, estimating prognosis, and a time-limited trial of dialysis where indicated. The adult recommendations are summarized in Table 2.2. Patients with advanced disease in an organ system other than the kidneys, or those with malignancy, have sometimes been excluded from chronic dialysis. For example, those with advanced liver disease might have ascites, encephalopathy, bleeding diathesis, and hypotension. These concomitant problems may make access difficult, and the dialysis treatments may create too much hypotension or fail to correct the accompanying fluid overload. In some such patients, dialysis may be futile. Futility is an ethical principle on which one can make a reasonable decision not to initiate dialysis. On the other hand, some such patients may achieve a good quality of life and "remission" of failure of other affected organ systems with fluid removal, electrolyte balance, and improved nutrition provided by multidisciplinary ESKD management.

TABLE 2.2 Renal Physicians Association Clinical Practice Guidelines (for Adult Patients)

Shared Decision-Making in the Appropriate Initiation of and Withdrawal From Dialysis
1. Develop a physician-patient relationship for shared decision-making.
2. Fully inform patients with AKI, stages 4 and 5 CKD, and ESKD about their diagnosis, prognosis, and all treatment options.
3. Give all patients with AKI, stage 5 CKD, or ESKD an estimate of prognosis specific to their overall condition.
4. Institute advance care planning.
5. If appropriate, forgo (withhold initiating or withdraw ongoing) dialysis for patients with AKI, CKD, or ESKD in certain, well-defined situations.
6. Consider forgoing dialysis for patients with AKI, CKD, or ESKD who have a very poor prognosis or for whom dialysis cannot be provided safely.
7. Consider a time-limited trial of dialysis for patients requiring dialysis, but who have an uncertain prognosis, or for whom a consensus cannot be reached about providing dialysis.
8. Establish a systematic due process approach for conflict resolution if there is disagreement about what decision should be made with regard to dialysis.
9. To improve patient-centered outcomes, offer palliative care services and interventions to all AKI, CKD, and

ESKD patients who suffer from the burdens of their disease.

10. Use a systematic approach to communicate about diagnosis, prognosis, treatment options, and goals of care.

AKI, acute kidney injury; CKD, chronic kidney disease; ESKD, end-stage kidney disease.
Source: Renal Physicians Association, Second Edition, 2010.

C. Older patients and dialysis. In the United States and elsewhere, the fastest-growing age group presenting for dialysis is the "oldest old" (patients older than 80 years). Access placement in this group is not particularly difficult, and cuffed venous catheters have been used with success in difficult cases. Time constraints are not a problem, and these individuals often arrive eager for their treatments. Transportation often is available from assisted-living providers, retirement community staff, or municipal programs. A high rate of compliance with all aspects of treatment often offsets a higher prevalence of comorbid (cardiac, vascular, malignancies) conditions in achieving a good outcome. As a result, many older patients placed on dialysis continue to enjoy a good quality of life and benefit from documented improvement in a variety of health outcome measures.

D. Adolescents on dialysis. The decision-making process for treating pediatric and adolescents with ESKD is complex. Multiple considerations are involved, including medical and social factors, quality of life, and patient/family preference. Other issues include depression and frustration with medical orders, interpersonal conflicts with family members, poor attendance at school due to frequent hospital admissions, and peer pressure because of the inability to participate in school sports. This may manifest as a flat affect (limited social interactions and evasion of communication) and nonadherence to medications, diet, and missed clinic visits. Psychological support and social worker input are key. Most pediatric patients use an external percutaneous catheter as their access at the time of initiation of dialysis. They usually start dialysis with the expectation that successful renal transplantation is an achievable goal and will provide the best survival and quality of life, perhaps explaining the relatively infrequent use of an arteriovenous (AV) fistula for vascular access in this population.

II. DIALYSIS ACCESS PLACEMENT ISSUES.

For hemodialysis, the preferred access is an AV fistula. For all patients for whom renal replacement therapy is anticipated, the veins in both arms should be preserved and the use of the nondominant arm should be considered first. All venipunctures should be drawn from the back of the hand where possible. Ideally, venous mapping using ultrasound should be performed before the creation of an AV fistula. The use of PICC (percutaneous intravenous central catheter) lines should be avoided especially in patients with serum creatinine (SCr) level greater than 1.5 or an eGFR less than 30 mL/min/1.73 m^2, as these often result in central vein stenosis with future access outflow problems. Because some patients have veins that are fragile, creating access early is important; that is, 6 to 9 months before the anticipated initiation of dialysis. A lead time of at least 6 months prior to anticipated dialysis may allow correction of suboptimal flow or placement of a second fistula if the initial fistula does not function properly. Vascular access issues are discussed in detail in several chapters of this handbook.

For PD, a peritoneal catheter should be in place at least 2 weeks prior to the anticipated start of dialysis. In the past, an AV fistula was recommended as a fallback option for patients who choose PD. This is no longer recommended but is practiced in some centers. In situations where urgent start of dialysis is needed, a recent trend is to place a peritoneal catheter, which then allows initial control of uremia by PD and buys time for subsequent

placement of an AV fistula.

III. WHEN TO INITIATE DIALYSIS

A. Uremia is associated with symptoms and signs that result from toxic effects of elevated levels of nitrogenous and other wastes in the blood.

1. **Symptoms.** Uremic patients commonly become nauseated and often vomit soon after awakening. They may lose their appetite such that the mere thought of eating makes them feel ill. They often feel fatigued, weak, and/or cold. Their mental status is altered; at first, only subtle changes in personality may appear, but eventually, the patients become confused and, ultimately, comatose.
2. **Signs.** Signs of uremia are less common because patients typically present at relatively early stages of uremia. Detecting uremic complications should remain a priority. Key complications include:
   a. **Uremic pericarditis.** This should be suspected in a uremic patient presenting with sudden chest pain that worsens on inspiration and in the supine position, a pericardial friction rub with typically three components, related to atrial systole, ventricular systole, and rapid ventricular filling during diastole. The electrocardiogram (ECG) is often normal. Tamponade should be suspected when the patient is tachycardic, hypotensive, and has distended neck veins and there is a paradoxical pulse pressure drop of more than 10 mm Hg during inspiration (pulsus paradoxus). Uremic pericarditis is an urgent indication for dialysis treatment.
   b. **Encephalopathy.** The presentation can be variable; in mild cases, one sees slowly progressive cognitive decline, restlessness, drowsiness, and diminished ability to concentrate. In more severe instances, there is confusion, delirium, seizures, disorientation, emotional volatility, and coma. Tremor, inability to perform calculations, impaired memory, hyperreflexia, asterixis, multifocal myoclonus, or seizures are signs of uremic encephalopathy. There is no specific confirmatory test to diagnose uremic encephalopathy. A computed tomography scan of the brain can exclude focal lesions. Magnetic resonance imaging shows widespread involvement with abnormalities in the cortex, subcortical white matter, basal ganglia, and hippocampus. Posterior reversible leukoencephalopathy syndrome may be seen in the cortex and subcortex. The electroencephalogram is usually nondiagnostic. Immediate initiation of hemodialysis with a deliberately low initial rate of solute removal (to avoid disequilibrium syndrome) is indicated.
   c. **Platelet dysfunction.** Bleeding may be observed in uremic patients because of abnormalities in platelet function and impaired platelet-vessel wall interaction. The main cause is the presence of uremic toxins present in the blood. Dialysis improves platelet abnormalities and reduces, but does not eliminate, the risk of hemorrhage.
3. **Signs and symptoms of uremia versus anemia.** The contribution of anemia to the uremic syndrome symptom complex remains uncertain. In one study, when the hemoglobin level in a range of 8.5 to 10.0 g/dL in adults with CKD stages 3 to 5 was corrected to achieve and maintain a target hemoglobin of 11 to 12 g/dL over 28 weeks with an oral novel hypoxia-inducible factor prolyl hydroxylase inhibitor

(HIF-PHI) and compared to placebo, there was a statistically significant improvement in a key patient vitality score (Johansen, 2023). Correcting anemia reduces the rate of blood transfusion, which mitigates the risk of allosensitization in potential kidney transplant recipients.

B. Indications for dialysis in the chronic setting. Usually, dialysis is initiated in adult patients when the eGFR/1.73 m^2 decreases to about 8 mL/min. There is now consensus among several high-quality clinical practice guidelines that initiating dialysis based on manifestations of the uremic syndrome and/or emergent complications of uremia, coupled with shared decision-making, is currently recommended (Salas-Gama, 2022). However, evaluation of the need for dialysis should begin at a higher eGFR/1.73 m^2 level, probably around 10 to 12 mL/min, and sometimes higher. Patients with heart failure and borderline eGFRs may have trouble with refractory fluid retention and may require earlier initiation of dialysis. Conditions that may argue for relatively early initiation of dialysis are listed in Table 2.3.

TABLE 2.3 Complications That May Prompt Initiation of Kidney Replacement Therapy

Intractable extracellular volume overload and/or hypertension
Hyperkalemia refractory to dietary restriction and pharmacologic treatment
Metabolic acidosis refractory to bicarbonate treatment
Hyperphosphatemia refractory to dietary counseling and to treatment with phosphate binders
Anemia refractory to erythropoietin and iron treatment
Otherwise unexplained decline in functioning or well-being
Recent weight loss or deterioration of nutritional status, especially if accompanied by nausea, vomiting, or other evidence of gastroduodenitis
Urgent Indications
Neurologic dysfunction (eg, neuropathy, encephalopathy, psychiatric disturbance)
Pleuritis or pericarditis without other explanation
Bleeding diathesis manifested by prolonged bleeding time

Data from the National Kidney Foundation's 2006 Kidney Disease Outcomes Quality Initiative (KDOQI) hemodialysis adequacy guidelines.

It should be noted that pericarditis or pleuritis without other cause is an indication for urgent dialysis, particularly pericarditis, where the risk of rapidly developing pericardial effusion and cardiac tamponade is present. Neurologic dysfunction, especially signs of encephalopathy (manifested by asterixis) or uremic neuropathy, is also an indication for prompt dialysis, as is prolongation of the bleeding time, which could lead to gastrointestinal or other bleeding.

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PART II

Blood-Based Therapies

3 Physiologic Principles and Urea Kinetic Modeling

John T. Daugirdas

Dialysis is a process whereby the solute composition of a solution, A, is altered by exposing solution A to a second solution, B, through a semipermeable membrane. Conceptually, one can view the semipermeable membrane as a sheet perforated by holes or pores. Water molecules and low-molecular-weight solutes in the two solutions can pass through the membrane pores and intermingle, but larger solutes (such as proteins) cannot pass through the semipermeable barrier, and the quantities of high-molecular-weight solutes on either side of the membrane will remain unchanged.

I. MECHANISMS OF SOLUTE TRANSPORT.

Solutes that can pass through the membrane pores are transported by two different mechanisms: diffusion and ultrafiltration (convection).

A. Diffusion.

The movement of solutes by diffusion is the result of random molecular motion. The larger the molecular weight of a solute, the slower will be its rate of transport across a semipermeable membrane. Small molecules, moving about at high velocity, will collide with the membrane often, and their rate of diffusive transport through the membrane will be high. Large molecules, even those that can fit easily through the membrane pores, will diffuse through the membrane slowly because they will be moving about at low velocity and colliding with the membrane infrequently (Figure 3.1).

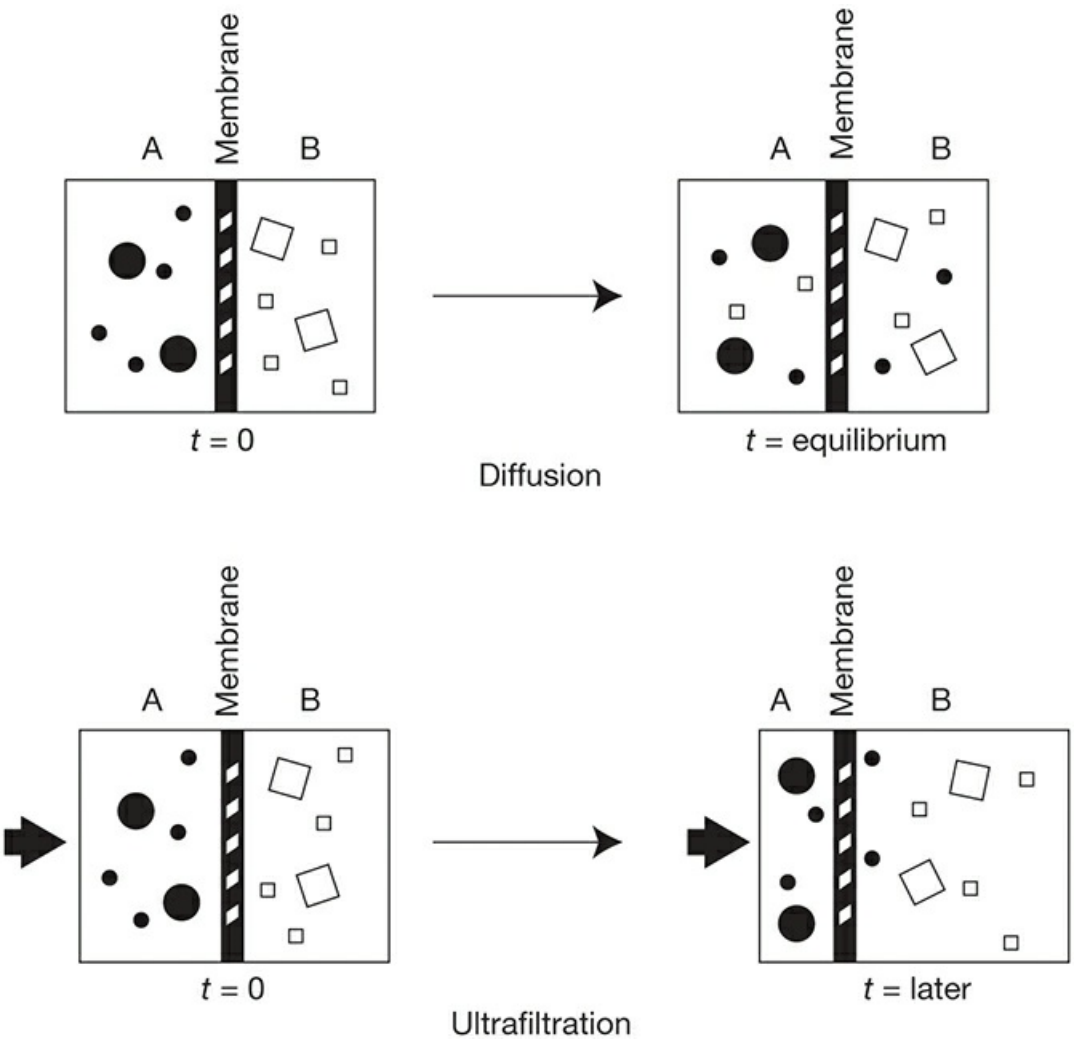


FIGURE 3.1: The processes of diffusion (top) and ultrafiltration (bottom). As shown, in both processes, low-molecular-weight solutes can cross the semipermeable membrane, whereas larger solutes are held back.

B. Ultrafiltration. The second mechanism of solute transport across semipermeable membranes is ultrafiltration (convective transport). Water molecules are extremely small (molecular weight, 18 Da [daltons]) and can pass through all semipermeable membranes. Ultrafiltration occurs when water driven by either a hydrostatic or an osmotic force is pushed through the membrane (Figure 3.1). Those solutes that can pass easily through the membrane pores are swept along with the water (a process called "solvent drag"). The water being pushed through the membrane carries solutes at close to their original concentrations. Analogous processes are wind sweeping along leaves and dust as it blows and current in the ocean moving both small and large fish as it flows. Larger solutes, especially those that are larger than the membrane pores, are held back. For such large solutes, the membrane acts as a sieve.

1. **Hydrostatic ultrafiltration**
   a. **Transmembrane pressure.** During hemodialysis, water (along with small solutes) moves from the blood to dialysate in the dialyzer as a result of a hydrostatic pressure gradient between the blood and dialysate compartments.

The rate of ultrafiltration will depend on the total pressure difference across the membrane (calculated as the pressure in the blood compartment minus the pressure in the dialysate compartment).

b. **Ultrafiltration coefficient (K_{UF}).** The permeability of dialyzer membranes to water, although high, can vary considerably and is a function of membrane thickness and pore size. The permeability of a membrane to water is indicated by its ultrafiltration coefficient, K_{UF}. K_{UF} is defined as the number of milliliters of fluid per hour that will be transferred across the membrane per millimeters of mercury (mm Hg) pressure gradient across the membrane.

2. **Osmotic ultrafiltration.** Osmotic ultrafiltration is described in Chapter 19. In hemodialysis, the amount of osmotic ultrafiltration usually is minimal, because the osmolality of standard dialysis solution is deliberately set to be close to that of normal serum. However, osmotic ultrafiltration may play a role when the dialysis solution sodium concentration is deliberately set to an elevated or reduced value.
3. **Purpose of ultrafiltration.** Ultrafiltration during dialysis is performed for the purpose of removing water accumulated either by ingestion of fluid or by metabolism of food during the interdialytic period. Typically, a patient being dialyzed thrice weekly will gain 1 to 4 kg of weight between treatments (most of it water), which will need to be removed during a 3.5- to 5-hour period of dialysis. Patients with acute fluid overload may need more rapid fluid removal. Thus, the clinical need for ultrafiltration usually ranges from 0.5 to 1.2 L/h.
4. **Use of ultrafiltration to enhance solute clearance**
   a. **Hemofiltration and hemodiafiltration.** Whereas diffusive removal of a solute depends on its size, all ultrafiltered solutes below the membrane pore size are removed at approximately the same rate. This principle has led to use of a technique called *hemofiltration,* whereby a large amount of ultrafiltration (more than is required to remove excessive fluid) is coupled with infusion of a replacement fluid in order to remove solutes. Although hemodialysis and hemofiltration often show comparable removal of small solutes such as urea (molecular weight 60 Da), hemofiltration can effect much higher removal of larger, poorly diffusible solutes, such as inulin (molecular weight 5,200 Da). More commonly, hemodialysis and hemofiltration are combined. The procedure is then called *hemodiafiltration.*

C. Removal of protein-bound compounds. The normal kidney detoxifies protein-bound organic acids and bases. Being protein bound, they are filtered to only a small extent and so bypass the glomerulus. However, in the peritubular capillary network, these substances are removed from albumin and are taken up by proximal tubular cells. Then they are secreted into the tubular lumen, to be excreted in the urine. Other protein-bound compounds (bound to albumin and small proteins) are filtered in the glomerulus along with their carrier proteins. In the proximal tubule, the filtered proteins are catabolized along with their bound compounds.

The serum concentration of such protein-bound substances is markedly elevated in patients undergoing dialysis (Lee, 2022), but the association between high blood levels of these compounds and mortality is not completely clear (van Gelder, 2020). Removal of protein-bound compounds by hemodialysis depends on the percentage of the “free” fraction of the compound in plasma (the fraction that is exposed to dialysis). Also,

removal depends on how quickly the free fraction is replenished by the protein-bound pool. Substances that are tightly bound to proteins with a low free fraction in the plasma will be removed to only a small extent by conventional hemodialysis.

II. SOLUTE REMOVAL FROM THE PERSPECTIVE OF THE DIALYZER. In clinical use, the box containing two solutions in Figure 3.1 becomes the dialyzer, containing blood and dialysis solution. The latter consists of highly purified water to which sodium, potassium, calcium, magnesium, chloride, bicarbonate, and dextrose have been added. The low-molecular-weight waste products that accumulate in uremic blood are absent from the dialysis solution. When uremic blood is exposed to dialysis solution, the flux rate of these waste solutes from blood to dialysate is initially much greater than the back-flux from dialysate to blood. Eventually, if the blood and dialysate were left in static contact with each other via the membrane, the concentration of permeable waste products in the dialysate would become equal to that in the blood, and no further net removal of waste products would occur. Transport back and forth across the membrane would continue, but the rates of transport and back-transport would be equal. In practice, during dialysis, concentration equilibrium is prevented, and the concentration gradient between blood and dialysate is maximized, by continuously refilling the dialysate compartment with fresh dialysis solution and by replacing dialyzed blood with undialyzed blood. Normally, the direction of dialysis solution flow is opposite to the direction of blood flow (Figure 3.2). The purpose of "countercurrent" flow is to maximize the concentration difference of waste products between blood and dialysate in all parts of the dialyzer.

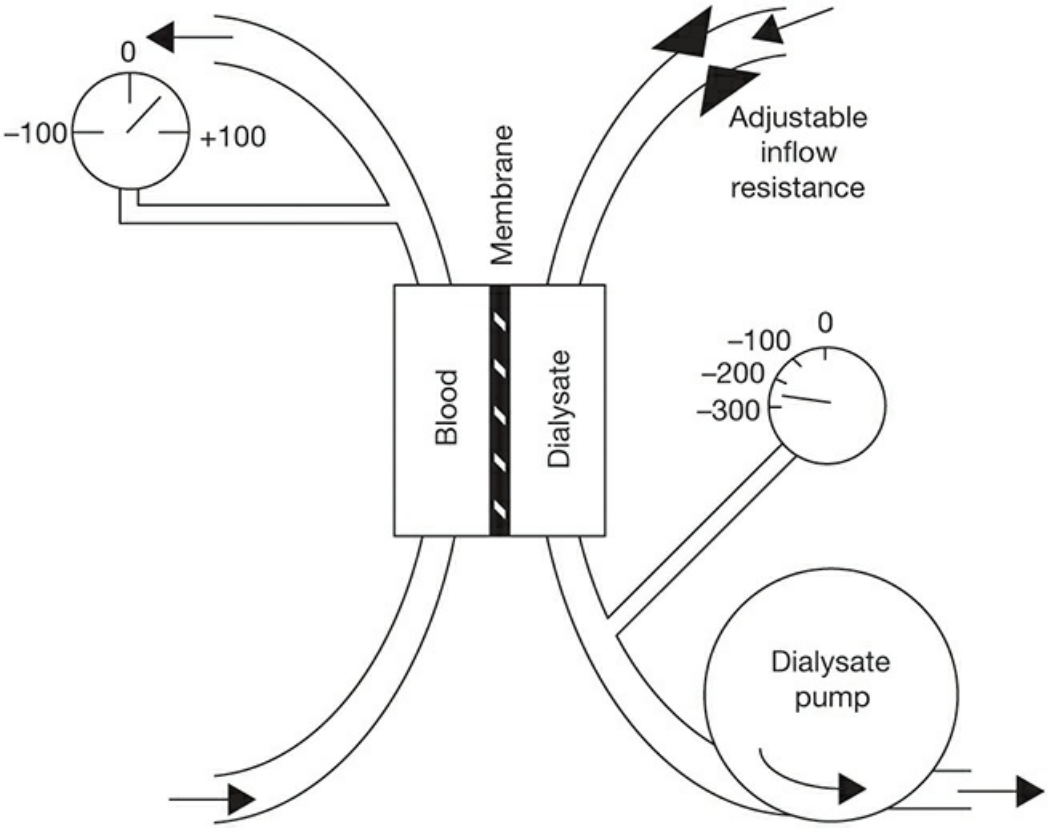


FIGURE 3.2: A dialyzer with blood flowing in one direction and dialysis solution flowing in the opposite direction. Hydrostatic pressure across the membrane (and ultrafiltration) is adjusted by varying the resistance to inflow of dialysis solution.

A. Extraction ratio. Figure 3.3 shows a schematic of a dialyzer and its effects on the serum urea nitrogen (SUN) concentration of blood entering and leaving the dialyzer. The extraction ratio is the percentage reduction of urea (or any other solute) across the dialyzer. In the case shown, with blood flow rate **(**Q_B) of 400 mL/min, the inlet SUN is 100 mg/dL and the outlet concentration is 40 mg/dL; hence, the extraction ratio is 60% (100 − 40)/100. The extraction ratio is not affected by the inlet SUN level. Under the same conditions, if the inlet SUN were 200 mg/dL, the outlet SUN would be 80, and if the inlet SUN were 10, the outlet SUN would be 4.

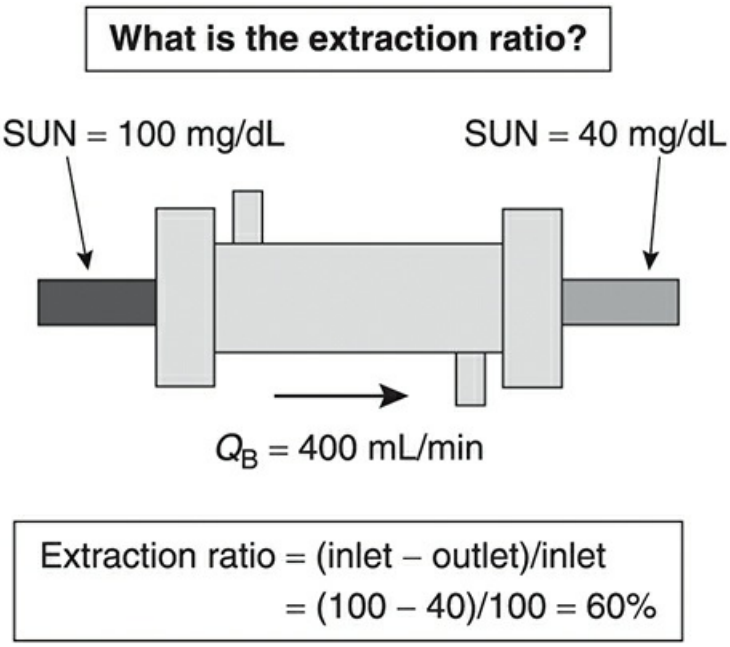


FIGURE 3.3: The dialyzer extraction ratio for urea as a function of inlet and outlet urea concentration. SUN, serum urea nitrogen.

The extraction ratio is affected by the rate of blood flow through the dialyzer (Figure 3.4). If blood flow rate were reduced from 400 to 200 mL/min, the outlet SUN would decrease from 40 to 12 mg/dL. If blood flow rate were reduced to 1 mL/min, the outlet SUN would be very low, about 1 mg/dL, and if a very high rate of blood flow were used, 20 L/min, the outlet SUN would increase to about 97 mg/dL. The faster the blood flows through the dialyzer, the less time it spends in the filter. The dialyzer blood compartment volume is about 100 mL, so at a flow rate of 400 mL/min, the blood is spending about 15 seconds in the dialyzer. On reducing the flow to 200 mL/min, the transit time doubles, to 30 seconds, and because of this, the blood has more time to be "cleaned," and the SUN in the blood exiting the dialyzer is only 12 mg/dL. On reducing flow to 1 mL/min, the blood would spend a full 100 minutes in the dialyzer, and the outlet blood would have a very low concentration of urea nitrogen. On the other hand, at a very rapid flow rate, much higher than could be achieved in practice, say 20,000

mL/min, the blood would spend only 0.3 seconds in the dialyzer. Still, the outlet SUN would be lower than the inlet and might be about 97 mg/dL. In effect, the dialyzer is a "washing machine," and the less time the blood spends in the machine, the lower the percentage of waste products removed from a given volume of blood.

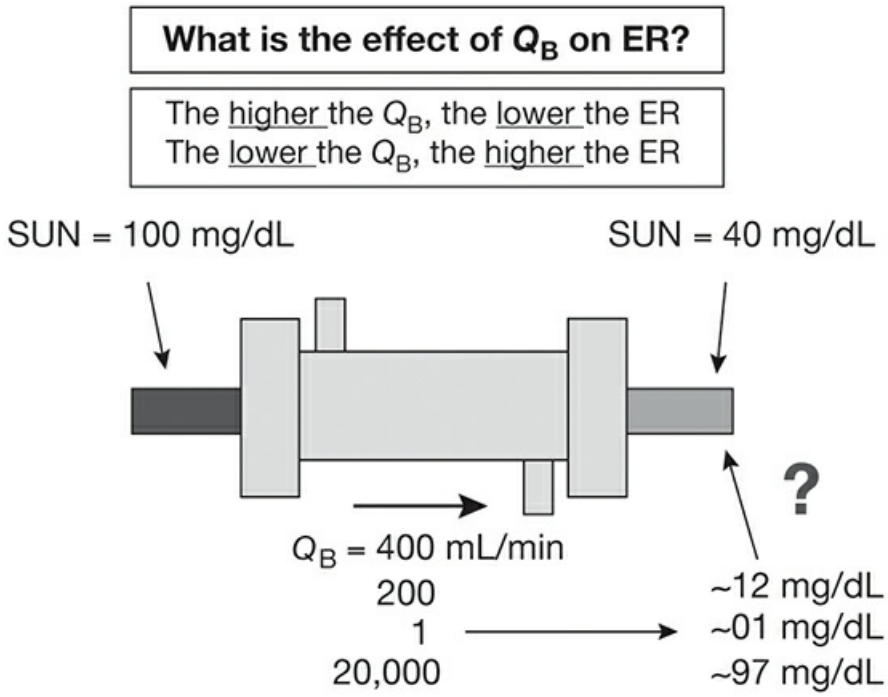


FIGURE 3.4: Effect of blood flow rate on the outlet serum urea nitrogen (SUN).

B. Concept of clearance. As shown in Figure 3.5, the blood exiting the dialyzer can be considered in one of two ways. One can consider the entire volume and the percentage reduction of solute in that volume, or one can separate out the flow exiting the dialyzer into two streams—in the first stream, the concentration of solute will be the same as the inlet concentration, and in the second stream, all urea nitrogen will have been removed. One can think of an extraction ratio or reduction in SUN of 60% for the combined outlet stream, or one can consider that 60% of the fluid flowing through the dialyzer has been completely cleared of urea. If we mix the unchanged stream with the cleared stream, the concentration of urea nitrogen in the mixed stream will be reduced by 60% relative to that in the dialyzer inlet. One can calculate what the relative flow rates of the unchanged stream and the cleared stream would need to be to achieve mass balance. In this case, the flow rate of the cleared stream is simply 60% of the inlet flow rate. If the inlet flow rate is 400 mL/min, the flow rate of the cleared stream would be 0.60 × 400 = 240 mL/min, and the flow rate of the unchanged stream would be 160 mL/min. Thus, a dialyzer extraction ratio of 60% translates into a dialyzer clearance of 0.6 × blood inflow rate (Q_B), or 240 mL/min. Clearance is usually abbreviated as "K" or "K_D." Flow rate is abbreviated as "Q," blood flow rate as "Q_B," and dialysate flow rate as "Q_D."

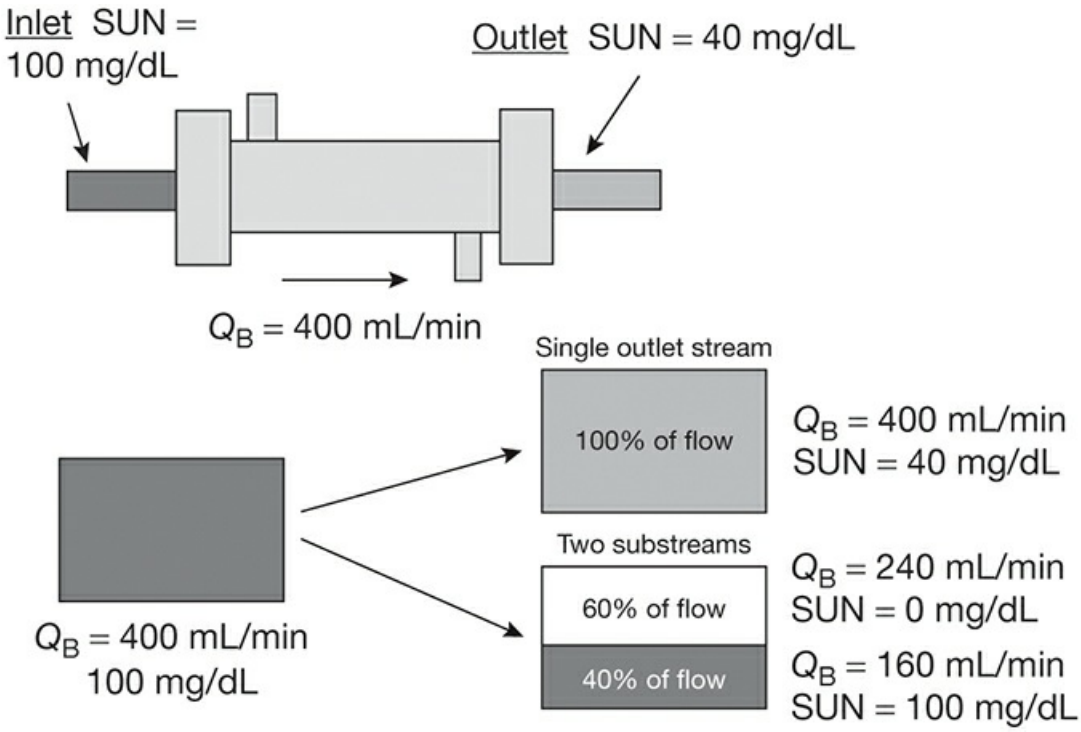


FIGURE 3.5: Concept of dialyzer clearance. The blood exiting the dialyzer can be looked at in two ways: (1) as one outlet stream where the solute concentration has been reduced by 60% (from 100 to 40 mg/dL) or (2) as two substreams: in one substream the solute concentration is unchanged, and in the other substream the solute has been completely removed. The flow rate of the cleared substream is the dialyzer "clearance" and is equal to the extraction ratio multiplied by the blood flow rate. SUN, serum urea nitrogen.

1. **Effect of dialyzer blood flow rate on clearance.** We now can look at the effects of blood flow (Q_B) on dialyzer clearance (K_D). From Table 3.1, we see that when blood flow is very low, 50 mL/min, the blood in the dialyzer is cleaned very well, due to a long residence time in the dialyzer, and the outlet SUN is only 1 mg/dL, with an extraction ratio of 99%. However, the amount of blood cleared is limited by the flow rate of 50 mL/min; although 99% of the blood is cleared, 99% of 50 mL/min is a low number. When the blood flow rate is increased, the blood is only partially cleared of urea due to less time spent in the dialyzer, but even though the extraction ratio falls as blood flow rate is increased, the volume of blood cleared of urea nitrogen keeps increasing as the blood flow rate is increased. Ultimately, when blood flow rate is very high, 20 L/min, the clearance in this particular example is 600 mL/min, even though the inlet SUN is reduced by only 3% at the dialyzer outlet.

TABLE 3.1 Effect of Dialyzer Blood Flow Rate on Extraction Ratio and Clearance (inlet SUN = 100 mg/dL)

Q_B (mL/min)	Outlet SUN (mg/dL)	Extraction Ratio (ER, %)	K_D (ER × Q_B)
50	1	99	50
200	12	88	176
400	40	60	240

500	48	52	260
20,000	97	3	600

SUN, serum urea nitrogen.

2. **The K_0A, mass transfer area coefficient.** If the extraction ratio remained constant at 60%, a doubling of the blood flow rate would double the clearance. However, removal efficiency falls at higher blood flow rates, and so the clearance does not increase with Q_B in a 1:1 ratio. Ultimately, at very high blood flow rate, the clearance will plateau. The theoretical maximum clearance of a dialyzer (for a given solute) at infinite blood and dialysate flow rates is called the K_0A and has units of mL/min. For the dialyzer in Table 3.1, the K_0A is close to 600 mL/min. The K_0A also has a physical aspect. It is the multiple of two quantities: K_0, the permeability coefficient of the dialyzer membrane for a given solute, and A, the total effective surface area of the membrane in the dialyzer. Doubling the surface area of the membrane in a dialyzer will roughly double the K_0A. Two dialyzers of the same surface area do not necessarily have the same K_0A, as the K_0 values of the membranes used in those dialyzers can be markedly different. The K_0 can be increased by making the membrane thinner, by adjusting its porosity, and by optimizing the fluid path of dialysate in the dialyzer using spacer yarns and other features.

   Figure 3.6 shows the relationship between blood flow rate (Q_B) on the horizontal axis and expected dialyzer clearance (K_D) on the vertical axis. Each isopleth (curved line) represents a different efficiency dialyzer, where dialyzer efficiency is expressed as dialyzer K_0A. The values of K_0A in Figure 3.6 range from 400 to 1,600 mL/min. Most dialyzers in common use today for adults have K_0A values of 1,000 to 1,600 mL/min. This figure shows that as the blood flow is increased, the clearance increases, but the increase tends to level off. You can see that when Q_B is low (~200 mL/min), dialyzers in the 1,000 to 1,600 mL/min K_0A range have similar clearances. This is because at this low blood flow rate, they are each extracting almost all of the urea in the blood entering the dialyzer. The benefits of a “high-efficiency” (high K_0A) dialyzer become apparent primarily when the blood flow rate is high. Then the larger dialyzers with thinner, more efficient membranes are able to keep the extraction rate high, maximizing the increase in dialyzer clearance.

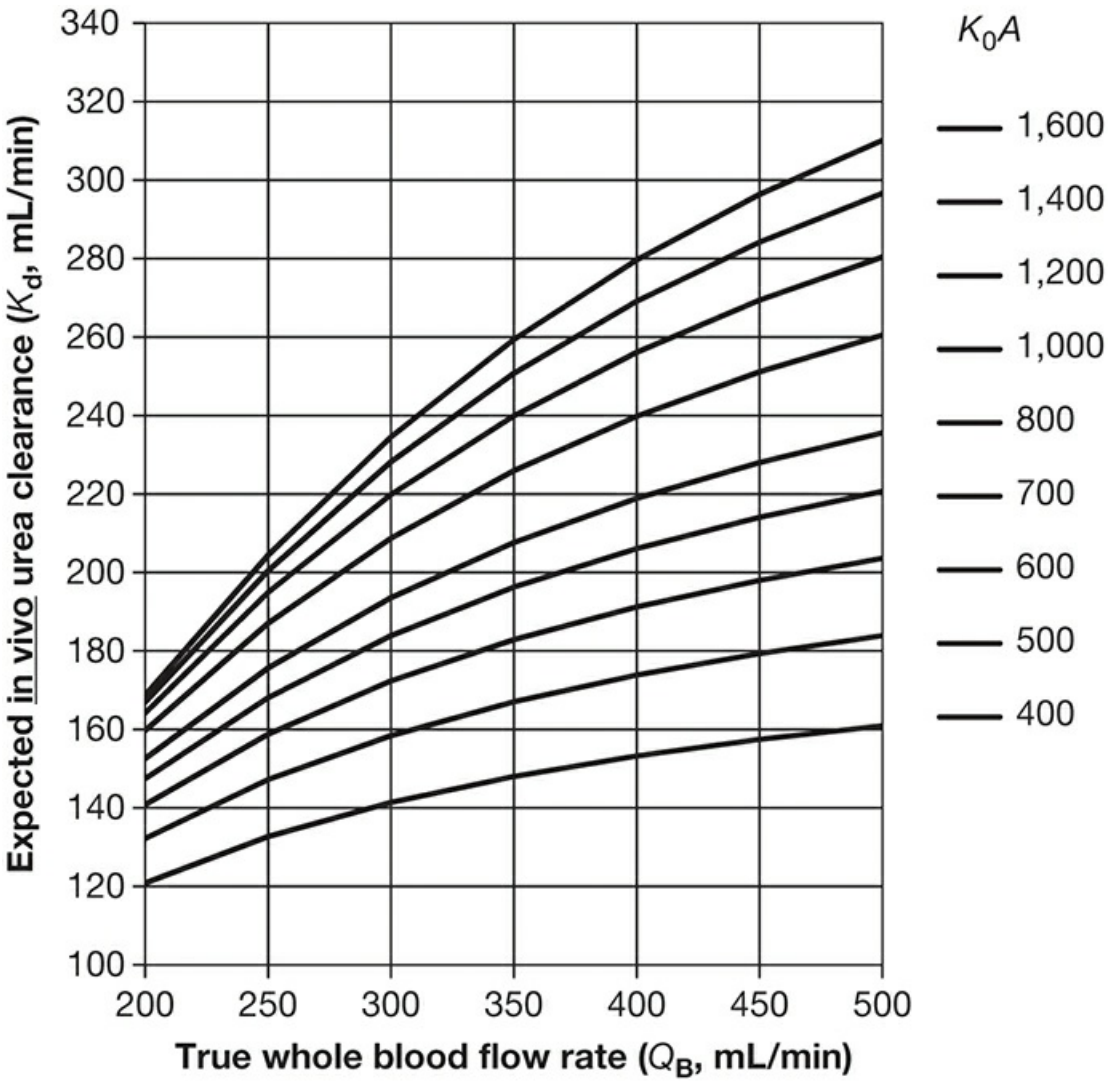


FIGURE 3.6: Relationship between blood flow rate (Q_B) and dialyzer blood water urea clearance (K) as a function of dialyzer efficiency (K_0A). Each isopleth (curved line) represents a different dialyzer having a different K_0A value. To use the nomogram, find the blood flow rate on the horizontal axis, then move up to the dialyzer K_0A being used, and read the expected dialyzer urea clearance on the vertical axis. Theoretical clearance values have been adjusted to more closely reflect expected values in vivo.

3. **Calculating the solute removal rate.** For a situation where a uniform solution is running through the dialyzer, one can calculate the removal rate (in mg/min or mmol/min) of a given solute. For example, if the inlet SUN is 1 mg/mL and we are clearing urea from 240 mL/min of blood, then we are removing 240 mg/min of urea nitrogen from the patient.
4. **Effect of erythrocytes.** In the concept of clearance described earlier, the blood was treated as a simple fluid. However, this is not the case. At a hematocrit of 30%, a blood flow of 400 mL/min is really a plasma flow rate of 280 mL/min and an erythrocyte flow rate of 120 mL/min. What is measured at the dialyzer inlet and outlet are the serum levels of a given waste product. For urea, the presence of erythrocytes is not a major problem because urea diffuses into and out of erythrocytes quickly. For example, if the outlet SUN level is 40 mg/dL, the urea

concentration in erythrocytes will also have been reduced to about that level. For creatinine and phosphate and many other solutes, the problem is more complex because these substances do not equilibrate quickly between plasma and erythrocytes. In fact, very little creatinine or phosphate is removed from red blood cells during passage through the dialyzer. When calculating the removal rate of creatinine or phosphate, one needs to use the plasma flow rate instead of the blood flow rate.

5. **Effect of blood water.** As noted, urea is dissolved in erythrocytes and plasma water and is removed from both during passage through the dialyzer. Approximately 93% of plasma is water (depending on its protein concentration), and about 72% of an erythrocyte is water. Some urea associates with the nonwater portion of erythrocytes. On average, urea is dissolved in a volume that is about 86% of the blood (the usual correction is 89% due to some urea binding within the red blood cell). The correction for blood water becomes important when using the dialyzer clearance to compute how much urea is being removed during a dialysis session.
   For solutes like creatinine and phosphate that are removed from the plasma compartment only, the volume of removal is about 93% of the plasma flow rate. Increasing the hematocrit (eg, from 20% to 40%) causes only a trivial reduction of the blood water urea clearance but will be associated with a noticeable reduction in the clearance of creatinine or phosphate, due to the effect of hematocrit on the plasma flow rate.
6. **Effect of dialysis solution flow rate.** Dialyzer clearance of urea (and other solutes) depends on the dialysis solution flow rate as well. A faster dialysis solution flow rate increases the efficiency of diffusion of urea from blood to dialysate although the effect is usually modest. The usual dialysis solution flow rate is 500 mL/min. A flow rate of 800 mL/min (typically, but not always) will increase urea clearance by about 5% to 8% when a high-efficiency dialyzer is used and when the blood flow rate is greater than 350 mL/min. On the other hand, in some daily, nocturnal, or intensive care unit-based applications, dialysate flow rate is markedly lower than 500 mL/min. Such a reduced dialysate flow rate can cause substantial reduction in dialyzer clearance. The optimum dialysis solution flow rate is 1.5 to 2.0 times the blood flow rate. Above that, the increase in efficiency is quite small, especially with some of the newer dialyzers where the dialysis solution flow path has been optimized.
7. **Effect of solute molecular weight on diffusive clearance.** Because high-molecular-weight solutes move slowly through solutions, they diffuse poorly through the membrane. As a result, the extraction ratio for molecules larger than urea will be less than that of urea; plus, to calculate clearance, this lower extraction ratio must be multiplied by the plasma flow rate and not the blood flow rate.
8. **Very large molecules.** Very large molecules, such as β_2-microglobulin (molecular weight 11,800 Da), cannot get through the pores of so-called “low-flux” dialysis membranes at all. Thus, dialyzer clearance of β_2-microglobulin when using a low-flux dialyzer will be close to zero! “High-flux” membranes have pores of sufficient size to pass this large molecule. A small minority of dialysis membranes also remove β_2-microglobulin by adsorption.
9. **Dialyzer efficiency versus flux.** When we speak of dialyzer efficiency, we refer

primarily to the ability of a dialyzer to remove small solutes. The dialyzer efficiency is best represented by the K_0A for urea. The flux of a dialyzer refers to its ability to remove very large molecules such as β_2-microglobulin. There is no single measure in common use to specify the flux of a dialyzer, though water permeability ($\boldsymbol{K_{UF}}$) can be used. Usually high-flux dialyzers will have a water permeability greater than 15 to 20 mL/h/mm Hg. One can have a small, low-efficiency (K_0A = 400 mL/min) dialyzer (eg, for use in children) that is high flux, or a high-efficiency dialyzer (K_0A = 1,200 mL/min) that is low flux and that removes urea very well but no β_2-microglobulin.

III. SOLUTE REMOVAL FROM THE PATIENT PERSPECTIVE

A. Importance of urea. Measurement of solute removal during hemodialysis focuses on urea. Urea is manufactured by the liver from amino acid nitrogen via ammonia and is the principal way in which nitrogenous waste products are excreted from the body. Urea is a small molecule, with a molecular weight of 60 Da. In the past, higher levels of serum urea in dialysis patients were thought to be only slightly toxic. However, the level of serum urea in end-stage kidney disease is associated with the amount of protein carbamylation (Kairaitis, 2000). Carbamylation is a nonenzymatic post-translational modification of proteins resulting from a reaction between those proteins and cyanate, a urea by-product. High levels of protein carbamylation are strongly associated with morality in dialysis patients (Koeth, 2013). Urea generation occurs in proportion to protein breakdown as reflected in the protein nitrogen appearance (PNA) rate. In stable patients, the PNA is proportional to dietary protein intake. Using a mathematical model known as urea kinetics, one can compute both the rate of removal and production of urea. The extent of urea removal gives a measure of the adequacy of dialysis, and the amount of urea nitrogen generation gives an estimate of dietary protein intake.

B. The weekly SUN profile. As a result of dialysis, the predialysis SUN level is typically reduced by about 70% so that postdialysis SUN is 30% of the predialysis value. During the subsequent interdialytic period (assuming a thrice-weekly dialysis schedule), the SUN will rise to almost the same level as that seen prior to the first treatment. The result is a sawtooth pattern. The time-averaged concentration (TAC) of SUN can be computed mathematically as the area under the sawtooth curve divided by time. Both the predialysis SUN and TAC SUN levels reflect the balance between urea production and removal. For a given level of dialysis therapy, predialysis SUN and TAC SUN will rise if urea nitrogen generation (g) is increased and will fall if g is decreased. Also, for any given rate of urea nitrogen generation, predialysis SUN and TAC SUN levels will rise if the amount of dialysis is decreased or will fall if the amount of dialysis is increased.

C. Pitfalls in targeting a predialysis SUN or TAC SUN. Early attempts to model dialysis adequacy focused on predialysis SUN or on the TAC SUN. Therapy was thought to be adequate as long as predialysis or TAC SUN was appropriately low. However, low predialysis or TAC SUN levels were found to be associated with a high mortality rate and were found to most often reflect inadequate protein intake rather than adequate dialysis.

D. Indices of urea removal

1. **Urea reduction ratio (URR).** The current primary measure of dialysis adequacy is the treatment-related URR. This is computed as follows: Assume that predialysis SUN is 60 mg/dL and postdialysis SUN is 18 mg/dL. The relative reduction in SUN (or urea) level is (60 − 18)/60 = 42/60 = 0.70. By convention, URR is expressed as a percentage, so the value of URR in this example would be 70%.
   SI units: Assume that predialysis serum urea is 21 mmol/L and postdialysis is 6.4 mmol/L. The relative reduction in SUN (or urea) level is (21 − 6.4)/21 = 14.6/21 = 0.70.
2. ***Kt/V* urea.** The *Kt*/*V urea* was popularized by Gotch and Sargent (1985) in their reanalysis of the National Cooperative Dialysis Study. In that study, a urea *Kt*/*V* value less than 0.8 was found to be associated with a high likelihood of morbidity and/or treatment failure, while a *Kt*/*V* greater than 1.0 was associated with a good outcome. Largely because of this study, guideline groups have recommended a minimum *Kt*/*V* value of at least 1.2 for hemodialysis patients being dialyzed 3 times/wk.

   The *Kt*/*V urea* is a dimensionless ratio representing volume of plasma cleared of urea (*Kt*) divided by the urea distribution volume (*V*). *K* is the dialyzer blood water urea clearance (L/h), *t* is dialysis session length (hours, h), and *V* is the distribution volume of urea (liters, L), which is close to total body water.

   $K \times t$ = L/h × h = L

   V = L

   $(K \times t)/V$ = L/L = dimensionless ratio

   If we deliver a *Kt*/*V* of 1.0, this implies that $K \times t$, or the total volume of blood cleared during the dialysis session, is equal to *V*, the urea distribution volume.
3. **How URR is related to *Kt/V*.** To understand this best, consider Figures 3.7 through 3.14. In a fish tank analogy (Figure 3.7), if one removes a fish from a 40-L tank, drains half (20 L) of the volume, and replaces the drained fluid with 20 L of clean water, the replaced and cleared volume can be thought of as *Kt*. The volume of the tank is 40 L, so the *Kt*/*V* is 20/40 or 0.5. The fish waste reduction ratio will be 50% after the 20 L of clean water is mixed with 20 L of uncleaned water. In this situation, *Kt*/*V* = fish waste reduction ratio = 0.5. In Figure 3.8, we clean the tank more completely. On removing the fish, the entire 40 L (*V*) is drained and replaced with clean water. Then the fish is replaced. In this case, the cleared volume (*Kt*) is 40 L; so, *V* = 40 L and *Kt*/*V* = 40/40 = 1.0, and now the fish waste reduction ratio is 100%. In this model, a *Kt*/*V* of 1.0 is a “perfect” dialysis or cleaning, one that cannot be improved upon.

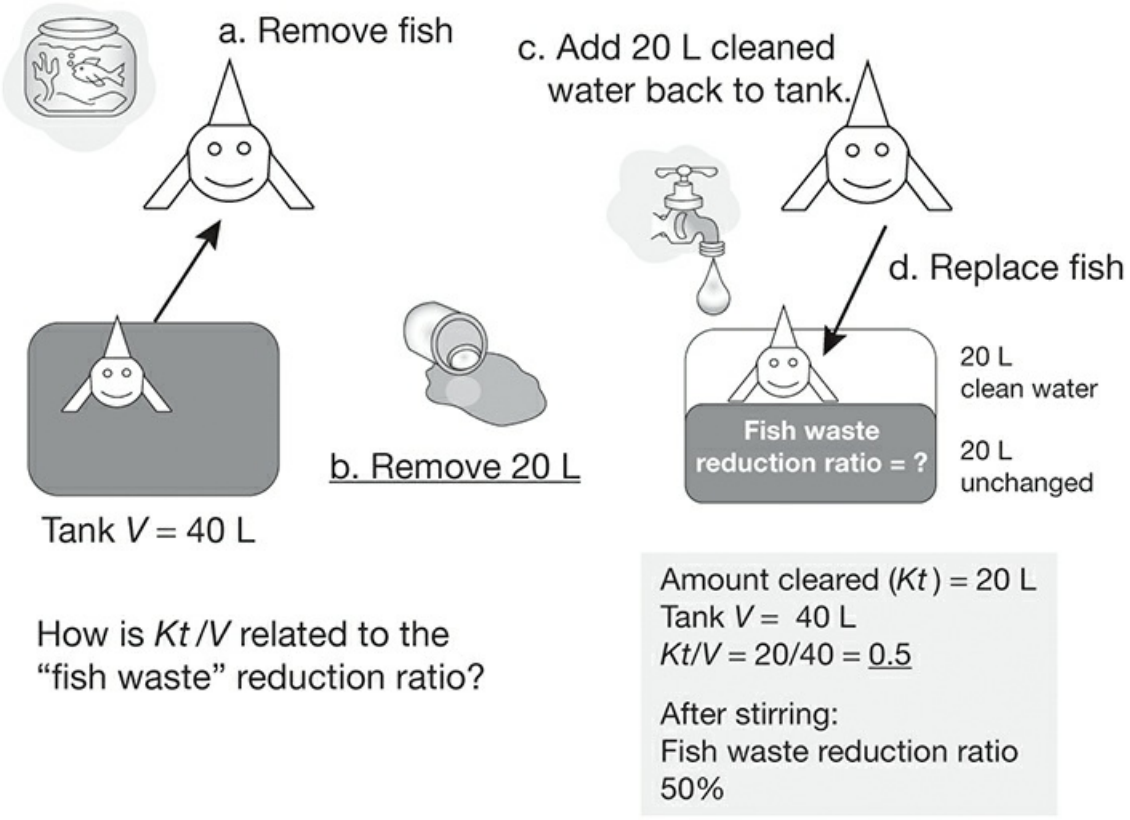


FIGURE 3.7: Fractional clearance of 50% (Kt/V = 0.5) in a fish tank model with the fish removed during cleaning. Note the fish waste reduction ratio is 50%, equal to the Kt/V.

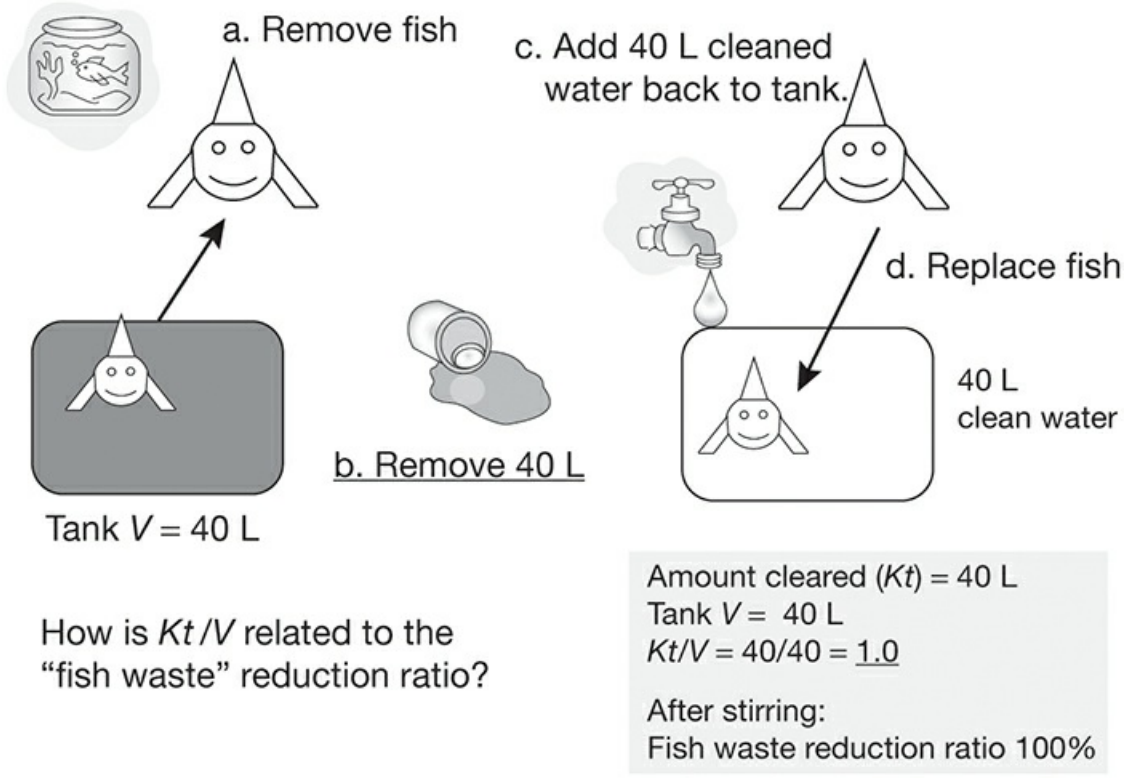


FIGURE 3.8: Fractional clearance of 100% (*Kt*/*V* = 1.0) in a fish tank model with the fish removed during cleaning. The fish waste reduction ratio is 100%, equal to the *Kt*/*V*.

A markedly different situation is shown in Figure 3.9. In this case, the cleaning takes place without removing the fish from the tank. With a 1-L cup, one removes 1 L of dirty water and replaces it with 1 L of clean water. Taking out only a small volume at a time keeps the fish happy and allows it to stay in the tank during cleaning. If one does this 40 times, then a total of 40 L (40 × 1 L) will have been "cleared," and the *Kt* will be 40. As the *V* is also 40, the *Kt*/*V* will again be 40/40, or 1.0. However, in this situation, the fish waste reduction ratio will be only 63% instead of 100%.

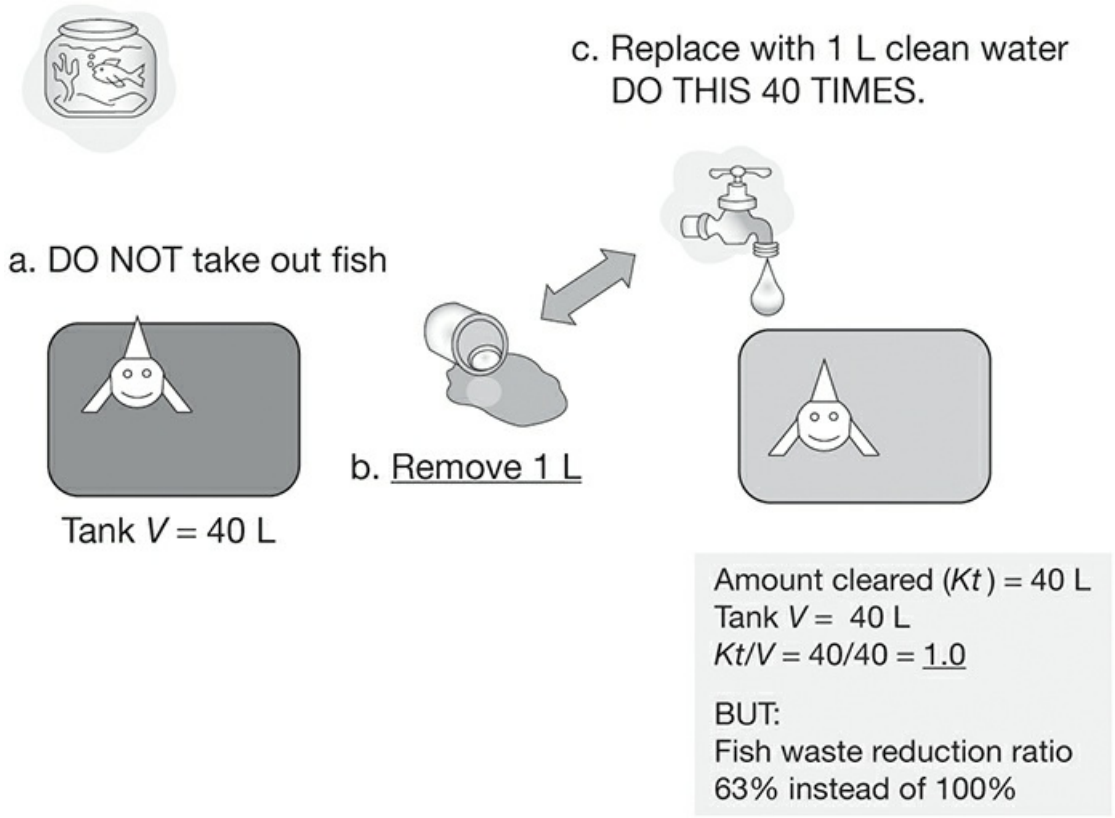


FIGURE 3.9: Fractional clearance of 100% (*Kt*/*V* = 1.0) in a fish tank model with the fish left in place during tank cleaning. In this situation, the fish waste reduction ratio is only 63%.

Figures 3.10 and 3.11 show this in a more formal sense. In Figure 3.10, we show a situation analogous to Figure 3.7, where the fish has been removed from the tank during cleaning. Here we consider a source tank containing 40 L, and a "perfect" dialyzer, such that the outlet SUN is always zero. The starting UN concentration in the source tank is 80 mg/dL. In Figure 3.10, the cleaning process is discontinuous. Cleaned fluid is collected in a separate holding tank, and the UN concentration of the cleaned fluid is zero. If one runs 20 L through this ideal dialyzer, then *Kt* is 20, and on adding this cleaned fluid back to the source tank, the URR will be 50%. If one runs 40 L through the ideal dialyzer, then the *Kt* volume is

40 L; on adding this completely cleaned fluid back to the source tank, the URR will be 100%. The bottom panel of Figure 3.10 shows a graph of the relationship between URR and Kt/V and it is simply URR = Kt/V. The middle panel shows the concentration of UN in the fluid entering the dialyzer from the source tank as dialysis progresses. The inlet SUN stays at 80 mg/dL throughout the dialysis, making this process extremely efficient.

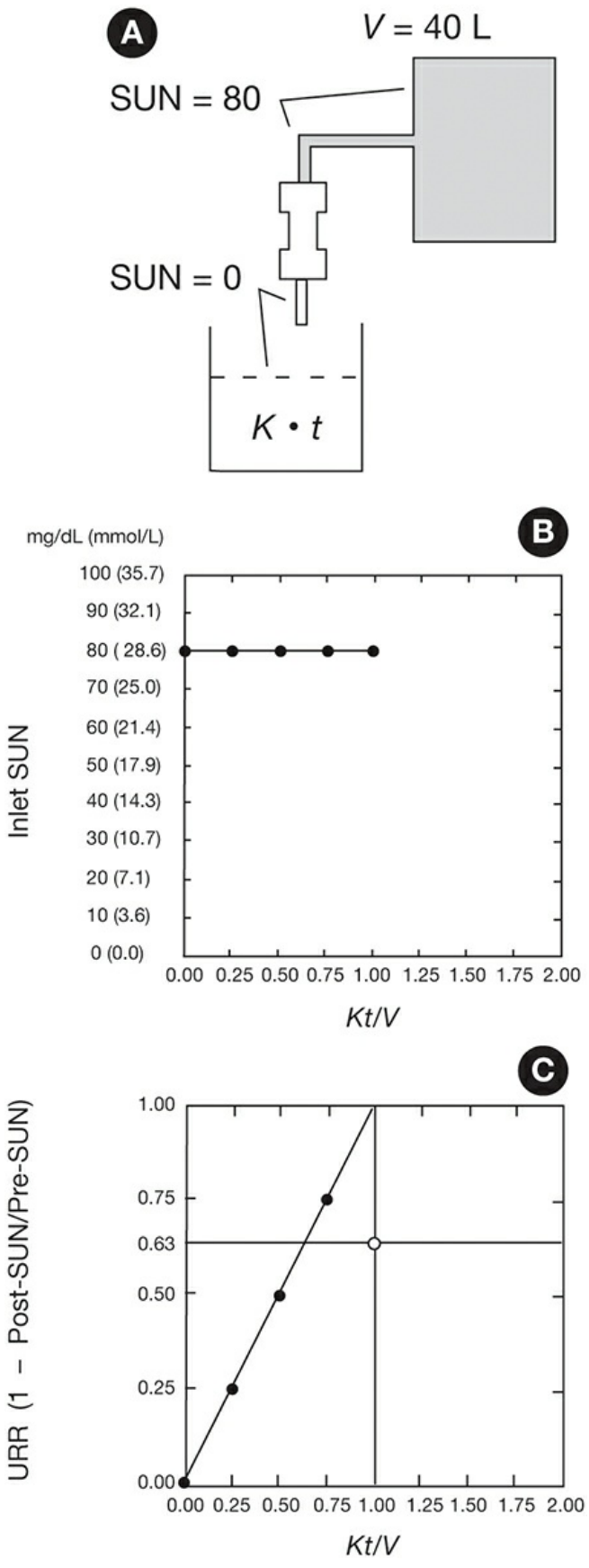
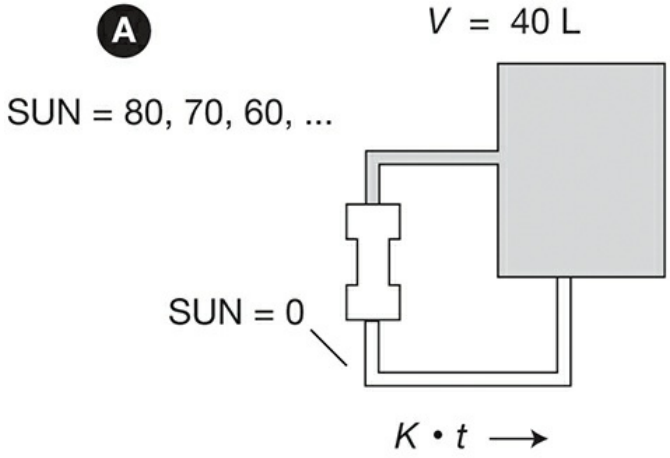
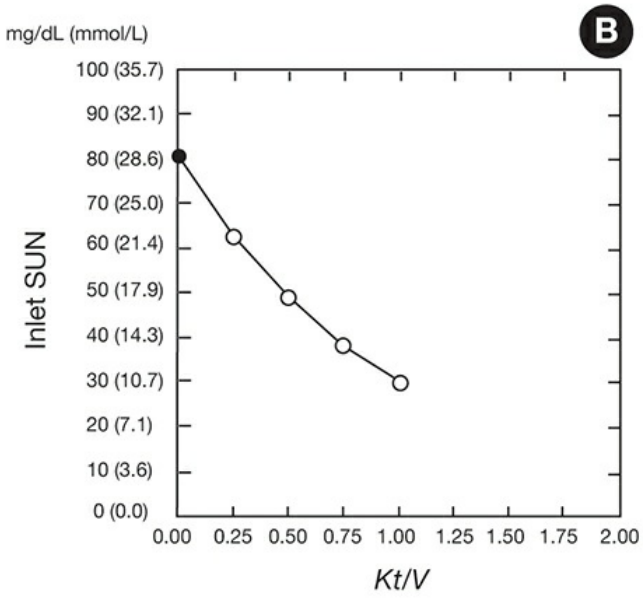

A
V = 40 L
SUN = 80
SUN = 0
K • t
B
mg/dL (mmol/L)
100 (35.7)
90 (32.1)
80 (28.6)
70 (25.0)
60 (21.4)
50 (17.9)
40 (14.3)
30 (10.7)
20 (7.1)
10 (3.6)
0 (0.0)
Inlet SUN
0.00 0.25 0.50 0.75 1.00 1.25 1.50 1.75 2.00
Kt/V
C
1.00
0.75
0.63
0.50
0.25
0.00
URR (1 – Post-SUN/Pre-SUN)
0.00 0.25 0.50 0.75 1.00 1.25 1.50 1.75 2.00
Kt/V

FIGURE 3.10: A. A fixed-volume model of urea removal (no urea generation) in which fluid from the dialyzer is routed to a holding tank and is mixed with the source "body" tank only at the end of dialysis. In this cartoon, blood flow rate is equal to dialyzer clearance as we are assuming a perfect dialyzer. B. The dialyzer inlet SUN (ie, blood urea nitrogen) remains constant (80 mg/dL [~28 mmol/L] in this example) throughout dialysis. C. In this model, *Kt*/*V* = URR and *Kt*/*V* = 1.0 represents a perfect dialysis (all toxins removed). SUN, serum urea nitrogen; URR, urea reduction ratio. (Reproduced from Daugirdas JT. Urea kinetic modeling tutorial. *Hypertens Dial Clin Nephrol*. http://www.hdcn.com)


A
V = 40 L
SUN = 80, 70, 60, ...
SUN = 0
K • t


B
mg/dL (mmol/L)
100 (35.7)
90 (32.1)
80 (28.6)
70 (25.0)
60 (21.4)
50 (17.9)
40 (14.3)
30 (10.7)
20 (7.1)
10 (3.6)
0 (0.0)
Inlet SUN
0.00 0.25 0.50 0.75 1.00 1.25 1.50 1.75 2.00
Kt/V

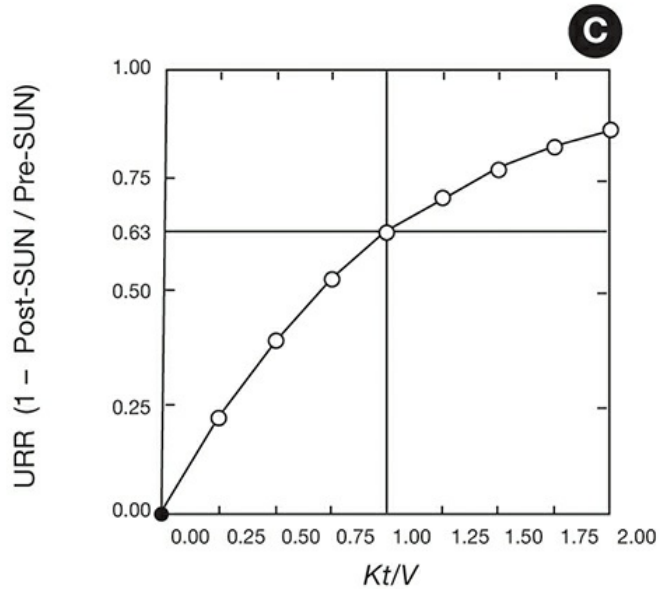

C
1.00
0.75
0.63
0.50
0.25
0.00
URR (1 – Post-SUN / Pre-SUN)
0.00 0.25 0.50 0.75 1.00 1.25 1.50 1.75 2.00
Kt/V

FIGURE 3.11: A. Another fixed-volume model, except this time the dialyzer outlet fluid is continually returned to the source tank throughout dialysis. As shown in B, the inlet SUN now falls exponentially during dialysis, reducing dialysis efficiency. C. With continuous outlet return, a URR of only 0.63 is reached when the total tank volume (*V*) is passed through the dialyzer, making *Kt*/*V* = 1.0. SUN, serum urea nitrogen; URR, urea reduction ratio. (Reproduced from Daugirdas JT. Urea kinetic modeling tutorial. *Hypertens Dial Clin Nephrol*. http://www.hdcn.com)

Figure 3.11 shows the situation similar to when the fish remains in the tank. In this situation, the UN concentration of the fluid exiting the dialyzer is still zero, but the dialyzer outlet fluid is routed back to the source tank. This results in a continuous dilution of the UN concentration in the source tank as dialysis progresses, and the inlet UN of the dialyzer over time decreases as shown in the middle panel. The system with continuous fluid return is far less efficient than when fluid is kept in a holding tank until the end of dialysis. With this new arrangement, even after running all 40 L through our ideal dialyzer (*Kt*/*V* = 1.0), and despite the outlet SUN being zero, there still will be urea left in the tank. The bottom panel in Figure 3.11 shows the relationship between URR and *Kt*/*V*. Similar to the fish tank analogy, when *Kt*/*V* is 1.0, the URR will be 0.63. Even if we run all 40 L through a second (*Kt*/*V* = 2.0) and a third (*Kt*/*V* = 3.0) time, the postdialysis SUN still will not be zero and the URR still will not be 100%. Because of this dilution factor, long dialysis sessions become progressively less efficient in removing small-molecular-weight solutes as the session continues.

Why is this? With each 1-L remove/replace cycle, the concentration of fish waste in the tank gets reduced so that the subsequent 1-L remove/replace cycle removes less fish waste than the cycle before. The progressive dilution of fish waste in the tank during this cleaning process reduces the efficiency of the process, and in this case, a *Kt*/*V* of 1.0 is no longer a perfect cleaning, and substantial fish waste remains in the tank at the end.

4. **Effect of urea generation.** In Figure 3.12, we are back to cleaning the fish tank. If one removes 40 L (1 L at a time × 40), and we do this quickly, the fish waste reduction ratio will be 63%, as discussed earlier. However, if we clean the tank *slowly*, while we are cleaning the tank, the fish in the tank continues to generate waste. If the "dialysis" or fish tank cleaning takes 2 hours, we expect a fish waste reduction ratio of 63%, but find instead a reduction ratio of only 61.5%, due to the additional waste added to the tank by the fish during the 2-hour cleaning period. Similarly, if the cleaning takes 4 or 8 hours, a *Kt*/*V* of 1.0 will result in a waste reduction ratio of only 60% or 57%, respectively. Finally, if the 40 L is replaced very slowly, over 24 hours, then we have a continuous renal replacement type of treatment, where a *Kt*/*V* of 1.0 per day results in a waste reduction ratio of close to 0%. This means that although URR and *Kt*/*V* are mathematically related, one needs to take the length of the dialysis session into account.

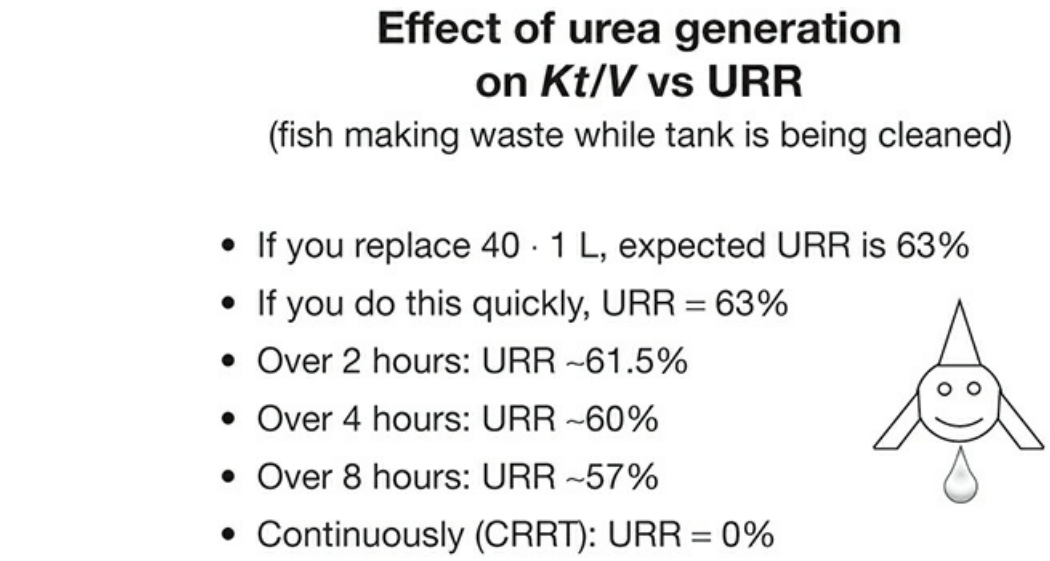


FIGURE 3.12: Effect of dialysis session length on the relationship between *Kt*/*V* and URR. Due to continued production of fish waste (eg, urea generation) during the removal process, the URR for any given *Kt*/*V* decreases as the session length increases. CRRT, continuous renal replacement therapy; URR, urea reduction ratio.

5. **Additional *Kt*/*V* associated with volume removal.** *Kt*/*V* by convention is based on the *postdialysis* value for *V*. Commonly during dialysis, some fluid is removed, such that postdialysis *V* will be several liters lower than the starting value. Along with fluid volume reduction, some wastes are removed, and this removal is not reflected by a change in concentration. To understand this better, consider the extreme case shown in Figure 3.13. Here we start with a fish tank that has a volume of 80 L. We simply drain 40 L and do not replace any fluid. We have "cleared" (*Kt*) 40 L, and the postdialysis volume of the fish tank now is 40 L, so *Kt*/*V* is 40/40 = 1.0, but the waste reduction ratio is 0. Thus, in the course of volume reduction, we always get some additional *Kt*/*V* that is not reflected in the waste reduction ratio.

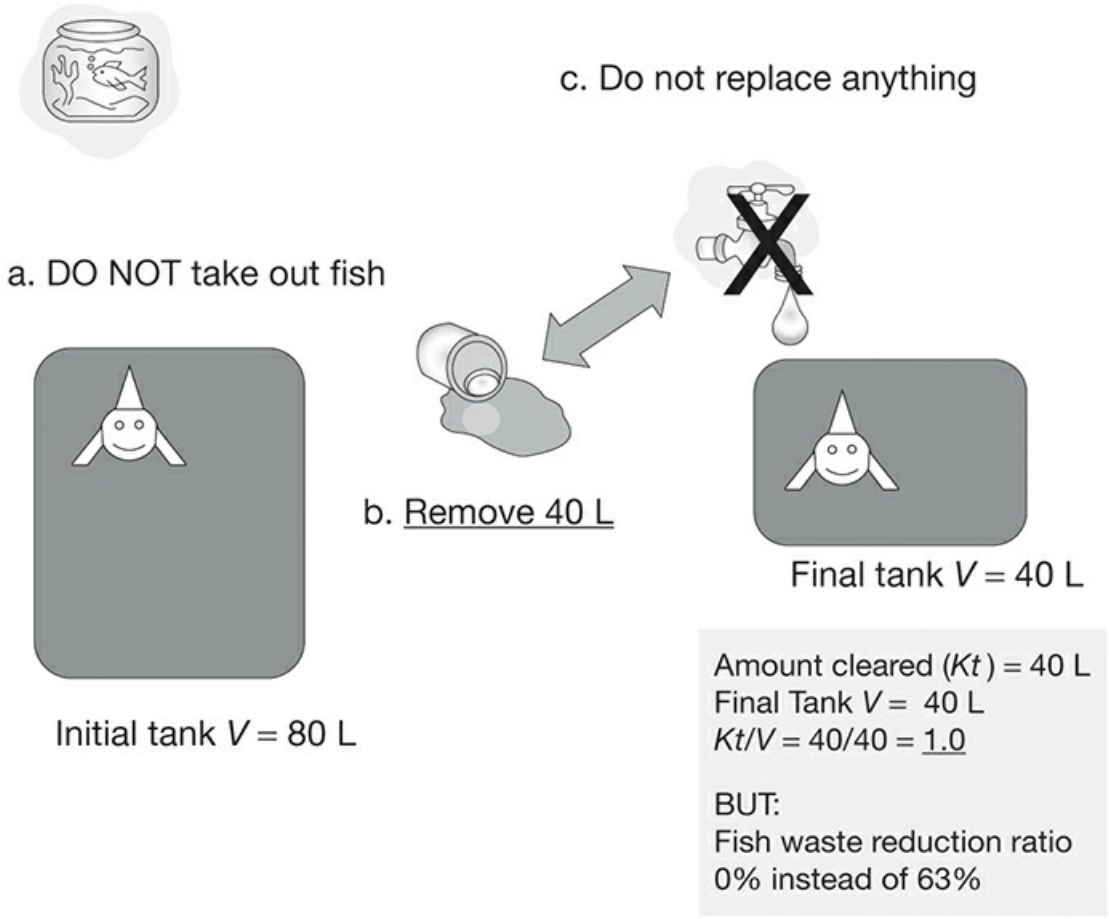


FIGURE 3.13: Effect of volume reduction on the relation between *Kt*/*V* and URR. Urea (or fish waste) removed in the process of volume contraction will not be reflected in the URR. *Kt*/*V* is calculated based on the postdialysis value for *V*. URR, urea reduction ratio.

6. **Quantification of the effects of urea generation and volume removal.** Figure 3.14 shows a nomogram that plots the relationship between *Kt*/*V* and URR, adjusting for urea generation and also volume removal. The dotted line is the same as the line in Figure 3.11C. Remember, a *Kt*/*V* of 1.0 was associated with a URR of 63%. With a 3.5- to 4.0-hour dialysis treatment, the URR will be reduced by about 3% due to urea generation; thus, because of urea generation, a *Kt*/*V* of 1.0 typically is reflected by a URR of around 60% (instead of 63%). The additional lines to the right and below the first solid curved line represent the relationship between URR and *Kt*/*V* when substantial fluid is removed. The heavy black line shows the relationship when 3% of body weight is removed, and the remaining two lines show the relationship when fluid removal is 6% or 9% of body weight, respectively. A 3% weight loss (2.1 kg in a 70 kg patient) might be thought of as typical. We can read off the URR corresponding to a *Kt*/*V* of 1.2 by moving up from 1.2 on the horizontal axis to the heavy black isopleth (curved line), and then moving left to the vertical axis. The intersection of 1.2 with the 3% weight loss isopleth (0.03) corresponds to a URR of 65%. This is why guidelines recommending a minimum *Kt*/*V* of 1.2 also recommend a URR of at least 65%. However, the relationship between *Kt*/*V* and URR is not entirely fixed. If one is removing 9% of body weight during dialysis

(0.09 line on the graph), a URR of 65% translates to a *Kt*/*V* of 1.4, with the extra 0.2 *Kt*/*V* units coming from waste product removal that is not reflected in a concentration change. Similarly, one can achieve a *Kt*/*V* of 1.2 in patients with a 9% fluid removal rate with a URR of only 58%. Other points of interest corresponding to a URR of 75% are also shown on the graph. When URR is 75%, *Kt*/*V* will be 1.5, 1.6, 1.7, or 1.8 when fluid removal is 0%, 3%, 6%, or 9% of body weight, respectively.

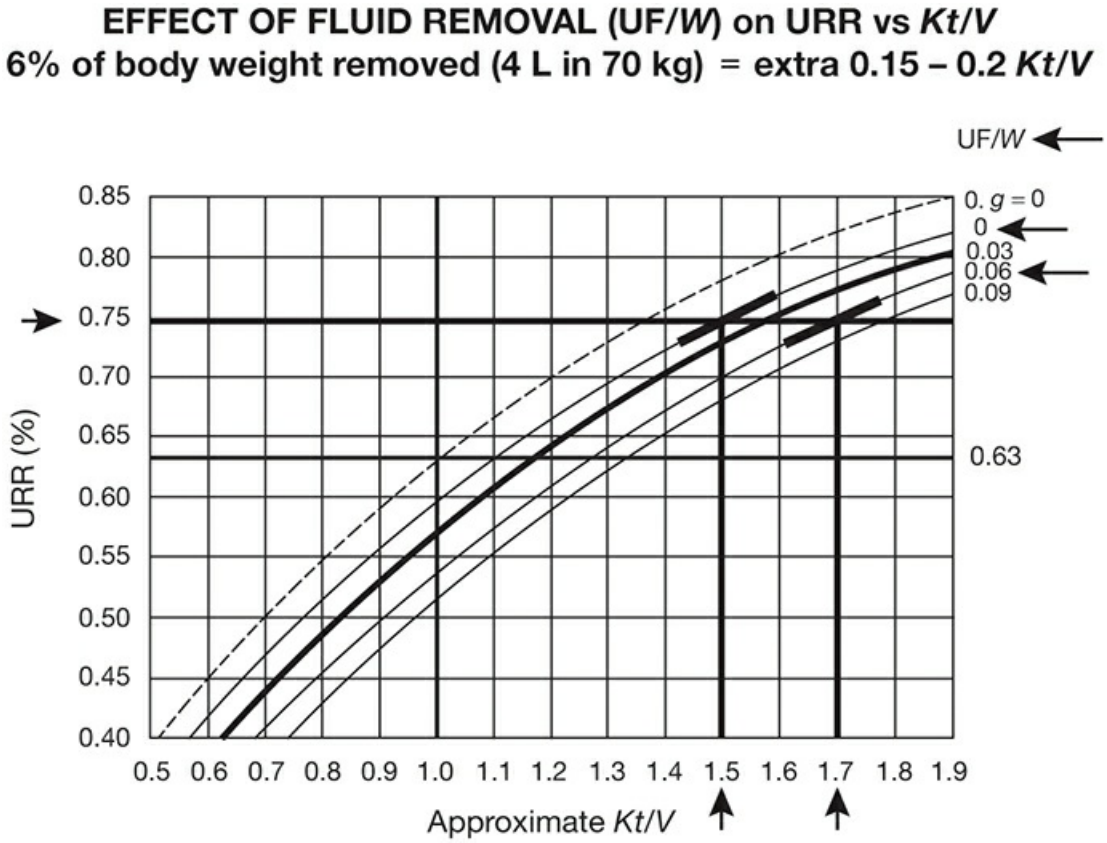


FIGURE 3.14: Actual relationship between *Kt*/*V* and URR, taking into account urea generation and the effects of volume contraction. We now see that a *Kt*/*V* of 1.0 corresponds to a URR of 0.60 instead of 0.63, due to urea generation. In fact, depending on how much fluid is removed as a percentage of the body weight, a *Kt*/*V* of 1.0 can be attained with URR values as low as 0.52, with an average URR of 0.57 (heavy line represents the usual UF/*W* of 3%). A URR of 75% can correspond to a *Kt*/*V* of 1.5 in a patient with no fluid removal, or to a *Kt*/*V* of 1.7 in a patient from whom 6% of body weight is being removed. URR, urea reduction ratio. (Reproduced from Daugirdas JT. Urea kinetic modeling tutorial. *Hypertens Dial Clin Nephrol*. http://www.hdcn.com)

Equations have been developed that can approximately translate URR to *Kt*/*V* by adjusting for the session length (urea generation) and fractional volume removal. One such equation follows:

$$Kt/V = -\ln(R - 0.008 \times t) + (4 - 3.5 \times R) \times 0.55\ \mathrm{UF}/V$$

where ln is the natural logarithm, *R* is the ratio of postdialysis to predialysis SUN, *t* is the session length (in hours), UF is the volume of fluid removed during dialysis (in liters), and *V* is the postdialysis urea distribution volume (in liters). The $0.008 \times t$ term adjusts the post-/pre-SUN ratio, *R*, for urea generation and is a function of

session length. For nonstandard dialysis schedules or blood draw dates, the 0.008 urea generation term can be optimized further (Daugirdas, 2013). The second adjustment term accounts for added *Kt*/*V* due to reduction in postdialysis *V*. If *V* is not known, an anthropometric estimate can be used or *V* can be assumed to be 55% of the postdialysis weight (*W*). The expression then simplifies to

$$Kt/V = -\ln(R - 0.008 \times t) + (4 - 3.5 \times R) \times \mathrm{UF}/W\mathrm{g}$$

This is the equation that was used to generate the curves in Figure 3.14. *Thus, both the URR and* Kt/V *are mathematically linked, and both are determined primarily from the pre- and postdialysis SUN levels. However, the* Kt/V *also takes into account ultrafiltration and urea generation. Neither is superior to the other as a measure of outcome.*

7. **Multipool models, urea inbound, and rebound.** The model shown in Figure 3.11 assumes that urea is contained in a single body compartment. This assumption leads to a monoexponential decline in the SUN during dialysis, as per hollow circles in Figure 3.11B, and to a minimal rebound after dialysis has been discontinued. In fact, the SUN profile during dialysis deviates from the decrease shown in Figure 3.11B, usually being lower than expected (Figure 3.15). Immediately after stopping dialysis, SUN rebounds to levels that cannot be explained on the basis of postdialysis urea generation (Figure 3.15). These observations suggest that urea is being sequestered somewhere during dialysis. Because urea is being removed from a smaller apparent volume during the early part of dialysis, the SUN during the initial part of dialysis falls more quickly than expected. We have designated this unexpected early fall in SUN during the early stages of a dialysis session as urea **inbound**. Toward the end of dialysis, as a concentration gradient develops between the sequestered compartment and the accessible compartment, the fall in SUN slows. After dialysis is complete, continued movement of urea from the sequestered to the accessible compartment causes the postdialysis urea **rebound** (Figure 3.15).

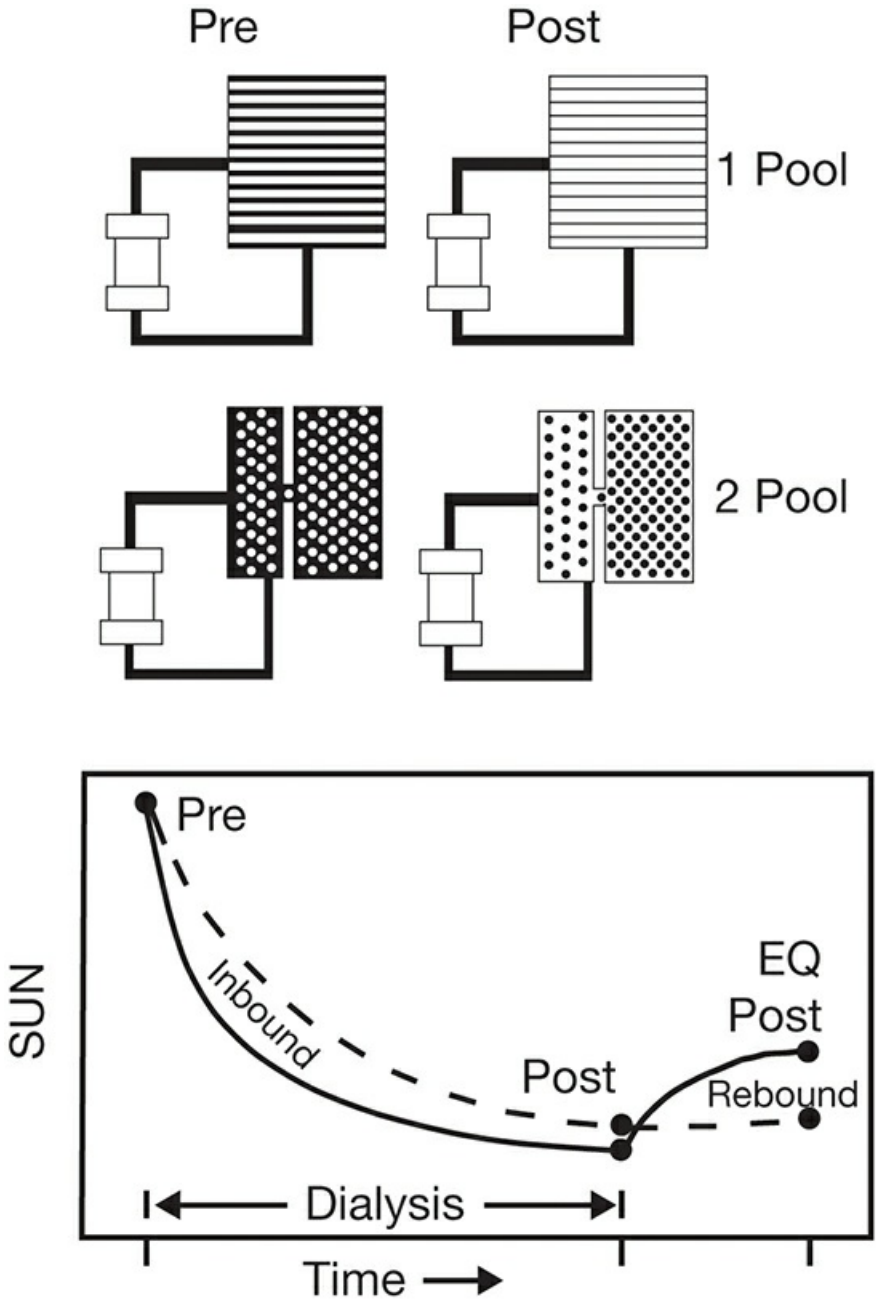


FIGURE 3.15: The effects of urea sequestration on the intradialytic fall in SUN (urea inbound) and the postdialysis increase in SUN (rebound). When there is sequestration, the intradialytic SUN level falls more quickly than expected (inbound) due to initial removal from a smaller apparent space. However, after dialysis is complete, continued entry of urea from the sequestered space to the proximal space causes urea rebound to occur. SUN, serum urea nitrogen. (Reproduced from Daugirdas JT. Urea kinetic modeling tutorial. *Hypertens Dial Clin Nephrol*. http://www.hdcn.com)

a. Regional blood flow model. Urea sequestration during dialysis was initially explained as being due to difficulties in removing urea from cells. It has now been shown that urea is sequestered during dialysis in tissues, primarily muscle, that contain a high percentage of total body water, and hence urea, but receive a low percentage of the cardiac output. Because of the low ratio of blood flow

through these tissues to their urea content, the transfer rate of urea from these tissues to the dialyzer by way of the central blood circulation is slow, causing urea sequestration.

b. Implications of urea inbound and rebound on measures of adequacy. The amount of urea removed during dialysis is dependent on the time-averaged dialyzer inlet urea concentration during the treatment. If there is sequestration, the time-averaged dialyzer urea concentration will be lower than that estimated by a single-pool model from the pre- and postdialysis urea values. As a result, the single-pool model will overestimate the amount of urea removal.

c. The concept of equilibrated *Kt/V* (e*Kt/V*). After dialysis, urea diffuses back from sequestered tissue sites into the blood to cause a postdialysis rebound, which is largely complete by 30 to 60 minutes. One can measure the postdialysis SUN at this time and compute a "true" or equilibrated URR, which will be less than the URR based on an immediate postdialysis sample. The equilibrated URR can be translated into an equilibrated *Kt*/*V*.

The amount of urea rebound depends on the intensity or rate of dialysis that was given relative to body size. The rate of dialysis can be expressed as the number of *Kt*/*V* units per hour, or (*Kt*/*V*) divided by *t* in hours. Based on urea modeling, a formula modified from one suggested by Tattersall (1996) can be used to predict the amount of rebound based on the rate of dialysis:

$$eKt/V = spKt/V \times Td/(Td + 30.7)$$

where e*Kt*/*V* and sp*Kt*/*V* are equilibrated and single-pool *Kt*/*V*, respectively, *Td* is the dialysis session length in minutes, and 30.7 is a time constant. The constant that we recommend, 30.7 minutes, is based on data from the Hemodialysis (HEMO) study (Daugirdas, 2009, 2013) and is slightly different from the value of 35 minutes originally suggested by Tattersall. Using this equation, one can calculate the e*Kt*/*V* values corresponding to a sp*Kt*/*V* of 1.2 delivered over 6, 3, or 2 hours.

sp*Kt/V*	*t* (h)	sp*Kt/V* per h	Rebound	e*Kt/V*
1.2	6	0.2	0.09	1.11
1.2	3	0.4	0.17	1.03
1.2	2	0.6	0.24	0.96

As is evident from the table, e*Kt*/*V* can be significantly less than sp*Kt*/*V*, especially during short dialysis treatments. Perhaps for this reason, the European Best Practices guidelines set their minimum recommended dialysis *Kt*/*V* of 1.2 in terms of e*Kt*/*V* rather than sp*Kt*/*V*.

IV. ACCESS RECIRCULATION.

Normally blood flow through an arteriovenous (AV) access averages about 1 L/min. The blood pump, which routes a portion of this flow through the dialyzer, usually is set to take a flow of 350 to 500 mL/min. Because flow through the vascular access normally exceeds the demand of the blood pump, nearly all of the blood entering the blood pump comes from the access upstream to the needle insertion site. The urea concentration of blood entering the dialyzer is the same as that in the

upstream access, and there is no access recirculation (assuming, of course, that the access needles have not been placed too close to one another, and that the arterial and venous needle positions have not been inadvertently reversed). In a failing AV graft or fistula, flow through the access can decrease markedly, to 350 to 500 mL/min or slower. In such circumstances, part of the flow leaving the dialyzer moves upstream instead of downstream through the access segment between the two needles and reenters the dialyzer via the inflow blood line. In such a case, the dialyzer inlet blood becomes admixed, or "diluted," with dialyzer outlet blood. This phenomenon is called *access recirculation*.

A. Impact of access recirculation on dialysis adequacy. When access recirculation occurs, the urea concentration in the blood entering the dialyzer may be reduced by 5% to 40% or more. The amount of urea removed in the dialyzer is equal to the volume of blood cleared × dialyzer inflow urea concentration. Although dialyzer clearance remains unchanged, the amount of urea removed is reduced because the concentration of urea entering the dialyzer inlet is reduced. In patients with access recirculation, if blood at the end of dialysis is drawn from the dialyzer inlet blood line, the urea level in this blood will be lower than that in the patient's upstream blood. Hence, the apparent postdialysis SUN will be artifactually low, and the URR and, consequently, the sp*Kt*/*V* will be overestimated.

B. Avoiding the impact of access recirculation on URR or sp*Kt*/*V* by slowing the blood flow or by stopping dialysate flow at the end of dialysis prior to blood sampling. To ensure that blood being sampled reflects patient blood, one needs to slow the blood pump to a flow rate (eg, 100 mL/min) that is assuredly below the access flow rate for a short period of time (10-20 seconds). Lowering the blood flow stops the backward flow of blood from the dialyzer outlet to inlet and now all blood entering the arterial needle is upstream blood. The length of the slow-flow period depends on the dead space between the tip of the arterial needle and the sampling port (usually about 9 mL in most adult blood lines). A 10- to 20-second period of 100 mL/min flow should be sufficient to allow the column of nonadmixed blood to reach the sampling port in most blood lines. Postdialysis blood should always be drawn after a short slow-flow period for this reason. Merely stopping the blood pump prior to drawing the sample at the end of dialysis does not prevent this problem, as the admixed blood in the inlet blood line is simply "frozen" in place. A sample taken from the inlet blood line after stopping the pump still reflects admixed blood.

Another clever method of avoiding this problem is to just shut off the dialysate flow for 3 minutes at the end of dialysis (or put dialysate flow into bypass) while letting the blood flow go full tilt. After 3 minutes, the SUN level in the blood leaving the dialyzer is similar to that going in. Recirculation continues to occur due to the unchanged blood flow rate, but the dialyzer outlet blood that is admixing with the inlet blood line now has the same urea concentration as the inflow blood, and so the dialyzer inlet SUN level correctly reflects the SUN concentration in the patient's blood. As a result, the URR and *Kt*/*V* can be correctly estimated.

V. CARDIOPULMONARY RECIRCULATION.

A recirculation can broadly be defined to occur whenever blood leaving the dialyzer outlet returns to the inlet without first having traversed the peripheral urea-rich tissues. In access recirculation, the recirculation occurs via the short access segment between the venous and arterial needles. Cardiopulmonary

recirculation occurs through the heart and lungs (which contain negligible amounts of urea) when the dialyzer is fed from the arterial circulation (eg, via an AV access). During dialysis, cleared blood from the dialyzer outlet returns to the heart. In the aorta, the cleared blood is partitioned; some of it gets routed to the nonaccess arteries that lead it to the tissues to pick up more urea, but a fraction goes directly back through the access to the dialyzer without having traversed a peripheral capillary bed. When a dialyzer is fed from a venous access, cardiopulmonary recirculation cannot occur. Although an AV urea gradient is still present, all of the blood leaving the dialyzer must go through the peripheral capillary bed before it sees the dialyzer again.

A. Impact of cardiopulmonary recirculation on dialysis adequacy. During dialysis using either an AV or a venous access, there is an AV gradient for urea that is established. With an AV access, the dialyzer "rides" the arterial intradialytic urea nitrogen concentration curve, which is 5% to 10% lower than the venous intradialytic urea nitrogen concentration curve. Hence, dialysis with an AV access is inherently less efficient (by about 5%-10%) than that using a venous access. This effect usually is outweighed by the higher blood flow rates achievable with AV access and the avoidance of venous catheter–related access recirculation.

VI. MODELING OF UREA DISTRIBUTION VOLUME.

Urea modeling can be used to determine the patient's apparent urea space, *V*. This is done using the "how many marbles in the box?" method. If one removes a certain number of marbles from a box, one can determine the size of the box if one also knows the concentration change. For example, if removal of 50 marbles causes a concentration change of 50%, we know that there was originally 100 marbles in the box, and if the starting concentration is 10 marbles/L, we can calculate that the volume of the box must be 10 L. If removal of 50 marbles causes a concentration change of only 5%, we know that the starting number of marbles must have been 1,000, and with an initial concentration of 10 marbles/L, the starting volume must have been 100 L.

A urea modeling program first has to calculate how many "marbles" (ie, how much urea) were removed. The program estimates the dialyzer clearance (from dialyzer K_0A and from the blood, and dialysate flow rates), and from the session length it calculates the volume of blood cleared (Kt) during the entire dialysis session. Next, it computes a urea concentration curve during dialysis based on either a single-pool or a double-pool model, as in Figure 3.15. From this it can compute an average urea concentration during dialysis. The amount of urea removed is then simply the dialyzer clearance × time × average dialyzer inlet urea concentration. Next, the program knows the concentration change, because predialysis and postdialysis SUN are measured and the laboratory values are put into the program. So now the program knows how many marbles were removed plus the concentration change, and from this information it can calculate the "size of the box," *V*, which is the urea distribution volume.

When following patients, one should always compare the modeled urea volume with the estimated (or bioimpedance-measured) total body water volume to see if the calculated value for *V* makes sense. *V* is approximately 90% of the total body water volume. An anthropometric estimate (Watson or Hume-Weyers) of *V* can be used to estimate total body water volume (see Appendix B). The modeled urea volume should be in the range of 60% to 120% of the anthropometric value for *V* in most cases, unless there is unusual body

weight or composition (eg, major amputations) or very severe fluid overload.

A more powerful use of *V* is to follow the modeled value over time. Although values for *V* have a substantial variation from treatment to treatment, a large change in *V* may reflect an error in blood sampling technique, an unrecorded change in the amount of dialysis ($K \times t$) given, or the presence of access recirculation.

A. *V* much smaller than usual. In this case, the URR is higher than expected, as is the *Kt*/*V*. Because the modeling program is told that *K* and *t* have not changed, the high *Kt*/*V* causes the program to conclude that the patient must have shrunk, and a smaller than usual value for *V* is calculated. Most often, if the *V* is reduced by about 100%, the problem is that the postdialysis blood sample was drawn from the dialyzer outlet line instead of the inlet.

B. *V* much larger than normal. In this scenario, the URR and *Kt*/*V* are lower than expected, and so the program concludes that if *K* and *t* are unchanged, then the patient must have somehow expanded to account for such a low *Kt*/*V*. In fact, the real problem is that either *K* or *t* is actually lower than recorded. The most common problems causing this are treatment interruption (full duration of dialysis session not given), lowering of the blood flow rate due to technical problems (*K* lower than expected), or some sort of dialyzer performance problem resulting in reduced dialyzer clearance. Access recirculation can also cause an apparent increase in *V* because effective clearance is reduced due to dilution of urea at the dialyzer blood inlet. One caveat: The effects of access recirculation on *V* will *only* be seen if blood is drawn properly (eg, after a slow-flow period). If blood drawn postdialysis is admixed with blood from the dialyzer outlet, then the URR will be artifactually increased. The expected lowering of URR due to access recirculation then may not be seen, and modeled *V* may not change.

VII. UREA NITROGEN GENERATION RATE (*g*) AND THE nPNA.

One of the benefits of urea modeling is that the generation rate of urea nitrogen (*g*) and the normalized PNA (nPNA) can be estimated. The way a computer modeling program does this is shown in Figure 3.16. From a pre- and postdialysis SUN and from other information regarding the dialysis session, an initial estimate of patient urea distribution volume is made, as described earlier. The program then puts in various estimates for urea nitrogen generation (*g*) and generates a separate sawtooth weekly SUN curve corresponding to each guess. Higher values of *g* will result in higher sawtooth curves. The program then looks to see which curve matches the actual measured predialysis SUN level. The level of *g* (and nPNA) corresponding to this curve is then chosen as the estimated value for that particular patient.

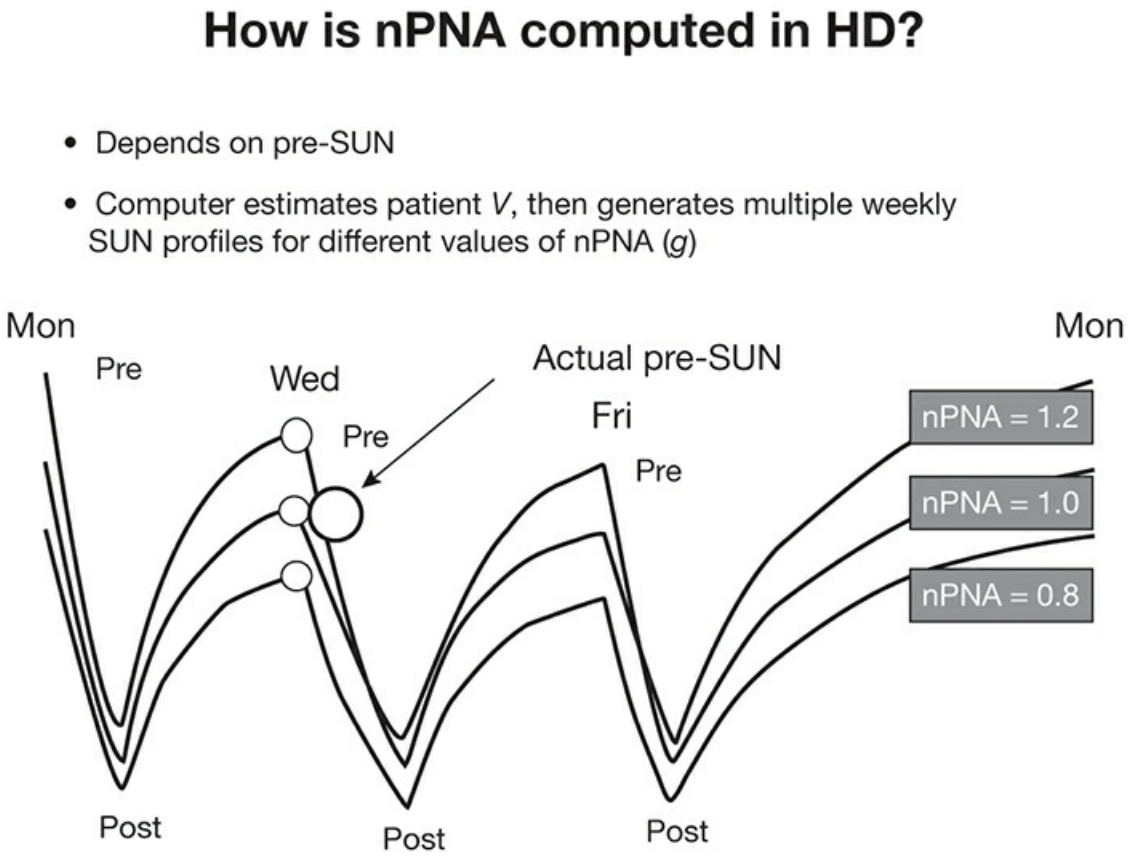


FIGURE 3.16: How a urea kinetic modeling program determines the PNA rate. From the pre- and postdialysis SUN, the session length, volume reduction, and an estimate of dialyzer clearance, the patient *V* is estimated. Then various values of urea generation (which corresponds tightly to nPNA) are plugged in, and weekly sawtooth SUN patterns are generated. The nPNA is assumed to be the value that generates a curve where the sawtooth peak for the day of the week when modeling values are drawn matches the laboratory value. HD, hemodialysis; nPNA, normalized PNA; PNA, protein nitrogen appearance; SUN, serum urea nitrogen.

The clinical utility of *g* or nPNA is somewhat debatable. nPNA is not a very robust predictor of mortality (once serum albumin and creatinine are controlled for). Generally, outcome is poor when nPNA is low, as this usually reflects poor dietary intake. Before one can make the assumption that a low nPNA reflects a low dietary protein intake, one needs to make sure that other sources of urea loss such as residual renal clearance have been properly accounted for. Rarely, a patient will have a low nPNA because they are improving markedly, and much of the dietary protein intake is being used for anabolism; in this happy but unusual circumstance, the urea nitrogen goes into building tissue and is not "appearing" in the blood. A high nPNA is not always a good thing, as it may be due to tissue breakdown (ie, to hypercatabolism).

VIII. RESIDUAL RENAL FUNCTION. Residual renal function has been shown to be of great survival benefit in patients undergoing dialysis, and its impact in patients receiving peritoneal dialysis appears to be greater than that of peritoneal clearance. In patients undergoing dialysis, residual kidney clearance can be approximated as the average of the creatinine and urea clearances. Urea clearance (K_{ru}) underestimates the glomerular filtration rate (GFR) due to proximal tubular urea reabsorption, whereas creatinine clearance

overestimates GFR because of tubular secretion. It is well established that patients with end-stage kidney disease (ESKD) with substantial residual renal function live longer, and so it is important to attempt to preserve residual function and to minimize potential injury to the end-stage kidney (eg, by avoiding nephrotoxic drugs and by minimizing intradialytic hypotension).

A. Measuring the K_{ru}. For this, one needs to collect all urine during a 24-hour period of the interdialytic interval. Usually, the patient starts the collection 24 hours before coming to the dialysis unit and then reports to the unit with the urine container. A blood sample at the end of the urine collection period is needed, and if the urine collection period is set to end just before dialysis, the needed blood sample can be drawn from the dialyzer bloodline at the start of dialysis. If the patient is receiving a usual amount of dialysis and if the collection interval is approximately 24 hours prior to dialysis, one can assume that the average serum urea level during the collection will be about 85% of the predialysis SUN. The K_{ru} is then calculated as:

$$K_{ru} = \left(\frac{UUN}{[0.85\,\text{predialysis SUN}]} \right) \times \text{urine flow rate}(\text{mL}/\text{min})$$

where UUN is the urine urea nitrogen concentration. The units for UUN and SUN do not matter, but they must be the same, as they cancel each other out (some labs will report urine results as urea and not as urea nitrogen). Typically, K_{ru} values of 0 to 8 mL/min will be obtained. The serum water UN concentration will be about 7% higher than the serum UN, and to calculate the residual kidney urea WATER clearance, one can divide UUN by 0.91 times the predialysis SUN instead of by 0.85 times this value.

Problem: If urine flow rate is 0.33 mL/min, or 20 mL/h, over 24 hours one would collect 480 mL of urine. Assume that the urine urea concentration is about 800 mg/dL (285 mmol/L) and that the collection was during the 24-hour interval immediately preceding a first-of-week dialysis session. Predialysis SUN for that dialysis is 56 mg/dL (20 mmol/L). What is the K_{ru}?

Solution in mg/dL units: First, compute the estimated mean SUN during the 24-hour collection interval. As discussed earlier, the estimated mean SUN during the collection period is 85% of the predialysis SUN, or 0.85 × 56 = 48 mg/dL. So K_{ru} = (800 mg/dL × 0.33 mL/min)/48 mg/dL = 5.5 mL/min.

Solution in SI units: First, compute the estimated mean SUN during the 24-hour collection interval. As discussed earlier, the estimated mean SUN during the collection period is 90% of the predialysis SUN, or 0.85 × 20 = 17 mmol/L. So K_{ru} = (0.285 mmol/mL × 0.33 mL/min)/0.017 mmol/mL = 5.5 mL/min.

1. **Estimating K_{ru} from levels of serum markers.** Because collection of urine is somewhat tedious and expensive, and always runs the risk of incomplete collection due to patient forgetfulness, a number of investigators have examined the accuracy of estimating K_{ru} based on levels of high-molecular-weight serum markers such as cystatin, β_2-microglobulin or β trace protein, and also of creatinine. These methods have been evaluated both in patients receiving peritoneal dialysis (Fan, 2020) and hemodialysis (Vilar, 2015). The accuracy was moderately good. Blood levels of such markers depend on both generation rate and removal, and the generation rate

can vary markedly among different patients.

2. **K_{ru} versus urine volume.** One simple way to get an idea of a patient's residual kidney function is to measure or estimate the amount of urine that he or she is producing over a 24-hour period. Patient-reported urine volume does show a relationship with measured urine volume, but no studies have attempted to question patients repeatedly or to get graded information regarding the amount of urine being produced (eg, none, at least two shot glasses, two coffee mugs, or 1-L or 1-quart milk container, corresponding to 60, 500, and 1,000 mL/d). While there is an association between urine volume and K_{ru}, with 1-L/d urine output corresponding to approximately 3.5 mL/min of K_{ru}, there is a wide scatter in this relationship. However, even a simple dichotomous questionnaire, asking whether a patient is making more or less than 200 mL of urine per day, is strongly associated with outcome (Hecking, 2019) and so may provide useful clinical information.
3. **Variation in K_{ru} and urine volume throughout the interdialytic interval.** During the initial 24 hours after a dialysis session, residual kidney function, both in terms of K_{ru} and urine volume, is reduced. These increase by 10% to 20% during the subsequent 24-hour period, and there is another even greater increase during the second nondialysis day. Preliminary data suggest that for patients undergoing dialysis 3 times/wk, a 24-hour urine collection performed during the 24 hours prior to the midweek session is representative of the average weekly value (Daugirdas, 2016).

IX. STANDARD *KT/V* UREA.

The so-called "standard" ***Kt/V*** urea grew out of two desires: (1) to come up with a measure of hemodialysis adequacy that was not dependent on number of treatments per week and (2) to have a measure where the minimum dose for hemodialysis would be similar to the minimum dose for peritoneal dialysis.

A. Casino Lopez EKRU.

One can compute the equivalent urea clearance (EKRU) for any given dialysis regimen using the same principle as computing a creatinine clearance: For creatinine, if one knows the per minute generation rate (from a 24-hour urine collection) and the mean plasma level, one can compute clearance as a ratio of the two.

$$\text{Creatinine clearance} = \frac{\text{UV}}{p}$$

where UV is the urine flow rate multiplied by the urine creatinine concentration, and P is the mean plasma (serum) concentration of creatinine during the collection period. From the timed urine collection, one knows how much creatinine is being generated per minute, and if we know the serum concentration during the collection period, we know how much plasma is being cleared to remove the amount of creatinine that is being generated to maintain steady state. This type of calculation was adapted to hemodialysis and urea removal by Casino and Lopez (1996). As discussed earlier and as shown in Figure 3.16, a urea modeling program can obtain a value for urea generation rate for any dialysis schedule, assuming steady state. The same modeling program can then calculate the TAC of SUN for the week. Once g and TAC are known, EKRU can be calculated for any dialysis regimen, similar to creatinine clearance, as follows:

$$\text{EKRU} = \frac{g}{\text{TAC}}$$

If one uses this approach to calculate EKRU corresponding to a 3 times/wk dialysis schedule with sp*Kt*/*V* of 1.2, the EKRU turns out to be about 11 mL/min. Theoretically, one can take any hemodialysis prescription, compute *g* and TAC using a modeling program, and then convert it to EKRU in mL/min. This EKRU value theoretically can be added to the measured residual renal urea clearance. The resulting EKRU can be expressed either in mL/min or in L/wk. When expressed as L/wk, EKRU can be thought of as a ($K \times t$) term, or volume of plasma cleared during the week, and this can then be normalized to *V* to calculate a weekly equivalent *Kt*/*V* urea.

Problem: In a patient with $V = 35$ L, EKRU is 11 mL/min. What is the equivalent weekly *Kt*/*V* urea?

Solution: 11 mL/min × 10,080 min/wk divided by 1,000 to convert milliliters to liters gives a weekly volume of plasma cleared of 110 L/wk. This is the $K \times t$ term of *Kt*/*V*. Dividing by $V = 35$, we get weekly *Kt*/*V* urea = 3.14.

B. Standard *Kt*/*V* urea. One problem with the EKRU metric was that the minimum sp*Kt*/*V* of 1.2 given 3 times/wk seemed to translate into a weekly equivalent *Kt*/*V* urea of 3.14, substantially higher than the weekly *Kt*/*V* urea of around 2.0 needed in patients receiving peritoneal dialysis. To fix this problem, Keshaviah, and later Gotch, proposed a "peak concentration hypothesis."

They surmised that one difference between peritoneal dialysis and hemodialysis is that in the latter there are peaks of urea and other uremic toxins. They also noticed that for a 3 times/wk schedule, the average peak concentration of urea was about one-third higher than the TAC. Accordingly, they suggested dividing *g* by the mean weekly predialysis SUN level instead of by the time-averaged urea level (Figure 3.17). Dividing by the higher mean predialysis value resulted in lowering the new measure of dialysis adequacy by about one-third. For a standard 3 times/wk hemodialysis regimen with a sp*Kt*/*V* of 1.2, the new equivalent clearance was about 7 mL/min versus 11 mL/min with EKRU, and the weekly equivalent *Kt*/*V* using the new measure, termed "standard *Kt*/*V*" by Gotch, was 2.0, similar to that for peritoneal dialysis.

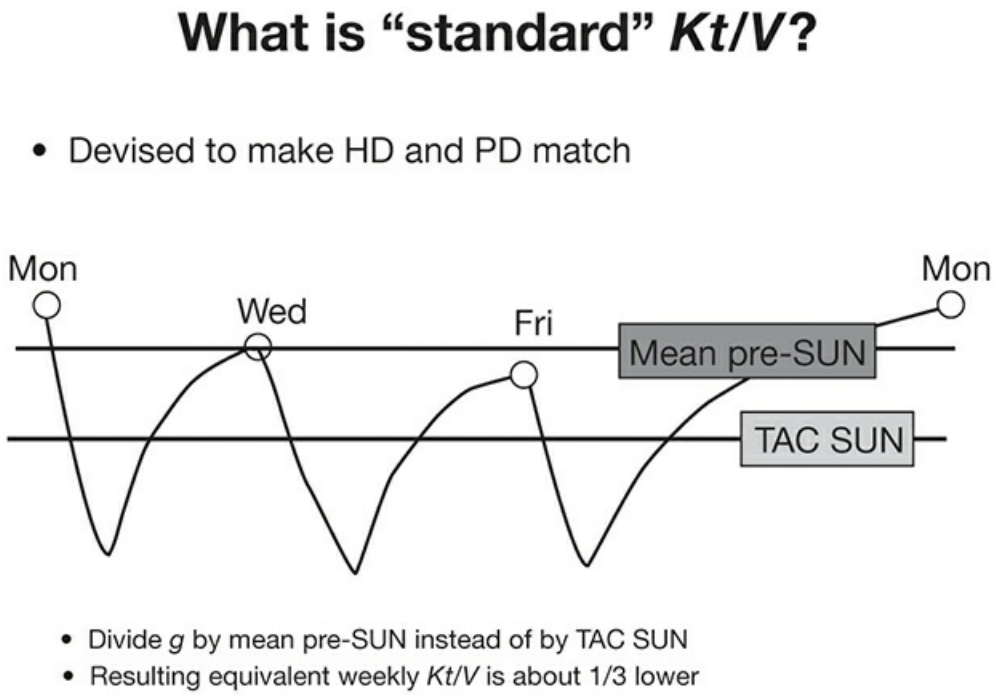


FIGURE 3.17: How standard *Kt*/*V* is calculated. The urea generation rate is determined along with the nPNA as in Figure 3.16, and then this figure is divided by the average predialysis SUN level. HD, hemodialysis; nPNA, normalized PNA; PD, peritoneal dialysis; SUN, serum urea nitrogen; TAC, time-averaged concentration.

1. **Sequestered solute and standard *Kt*/*V*.** It has been pointed out by Depner that standard *Kt*/*V* might be thought of as modeling a solute other than urea. The solute representing standard *Kt*/*V* would be easily removed by dialysis, but would be highly sequestered, with a very high postdialysis rebound. The mean predialysis level of such a highly sequestered solute would be similar to its time-averaged value. Removal of such a highly sequestered solute would be markedly improved by increasing dialysis frequency. If one looks at the relationship between standard *Kt*/*V* and dialysis frequency (Figure 3.18), it is clear that standard *Kt*/*V* can only be increased above 3.0 or so if dialysis frequency is more than 3 times/wk.

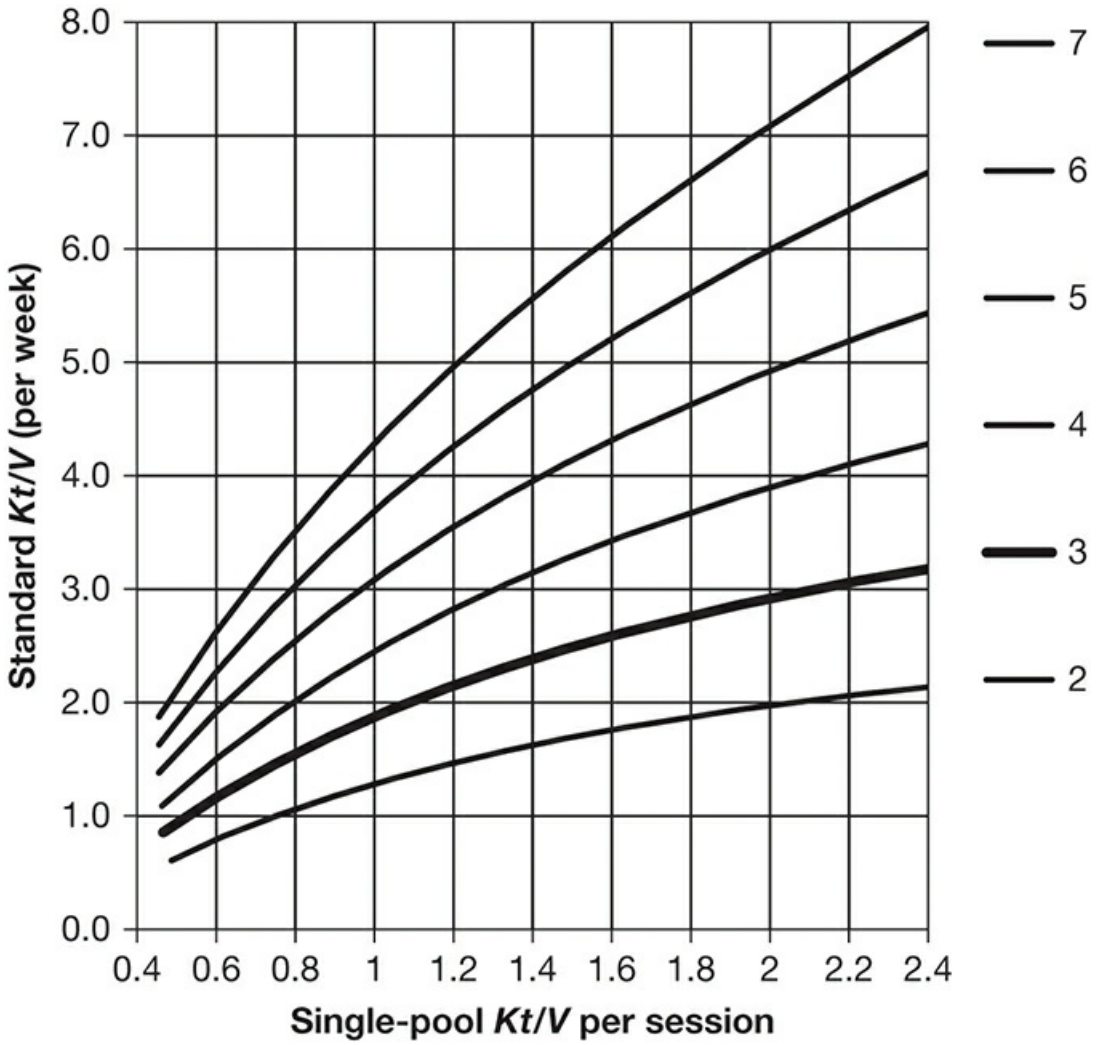


FIGURE 3.18: Standard *Kt*/*V* as a function of treatment *Kt*/*V* (single pool) and number of treatments per week (shown on the right). This is the modeled standard *Kt*/*V*, using a dialyzer clearance of 220 mL/min in a patient with a *V* of 40 L. As shown, it is difficult to get to a standard *Kt*/*V* greater than 3.0 with a 3 times/wk schedule. Dialysis times ranged from 30 to 450 minutes.

2. **Calculating the dialysis-related standard *Kt*/*V* in clinical practice.** This can be done using a urea kinetics modeling program. An open-source version of a formal urea kinetic modeling program is available at http://ureakinetics.org (Daugirdas, 2009).

   Dialysis-related standard *Kt*/*V* can also be computed using a simplified equation developed by the FHN group of investigators (Daugirdas, 2010a), as described in Appendix C.
3. **Adding the residual renal urea clearance to standard *Kt*/*V* urea.** Direct addition of residual renal urea clearance to standard *Kt*/*V* is problematic, as the standard *Kt*/*V* is an artificial construct. Some people do this, some do not. One needs to calculate the dialysis component of standard *Kt*/*V* and express it as mL/min format by multiplying by *V* and dividing by the number of minutes in a week. Then one can add residual renal urea clearance. After the residual renal clearance has been added, one can convert back to a weekly value.

C. Issues relating to normalizing dialysis dose by *V*.

Normalizing *Kt* to *V* is convenient and makes sense, because urea is distributed in total body water and its generation rate is proportional to *V*. However, because *V* represents largely muscle mass, it is not entirely clear that someone with 10% more muscle needs 10% more dialysis. Dosing dialysis by *Kt*/*V* may result in lower doses of dialysis for smaller people, including women and children (Daugirdas, 2010b). An alternative approach is to scale the dialysis dose ($K \times t$) to body surface area. This will result in relatively more dialysis for smaller people, women and children, and relatively less dialysis for larger patients. Some observational data support use of such an alternative. For example, when surface-area-normalized standard *Kt*/*V* is used, higher amounts of dialysis continue to result in better outcomes in both men and women (Pattharanitima, 2020). Scaling of dialysis by *V* instead of surface area results in relatively low doses of dialysis in small children (Daugirdas, 2010c).

See Appendix C for a method of calculating surface-area-normalized standard *Kt*/*V*.

X. MACHINE-ESTIMATED MEASURES OF HEMODIALYSIS ADEQUACY

A. Estimating dialyzer clearance by pulsing dialysate with sodium and analyzing resulting changes in dialysate conductivity.

Measuring adequacy using urea is time consuming and involves the use of needles, exposure of staff and patient to blood, and considerable effort in processing and analyzing blood samples. One alternative approach is to measure the clearance of the dialyzer online by causing a step increase in dialysate sodium and then measuring the conductivity of the dialysate flowing into the dialyzer and comparing this to the conductivity of the dialysate exiting the dialyzer over a short period of time. Many of the technical issues have been solved, and dialyzer conductivity–based clearances reflect in vivo dialyzer urea clearances quite well. An advantage of this method is that clearances can be computed multiple times throughout a dialysis session. Conductivity-based clearances can estimate *K*, and we know the dialysis session length *t*, but we don't know the urea distribution volume, *V*. The latter can be estimated as 90% of the anthropometric total body water value, or a previously determined value for *V*, using either bioimpedance or urea modeling, can be used. The value for *V* in patients undergoing dialysis is quite stable, as long as marked changes in weight do not occur (Raimann, 2020). Use of conductivity-estimated dialyzer clearance can reduce the need to measure postdialysis SUN: After an initial period of monthly pre- and post-SUN measurements to establish a urea-modeled value for *V*, subsequently, *Kt*/*V* based on a conductivity-estimated value for *K* can be used to monitor further adequacy of therapy (Raimann, 2020).

B. UV absorbance of spent dialysate.

Another approach to machine-measured hemodialysis adequacy is to monitor the ultraviolet (UV) light absorbance of spent dialysate. UV light absorption at selected wavelengths corresponds to dialysate concentration of uric acid and other small-molecular-weight solutes. Analysis of the spent dialysate UV absorption curve over time mirrors what goes on in the blood, and the ratio of the early and late dialysate UV absorption mirrors the predialysis and postdialysis SUN. From this the *Kt*/*V* of a treatment can be computed as it progresses, and the information reflects what is happening in the patient (Uhlin, 2006). One potential drawback of this dialysate-based method is that it has not been completely validated in patients with severe access recirculation (Ross, 2018), and access

recirculation is one important cause of covert underdialysis. In contrast, access recirculation will cause a drop in conductivity-based clearance, and so should be promptly detectable by analysis of serial conductivity measurements (Mohan, 2010).

XI. REMOVAL OF HIGH-MOLECULAR-WEIGHT SUBSTANCES

A. β_2-microglobulin, molecular weight 11,800 Da. The native kidney removes many uremic waste products of various molecular weights, all the way up to the molecular weight of albumin (about 60 kDa). Dialyzers initially developed in the 1970s using membranes made of cuprammonium cellulose did not have pores large enough to pass β_2-microglobulin, and the clearances of this molecule as well as molecules in the 10 to 40+ kDa range were minimal. The β_2M reduction ratio with such low-flux membranes is actually negative, with the postdialysis serum level being higher than the predialysis level due to concentration of plasma proteins because of fluid removal from the extracellular space. At the time, complications related to β_2-microglobulin amyloid accumulation were prevalent, including soft-tissue infiltration of joints and carpal tunnel syndrome as well as β_2M amyloid bone cysts. Synthetic membranes were developed then, having pores large enough to pass this large molecule, and some of the newer membranes also adsorbed some β_2M. With these high-flux membranes, the β_2M reduction ratio was similar to, though somewhat less than, URR. Today, such high-flux membranes that easily pass β_2M and similar-sized molecules are the norm, and guideline bodies in Europe recommend use of high-flux membranes for all patients. The 2015 KDOQI hemodialysis adequacy guideline update was not as supportive, given the lack of definitive randomized trial evidence that use of high-flux versus low-flux membranes reduced mortality or hospitalizations. The removal of such large molecules can be further enhanced by use of hemodiafiltration, where provision of substitution fluid and a high convective flow through the dialyzer membrane result in enhanced β_2M removal. Typically, use of hemodiafiltration increases the β_2M reduction ratio from 40%-60% to 70%-90%.

Although use of high-flux membranes and hemodiafiltration enhances β_2M removal during an individual treatment, the impact on predialysis and time-averaged serum levels is less pronounced. The serum β_2M in patients with normal kidney function is in the range of 0.8 to 1.5 mg/L. In patients dialyzed with a low-flux membrane, which removes no β_2M, the predialysis serum values are about 25 times higher, in the range of 30 to 40 mg/L. With use of a high-flux membrane and 3 times/wk treatments, the β_2M levels are in the 22 to 26 mg/L range, and they are not much affected by the additional removal due to the inclusion of hemodiafiltration. So, the question remains, whether reduction of β_2M levels with high-flux dialysis or hemodiafiltration to levels that are still almost 20 times the normal value is of clinical importance. In one randomized trial done in the Netherlands, survival was indistinguishable in patients dialyzed with high-flux membranes and hemodiafiltration versus those dialyzed with a low-flux membrane, despite a marked difference in predialysis serum β_2M levels (Grooteman, 2012). However, two other randomized trials, both comparing hemodiafiltration and high-flux hemodialysis, have shown a substantial survival benefit for hemodiafiltration, despite very modest measured or modeled differences in predialysis or time-averaged serum

β_2M levels. Hemodiafiltration is discussed in detail in chapter 16.

B. Medium Cutoff membranes and removal of extremely high-molecular-weight substances. As one increases membrane pore size beyond levels used in conventional high-flux dialyzers, the risk of losing some albumin during dialysis through the dialyzer increases. So-called medium cutoff (MCO) membranes were developed to help remove immunoglobulin light chains in the treatment of multiple myeloma. There are a number of potential uremic toxins with molecular weights in the 20 to 40 kDa range that are not well removed by conventional high-flux membranes, but which are removed to a substantial extent by MCO membranes. A small amount of albumin removal, which results in either no reduction or a trivial reduction in predialysis serum albumin levels, is the price that needs to be paid. Some of the high-molecular-weight substances that are removed by MCO membranes are involved in inflammation or vascular calcification. Usually, however, the predialysis level of such substances is reduced by only a modest amount, and the baseline levels are elevated to many times the values in patients with normal kidney function. There are some encouraging results suggesting clinical improvement with use of MCO membranes versus conventional high-flux dialyzers, and this remains an area of active investigation (Yang, 2022). Dialysis using MCO membranes does not markedly reduce predialysis serum levels of highly protein-bound uremic toxins.

XII. CONTROL OF EXCESS FLUID VOLUME AS A DIMENSION OF HEMODIALYSIS ADEQUACY.

It has become clear that removal of excess fluid accumulated by ingestion during the interdialytic interval is an additional key feature of dialysis adequacy. Numerous studies have shown that patients with ESKD with fluid overload are at increased risk of mortality and hospitalization (Zoccali, 2017). An additional risk factor is the rate at which fluid is removed, the so-called ultrafiltration rate (Mermelstein, 2023). The extent of fluid overload and the need for rapid ultrafiltration can be minimized by (1) maintaining residual urine output if possible, (2) preventing excess ingestion of salt, which tends to drive fluid intake, and (3) allowing a liberal amount of dialysis time in the course of the week during which fluid can be removed. These issues are discussed in Chapter 31.

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4 Hemodialysis Apparatus

Nicholas Hoenich

I. HEMODIALYSIS MACHINES.

The primary components of a hemodialysis machine comprise (1) the extracorporeal blood circuit containing the blood pump and the dialyzer, (2) the dialysis fluid delivery and ultrafiltration system, and (3) a monitoring system that checks parameters in both the blood and dialysis fluid circuits to ensure patient safety. The dialysis machine is controlled by a user interface usually in the form of a touch screen. It may contain optional modules for online clearance measurement and blood volume monitoring during treatment. Modern machines output treatment data to computerized medical information systems, allowing for both cross-sectional monitoring at a given time and monitoring trends over time.

A. Blood circuit.

A typical blood circuit is shown in Figure 4.1. The circuit is normally supplied as sterile sets of tubing making up the arterial and venous blood lines or for newer systems as cassettes. Integral Luer connectors provide connections to the patient's vascular access, the hemodialyzer, as well as to monitoring points. The tubing sets also contain injection sites to link the circuit to the infusion solution for priming and reinfusion at the termination of treatment.

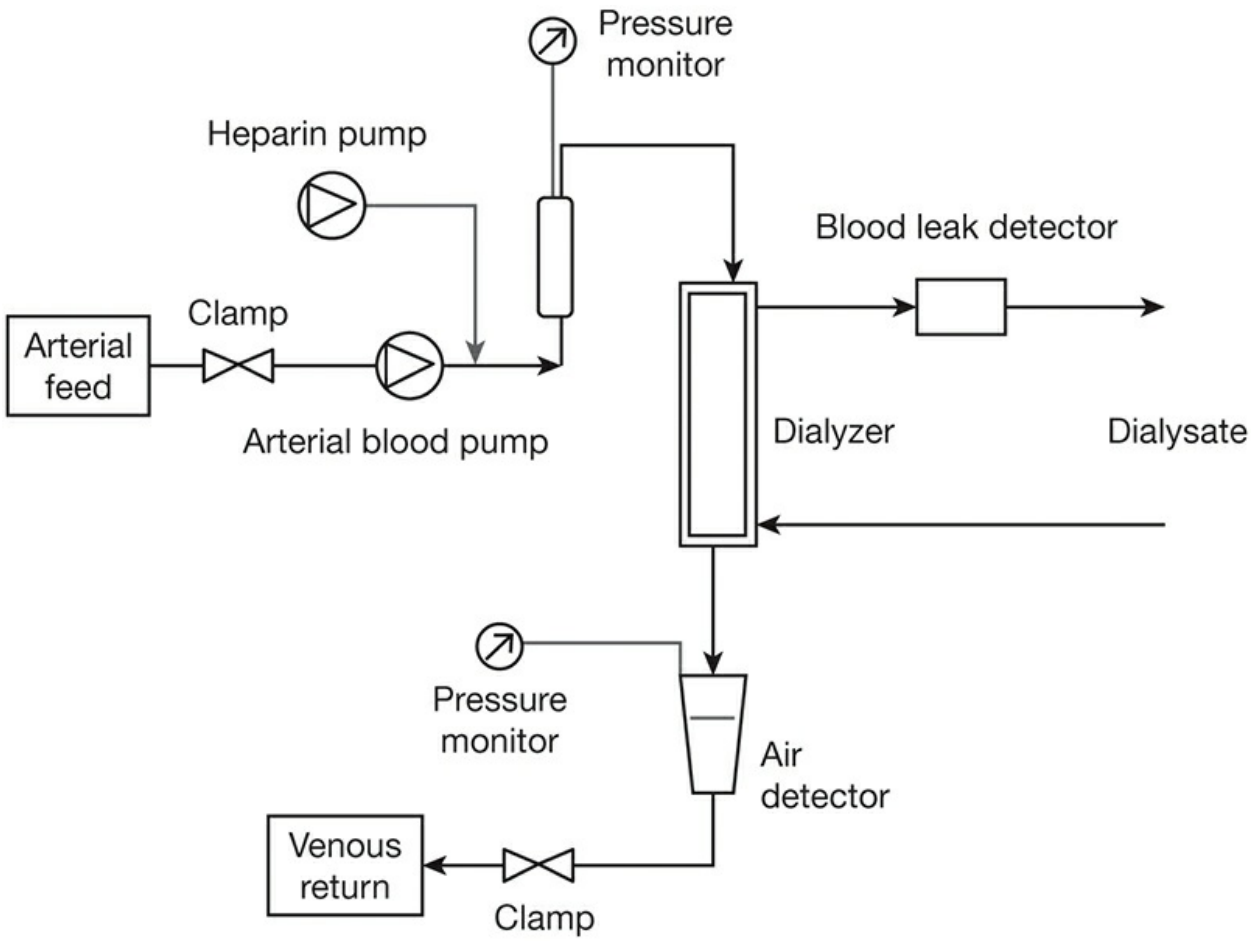


FIGURE 4.1: A typical blood circuit.

1. **Arterial blood line.** The "arterial" blood line takes blood from the patient via the arterial vascular access and delivers it to the inlet of the dialyzer using a blood pump. It consists of three elements: a prepump segment, the blood pump segment, and the postpump segment.
   a. **Prepump segment.** The prepump segment starts at the patient's access and ends at the blood pump insert. This segment usually contains a sampling port, a connector to a saline infusion line, and a "prepump" pressure monitor. The sampling port is used to draw blood samples for laboratory tests. The saline infusion "T" line is used to prime the dialyzer circuit and also to rinse back the contents of the blood compartment at the end of dialysis. Most, but not all, blood lines contain a connection to a pressure monitor. This is in the form of a small drip chamber incorporating a narrow-bore pressure line terminating in a hydrophobic pressure isolator that links the chamber to a pressure transducer.

      During dialysis, as blood is drawn from the patient's access by the blood pump, the pressure in the blood tubing upstream to the blood pump is subatmospheric (negative). If any connection is broken in this segment during dialysis, air can enter the blood line. An incompletely made connection here will not result in blood leakage but may result in ingress of air into the blood line. This air can form microbubbles that can get trapped in the hollow fibers of the

dialyzer, reducing the efficiency of dialysis. If the incomplete connection is not noted, the passage of the microbubbles through the dialyzer can accumulate in the venous drip chamber, as described below. In the venous drip chamber, a "blood level detector" may then be activated, stopping the blood pump and activating an alarm.

The negative pressure in the prepump bloodline segment is a function of the blood flow rate, the bore size of the arterial needle or catheter, and the blood viscosity (which increases with hematocrit). The negative pressure here can increase when the end of the arterial needle or the catheter inflow port is obstructed (either by a clot or by proximity to a blood vessel wall). During dialysis, the pressure limits of the prepump monitor are set automatically by the application of a window around the prevailing pressure. The window may be symmetrical or asymmetrical depending on the dialysis machine used. If the pressure moves beyond the window, an audible alarm is activated and the blood pump stops until the reason for the pressure changes is addressed.

For example, if the mean pressure measured is −100 mm Hg, the alarm window may be set at −50 and −200 mm Hg. An upstream constriction or kink in the blood tubing will trigger the −200 mm Hg alarm setting, while a dislodged needle may suddenly alter the inflow pressure, resulting in the triggering of the lower (−50 mm Hg) alarm pressure. However, this prepump pressure alarm should never be relied upon to detect a line separation, as the pressure may remain in range, even after a separation of the bloodline feeding the dialyzer.

b. Blood pump segment. The blood flow through the circuit and the dialyzer is driven by a roller pump. The rollers compress a section of tubing, preventing backflow, and push the blood forward each time the pump head rotates. The roller passes over a fixed length of tubing during each revolution, and the volume of the cylinder of tubing that is being compressed (stroke volume, calculated as $\pi r^2 \times$ length, where r is the internal radius of the blood tubing at the pump segment) will be the volume of blood that is pumped during each revolution. The dialysis machine displays the prevailing flow rate based on the revolutions per minute multiplied by this "stroke volume."

During dialysis, due to the repeated compression and relaxation of the pump tubing insert with each passage of the rollers, the blood pump tubing may not recoil to a fully circular geometry, but becomes slightly ovoid, which reduces its "stroke volume." This then requires a correction to be made to the estimated blood flow rate being delivered. A similar effect may occur in the presence of a high-inflow (negative) pressure. Dialysis systems incorporate a corrective algorithm linking the blood flow rate displayed to the magnitude of negative prepump pressure to correct for this effect, but with more resilient materials, the failure to snap back to a circular shape at high negative pressure is no longer much of a problem.

Roller pumps can damage the blood due to high shear rates induced in the vicinity of the rollers during occlusion, particularly during the reopening of the tubing once the roller has passed. During reopening, there may be momentary high-velocity backflow leading to red cell damage, causing premature "aging" of the red blood cells or, in extreme cases, hemolysis.

c. **Postpump segment.** The postpump segment, from the blood pump to the dialyzer blood inlet, contains a fine bore tube via a T piece for heparin infusion. Heparin during dialysis can be administered either as bolus doses or as a continuous infusion. When the infusion option is chosen, the rate of infusion into this segment is controlled by a separate heparin pump. Different rates and/or regimens of heparin administration can be programmed in by the user.

In some tubing sets, there is a pressure monitoring connection in the postpump blood tubing segment. The pressure in the postpump segment is positive, as the blood pump is pushing against resistance to flow in the dialyzer as well as the downstream "venous" blood line and access. This pressure in this segment will increase at high rates of blood flow through the dialyzer and is also affected by blood viscosity, which depends on inflow hematocrit as well as the level of ultrafiltration in the dialyzer. A high postpump arterial pressure may be due to a kink in the segment leading from the blood pump to the dialyzer inlet or to partial clotting of the fibers in the dialyzer.

2. **Venous blood line.** The "venous" blood line takes the blood from the dialyzer and delivers it to the patient's venous vascular access. Its primary components are a venous "drip chamber," which contains a detector for air that may have inadvertently been introduced into the blood circuit, and a pressure monitor.

a. **Venous drip chamber and air/foam detector with stop flow clamp.** The purpose of the venous "drip chamber" is to help remove any air that may have entered the blood circuit from various upstream sources. When blood enters this chamber, air bubbles contained in the incoming blood are forced by their buoyancy and reduction in velocity to rise into space containing air in the upper part of the chamber. Blood flow out of the bottom section of the chamber is "degassed" in this manner. The venous blood line immediately downstream to the drip chamber is inserted into a clamping device that is linked to an ultrasonic air and foam detector within which the drip chamber sits during use. Activation of the detector by air or foam stops the blood pump and activates this clamp, immediately shutting off flow through the venous blood line and preventing air from entering the patient. Although the presence of large amounts of air is detected by the above system, microbubbles in the extracorporeal circuit are less easy to detect and can pass into the patient during treatment. Such microbubbles are a consequence of (1) high blood flow rates leading to high negative pressures at the fistula needle site leading to microcavitation or (2) the jet effect of the discharge of the blood into the drip chamber (which can be mitigated by keeping the level of blood in the drip chamber at a high level). Microbubbles may also form at the beginning of treatment from air retained in the fibers of the dialyzer due to inadequate priming (Forsberg, 2013).

The pathophysiology and clinical implications of microbubble exposure during a hemodialysis session are largely unknown. It has been suggested that microbubble entry into the blood can result in lung microemboli (Stegmayr, 2016). A practical strategy to ensure that the passage of such bubbles back to the patient during dialysis is minimized is to maintain a high blood level in the venous drip chamber (Forsberg, 2012).

The drip chamber may also contain a mesh filter that prevents transfer of

any small clots that may have formed in the drip chamber from entering the patient. Incipient clotting of the blood circuit will usually first take place at the venous drip chamber.

b. **Venous pressure monitor.** The pressure monitored via the drip chamber is governed by the resistance to flow in the downstream vascular access, which in turn is a function of the size of the venous access needle, the blood flow rate, and blood viscosity. The pressure at this point in the circuit is always positive (above atmospheric in relation to the level of the patient's heart). In patients with arteriovenous (AV) access, trends in venous pressure from dialysis to dialysis, measured at a standard, low blood flow rate, corrected for patient blood pressure, height of the drip chamber, and needle size, have been used to predict the occurrence of stenosis of the downstream vascular access.

   During dialysis, the pressure limits at the venous pressure monitor are set automatically by the application of a window around the prevailing pressure. If the pressure moves outside the preset limits, an audible alarm is activated and the blood pump stops until the reason for the pressure change is addressed.

   A sudden line disconnection of the blood line from the access downstream to the venous pressure monitor, such as an inadvertent pullout of the venous needle, will lower the pressure at the venous monitor because resistance to flow will almost always be reduced.

   Ideally, this should cause the lower pressure limit to be breached and should activate the low-pressure alarm and stop the blood pump. However, the amount of fall in venous pressure associated with a line disconnection or a venous needle pullout not uncommonly is insufficient to trigger the alarm, especially when the operating venous pressure is low (eg, when a low blood flow rate is being used). **For this reason, the venous pressure alarm absolutely cannot be relied upon to detect venous line separation, and patients have been reported who bled to death after venous line dislodgment that went unnoticed, after which the blood pump continued to operate.**

c. **Bloodline disconnect wetness monitors.** To minimize the risk of inadvertent bloodline disconnections in patients treated overnight in the home or in patients who are at high risk for line separation, such as those with cognitive defects or agitation, attention must be paid to properly taping access needles and connections. The site of the vascular access should always be exposed to the caregiver view (Speranza-Reid, 2021). Detection of needle dislodgment or bloodline disconnection can be monitored using either stand-alone devices or devices that form part of the dialysis machine. One example of an ancillary device that is designed to help detect bloodline separation or needle pullout is the WetAlert, which is designed to work with the Fresenius 2008K home hemodialysis machine. If the device detects conductive fluids such as blood, a radio signal is sent to the hemodialysis machine that triggers an audiovisual alarm, stops the blood pump, and closes the clamp around the venous blood line.

   The Redsense device (Redsense Medical Ab) is a stand-alone sensor that is positioned at the venous access and is linked via a fiberoptic cable to an alarm that is activated if blood seepage is detected. The sensor is in the form of a patch, which is a single-use disposable item. The accompanying alarm unit and

fiberoptic extension are reusable. The HEMOdialert alarm and HEMOsensor (Anzacare) is a stand-alone reusable device with an independent audio alarm that triggers if blood is detected at the site of the sensor. As with the Redsense, it is not linked to the blood pump but does activate an alarm when blood is detected (Axley, 2012).

B. Dialysis fluid circuit. The term "dialysis fluid" is used throughout this section to mean the fluid made from treated water and concentrated electrolytes. The dialysis fluid circuit produces and delivers dialysis fluid to the dialyzer and then routes spent dialysate to the drain. The dialysis fluid circuit incorporates a number of sensors that monitor the dialysis fluid for temperature, conductivity, pressure, flow, and presence of blood. Alarms are activated when any of these monitored parameters move outside of preset limits. Such alarms work in conjunction with valves within the circuit to prevent dialysis fluid which may place the patient at risk from reaching the dialyzer. The alarm systems are linked to a user interface, generally in the form of a touch-sensitive screen. These screens replace the individual displays used in the older dialysis system. In some dialysis systems, the user interface also suggests procedures to rectify the particular alarm that has been triggered.

Hemodiafiltration is discussed in Chapter 16. Equipment used in the delivery of hemodiafiltration retains the primary elements used in the preparation and delivery of hemodialysis fluid, but the dialysis fluid pathway is more complex. With online hemodiafiltration, the dialysis fluid produced undergoes additional filtration to further increase its purity to a very high level. A portion of this ultrapure fluid, now termed "replacement fluid," is then infused directly into the blood side of the extracorporeal blood circuit, increasing the amount of convective transport.

All clinically used hemodialysis systems must be in compliance with American National Standards Institute/Advancement of Medical Instrumentation (AAMI)/International Electrotechnical Commission (IEC) 60601-2-16: Medical electrical equipment—Part 2-16: "Particular requirements for basic safety and essential performance of hemodialysis, hemodiafiltration and hemofiltration equipment." This standard defines basic safety and essential performance. This standard replaces the ANSI/AAMI RD5 document that dealt with hemodialysis systems. It does not cover systems intended for the central delivery of dialysis fluid.

The dialysis fluid produced is not sterile, and the current ANSI/AAMI standards define three levels of dialysis fluid in terms of microbiology: standard dialysis fluid, ultrapure dialysis fluid, and online-prepared substitution fluid used for hemodiafiltration. Ultrapure dialysis fluid and online-prepared substitution fluid used for hemodiafiltration are derived from standard dialysis fluid by additional filtration. Testing for conformity is outside the scope of this section, and it should be noted that within the United States, there is a conflict between the methodology required by the CMS (Centers for Medicare and Medicare Services) Conditions for Coverage and those given in the ANSI/AAMI standards.

The dialysis fluid circuit is linked to a separate water purification system, which in hospitals and clinics supplies treated water (see Chapter 5) to the multiple dialysis machines in the unit. In this section, only elements of the dialysis fluid circuit within the dialysis machine are considered.

1. Endotoxin filter. One or more bacterial- and endotoxin-retentive ultrafilters are an

integral component of the machine's dialysis fluid pathway. These help ensure that the concentration of microbial-derived substances in the dialysis fluid will be extremely low. Filter integrity is automatically tested during start-up. Such filters are disinfected whenever the dialysis machines are disinfected. Some older dialysis machines can be retrofitted with such filters.

2. **Heating and degassing.** The dialysis fluid is required to be delivered to the dialyzer at the correct temperature (usually 35–37 °C) and requires heating. On heating, any dissolved gases expand. Any bubbles formed due to heating are removed by degassing, which is done by exposing the heated water to a negative pressure. Heating and degassing are done before the water is mixed with dialysate concentrate.
3. **Dialysis fluid temperature control.** The temperature of the dialysis fluid is controlled by varying the amount of time that a heater is turned on. The temperature of the water is measured at points in the flow path close to the heater and at the dialysis machine outlet leading to the dialyzer. A feedback system maintains the temperature at the desired value and minimizes temperature fluctuations with a typical accuracy of 0.1–0.2 °C. Some systems utilize a heat exchanger in the fluid circuit to reduce the effect of variation in the incoming water temperature. A heat exchanger also results in energy savings, as the temperature rise needed is lower. All systems have an overtemperature cut-off. Undesirably high temperatures can result if the water supply to the dialysis machine is reduced.
4. **Proportioning system.** The dialysis machine proportionating system mixes treated water that has been heated and degassed with acid and bicarbonate concentrates. Some systems are designed to be used with a single mixing ratio of water to concentrate, while others can be set to different mixing ratios, with each mixing ratio designed for a specific acid or bicarbonate concentrate solution. The mixing of water with the concentrates is achieved either using fixed volume proportionating or by dynamic proportionating, where the mixing ratio is varied accordingly to achieve the desired dialysis fluid conductivity. The proportioning system is discussed in detail in Chapter 5.
5. **Conductivity.** If the proportioning system malfunctions, an excessively dilute or concentrated dialysis solution can be produced. Exposure of blood to a severely hyperosmolar dialysis solution can lead to hypernatremia and other electrolyte disturbances. Exposure to a severely hypo-osmolar dialysis solution can result in rapid hemolysis and severe hyponatremia.

   Monitoring of proportioning of water with acid and base concentrates is done by measuring the conductivity of the product dialysis fluid. The conductivity of a solution will increase or decrease depending on its concentration of ions. Conductivity is measured in terms of milliSiemens (mS) per centimeter (cm). One Siemen (S) is equal to the reciprocal of 1 ohm (an alternative term for a Siemen is "mho"). Common causes of dialysis fluid conductivity being out of range include an empty concentrate container or low water pressure.
6. **Bypass valve.** Dialysate temperature and conductivity are continuously monitored throughout treatment. If either goes out of the desired range, an alarm is triggered and a bypass valve is activated which blocks the dialysis fluid from entering the dialyzer and diverts it directly to the drain. The dialysis fluid continues to bypass the

dialyzer until the cause of the alarm has been rectified.

7. **Blood leak detector.** Small leaks of blood can occur through defects in the dialyzer membrane, and the small amount of blood entering the spent dialysate will be invisible to the naked eye. To detect this problem, a blood leak detector is placed in the dialysis fluid outflow line. If the detector senses the presence of blood, an alarm is activated and blood flow through the dialyzer is halted. False alarms can occur due to the presence of hydroxycobalamin in the blood. Hydroxycobalamin is dialyzable and easily passes through the membrane. Levels high enough to trigger a false alarm have been reported in patients receiving hydroxycobalamin to treat cyanide poisoning or postcardiopulmonary bypass vasoplegic syndrome (Datar, 2019). Air bubbles or deposits of grease or scale on the blood leak detector can also trigger it to alarm.
8. **Ultrafiltration delivery and control.** Fluid removal in older dialysis systems was based on the manual adjustment of pressures across the membrane. The amount of ultrafiltration due to a given pressure difference depended on the water permeability (K_{UF}) of the membrane. With the use of high-flux dialyzers, this approach has been replaced by systems that can accurately deliver, monitor, and control the ultrafiltration rate throughout treatment. The most common method is volumetric control. The dialysis fluid circuit is set up as a closed loop that includes two compartments or chambers within the dialysis machine separated by a flexible membrane. An ultrafiltration pump that can remove fluid from the closed loop is part of the circuit. Valves are connected to the inflow and outflow of each chamber, and these valves allow a fixed volume of fluid to enter the inflow chamber and the removal of an equivalent amount of spent dialysate from the outflow chamber. A separate ultrafiltration pump removes fluid from the closed dialysate loop, which results in an equal amount of fluid being transferred across the dialyzer, because the volume of the loop with its contained chambers is fixed.

   Less commonly used approaches include a single “mini” balance chamber with accurate flow meters measuring precisely the dialysis fluid inflow and outflow rates. Setting the difference between the two flowmeters controls the amount of fluid removal.

C. Advanced options

1. **Adjustable bicarbonate concentration.** The base buffer content of the dialysis fluid is dependent on the amounts of bicarbonate present in the bicarbonate concentrate and on the amount of acetate or citrate equivalents present in the acid concentrate. In certain machines, the bicarbonate concentration of the final dialysate can be changed from the default value by changing the default mixing ratio of water to the acid and base concentrates. This feature allows the delivery of final bicarbonate concentrations of 20 to 40 mM, which is quite useful in the treatment of patients with either acidosis or alkalemia. However, changing the concentration of bicarbonate by changing the mixing ratio will be associated with minor changes in the final dialysis fluid concentration of calcium, magnesium, and potassium, as the change in proportioning required affects elements contained in both the acid and base concentrates.
2. **Sodium profiling.** Most dialysis prescriptions utilize a constant dialysate sodium concentration, and different concentrates can be purchased that will produce

different default sodium concentrations in the product dialysis fluid. Because sodium ions are a major component of conductivity of the dialysis fluid, a desired dialysis fluid sodium can also be set by adjusting the desired dialysis conductivity.

Most dialysis machines allow the option of varying the dialysis fluid sodium concentration during the course of a given treatment. Typically, a higher dialysis fluid sodium is set for the early part of treatment with a progressive reduction over the course of dialysis, such that the dialysis fluid sodium level at the end of treatment is similar to or lower than the predialysis serum value. This approach promotes hemodynamic stabilization through a diffusive influx of sodium during the initial part of the dialysis session, when there is a relatively rapid fall in plasma osmolality due to the removal of urea and other osmotically active solutes. As the treatment progresses, the rapid decline in plasma osmolality abates and the dialysis solution sodium is lowered, minimizing the added sodium load from the dialysis solution over the entire treatment. Despite lowering dialysis solution sodium during the latter part of a dialysis session, such sodium profiling can often lead to sodium loading as patients are still exposed to a higher time-averaged dialysate sodium concentration during treatment. Another approach that has been tried is to align the dialysis fluid sodium concentration with the predialysis serum sodium level on a patient-specific basis. This approach has been termed isonatric dialysis and is based on the concept that patients undergoing dialysis have their own predialysis sodium values that change very little over time. This value, the sodium "set point," can be established by calculating the monthly mean of the patient's sodium values and adjusting the dialysis fluid sodium level accordingly. However, patients with lower predialysis serum sodium values have a worse outcome, and it is not clear whether their lower predialysis sodium should be maintained or increased to more normal values in the course of dialysis.

3. **Programmable ultrafiltration.** Normally, ultrafiltration is performed at the same rate throughout the dialysis session. Varying ultrafiltration rates to maximize fluid removal during periods of greatest hydration and dialysate-to-plasma sodium gradient may reduce ultrafiltration-related cardiovascular complications and symptoms. Generally, it is used primarily in the context of concomitant sodium profiling.
4. **Modulation of dialysis fluid temperature.** During dialysis, patients experience an increase in energy production, leading to a slight increase in body temperature over the course of a dialysis session. This may be enhanced by cutaneous vasoconstriction in response to ultrafiltration, which can serve to reduce the rate of heat loss. Studies undertaken in the 1980s demonstrated that the use of a low (34.0–35.4 °C) dialysis fluid temperature improved hemodynamic stability compared to the use of dialysis fluid delivered at 37 °C. A recent Cochrane study found very low-quality evidence that fixed reduction of dialysis fluid temperature decreased the incidence of hypotension during dialysis compared with standard dialysis fluid temperature. Use of lower temperature dialysis solution was associated with some increase in patient discomfort (feeling cold) (Tsujimoto, 2019).

   The multicenter "MyTEMP" study found no benefit in terms of either a higher intradialytic blood pressure or survival in patients dialyzed using a slightly cooler dialysis solution, adjusted to be 0.5–0.9 °C below each patient's measured

temperature (MyTEMP Writing Committee, 2022).

One alternative to using a dialysis solution at a fixed lower temperature is to adjust dialysate temperature continuously online while monitoring the patient's thermal balance. This is possible with the use of a temperature control mode that forms part of current Fresenius hemodialysis machines. The dialysis solution temperature can be set to maintain a constant body temperature or to reduce body temperature slightly over the course of the dialysis session.

5. **Measurement of the delivered dose of dialysis during treatment.** Hemodialysis adequacy can be quantified using ultraviolet absorbance of the spent dialysate or by analysis of dialysate conductivity at the dialyzer inlet and outlet in response to changes in dialysate electrolyte concentration. Such measurements can be made at every dialysis. Ultraviolet absorbance is used in the Adimea (B. Braun) and Dialysis Dose Monitor (Nikkiso) systems (Castellarnau, 2010).

   The second approach to monitoring dialysis adequacy is based on dialysate conductivity, and is available on specific dialysis machines made by Baxter or by Fresenius Medical Care. As sodium clearance is similar to urea clearance, it can be used to estimate the urea clearance of a dialyzer. Two conductivity sensors are used to calculate ionic clearance. Using such an approach, the dialyzer in vivo sodium clearance can be calculated, which is close to the urea clearance (K). This value can then be combined with the dialysis session length (t) and divided by the patient's estimated urea distribution volume V (derived either from anthropometric data or from prior urea kinetic modeling) to give an online estimate of Kt/V during each treatment.
6. **Modules to measure access recirculation or access blood flow.** The ability to accurately measure access recirculation is of importance because its presence indicates access dysfunction and may explain why a prescribed Kt/V has not been delivered. The ability to measure access blood flow rate allows access monitoring and the detection of impending access dysfunction. A variety of different approaches, either in the form of stand-alone or dialysis machine integral modules, exist for this purpose and are based on ultrasonic, thermal, or ionic measurements (Badr, 2014; Lindsay, 1998).
7. **Modules to monitor blood volume changes during treatment.** In clinical practice, the goal of blood volume monitoring is to monitor the patient's response to ultrafiltration and to reduce the occurrence of intradialytic hypotensive episodes (Mahony and Ward, 2021). Changes in patient blood volume during dialysis are estimated based on the increase in hematocrit or plasma protein concentration which take place in the course of a dialysis session. Monitoring is done by use of an ultrasonic or optical sensor scanning the blood in the inflow blood line. Measurements are not absolute but relative to the first measurement made during treatment. In this way, the degree of blood volume reduction can be monitored, and with some machines, the ultrafiltration rate and/or the dialysis solution sodium level can be adjusted to limit the amount of hematocrit increase according to desired parameters. One randomized crossover trial attempting to use blood volume monitoring to guide the ultrafiltration rate failed to find a reduction in intradialytic hypotensive episodes (Leung, 2017), but some studies have found that such devices reduce the incidence of dialysis hypotension.

D. Single-blood pathway ("single-needle") devices.

The technique of single-needle dialysis in which the arterial and venous blood circuits are linked to a common pathway or single needle was invented in the 1960s and enjoyed great success during the 1970s and 1980s. Although single-needle dialysis lost popularity thereafter, it has become more popular again recently. With single-needle hemodialysis, there is a decrease in the number of punctures, translating into reduced potential access damage and an improved quality of life by reducing puncture-related pain, stress, and complications. One disadvantage is the occurrence of some degree of recirculation due to the use of a common pathway to withdraw and return the blood to the patient. This does have some impact on reducing the delivered dialysis dose (Vanholder, 2020).

Many current dialysis machines incorporate an option to perform single-needle dialysis. To perform single-needle dialysis, either a two-pump or a single-blood pump system can be used. In the two-pump setup, the pumps are placed in the arterial and venous blood circuits and operate in conjunction with clamps and expansion chambers. The arterial pump pumps blood into the expansion chamber until either a planned volume has been transferred or a preset pressure threshold has been reached. Then the arterial pump stops, a clamp on the arterial line is activated, and the venous pump returns blood to the patient, stopping after the preset volume has been reached or a low-pressure threshold is breached.

Alternatively, a single pump may be used, such as in the B. Braun Dialog iQ system (B. Braun). The phase volume is specified and the blood flow is regulated automatically. This system offers a reduction in the standstill periods coupled with an increased total treated blood volume and automatic adjustment of the optimal blood flow without user interaction at the machine (Bieser, 2018).

II. THE DIALYZER.

Blood tubing sets link the patient to the dialyzer, where the blood and dialysis solution circuits meet and where the movement of molecules between dialysis solution and blood across a semipermeable membrane occurs. To maximize the transport of molecules, the blood and dialysate flows are set to flow in opposite directions (countercurrent). The usual dialysis fluid flow rate is 500 to 750 mL/min, and the usual blood flow rate is 250 to 400 mL/min. For maximum practical efficiency, dialysis fluid flow rate should be set at 1.5 to 2.0 times that of the blood flow rate.

A. Construction

1. Hollow-fiber or capillary dialyzers.

Most commonly, the dialyzer is a hollow-fiber design (also referred to as a capillary dialyzer) in which a hollow-fiber bundle forms the blood compartment. The fiber bundle is enclosed in an outer housing that forms the dialysate compartment, which incorporates connectors for dialysis fluid. To obtain even spacing and to prevent dialysis fluid channeling, in many dialyzers, the fibers' outer wall may contain undulations (Moiré structure) and interspersed spacer yarns. Internal baffles have also been used to facilitate an improved dialysate fluid flow through the fiber bundle.

The fibers are held in a polyurethane potting material that also forms a barrier between the blood and dialysate compartments. The number of fibers in the bundle and their effective length (ie, the length between the polyurethane potting material) determine the dialyzer membrane surface area. The fibers terminate in a space at each end of the dialyzer cylinder. The cylinder ends are enclosed by so-called end

caps or headers that incorporate fittings to permit the attachment of the blood tubings. Blood flows into the chamber formed by the header at one end of the cylindrical shell. From there, blood enters the fiber lumens and an equivalent arrangement at the other end collects the blood which enters the venous blood circuit (Figure 4.2).

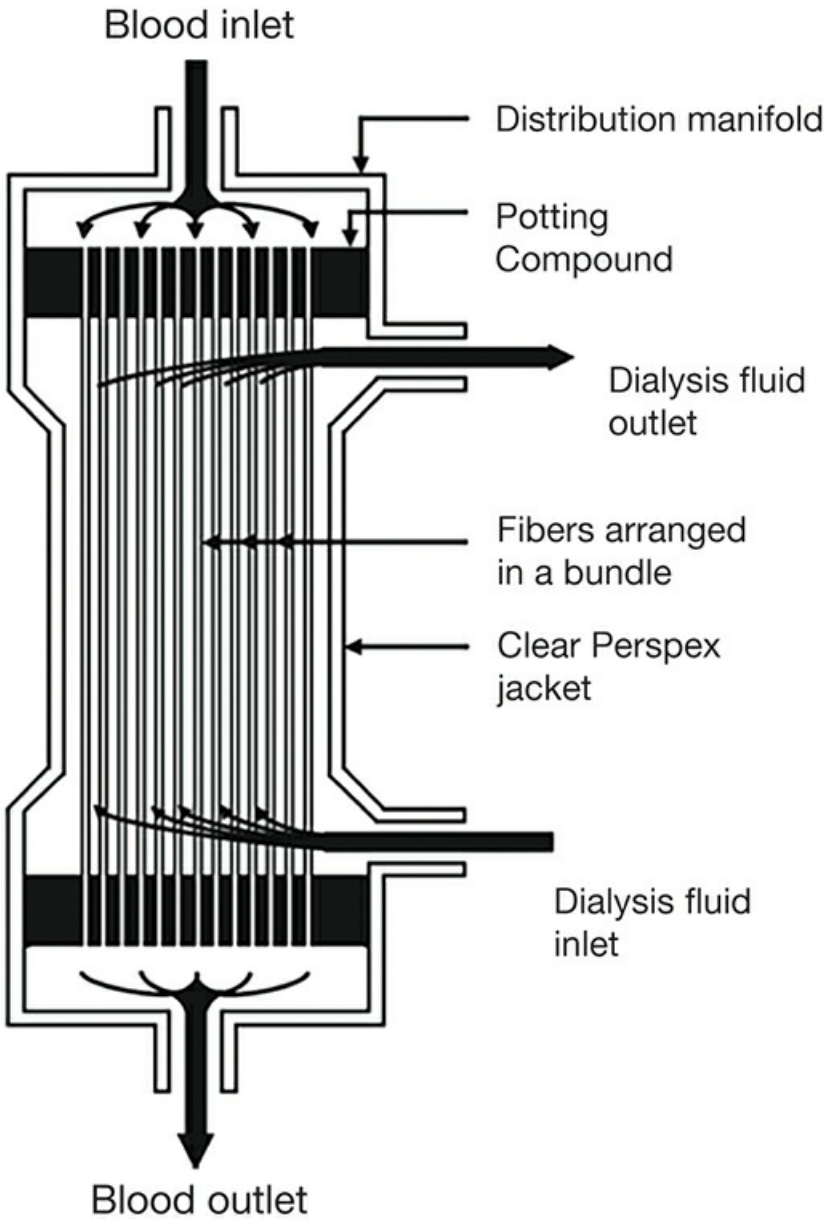


FIGURE 4.2: A schematic diagram of a typical hollow-fiber dialyzer. The patient's blood enters a distribution manifold at the dialyzer header that has been connected to the blood tubing set. Blood then flows through the fiber bundle, which is held in place at both ends by a polyurethane potting compound. Blood leaves the bundle via a second manifold at the distal end of the fiber bundle. The dialysis fluid flows in a countercurrent direction, bathing the fibers and enabling the transfer of molecules from the blood into the dialysis fluid. The entire assembly is contained in a transparent plastic housing. (Adapted from an illustration from the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.)

2. **Parallel plate dialyzers.** Historically, parallel plate dialyzers were also used, in

which blood and dialysis solution pass through alternate spaces between the membrane sheets supported on channeled plates along which the dialysis fluid flows.

B. Membranes. Historically, membranes based on cellulose were used. Those membranes were most often prepared by first dissolving cellulose using an ammoniac solution of cupric oxide and so were called "cuprophane" membranes. Today, membranes are either manufactured from synthetic polymers or modified cellulose.

1. **Synthetic polymer membranes.** Synthetic polymer blend membranes include polysulfone, polyethersulfone, polyacrylonitrile (PAN), polyamide, polyester polymer alloy (PEPA), ethylene vinyl alcohol (EVAL) copolymer, and polymethyl-methacrylate (PMMA). There are several manufacturers of polysulfone membranes; subtle differences exist between them, and consequently, they cannot be considered identical.
2. **Modified cellulose membranes.** In modified cellulose membranes, the bioreactive hydroxyl (OH) groups of the cellulose molecule have been acylated with acetate groups and are named according to the number of acetate groups in each cellulose unit. For example, cellulose acetate, cellulose diacetate (CDA), or cellulose triacetate (CTA). More recently, asymmetric cellulose triacetate (ATA) has been produced and is used in dialyzers manufactured by the Nipro Corporation.
3. **Vitamin E–coated membranes.** Vitamin E has been used since the early 1990s to modify surfaces that contact blood. Initially, cellulose-based and later synthetic hollow-fiber membranes were coated with vitamin E to enhance biocompatibility and provide antioxidant protection. One meta-analysis indicated that the use of such membranes reduced the resistance to erythropoietin but had no impact on other anemia parameters. Use of vitamin E–coated membranes was associated with a decrease in some markers of inflammation and oxidative stress, but there was no impact on the serum lipid profile, dialysis adequacy, or blood pressure, nor on serum levels of albumin or uric acid (D'Arrigo, 2017).
4. **High-flux versus low-flux membranes.** The permeability to solutes and water of membranes can be altered by adjusting the manufacturing process and changing the polymer ratios, which influence the membrane pore size distribution. The pore size of dialyzer membranes determines the maximum size of molecules that they will allow to pass. Although dialysis adequacy has traditionally focused on the removal of low-molecular-weight substances such as urea (molecular weight [MW] 60) and creatinine (MW 113), it has long been known that so-called middle molecules with MW range originally defined in the 500 to 2,000 Da range are also uremic toxins. All dialysis membranes, whether "low-flux" or "high-flux," allow passage of molecules in this weight range. However, it became clear that molecules in the 2,000- to 45,000-Da range were also often associated with uremic toxicity and were markedly elevated in patients undergoing dialysis. A number of dialysis membranes, whether based on cellulose or synthetic polymers, had pore sizes that allowed almost no passage of molecules in the 11-kDa size range, for example, of β-2-microglobulin. Increasing the pore size led to a family of so-called high-flux membranes, which allowed the passage of 11-kDa molecules while still limiting the passage of albumin (MW about 65 kDa). The use of high-flux membranes has been associated with a number of potential benefits, as detailed in Chapter 11.

5. **Medium cut-off membranes.** Medium cut-off membranes were designed to achieve substantial removal of middle-to-high-weight molecules (20- to 40-kDa range) with little albumin loss. This was achieved primarily by narrow pore size distribution and relatively small fiber diameter, which promotes increased convective transport within the dialyzer. The goal is to be able to achieve the same or better degree of removal of such molecules as obtained with hemodiafiltration using conventional high-flux membranes without the need for replacement fluid or ultrapure dialysis solution.

C. Dialyzer performance

1. **Clearance.** The solute removal of any dialyzer can be expressed in terms of clearance. Dialyzer clearance (K) can be expressed in terms of concentrations and flow rates as follows:

$$K_{\mathrm{d}} = Q_{\mathrm{B}} \frac{(C_{\mathrm{bi}} - C_{\mathrm{bo}})}{C_{\mathrm{bi}}}$$

where K is the dialyzer clearance of the solute in question, C_{bi} is the blood concentration of that solute at the dialyzer blood inlet (arterial), C_{bo} is the blood concentration of the solute at the dialyzer blood outlet (venous), and Q_{b} is the blood flow rate. This simple expression does not take into consideration the solute transport arising from fluid removal (ultrafiltration). For a detailed discussion of dialyzer urea clearance, see Chapter 3.

2. **Mass transfer area coefficient (K_0A).** The mass transfer area coefficient (K_0A) is a useful way of characterizing the ability of a given dialyzer to clear a particular solute. It is a multiple of two terms: the K_0, which is the maximum clearance per unit surface area of the membrane for a particular solute, and A, the effective membrane surface area within the dialyzer. Functionally, the K_0A is also the maximum theoretical clearance of a given dialyzer (in mL/min) for a given solute at infinite blood and dialysis solution flow rates. Theoretically, K_0A can be used to predict the performance of the dialyzer at any blood and dialysis fluid combination. In terms of urea removal, super high-efficiency dialyzers will have a K_0A value greater than 1,400 mL/min. High-efficiency dialyzer will have a K_0A value for urea greater than 1,000 mL/min. Ordinary, relatively low- efficiency dialyzers will have K_0A urea values between 600 and 1,000 mL/min, and dialyzers with K_0A urea values less than 600 mL/min are usually reserved for small patients and children.

3. **Ultrafiltration coefficient (K_{UF}).** Fluid removal across the dialyzer is governed by the membrane's hydraulic permeability and the applied pressure. A standardized measurement of ultrafiltration rate for dialyzers (K_{UF}) is commonly reported as mL/h per mm Hg. Most so-called low-flux dialyzer membranes have a K_{UF} value less than 15, whereas with high-flux membranes the typical K_{UF} value is much higher.

   Within the dialyzer, due to differences in pressure along the length of the hollow-fiber bundle, especially when using a membrane that is highly permeable to water, there is ultrafiltration both from the blood to dialysate compartment (mostly in the upstream portion of the fiber bundle) as well as the so-called backfiltration

that occurs mostly in the downstream portion of the fiber bundle. Backfiltration is clinically important because it presents a pathway whereby microbial contaminants present in the dialysis fluid can be transferred to the blood (Bowry, 2021; Tao, 2014).

4. **Sieving coefficient.** The sieving coefficient describes a membrane's ability to pass a solute in convective mode. It ranges from 0 (no transport) to 1 (unrestricted transport). The sieving coefficient is usually of interest for large molecular weight solutes, with an MW range of 10 kDa and higher.
5. **The dialyzer specification sheet and its interpretation.** The specification sheet for any dialyzer in current clinical use contains data relating to the device and is presented in a standardized form. The data shown, unless specified otherwise, typically has been obtained from in vitro studies performed in a laboratory rather than under clinical conditions. Standardized test methodology is detailed in ISO/AAMI/ANSI 8637-3.
    a. **In vitro urea clearance.** Clearances are reported at standard "blood" flow rates of 200, 300, and 400 mL/min and a dialysis fluid flow rate of 500 mL/min for blood flow rates of 200 and 300 mL/min and 700 or 800 mL/min for blood flow rates above 300 mL/min. Clearance increases somewhat with ultrafiltration, and the results shown typically were measured at an ultrafiltration rate of zero. For dialyzers that are intended for use in hemodiafiltration, data are often presented at higher dialysis fluid flow rates for blood flow rates of 300 to 500 mL/min. The values in the specification sheet for urea clearance are substantially higher than those obtained during actual dialysis but are nevertheless useful for comparing dialyzers, although the best way to compare dialyzer clearances for a given solute is to compare K_0A values.
    b. **In vitro urea K_0A.** This value is not always given for a dialyzer. It can easily be backcalculated from the urea clearance information at a particular blood and dialysate flow rate, also taking into consideration whether ultrafiltration was zero or not during the clearance measurement. A calculator for this purpose is available at www.ureakinetics.org. The backcalculated K_0A values may differ slightly when inputting the urea clearances at different blood and dialysate flow rates. Usually, the clearances obtained at the higher blood flow rates will give more reliable values.
    c. **Creatinine clearance.** Creatinine clearance data are provided in an identical manner to that described for urea. The inclusion of creatinine as a parameter of interest is linked to the use of creatinine to measure native renal function. Creatinine clearances on the spec sheet usually provide no useful additional clinical information.
    d. **Phosphate clearance.** Phosphate clearance data are provided in an identical manner to that described for urea. This information is not usually of clinical utility. Phosphate and urea removal usually correlate fairly well, although some dialyzer membranes have been optimized for increased phosphate removal.
    e. **Vitamin B_{12}.** In vitro clearance of vitamin B_{12} (MW 1,355) is an indication of how well the membrane allows the passage of larger molecular weight solutes and is relatively easily measured in the laboratory. Clearance data together with membrane sieving coefficient are generally presented.

f. **β_2-Microglobulin, inulin, myoglobin, and albumin.** Sieving coefficients for β_2-microglobulin (MW 11,800), inulin (MW 5,200), myoglobin (MW 17,000), and albumin (MW 66,400) are often provided and are of particular interest for those wishing to optimize the removal of such large MW substances.

g. **Ultrafiltration coefficient, K_{UF}.** A test solution of anticoagulated bovine or human blood, with a hematocrit of 32 ± 3% and a protein content of (6.0 ± 0.5) g/dL (60 g/L), is used for the determination of the ultrafiltration coefficient.

h. **Surface area.** The membrane surface area of most dialyzers suitable for the treatment of adult patients ranges between 0.8 and 2.5 m^2. Smaller size dialyzers are available from many manufacturers for pediatric patients. An association between dialyzer surface area and mortality has been reported (Abe, 2021).

i. **Membrane characteristics.** Characteristics of the membrane in terms of materials used are generally listed. Membrane internal diameter and wall thickness are specified. Hollow fibers used typically have an internal diameter of 180 to 200 mcm and a wall thickness of 30 to 40 mcm. A low internal diameter of the hollow fibers can result in increased blood compartment resistance, resulting in increased rates of internal filtration and backfiltration.

j. **Blood compartment volume and priming volume.** The blood compartment volume is usually 60 to 120 mL. This excludes the volume of the blood lines used to connect the dialyzer to the patient. This together with the volume of the blood lines makes up the extracorporeal volume and is an important consideration when treating pediatric patients. Priming volume refers to the volume that is required to prime the dialyzer and ensure that all the air in the blood compartment has been removed. Generally, this volume is 2 to 2.5 times the blood compartment volume.

k. **Mode of sterilization.** The primary methods of sterilization of currently used hemodialyzers are electron beam, γ- or β-irradiation, and steam. Historically, ethylene oxide gas (ETO) was commonly used; however, its use has declined for operational and clinical reasons. Lengthy cycle times are often needed to ensure complete dissipation of ETO from the device, as ETO is adsorbed by many materials in the dialyzer following sterilization, including potting compound.

l. **Limitations of use.** Limitations of use are not given in the product specification but form an important part of the instructions for use and should be read before any new type of device is introduced clinically. This includes information regarding the use of the dialyzer in a reprocessing environment.

m. **Dialyzer table.** A table of commonly used dialyzers is presented in Appendix D. This table includes membrane material, membrane surface area, sterilization mode, K_{UF}, blood compartment volume, and urea clearance metrics, including K_0A.

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5 Dialysis Water and Dialysis Solution

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I. PRODUCT WATER FOR HEMODIALYSIS. Patients are exposed to 120 to 200 L of dialysis fluid during each dialysis treatment. Any low-molecular-weight contaminants in that fluid can enter the blood unimpeded and accumulate in the body in the absence of renal excretion. Therefore, the chemical and microbiologic quality of dialysis fluid is important if patient injury is to be avoided. Dialysis fluid is prepared from treated water (product water) and concentrates, the latter containing the electrolytes necessary to provide dialysis fluid of the prescribed composition. Most concentrates are obtained as powder from commercial sources. Although the quality of that powder is subject to regulatory oversight, the quality of the water used to reconstitute the powder at a dialysis facility, and to prepare the final dialysis fluid, is the responsibility of the dialysis facility.

A. Water contaminants harmful to patients undergoing dialysis. Some substances added to municipal water supplies for public health reasons pose no threat to healthy individuals at the concentrations used but can cause injury to patients with renal failure if those substances are allowed to remain in the water when it is used to prepare dialysis fluid. Therefore, all municipal water supplies should be assumed to contain substances harmful to patients undergoing dialysis, and all dialysis facilities require a system for treating municipal water before it is used to prepare dialysis fluid. Contaminated water should be suspected when multiple patients in the same dialysis facility present with toxicity associated with any of these substances. What follows is a short list of the most common offending substances. Please refer to References and Suggested Readings for a more complete discussion of these and other contaminants.

1. **Aluminum.** Aluminum is added to water as a flocculating agent by many municipal water suppliers (aluminum sulfate is used to remove nonfilterable suspended particles). Aluminum causes bone disease, a progressive and often fatal neurologic deterioration known as the dialysis encephalopathy syndrome, and anemia.
2. **Chloramine.** Chloramine is added to water to prevent bacterial proliferation. Because chlorine can combine with organic substances in the water to form potentially cancer-causing compounds, many municipalities now use chloramine rather than chlorine to suppress bacterial proliferation. In the past, some municipalities did not notify dialysis facilities of the change from chlorine to chloramine, leading to outbreaks of hemolytic anemia. Chloramine also damages reverse osmosis (RO) membranes.
3. **Fluoride.** Fluoride is added to water supplies to reduce tooth decay. Large amounts of fluoride can elute into water from an exhausted deionizer and cause severe pruritus, nausea, and fatal ventricular fibrillation.
4. **Copper and zinc.** Copper and zinc can leach from metal pipes and fittings and cause hemolytic anemia. Lead and aluminum can enter the water stream in a similar

fashion.

5. **Bacteria and endotoxin.** Both the water used to prepare dialysis fluid and the final dialysis fluid are susceptible to microbiologic contamination by bacteria and their endotoxins. Endotoxins, endotoxin fragments, and other bacterial products, such as short bacterial DNA fragments, some of which can be as small as 1,250 Da, can cross dialyzer membranes and enter the bloodstream to produce pyrogenic reactions and other untoward effects. The substances added to municipal water to suppress bacterial proliferation are removed by a dialysis facility's water treatment system, increasing the importance of preventing bacterial growth in the treated water.
6. **Toxins from blue-green algae.** Contamination of municipal water supplies by other microbial products, such as microcystins derived from blue-green algae, can also prove toxic to patients undergoing hemodialysis (Carmichael, 2001). Dialysis centers should be aware of the potential presence of such toxins, particularly in areas subject to seasonal algae blooms.
7. **Peroxides.** Silver-stabilized peroxide and hydrogen peroxide can be added to hospital water supplies to suppress the growth of Legionella in the hospital's water distribution system. Residual hydrogen peroxide and silver-stabilized hydrogen peroxide have been associated with cyanosis and methemoglobinemia in patients undergoing hemodialysis. Where possible, dialysis programs located in a hospital should have a dedicated water supply independent of the hospital water systems to avoid inadvertent exposure to peroxides.

B. Water and dialysis fluid quality requirements

1. **Fluid quality standards.** The International Organization for Standardization (ISO) has published minimum standards for the quality of the water used to prepare dialysis fluid and the quality of the final dialysis fluid. These standards have been adopted by the Association for the Advancement of Medical Instrumentation as national standards for the United States and are also followed by regulatory organizations in many other countries. The standards set maximum levels for chemicals known to be toxic to patients undergoing hemodialysis, for chemicals known to be toxic to the general population, and for bacteria and their endotoxins. In the United States, fluid quality is also subject to regulation by the Centers for Medicare and Medicaid Services (CMS) via its conditions for coverage of end-stage renal disease facilities (Conditions for Coverage). While ISO and CMS agree regarding the limits for chemical contaminants, they differ for bacteria and endotoxin. Current ISO recommendations are that product water used to prepare dialysis fluid should contain **less than 100 colony-forming units (CFU)/mL** of bacteria and **less than 0.25 endotoxin units (EU)/mL** of endotoxin. The maximum levels for the final dialysis fluid are 100 CFU/mL and 0.5 EU/mL, respectively. The current CMS regulations, which set maximum levels of 200 CFU/mL for bacteria and 2 EU/mL for endotoxin in both water and dialysis fluid, were published in 2008 and reflect the standards of that time. Although pyrogenic reactions do not occur when levels of bacteria and endotoxins in the dialysis fluid are maintained below the limits set by either ISO or CMS, the lower levels set by ISO are thought to provide greater protection against chronic inflammation as described below for ultrapure dialysis fluid.

2. **Ultrapure dialysis fluid.** Low levels of endotoxins and endotoxin fragments in dialysis fluid, while not causing pyrogenic reactions, may contribute to a chronic inflammatory response that may be associated with long-term morbidity in patients undergoing dialysis. In observational studies, the use of so-called ultrapure dialysis fluid, which is characterized by a **bacteria level below 0.1 CFU/mL** and **endotoxin level below 0.03 EU/mL**, has been linked to reduced plasma levels of markers of inflammation, such as C-reactive protein and interleukin-6, an improved response of anemia to erythropoietin therapy, better nutrition as evidenced by increases in plasma albumin value, and higher estimated dry body weight, midarm muscle circumference, and urea nitrogen appearance rate. Ultrapure dialysis fluid has also been associated with reduced plasma levels of β_2-microglobulin and pentosidine (a surrogate marker of carbonyl stress), and a slower loss of residual renal function (Susantitaphong, 2013). Whether or not these benefits extend to mortality is unclear, however, with both a reduction (Hasegawa, 2015) and no change (Asci, 2013) in all-cause mortality being reported for ultrapure dialysis fluid compared to standard dialysis fluid.

   Although some of the above benefits have not been confirmed, many authorities believe that ultrapure dialysis fluid should be used routinely for standard hemodialysis. Although the use of ultrapure dialysis fluid is highly desirable for hemodialysis, it is mandatory for online convective therapies, such as online hemodiafiltration, to prevent the transfer of bacterial fragments into the blood via the replacement fluid, which is prepared from dialysis fluid and infused directly into the blood.

C. Methods of treating water for hemodialysis. Systems used to treat water for dialysis consist of three parts: pretreatment, primary purification, and distribution to the point of use.

1. **Pretreatment.** The pretreatment cascade is designed to prepare the water for optimal operation of the primary purification process. Components usually include a valve to blend hot and cold water to a constant temperature; a pump to boost the incoming water pressure to a level sufficient for operation of the system; and some form of preliminary filtration, softening, and filtration through activated carbon. Correction of pH (using injection of hydrochloric acid) is sometimes needed to correct excessive alkalinity, which can impede the ability of carbon to remove chlorine and chloramine and can cause fouling of RO membranes by calcium and magnesium salts. The pump used to inject acid must be regulated to tightly control the addition of acid to protect patients and the performance of other components of the water treatment system.
   a. **Water softener.** A water softener is used to remove calcium and magnesium from water in exchange for sodium bound ionically to a resin bed. The resin exchanges Na^+ ions for Ca^{++} and Mg^{++} as well as for other cations such as iron and manganese. The water softener protects the downstream RO membrane from scaling by calcium and magnesium in the source water. Such mineral scale can foul an RO membrane quickly. Water softener resins need to be backwashed and regenerated frequently on a routine basis using a concentrated sodium chloride solution (brine). During backwash, water is drawn into the softener in a reverse direction to wash and fluff the resin, and then the brine solution is introduced to

regenerate the resin, replacing the recently bound Ca^{++} and Mg^{++} ions with Na^{+} ions.

b. Carbon. Carbon is used to remove chlorine and chloramine, which are not removed by RO. Carbon also removes other small organic compounds that may be in the water. Although granular activated carbon (GAC) beds are most commonly used for this purpose, other forms of carbon can be used in some circumstances, for example, block carbon filters may be used in portable dialysis systems.

The kinetics of chloramine removal by carbon are slower than those for the removal of chlorine, and a system that adequately removes chlorine might not adequately remove chloramine. As a result, care is required in designing and monitoring carbon beds used for chloramine removal. The carbon beds should be sized to provide an "empty bed contact time" of at least 10 minutes and backwashed regularly to fluff the beds and prevent the formation of channels in the carbon, which can reduce their efficiency. Redundancy is created by using two carbon beds in series. The upstream "worker" carbon bed will become exhausted first, with the downstream or "polisher" bed serving as a backup. This strategy permits sequential replacement as the upstream carbon bed becomes exhausted. Although the levels of chlorine and chloramine can be determined separately, it is simpler to measure total chlorine—the sum of chlorine and chloramine—and replace exhausted carbon beds based on that measurement. The total chlorine level in the water exiting the primary "worker" carbon bed should be checked before each dialysis shift. If a breakthrough is noted, the total chlorine level should be checked downstream of the "polisher" bed. If no breakthrough is noted at that point, treatments can be continued while closely monitoring the outflow from the downstream "polisher" carbon bed. If total chlorine breakthrough is noted downstream of the "polisher" bed, treatments must cease immediately.

Optimal removal of chloramine by carbon may require adjustment of the pH of the feed water. Even with pH adjustment, carbon may provide inadequate removal of chloramine if the water contains corrosion inhibitors or other substances that prevent chloramine molecules from reaching the surface of the carbon. In such situations, it may be necessary to use alternative methods of chloramine removal, such as injection of sodium bisulfite.

2. Primary purification process. The primary purification process is almost always RO. A filter is normally placed just upstream of the RO membrane to catch any carbon particles and resin beads that may have been inadvertently released from the pretreatment system.

a. Reverse osmosis. RO uses high-pressure filtration of water through a semipermeable membrane that will hold back dissolved solutes. RO will remove more than 95% of ionic contaminants and nonionic contaminants as small as glucose. In addition, it provides an effective barrier against bacteria and endotoxins. In many cases, RO will provide water of sufficient quality for the preparation of standard dialysis fluid without further treatment. RO systems are monitored using in-line meters that measure product water conductivity or total dissolved solids (TDS). These measurements are used to calculate the percent

rejection of solutes by the membrane and are incorporated in most RO systems to provide a continuous measure of equipment performance.

b. Deionization. Deionization may be used as an alternative to RO but is more frequently used to further treat water following RO. A solid-phase deionizer contains both cationic and anionic resins. These can be configured as either two beds (one for the cationic resin and the other for the anionic resin) or as a single bed containing a mixture of both resins. Cationic resins contain sulfuric groups, and these exchange hydrogen ions for other cations such as sodium, calcium, and aluminum. Anionic resins contain ammonium groups, which exchange hydroxyl ions for other anions such as chloride, phosphate, and fluoride. The hydrogen and hydroxyl ions released during the exchange process then combine to become water, resulting in a product water that contains very few residual ions. Deionizers do not remove nonionic contaminants, bacteria, or endotoxins.

Deionizer function is monitored by checking the conductivity of the outflow water; the fewer the ions that remain in the water, the lower the conductivity. When the resins in a deionizer tank have exchanged all their available hydrogen and hydroxyl ions for cations and anions from the water, the capacity of the tank to remove ions is "exhausted" and the outflow conductivity increases, signaling that the tank needs to be replaced. It is important to know that an "exhausted" deionizer resin is not inactive but will rapidly release the ions that are most weakly bound to the resin if it continues to be used, with potentially serious adverse consequences for the patient. For example, failure to remove exhausted deionizer tanks led to patient deaths following the release of massive amounts of fluoride into the dialysis water (Arnow, 1994). For this reason, it is important to move exhausted deionizer tanks offline as soon as evidence of increased conductivity appears. All ion exchange tanks are required to be fitted with online monitors that continuously monitor the conductivity of the outflow water and divert that water away from the patients should it exceed 1 mS/cm (a resistivity of 1 MΩ-cm). Additionally, some tanks have a light that is normally off, and then turns on when the outflow conductivity increases, or a light that is normally on, and which turns off when conductivity monitoring fails. If there is a light, it is very important to know which type it is.

The resin of deionizers presents a large surface area for bacterial proliferation. Since all bacteriostatic substances such as chlorine and chloramine will have been removed from the water by the time it reaches a deionizer, the level of bacterial contamination of the water flowing through deionizer tanks is subject to increase. For this reason, an ultrafilter should be placed downstream of the deionizer to remove any bacteria or endotoxin that may have accumulated from the deionizer tanks. Some centers also prefer to destroy bacteria (whether in a vegetative or a sporulated state) with ultraviolet (UV) radiation. However, the UV process can increase the lipopolysaccharide and peptidoglycan content of the treated water due to bacterial death and may become ineffective if not kept clean.

3. Distribution of treated water. Treated water intended for the preparation of dialysis fluid must be distributed to the individual dialysis machines to produce dialysis fluid that remains free of contaminants. Chemical contaminants are avoided

by using inert materials, such as plastics, for all components that contact the treated water and dialysis fluid. Microbiologic contamination is avoided by using appropriately designed and constructed piping systems in combination with regular disinfection. The water distribution system is configured in a loop without multiple branches or dead ends. If the distribution system includes a storage tank (ideally, the use of a storage tank should be avoided), the tank is of the minimum required size, has a tight-fitting lid, and is designed for ease of cleaning and disinfection.

Water storage and distribution systems are disinfected on a regular schedule to prevent bacterial colonization of the system and minimize the formation of biofilm, which, once established, is very difficult to remove. The frequency of disinfection should be based on serial measurements of bacteria and endotoxin in treated water and dialysis fluid that demonstrate routine compliance with the quality standard for the given frequency of disinfection. When chemical germicides are used, disinfection is generally performed at least monthly. The disinfection schedule should be designed to minimize biofilm formation in the storage and distribution system, not to eliminate biofilm after it has formed. Distribution systems are now available that can be disinfected with hot water or ozone. These systems allow more frequent disinfection because there is no need to rinse the system free of residual germicide.

4. **Bicarbonate concentrate mixing and distribution systems.** These include containers used to distribute centrally prepared concentrate to individual dialysis machines, which are disinfected frequently because bicarbonate concentrates are particularly susceptible to bacterial contamination.

D. Safety and monitoring. Water treatment systems should be designed and operated with an emphasis on patient safety. They should be located in secure areas and isolated from the potable water system by a backflow prevention device. There should be a contingency plan in the event of a failure of the source water supply or a critical component of the water treatment and distribution system. There should be detailed procedures for the operation and monitoring of all the individual components of the water treatment and distribution systems, as well as the quality of the final water and dialysis fluid. In general, the greater the risk to patient safety from a component failure, the more frequent should be the monitoring of that component. For example, the acute nature of hemolytic anemia arising from exposure to chloramine requires that chloramine levels be measured at least daily, while the risk of fatal fluoride intoxication from exhaustion of a deionizer requires continuous monitoring of its product water conductivity. In contrast, although the quality of water and dialysis fluid must be checked using high-sensitivity methods for bacterial growth and presence of endotoxin, the frequency of that monitoring might only be monthly once an effective disinfection schedule has been established. It is also important to monitor the patients themselves, being always alert for evidence of unexplained clusters of hemolytic, pyrogenic, or other unusual reactions that may be linked to fluid quality.

ISO has developed standards for equipment used to treat water for dialysis that are designed to maximize patient safety (ISO 23500-2). These standards have been adopted for use in the United States and many other countries. Other guidance on the monitoring of water treatment systems has been published by the European Renal Association (Best Practice Guidelines) and in the United States, the Forum of ESRD Networks has

prepared a Medical Director Toolkit to assist dialysis units in meeting the requirement of the CMS Conditions for Coverage (Forum of ESRD Networks, 2021). The CMS requirements include monitoring the various parts of the water treatment and distribution system as well as the need to comply with required remote alarms, training, and planning in the event of emergencies.

II. DIALYSIS SOLUTION PREPARATION

A. Proportioning machines. To reduce bulk and shipping costs, dialysis fluid is manufactured in concentrated form and machines proportion it with water before delivering it to the dialyzer. The dialysis machine incorporates pumps and one-way valve systems that make the final dialysis fluid by taking fixed volumes of dialysate concentrates and mixing them with a fixed volume of heated treated water, or by using conductivity-based servocontrol systems to mix the concentrates and water. As discussed in the previous chapter, the ionic composition of the final dialysis fluid is checked by conductivity, which is kept in a very tight range. As long as the solution remains in the target conductivity range, the dialysis fluid is allowed to pass on to the dialyzer. If conductivity gets outside the range, an alarm sounds and dialysis stops.

B. Dual-concentrate system for bicarbonate-based solutions. Almost all dialysis fluid used today is bicarbonate based, and this engenders a solubility issue. When making a bicarbonate solution of about 30 mM, the pH will be close to 8.0. At this pH, calcium and magnesium will precipitate out from the solution, reducing their diffusible concentration and also contributing to scaling on dialysis machine lines and passages. To circumvent the problem of calcium and magnesium precipitation, a bicarbonate-based dialysis fluid–generating system utilizes two concentrates: a “bicarbonate” concentrate and an “acid” concentrate. The “acid” concentrate contains a small amount of acetic or citric acid plus sodium, potassium (as needed), calcium, magnesium, chloride, and dextrose (optional). The low pH of the acid concentrate keeps the calcium and magnesium in solution, even in concentrated form.

Specially designed double-proportioning systems mix the two concentrates sequentially with treated water to make the final dialysis fluid. During mixing, the small amount of acetic acid in the “acid” concentrate (about 2-4 mM) reacts with an equimolar amount of bicarbonate in the “bicarbonate” concentrate to generate carbon dioxide. The carbon dioxide generated forms carbonic acid, which lowers the pH of the final bicarbonate-containing solution to approximately 7.0 to 7.4. At this pH range, the calcium and magnesium in the product dialysis fluid remain dissolved. The ratio of “acid” concentrate to “base” concentrate to water in the various proportioning systems available depends on the machine manufacturer. Liquid “acid” concentrates are available between 35 times and 45 times concentrated, and the corresponding liquid “bicarbonate” concentrates are also concentrated differently. In units using more than one brand of dialysis machine, it is important to use concentrate designed for the proportioning ratio of a given machine.

The bicarbonate level shown on the monitor of many dialysis machines that allow for adjusting dialysis solution bicarbonate by altering the concentrate proportioning ratio is the final bicarbonate concentration and does not take into account the acetate of sodium acetate that was produced from the reaction of acetic acid with an equimolar amount of sodium bicarbonate. This acetate will generate bicarbonate as it is

metabolized in the body on an equimolar basis. Thus, the actual base content of the dialysate used will be higher than that shown on the monitor (Kohn, 2012). With most liquid acid concentrates containing acetic acid, the amount of acetic acid, and hence that of acetate present in the dialysis fluid after mixing commonly, is about 4 mM.

C. Dry concentrates

1. **Bicarbonate.** In some machines, a cartridge containing dry sodium bicarbonate is used in place of a liquid "bicarbonate" concentrate. Use of dry bicarbonate cartridges obviates the problem of bacterial growth in "bicarbonate" concentrate and the concern of subsequent contamination of the final dialysis solutions. Use of dry bicarbonate cartridges is considered by many to be essential for online hemodiafiltration.
2. **Acid (citric acid or sodium diacetate).** Although acetic acid is a liquid, dry "acid" concentrates can be made using either citric acid or sodium diacetate. The low concentration of citrate generated in citric acid–based dialysis fluid may chelate plasma calcium that is adjacent to the dialysis membrane, impeding coagulation, improving dialyzer clearance slightly, and increasing the dialyzer reuse number. In dry acid concentrates containing citric acid (0.8 mM) plus a small amount (0.3 mM) of acetic acid, after mixing, the dialysis fluid will contain 0.8 mM citrate (2.4 mEq/L) and 0.3 mM acetate, yielding about 2.7 mEq/L of bicarbonate-generating base.

   Sodium diacetate is a compound containing acetic acid and sodium acetate. Acid concentrates formulated with sodium diacetate typically contain twice the concentration of acetate in the final dialysis fluid compared to those using acetic acid. It is important to take this relatively high concentration of acetate (up to 8 mM) into account as an additional source of bicarbonate generation (Kohn, 2012; Lew, 2017).

D. Final dialysis fluid composition.

The composition range of typically used dialysis fluids is given in Table 5.1. The concentrations of sodium, potassium, and calcium can be varied by choosing different "acid" concentrates or by adding salts of these cations to the appropriate "acid" concentrates prior to use. In addition, some dialysis machines allow the concentration of sodium in the dialysis fluid to be varied during the course of an individual treatment—a practice known as sodium profiling. Sodium profiling may help reduce the tendency to intradialytic hypotension and the postdialysis washed-out feeling in some patients, but whenever the average dialysis solution sodium level is increased, this may predispose to increased thirst, excessive fluid intake, and hypertension (see Chapter 12). Most dialysis machines allow the bicarbonate level to be varied without changing to a different concentrate by altering the proportioning pump ratio. This allows the use of dialysis solution bicarbonate levels from 20 to 40 mM, and such a feature is particularly useful when more frequent dialysis is employed when dialyzing nonuremic patients (eg, to treat poisoning) or to treat patients with alkalemia. Minor changes in calcium, magnesium, and potassium (if present) will take place whenever the dialysis fluid bicarbonate level is altered.

TABLE 5.1 Composition of a Standard Hemodialysis Solution

Component	Concentration (mM)

Sodium	135-145
Potassium	2-3
Calcium	1.25-1.75 (2.5-3.5 mEq/L)
Magnesium	0.25-0.375 (0.5-0.75 mEq/L)
Chloride	98-124
Acetate[a]	3-8
Citrate[a]	0.8-1.0 (2.4-3.0 mEq/L)
Bicarbonate	25-35
Glucose	0-11
PCO_2	40-110 (mm Hg)
pH	7.1-7.3 (units)

[a]The acetate or citrate is added in the form of acetic acid, sodium diacetate, or citric acid to the "acid concentrate." When mixed with the "bicarbonate concentrate," the hydrogen ion from either of these acids reacts with bicarbonate to form CO_2 (ie, carbonic acid) to establish a buffer system.

E. Disinfection of dialysis machines. Dialysis machines are disinfected according to the manufacturer's recommendations. The water inlet lines to the dialysis machines are disinfected at the same time as the water distribution system. Dialysis machines are now available that incorporate a bacteria- and endotoxin-retentive ultrafilter located in the dialysis machine itself. This filter intercepts the dialysis solution flow just before it is passed to the dialyzer. These dialysis fluid ultrafilters, which are rated for a certain number of treatments or months of operation, are disinfected when the dialysis machine is disinfected. Such ultrafilters facilitate the routine preparation of "ultrapure dialysis solutions," and their use is central to the preparation of sterile replacement fluid from dialysis fluid in online hemodiafiltration.

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6 Arteriovenous Fistulas and Grafts: The Basics

Tushar Vachharajani, Loay Salman, Deborah Brouwer-Maier, and Arif Asif

I. INTRODUCTION: TYPES OF VASCULAR ACCESS.

Arteriovenous (AV) fistulas and grafts are the most common forms of vascular access used for maintenance hemodialysis. An AV fistula involves creating an anastomosis between an artery and a native vein, allowing the blood to flow directly from the artery to the vein. Traditionally, anastomosis is made at the wrist between the radial artery and the cephalic vein, although there are many variations possible, with anastomoses in the snuffbox, in the forearm area, or at the elbow or upper arm. An AV graft is similar, except that the distance between the feeding artery and vein is bridged by a tube made of prosthetic material. The most commonly used bridging material is polytetrafluoroethylene (PTFE) polymer. A third type of access, the cuffed venous catheter, is discussed in the following chapter.

An AV fistula cannot be used immediately, as the fistula maturation process generally takes about 6 to 8 weeks. During the maturation process, blood flow through the newly created fistula will gradually increase due to dilatation of both artery and vein. Pressure and flow–induced remodeling (thickening) of the wall of the fistula vein, which is the section where the needles will be inserted, strengthens the fistula and limits tearing and extravasation, while dilatation of the vein facilitates future needle insertion. An AV graft can be used earlier than a fistula, generally within 1 to 3 weeks after placement.

A well-functioning fistula remains the preferred access compared to a graft due to a fistula's lower incidence of infection, higher patency rates, and overall better patient survival. However, AV fistulas have their problems as well, one important downside being a poor maturation rate in those with unsuitable blood vessels, including many older patients. An AV graft can be a suitable initial choice of access in patients with insufficiently large or poorly distensible blood vessels. With prolonged use, some dilatation of the vein downstream to an AV graft typically occurs, and sometimes this newly enlarged vein segment can then be connected directly to an artery, converting the graft to a fistula (secondary AV fistula).

A. Neointimal hyperplasia.

Mechanistically, an AV graft is a less desirable vascular access option than an AV fistula because with a graft there is a higher risk of neointimal hyperplasia. Most commonly, this occurs in the venous segment downstream from the graft-vein anastomosis. Hyperplasia obstructs the lumen of the downstream vein, leading to poor flow in the graft and prolonged bleeding after the removal of dialysis needles (due to increased intragraft pressure). Eventually, this can lead to graft thrombosis. The cause of accelerated neointimal hyperplasia in AV grafts is thought to be turbulence downstream to the graft-vein anastomosis and also to a compliance mismatch between the relatively rigid graft and the more flexible vein. Periodic exposure of this vulnerable vein segment to immunologically activated blood exiting the

dialyzer may accelerate the process, although stenosis can develop downstream to an AV graft even when the graft is left unused.

Although an AV graft is an inferior access option compared to a mature AV fistula, it is superior to a central venous catheter. Patients with either AV fistula or AV graft have less serious infections, lower morbidity, and higher survival rates than patients managed with venous catheters. Recently, some of the poorer results with central venous catheters have been shown to be due to selection bias (venous catheters tend to be used in sicker patients), and the infection risk with venous catheters, especially in older patients, has been found to be relatively low (Murea, 2014). Thus, in certain clinical circumstances discussed more thoroughly in the next chapter, the chronic venous catheter remains a useful form of vascular access.

II. GUIDELINES TARGETING INCREASED USE OF AV FISTULA. Early guidelines developed by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) and the "Fistula First" initiative (see web references) promote the construction of AV fistulas, targeting at least 68% use in patients on prevalent dialysis. Early referral of patients with chronic kidney disease (CKD) to nephrologists prior to the start of hemodialysis allows more time for the construction of an AV access, thus avoiding the risks associated with a central vein catheter that is usually required when the patient is referred for dialysis late in the course of CKD. Recently, "urgent start peritoneal dialysis" has been advocated as an initial treatment method for patients who urgently need dialysis. This allows such patients to be stabilized without subjecting them to a chronic venous catheter. One key factor in increasing AV fistula use is the presence of a dedicated and trained access surgeon functioning as part of a vascular access team.

Over the past two decades, since the implementation of the US government–sponsored Fistula First breakthrough initiative, the AV fistula rate in the US patients undergoing prevalent hemodialysis has increased from 26% to 61%. Many US Centers and European centers achieve much higher percentages (≥90%). In the United States, however, the central venous catheter use rate has not declined as much as planned in the incident patient population on dialysis. The lessons learned following the implementation of these earlier guidelines lead to a better understanding of the unique and individualized need for access planning. The 2019 KDOQI Vascular Access update highlights this concept (Lok, 2020). The introduction of an individualized plan while incorporating patient autonomy was outlined with the concept of an "ESKD Life Plan." The shared decision process should account for patient goals and values along with multidisciplinary input before selecting the best possible access for a given patient. An AV fistula is not always the preferred access. For example, an individual with limited life expectancy may preferentially be dialyzed with an AV graft or a central vein catheter.

III. VESSEL PRESERVATION. In patients with progressive CKD who are expected to require dialysis, superficial and deep veins of both arms must be protected, anticipating their possible use for vascular access. Accordingly, one should minimize venipunctures and the placement of peripheral infusion lines in the upper extremity, especially in the cephalic and antecubital veins of either arm. The veins on the dorsum of the hand should be used whenever possible. Because of the risk of subsequent central vein stenosis, the subclavian vein should not be cannulated unless absolutely necessary and the use of percutaneously

inserted central catheters (PICC lines) and midline catheters should be avoided as far as possible (Vachharajani, 2020a). In order to preserve the radial and brachial arteries, preferably one should avoid a transradial or transbrachial approach for endovascular interventions in patients with advanced CKD. Placement of endovascular leads for a cardiac implantable electronic device should be avoided as well, as this can adversely affect the patency of the central veins; plus, the long-term risk of infection will be high. Instead, patients with CKD who require a pacemaker or similar device should be evaluated for approaches utilizing epicardial as well as subcutaneous lead placement. The use of a leadless pacemaker when applicable can further reduce the risk of developing central vein stenosis (Maradey, 2018).

A. "Save the Vein" projects. Various dialysis-related organizations in the United States, the United Kingdom, and Canada have put together patient-targeted brochures, sometimes in both English and Spanish, describing the importance of preserving arm veins. Patient wristbands bearing the inscription: "Save Veins • No IV / LAB Draws" are also available.

IV. ARTERIOVENOUS ACCESS PLANNING

A. Patient education and timing issues. Patients with a glomerular filtration rate (GFR) of less than 20 mL/min/1.73 m^2 should be educated about all modalities of kidney replacement therapies including peritoneal dialysis and renal transplantation. For those choosing hemodialysis, an AV fistula should be placed at least 6 months prior to the planned initiation of dialysis. In patients planning to start peritoneal dialysis, the creation of an AV fistula is optional. A backup AV fistula is sometimes created in a peritoneal dialysis patient to avoid the risks associated with central vein catheters when peritoneal dialysis must be stopped for a time; for example, to replace the catheter because of malfunction or severe peritonitis. However, peritonitis rates are much lower now than in the past, so most centers no longer create such backup fistulas to minimize the risk of developing heart failure. Patients who are planning to receive a live donor kidney in the near future but who need dialysis for a short time can be managed without a permanent AV access. In such patients, short-term use (<6 months) of a cuffed venous catheter for access may be appropriate unless the patient has a relative contraindication to venous catheter use (such as valvular heart disease, which might predispose to endocarditis).

B. Predicting the need for dialysis. Anticipating the need for dialysis correctly is not always easy. Premature creation of an AV access is an unnecessary utilization of resources, and many older patients, especially, have been shown to die before needing dialysis. One tool that may help in predicting the need for renal replacement therapy was developed by Tangri, though their equations predict the risk of developing end-stage renal disease (ESRD) over a time window of 3 years (Lerner, 2017). A similar predictive equation based on male US Veterans Affairs patients was developed by Drawz (2013), which predicts the risk of ESRD over a 1-year period. Use of such risk equations in vascular access planning has been promising (Atiquzzaman, 2024).

V. PREOPERATIVE EVALUATION

A. Patient history. A thorough history is required, querying about previous episodes of central vein catheters or intravenous pacemaker/cardiac electronic device implantation,

prior use of PICC lines, and prior vascular surgery. Comorbid conditions such as congestive heart failure, diabetes mellitus, or peripheral vascular disease may limit options for access construction. Patients with severe heart failure may not tolerate the additional cardiac output required to circulate blood through the access. Patients with severe vascular disease due to atherosclerosis or diabetes or patients with extensive damage to their arm veins due to prior needle sticks or failed AV fistula may not have adequate blood vessels to support the creation of an AV access, although even in such patients an AV fistula often can be created in the upper extremity using innovative surgical techniques.

B. Physical examination. The presence of all pulses in the upper extremity (axillary, brachial, radial, and ulnar) should be evaluated and recorded. The blood pressure in both arms should be measured, and the difference between the arms should be graded as normal if less than 10 mm Hg, borderline if 10 to 20 mm Hg, or problematic if greater than 20 mm Hg. The Allen test, which measures collateral flow between the radial and ulnar arteries at the palmar arch, can be performed by physical exam or aided by Doppler (see what follows). The sensitivity of the Allen test can be increased if combined with pulse oximetry (Paul and Feeny, 2003). Details of how to perform the Allen test are given in Table 6.1. The patient should be examined for evidence of previous central or venous catheterization and for signs of trauma or surgery of the arm, chest, or neck, including previous AV access surgery. The presence of arm edema, collateral veins, or differential extremity size should prompt an evaluation of the central veins.

TABLE 6.1 Allen Test (Test of Palmar Arch Patency)

1. Position the patient so that they are facing you with their arm extended with the palm turned upward.
2. Compress both the radial and ulnar arteries at the wrist.
3. With the arteries compressed firmly, instruct the patient to create a fist repetitively in order to cause the palm to blanch.
4. When the patient's hand is blanched, release the compression of the ulnar artery and watch the palm to determine if it becomes pink. Then release all compression.
5. Repeat steps 2-4 for the radial artery.

Interpretation: When color returns to the blanched palm upon release of the arterial compression, it indicates arterial patency and reflects upon adequacy of flow. Blanching that persists for ≥5 s after release of the ulnar artery is a positive test for ulnar artery insufficiency. Likewise, blanching that persists for ≥5 s following the release of the radial artery is positive for radial artery insufficiency.

Modified from Beathard GA. Physical examination of the dialysis vascular access. *Semin Dial*. 1998;11:231-236.

C. Imaging studies. Routine preoperative mapping of the arm to evaluate veins and arteries helps with the selection of the most appropriate vein and the best location to create an access. Use of imaging studies has been shown to increase the rate of well-functioning fistula placements.

1. **Doppler ultrasonography.** Doppler ultrasonography, which can measure flow velocity as well as the inner diameter of the brachial and radial arteries and peripheral veins, should be performed in all patients to identify suitable arteries and veins for access placement. The poor visualization of central veins on Doppler ultrasonography is a limitation of this method. Doppler ultrasonography is best performed in the operating room after regional anesthesia of the arm using a

regional nerve block, as the veins tend to dilate postanesthesia administration; under normal circumstances, these veins can be constricted due to cooler ambient temperatures in the operating room and may not be visualized properly.

a. **Minimal vein and artery size.** Controversy exists about the minimum luminal size of the feeding artery and target vein for a fistula to mature. Studies suggest that the minimum vein lumen diameter should be about 2.5 mm for successful surgical anastomosis (Okada and Shenoy, 2014) and the minimal arterial diameter should be 2.0 mm. Smaller, "borderline" vessels down to 1.5 mm (for both artery and vein) have been used to create successful fistulas, but this may require an experienced surgeon with skills to operate on such small vessels (Pirozzi, 2010). More important may be the ability of the artery and vein to dilate after anastomosis, to allow an increase in flow.
b. **Vein dilation test.** During the Doppler study, the proximal vein is occluded using a tourniquet and the increase in vessel size is recorded. An average increase in internal diameter of 50% has been associated with successful fistula outcome (Malovrh, 2002).
c. **Arterial dilation test.** During the Doppler study, the pulse contour of the artery is examined. The pulse contour of the artery is normally triphasic due to high peripheral resistance. The patient is asked to clench the fist for 2 minutes and then to open the hand; the resulting hyperemic response normally converts the triphasic arterial pulse contour to a biphasic pattern in patients capable of a healthy arterial dilation.
d. **Mapping.** The cephalic and ulnar venous systems should also be evaluated for continuity and absence of strictures. Some surgeons perform venous mapping with a proximal tourniquet in place to distend and better identify veins suitable for AV fistula construction.

2. **Venography.** Venography is reserved for evaluating the central veins, especially in patients with a history of transvenous placement of a pacemaker, physical findings of upper extremity edema, collateral veins around the shoulder or on the chest wall, and/or unequal extremity size. If venography is performed, 30 mL or less of nonionic, low osmolality contrast, diluted 1:4, should be used to avoid nephrotoxicity. Full-strength contrast is usually not required for venography. Venography alone does not help evaluate the arterial tree.
3. **Arteriography.** Arteriography is indicated when pulses in the desired access location are markedly diminished or absent or there is a greater than 20 mm Hg difference in mean arterial pressure between the two arms.

VI. POSSIBLE LOCATIONS FOR UPPER EXTREMITY AV FISTULAS.

For an overview, see Okada and Shenoy (2014) (Table 6.2).

TABLE 6.2 Sites for AV Fistula Creation in the Upper Extremity

Conventional
Snuffbox (distal-most site)
Radiocephalic or Brescia-Cimino (radial artery to forearm cephalic vein at the wrist)
Ulnar artery to forearm basilic vein (uncommon)

Brachial artery to upper arm cephalic vein (at the elbow)
Transposed
Forearm basilic vein to radial artery at the wrist
Forearm basilic vein to the brachial artery (loop configuration)
Forearm cephalic vein to the brachial artery (loop configuration)
Transposed basilic vein in the upper arm to the brachial artery
Perforating veins in the proximal forearm to the proximal radial artery (Konner modification of the Gracz fistula)

AV, arteriovenous.

A. Arm fistula locations. An AV fistula can be categorized as conventional or transposed, depending on its connection to the arterial and venous circulations. A **conventional AV fistula** is created by connecting a superficial artery and vein and generally does not require extensive mobilization of the vessels. A **transposed AV fistula** utilizes deeper veins and requires extensive mobilization of the vein into a subcutaneous tunnel for easy needle access. Compared to conventional AV fistulas, transposed AV fistulas are technically more challenging to create and require greater healing time. Generally, conventional AV fistulas are created as a single-stage surgical procedure, whereas the creation of a transposed AV fistula can be either a one-stage or two-stage procedure.

At least nine potential sites for AV fistula can be used in the upper extremity (Table 6.2). The **anatomic snuffbox** fistula is the distal variant of the radiocephalic fistula created between the tendons of *extensor pollicis longus* and *brevis*. The classic wrist **radiocephalic** or Brescia-Cimino fistula (Figure 6.1) placed in the nondominant arm is the preferred access. Other forearm AV fistulas, such as the **ulnar artery–basilic vein** fistula, should be considered when a radiocephalic fistula is not an option. Before considering an upper arm site, several other transposed forearm sites should be evaluated; for example, the **forearm cephalic vein to proximal radial artery or brachial artery**, and the **transposed forearm basilic vein to radial artery or brachial artery**. If creating a forearm fistula is not possible, which happens not uncommonly in patients with diabetes or older patients with atherosclerosis, then an **upper arm brachial artery–cephalic vein** fistula (Figure 6.2) or a **transposed basilic vein–brachial artery** fistula (Figure 6.3) are potential options. Less commonly used options are the **Gracz fistula** (which uses a perforating vein that arterializes both upper arm cephalic and basilic veins) and the **brachial bidirectional cephalic** fistula (which arterializes both forearm and upper arm cephalic veins). When a perforating vein fistula is used, it has been suggested that the original surgical procedure be modified (Konner, 1999). When all sites in the nondominant arm have been exhausted, then the dominant arm can be used. A recent advancement in endovascular devices has led to successfully creating mid-forearm AV fistulas using the perforating veins as an outpatient procedure in an interventional suite equipped with fluoroscopy and ultrasound machines (Vachharajani, 2021).

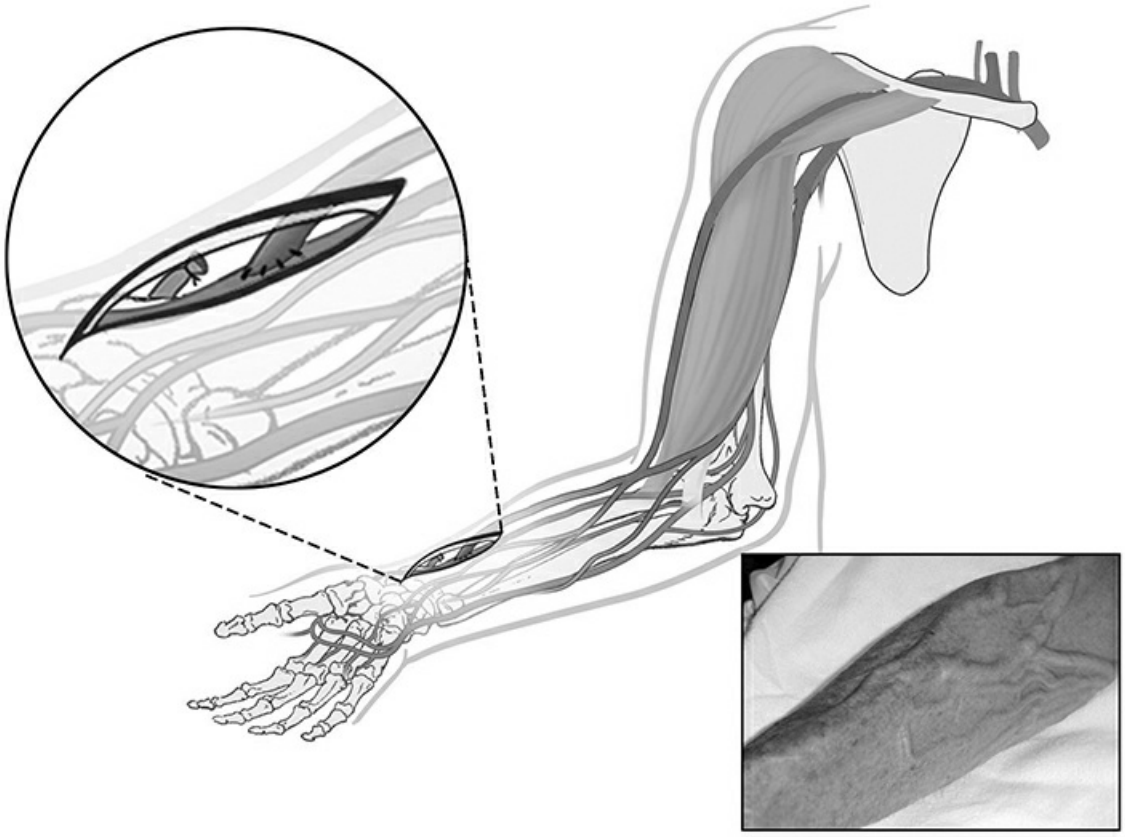


FIGURE 6.1: Radiocephalic AV fistula. AV, arteriovenous. (Reprinted with permission from Atlas of Dialysis Vascular Access by Tushar Vachharajani, MD, FACP, FASN.)

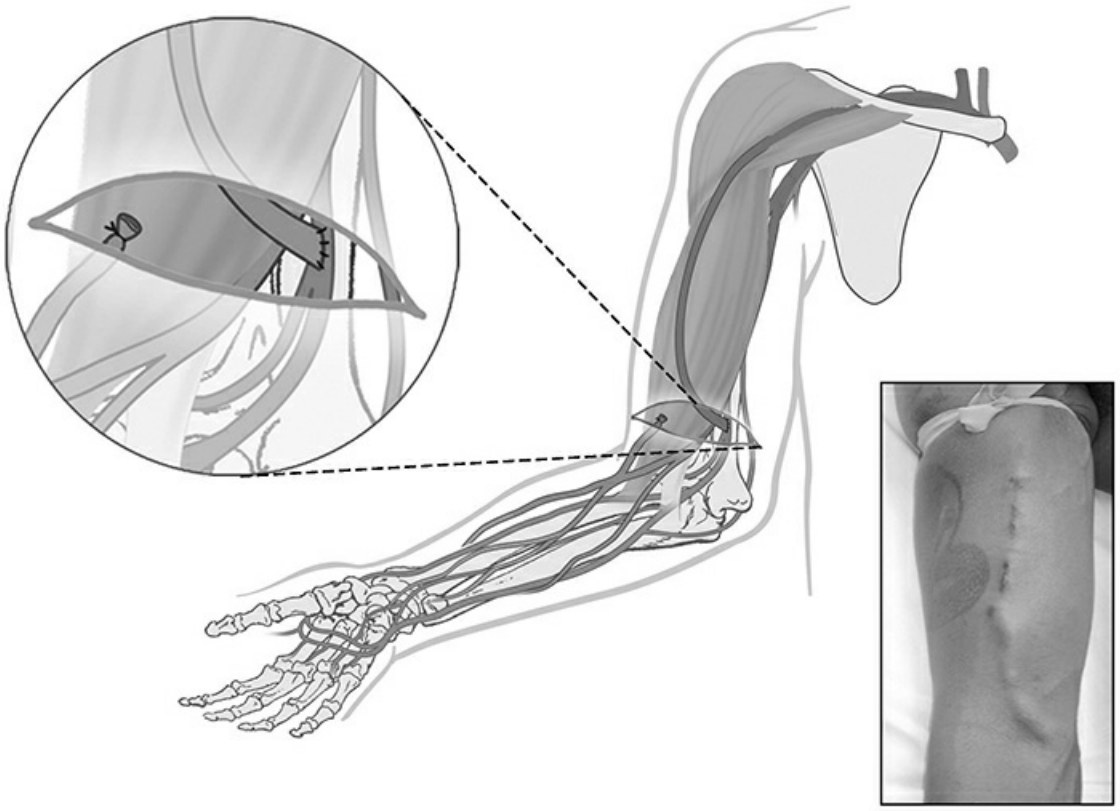


FIGURE 6.2: Brachiocephalic AV fistula. AV, arteriovenous. (Reprinted with permission from Atlas of Dialysis Vascular Access by Tushar Vachharajani, MD, FACP, FASN.)

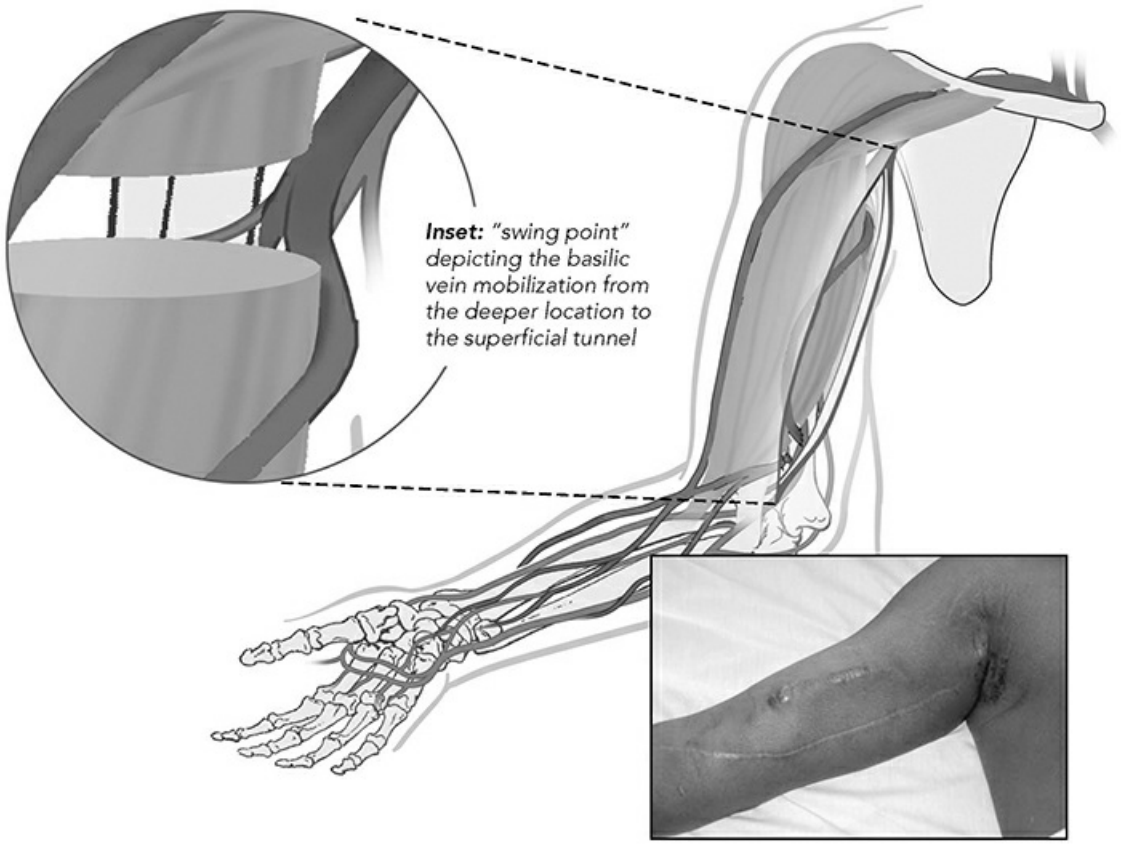


FIGURE 6.3: Transposed basilic vein to brachial artery AV fistula. AV, arteriovenous. (Reprinted with permission from Atlas of Dialysis Vascular Access by Tushar Vachharajani, MD, FACP, FASN.)

1. **Initial selection of elbow perforating vein fistula for older patients or patients with comorbidities.** In such patients, a calcified radial artery with a small lumen and thickened wall is a common finding, and fistulas fed by such arteries are likely to fail. In one small study (Palmes, 2011), a forearm fistula was performed only if the diameters of the radial and ulnar arteries were greater than 2.0 mm at the wrist and no calcification or segmental stenosis was detected. Also, with a tourniquet in place at the wrist, the cephalic vein diameter had to be at least 2.5 mm. If not, and if a perforating vein was present at the elbow, and the brachial artery and cephalic vein were of suitable diameter, a perforating vein AV fistula was created at the elbow, using the Konner modification (discussed earlier) of the Gracz approach. In the group of older patients with poor blood vessels getting the perforating vein elbow fistula, the fistula patency rate at 24 months was an impressive 78%.

B. Fistulas in the leg. AV fistulas in the lower extremity are created rarely, because of a higher complication rate and poorer outcome, but they remain an option once all potential sites in the upper extremity have been exhausted. The possible sites include fistulas connecting the superficial femoral artery to the femoral vein or the saphenous vein to the popliteal artery.

C. Steal due to fistula on the same side as an internal mammary artery–coronary artery bypass graft. This has now been widely reported, and in such patients, a contralateral AV fistula should be inserted to avoid this problem (Coskun,

2013).

VII. OPERATIVE PROCEDURE FOR AN AV FISTULA. Open surgical technique remains a common approach to creating an AV fistula. However, as mentioned above, endovascular or percutaneous creation with newer devices has been introduced in clinical practice with variable outcomes (Malik, 2021). AV fistula surgery is usually performed in the operating room under regional anesthesia. The anastomosis can be either side of the artery to side of the vein or side of the artery to end of the vein. In both instances, distal blood flow through the artery is preserved. With the side-to-side method, higher pressures may sometimes be transmitted to the distal veins in the hand, causing swelling and the so-called red hand syndrome. The side-of-artery to end-of-vein anastomosis prevents venous hypertension in the hand because the distal vein is ligated. A modified "piggyback SLOT" technique has been shown to substantially reduce torsion in the anastomosed vein and to reduce juxta-anastomotic stenosis (Bharat, 2012). The details of the operative techniques are beyond the scope of this handbook. It is important to emphasize that AV fistula placement is not something that can be relegated to a junior or inexperienced vascular surgeon but is best done by a surgeon with both experience and interest in performing these sometimes complex and demanding procedures.

A. Measuring radial artery fistula blood flow at the time of surgery. The radial artery normally has a flow rate of 20 to 30 mL/min, and this flow increases to 200 to 300 mL/min immediately after creation of the anastomosis (Konner, 1999). In one study of forearm fistulas, the flow in the anastomosed vein was measured immediately after surgery, and an immediate flow rate less than 120 mL/min was highly predictive of subsequent fistula failure (Saucy, 2010).

B. Predicting matured fistula blood flow using a computational algorithm. A consortium of investigators has developed an algorithm to predict ultimate fistula flow rate for various types of fistula, based on baseline patient demographic variables, and preoperative Doppler measurements of vessel diameters and flows (Caroli, 2013). This algorithm is not widely used clinically.

VIII. PERIOPERATIVE CARE AND FISTULA MATURATION. Some centers prepare the patient for AV fistula surgery by having the patient perform arm exercises for several weeks prior to surgery, with the idea that this might help the vein to dilate and achieve a luminal size of more than 2.5 mm (Wilschut, 2024). Following surgery, the arm should initially be kept elevated. Tight circumferential dressings should be avoided. Hand exercises (eg, squeezing a rubber ball or a soft handgrip device for a forearm AV fistula or bicep curls with a dumbbell for an upper arm AV fistula) may help increase fistula blood flow and pressure and are believed by some to assist with the maturation of an AV fistula. The fistula should never be used for venipuncture. Fistula blood flow should be checked daily (more frequently initially) by feeling for a thrill at the anastomotic site and by listening for an associated bruit. A physician, nurse, dialysis technician, or even a well-informed patient should be able to perform a physical examination of an AV fistula. The basics of physical examination of an AV access are described later in this chapter.

A. Rule of sixes. All new AV fistulas should be examined within 4 to 6 weeks of creation for signs of maturation. The prevailing wisdom has been that at the time of intended use, the vein diameter should be at least 6 mm. A mature AV fistula should

follow the “rule of 6”—it should be 6 mm in diameter, less than 6 mm below the skin, have a blood flow of at least 600 mL/min, and include a straight segment for cannulation that is at least 6 cm in length. Generally, maturation should occur by around 6 weeks after surgery. However, the 2019 KDOQI Vascular Access Guidelines consider a 5 mm vein diameter and a greater than 500 mL/min blood flow rate as adequate criteria to consider an AV fistula to be mature (Lok, 2020).

B. Details of fistula maturation. An experienced and well-trained examiner can clinically differentiate between a mature and an immature AV fistula. The fistula must be allowed to mature, as premature attempts to cannulate it can be associated with infiltration, compression of the vessel, and permanent loss of the fistula. Primary maturation failure of an AV fistula can result from an atherosclerotic artery, inadequate anastomosis, or an inability of the artery and/or vein to dilate due to vessel damage, for example, due to preexisting vascular calcification or sclerosis. One remediable cause is the presence of multiple tributary branches in the vein draining the AV fistula. These branches can siphon off the increased venous flow, lessening the amount of flow-induced vessel dilation. Often, ligation of such side branches can bring about or hasten the maturation process. If a fistula cannot be cannulated or support dialysis therapy for more than 6 weeks after placement, an imaging fistulogram should be obtained to determine the source of the problem.

IX. INITIAL TRIAL CANNULATION OF A NEW AV FISTULA.

If physical assessment has shown that the fistula has adequately matured, the next step is to perform a trial cannulation.

A. Day of the week. If possible, the initial trial cannulation should be done on a nondialysis day. This eliminates potential complications associated with the administration of heparin. If a trial cannulation is not possible, it is best to perform the initial cannulation of the new access at the patient’s midweek treatment. Performing the initial cannulation midweek helps minimize such complications as fluid overload and elevated chemistry test results associated with dialysis after a long weekend interval.

B. “Wet needle” technique. To ensure that the needle is placed properly, needle placement should be confirmed with a normal saline flush before connecting the needles to the blood pump and starting the pump. Blood return alone is not enough to show good needle placement. One option to check for proper needle placement is the use of “wet” needles. The needle is purged of air and the saline in the attached syringe is used to flush the needle. If an infiltration has occurred, the normal saline is less harmful to the surrounding AV fistula tissue. The wet needle also prevents the risk for a blood spray or spill if dry needles are used for cannulation and the caps are opened to “bleed out” air from the needle. Opening the needle tubing cap creates a risk for blood exposure to the dialysis team member, patient, and nearby patients.

C. Needle with a “backeye.” A needle with a backeye should always be used for the arterial needle to maximize the flow from the access and reduce the need for flipping (rotating) the needle after insertion.

D. Needle size selection. Needle size selection for the initial cannulation is critical. Visual and tactile examinations allow the cannulator to determine which needle gauge would be most appropriate, based on the size of the vessel. One can place a 17G or a 16G needle with its protective cap in place over the cannulation site. One then compares the vein size with the needle size with and without a tourniquet being applied. If the

needle is larger than the vein when the tourniquet is applied, then that particular needle size is too large and such a needle may infiltrate in the course of cannulation. One should use a needle size that is equal to or smaller than the vein (without the tourniquet). The smallest needle available, usually a 17G, typically is used for initial cannulation attempts. It is important to keep in mind that blood flow delivered by a 17G needle is limited.

Prepump arterial monitoring is recommended to ensure that blood pump speed does not exceed a flow that the needle can easily provide. Prepump arterial pressure should not exceed −250 mm Hg. Based on the performance of the fistula using a 17G needle, the decision to increase the needle size for subsequent cannulation can be made. A 17G needle ordinarily will not deliver more than 250 mL/min blood flow, and a 16G needle will not deliver a blood flow rate greater than 350 mL/min. Progression from the 17G to larger needles depends on adequate vessel size and access flow.

E. Initial cannulation procedure

1. Apply a tourniquet to the access arm.
2. Disinfect the access site per unit protocol.
3. Attach a **10-mL syringe filled with 8 mL of normal saline solution** to the needle, but do not prime the needle until immediately before the cannulation.
4. Grasp the needle by its butterfly wings and **prime the needle with normal saline** until all the air has been purged. Clamp the needle closed. Remove the protective cap and immediately proceed with cannulation.
5. Carefully cannulate the fistula using a 25° insertion angle. When **blood flashback** is observed (the needle may need to be unclamped to see the blood flashback), flatten the angle of the needle, parallel to the skin, and advance it slowly into the fistula lumen.
6. When the needle is in the vessel, remove the tourniquet and tape the needle securely per unit protocol. If blood flashback is visible, **aspirate back 1 to 5 mL** with the 10-mL syringe.
7. **Flush the needle** with the normal saline solution and clamp. The syringe must aspirate and flush with ease. Monitor for signs or symptoms of infiltration. Patients usually experience immediate sharp pain upon infiltration of saline or blood into the tissues.
8. Repeat the above steps for the second needle unless blood return via a venous catheter is planned (see what follows).

F. One needle technique with return using a venous catheter.

In patients who still have a venous catheter in place, one does not need to necessarily begin dialysis with the new fistula using two needles. The risk of infiltration is much higher with the blood return (dialyzer outflow) needle. For the first two or three treatments, the blood can be returned via the venous catheter. Next, dialysis can be done using two needles in the fistula, and only after several treatments have been successful is the venous catheter removed. The approach helps minimize the fear of needle sticks and allows the patient to accept the concept of pain and discomfort during needle puncture.

X. ARTERIOVENOUS GRAFTS.

As described at the outset of this chapter, AV grafts are less desirable than AV fistulas, primarily because of their lower long-term patency rates and greater need for endovascular interventions to maintain patency. AV grafts do have some

advantages, including a large surface area for needle placement, easy cannulation, short maturation time, and easy surgical handling characteristics.

Most AV grafts placed in the United States are composed of expanded PTFE. The choice of synthetic or biologic material should be based on the surgeon's preference and experience. Use of cryopreserved vein grafts, especially those placed in the thigh, is associated with a higher risk of infection. Short grafts have no advantage over long grafts in terms of patency and longevity. Tapered grafts, externally supported grafts, or elastic grafts do not provide results better than standard PTFE grafts. Modification of the distal anastomosis of PTFE grafts with a venous cuff may decrease venous stenosis and increase graft patency. Newer heparin-bonded materials in grafts are being used, but they do not appear to have any long-term advantages. The introduction of bioengineered grafts into clinical practice offers a novel alternative for the future. Outcomes of some clinical trials are promising (Agarwal, 2019; Lawson, 2020).

A. Potential AV graft locations

1. **Common locations.** Grafts may be placed in straight, looped, or curved configurations (Figure 6.4). The common initial sites for AV graft placement are a straight graft from the radial artery at the wrist to the basilic vein; a loop graft in the forearm from the brachial artery to the basilic vein (Figure 6.5); or an upper arm graft from brachial artery to axillary vein (Figure 6.6). Patient-specific features and projected time on dialysis help determine location; a distal graft in the nondominant arm is generally preferred initially. While this approach preserves proximal arm sites for future placement of a fistula, distal grafts are associated with more frequent episodes of thrombosis. A distal graft (eg, straight forearm graft from radial artery to an antecubital fossa vein) can sometimes be used to mature a proximal downstream vein for a future AV fistula construction.

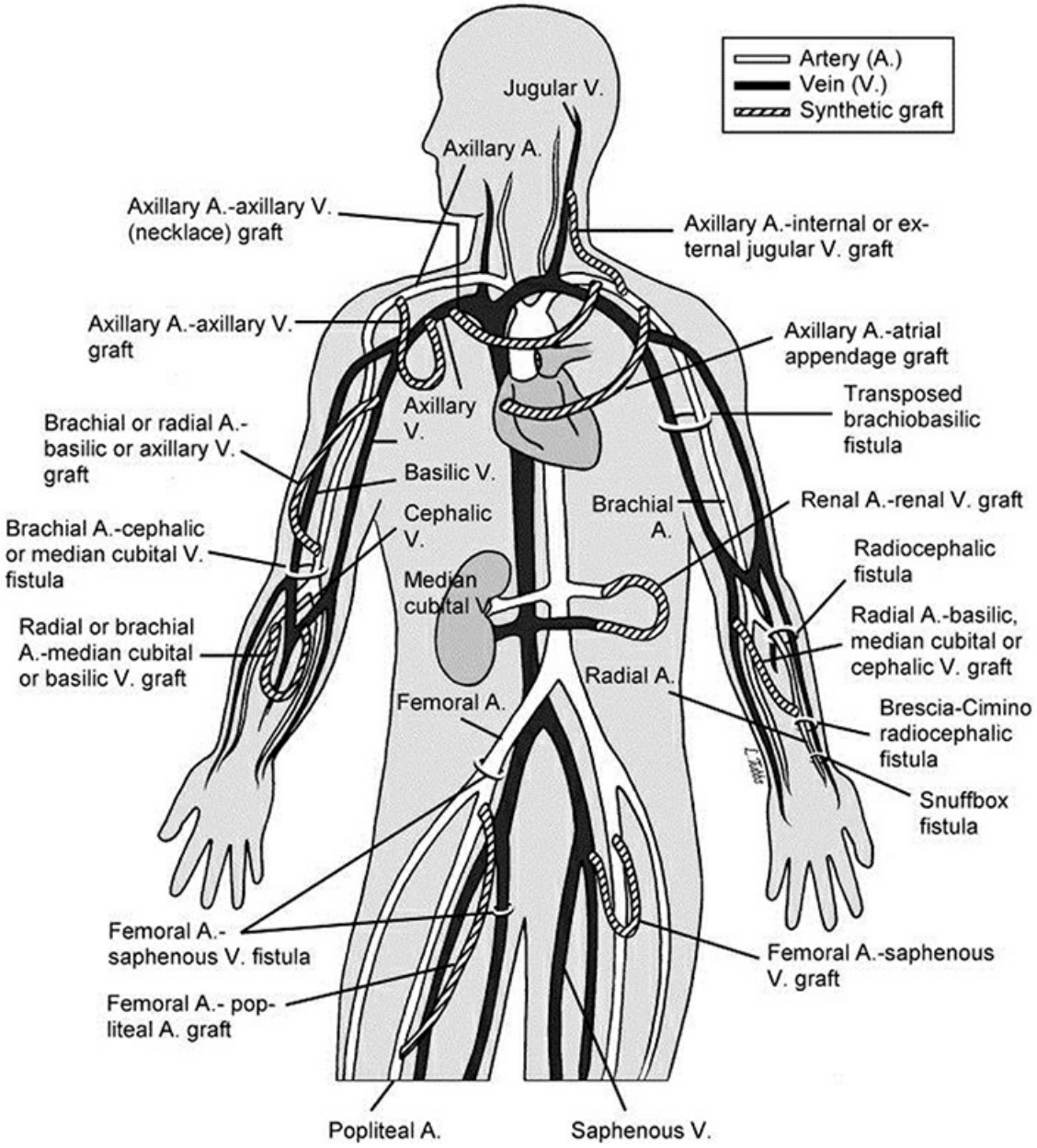


FIGURE 6.4: Various configurations and sites for AV graft placement. AV, arteriovenous. (Reprinted with permission from Paulson WD, et al. Vascular access: anatomy, examination, management. *Semin Nephrol.* 2002;22:183-194.)

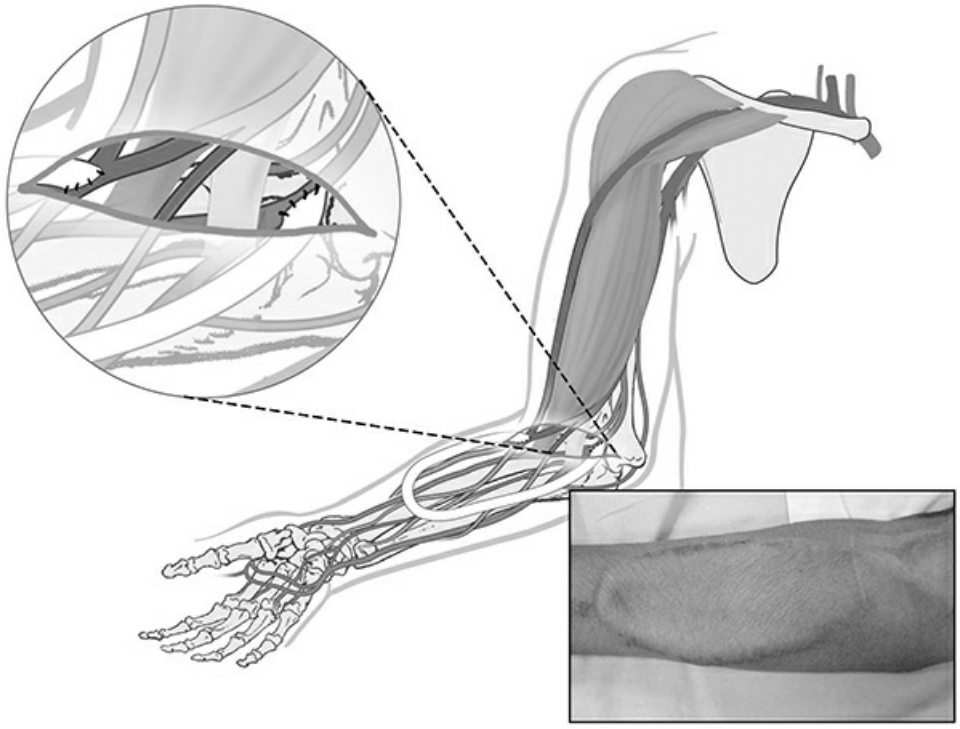


FIGURE 6.5: Forearm loop AV graft. AV, arteriovenous. (Reprinted with permission from Atlas of Dialysis Vascular Access by Tushar Vachharajani, MD, FACP, FASN.)

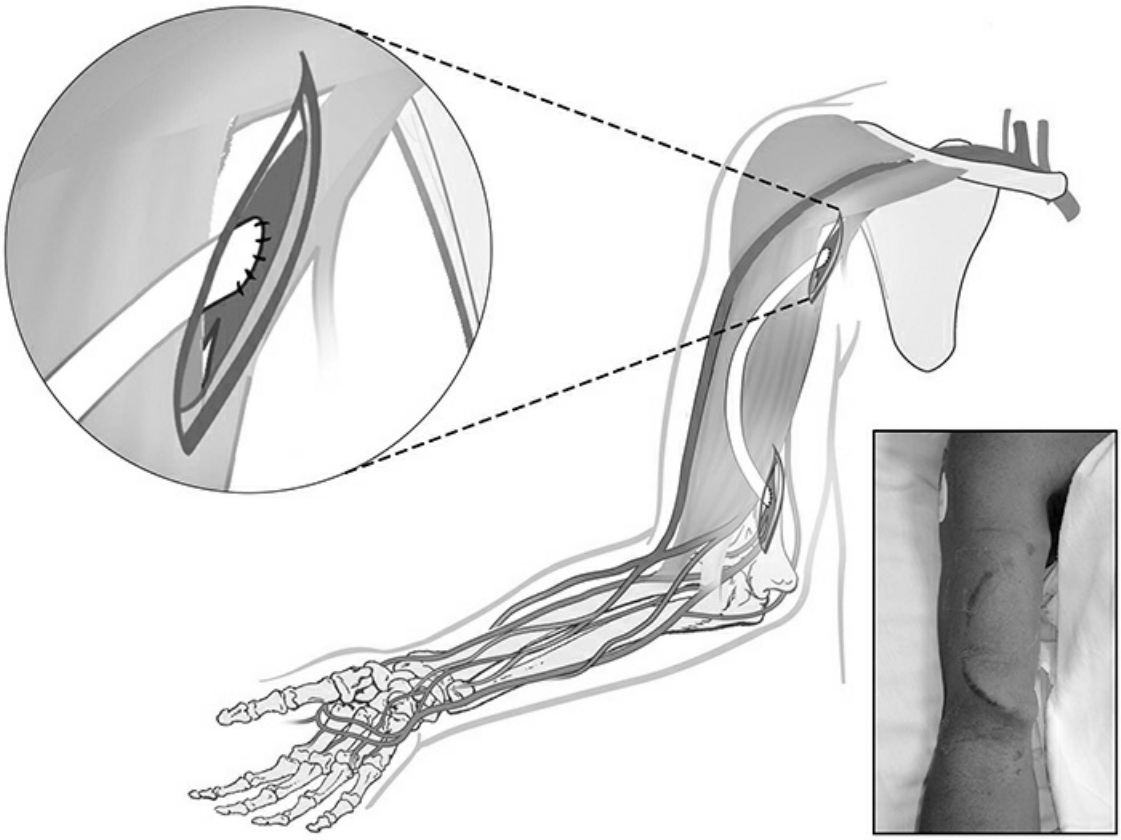


FIGURE 6.6: Upper arm AV graft. AV, arteriovenous. (Reprinted with permission from Atlas of Dialysis Vascular Access by Tushar Vachharajani, MD, FACP, FASN.)

2. **Uncommon locations.** The axillary artery can be used as the source of a loop graft in the upper extremity. The graft can extend from the arm to the internal jugular vein to bypass ipsilateral subclavian vein stenosis. An AV graft can also be placed in the thigh, but then there is a higher associated complication rate. A chest wall axilloaxillary (necklace) graft is another option when other sites have been exhausted. Multiple other sites including an axillary artery-to-femoral vein graft can be used, depending on the individual patient and the experience and skills of the surgeon (Vachharajani, 2018).

B. Surgical placement. Prophylactic antibiotics are often administered just prior to the operation. The anastomosis should be made between the end of the graft and the side of the vein or artery to minimize interference with blood flow through the native vessels. Some studies suggest that nonpenetrating clips may be superior to conventional sutures by avoiding endothelial penetration. A clip should be placed at the arterial and venous anastomoses for identification during subsequent angiography.

C. Postoperative care. This is similar to care after the creation of an AV fistula. The extremity is kept elevated for several days. Graft function is checked regularly by assessing for venous pulsation, thrill, and bruit. There is no point in doing arm exercises to hasten maturation.

D. Maturation (healing process). AV graft maturation is a misnomer as technically it is a healing process. A PTFE graft should not be cannulated for at least 2 weeks after placement and is considered healed when edema and erythema have resolved and the graft course is easily palpable. Adhesion between the graft and the subcutaneous tunnel to prevent hematoma formation requires at least 2 to 3 weeks. Cannulation of a graft that cannot be easily palpated or in an edematous site invites inaccurate needle insertion, leading to hematoma formation or frank laceration. Patients with persistent arm edema that fails to respond to arm elevation should have an imaging study to evaluate the status of their central veins.

1. **Early-use grafts.** Several early-use grafts have been introduced for immediate postoperative access to avoid risks associated with central venous catheters. The performance of a multilayered, self-sealing polyurethane graft is comparable to that of a conventional PTFE graft and allows for early access. Its placement requires more skill than the placement of a conventional PTFE graft because the risk of graft kinking and twisting within the tunnel is somewhat higher. Composite grafts should not be cannulated for at least 24 hours after placement, and not until swelling around the surgical wound has resolved and the graft can be easily palpated. A self-sealing graft composed of heparin-bonded polycarbonate that is immediately available for puncture has been developed.
2. **Autologous tissue grafts.** Preliminary experience with autologous, tissue-engineered vascular grafts has been encouraging. A phase 2 long-term follow-up study using bioengineered grafts reported a secondary patency rate of 58% at 5 years (Jakimowicz, 2022).

XI. PHYSICAL EXAMINATION OF AV FISTULAS AND GRAFTS.

Physical examination

is a noninvasive and cost-effective test that is an important tool in the evaluation of an AV access. Multiple studies have demonstrated that physical examination can accurately detect and localize stenotic lesions in a great majority of patients with an AV access. Physical examination can be very helpful not only in the postoperative monitoring of a new graft or fistula but also in the evaluation of access dysfunction. The latter topic is discussed in more detail in Chapter 8.

A. Inspection. Examination should not be limited to the site of the AV access but should also include the entire arm, shoulder, breast, neck, and face. Presence of swelling in any of these areas should be recorded and raises the suspicion of a downstream stenosis. The presence of collateral veins suggests downstream stenosis. Any scars on the chest wall should be carefully examined for evidence of previous catheter insertion sites. The presence of face, neck, or breast swelling is usually due to central venous stenosis.

B. Palpation and auscultation

1. **Pulse.** Normally, an AV access demonstrates a soft pulse that is easily compressed by the application of gentle pressure. In the presence of a downstream stenosis (outflow stenosis), the pulse becomes augmented (hyperpulsatile, water-hammer pulse). Often, a water-hammer pulse can be seen as a strong pulsation on inspection. The clinical history that goes with this scenario is frequently the presence of prolonged bleeding after removal of the access needles. In contrast to the water-hammer pulse, a feeble pulse (flat access, hypopulsation) indicates an upstream stenosis. The clinical history that goes with a feeble pulse often includes the inability to aspirate blood from the arterial needle (needle pulling high negative pressure). The access is usually "plump" upstream to a stenosis and "flat" downstream from a stenosis.
2. **Thrill.** The thrill of an AV access is a "buzz" that can be felt by the examining fingers. The thrill can be continuous or discontinuous. Normally, there is a continuous nature to the thrill except at the arterial anastomosis where the thrill normally is discontinuous. The quality of the thrill should be evaluated from the anastomosis all the way to the chest wall (many a time, cephalic arch stenosis gives a discontinuous thrill at the cephalic arch area in the anterior part of the shoulder). In the presence of a stenosis, the thrill becomes discontinuous; frequently, a systolic thrill can be felt immediately downstream from a stenosis.
3. **Auscultation.** Auscultation can be performed to assess the quality of the bruit in the AV access. As with palpation for a thrill, auscultation for a bruit allows for the detection and localization of a stenosis by the presence of a discontinuous versus continuous bruit.

C. Pulse augmentation and arm elevation tests. There are two additional tests that can be used to quickly examine an AV access: the **pulse augmentation test** and the **arm elevation test**.

1. **Pulse augmentation.** This is performed by a complete occlusion of the access downstream to the arterial anastomosis. The test is considered normal when the portion of the fistula upstream from the occluding finger demonstrates an augmentation of the pulse. With an AV fistula, the presence of side branches can be detected using the pulse augmentation test. Upon occlusion of the outflow of an AV access by the examining finger, two things should normally occur. (1) The thrill should disappear. (2) The part of the access upstream to the occluding finger should

become hyperpulsatile (augment). If the thrill persists after the occlusion of the access, the presence of an accessory outflow pathway should be suspected. In this case, the access pulse does not augment as the anticipated increase in pressure is dissipated by the presence of the accessory pathway. One can often pinpoint the location of the side branch by moving the occluding finger toward the anastomosis of the fistula. When the thrill disappears and the access augments, the examiner's occluding finger will have just passed the site of the side branch. Moving the finger away from the anastomosis should bring the thrill back. This maneuver confirms the location of the side branch.

2. **Arm elevation test.** This is performed by elevating the extremity and examining the normal collapse of an AV fistula. The test is considered abnormal when the fistula remains plump after arm elevation and fails to collapse. This indicates the presence of downstream stenosis. This test especially should be taught to the patient so they can check their AV fistula every day and be empowered in their own care.

XII. GENERAL ISSUES RELATING TO CANNULATION OF EITHER AV FISTULAS OR GRAFTS

A. Skin preparation. An aseptic technique must be used for all cannulation procedures.

B. Anesthesia. In pain-sensitive patients, a topical anesthetic cream can be applied to the skin about 30 minutes prior to puncture, but this is rarely required. Most patients, especially those with new accesses, require subcutaneously injected lidocaine prior to needle cannulation. Injected anesthetic is especially helpful when manipulation of the needle is anticipated. Patients with established needle tracts often tolerate direct puncture without anesthesia, and some find the anesthetic injection more painful than a direct stick. In at least one randomized trial, local cooling of the skin using an ice pack was more effective than the application of local anesthetics (Al-Jubouri, 2024).

C. Use of tourniquets for AV fistulas. A tourniquet or blood pressure cuff should be used to enlarge and stabilize the vein for easier cannulation of AV fistulas. A tourniquet should not be used during the dialysis treatment; a fistula that works only when a tourniquet is in place is still underdeveloped, usually because of inflow stenosis, and such a fistula needs more time or reevaluation by the vascular access team prior to use.

If a tourniquet is not required for cannulation and the fistula does not soften with arm elevation, a downstream (outflow) stenosis may be present and should be searched for using imaging studies.

D. Needle size. As noted above, during the initial use of a permanent vascular access, especially a fistula, some nephrologists recommend the use of small (16G-17G) needles and low blood flow rates. In mature accesses, larger (15G) needles are needed to support blood flow rates (>350 mL/min) required for high-efficiency dialysis.

E. Needle position, spacing, and orientation. Whether the needles should be inserted with the bevel facing upward or downward toward the skin is an unresolved question. Some studies have suggested less pain and fewer complications with bevel-down insertion, but this has not been a universal finding. Two needles are placed into the dilated vein(s) of the fistula or into the graft. The needle leading to the dialyzer blood inlet is always placed in the more upstream segment but at least 3 cm away from the arterial anastomotic site. This upstream or "arterial" needle may point either upstream or downstream. Pointing the upstream needle in a downstream direction is

popular in some countries, the rationale being that the "flap" left behind when the needle is withdrawn tends to close more naturally with the flow of blood. However, there is no controlled evidence to suggest that this is the case. The downstream (outlet or "venous") needle should be inserted pointing downstream, approximately 5 cm downstream to the upstream (arterial) needle (to minimize recirculation). One study found that recirculation does not occur, even with needles spaced as closely as 2.5 cm from one another (Rothera, 2011). Some caregivers rotate each needle 180° along the needle axis after insertion to prevent potential injury to the deep wall of the vessel by the needle point. This issue has not been systematically studied but generally is not recommended.

1. **Risk of inflow/outflow needle reversal.** Special care must be taken when cannulating forearm loop grafts. In more than 80% of such grafts, the arterial limb will be medial (ulnar), but in the remainder, the arterial limb may lie on the radial side of the forearm. Reversal of needle placement may occur unless the dialysis clinic staff knows that blood in this particular graft flows in the opposite-to-usual direction. Reverse needle placement substantially increases the amount of recirculation (to >20%) and can result in inadequate delivery of dialysis. This happens more commonly than one would expect, as patients may have access to surgery at another center and a diagram of the inserted access might not be readily available. When in doubt, a careful physical examination with transient occlusion of the access and palpation on either side of the occluding finger for pulsations will reveal the direction of blood flow in most cases. For reference, a "road map" diagram of the access from the surgeon who placed the access is very helpful.

F. Point-of-care ultrasound guidance for needle insertion. Small, portable ultrasound devices can be used to guide nurses and technicians when inserting needles into AV fistulae. This practice has not achieved widespread acceptance, and the potential outcome benefits in terms of increased fistula longevity and fewer complications are still being evaluated (Schoch, 2020).

G. Repeated punctures: Needle rotation. The manner in which needles are inserted affects the long-term patency and survival of accesses, particularly of AV fistulas. The "ladder" or rotational approach uses the entire length of the access without localizing needle sticks to any two areas. Grouping needle sticks in one or two specific areas can weaken the wall of a fistula, producing an aneurysm.

H. Buttonhole cannulation tips. In AV fistulas, one technique of placing access needles is the so-called buttonhole method. The AV fistula is always punctured through a limited number of sites, the use of which may be rotated. The needle must be placed precisely through the same needle tract used previously. After the buttonhole has been developed using sharp needles, special "dulled" needles are used to minimize laceration of the buttonhole tract. Initial enthusiasm for the buttonhole approach has been tempered with suggestions that its use may lead to increased infectious complications and may do little to prolong AV fistula longevity (MacRae, 2014; Muir, 2014). The degree of success with the buttonhole approach may be highly technique dependent. The buttonhole technique is to be avoided in AV grafts.

Overall, use of the buttonhole technique remains controversial when access cannulation is routinely done by the same person, such as the patient during self-care or home hemodialysis (Vachharajani, 2020b). Buttonhole cannulation requires strict

adherence to proper infection control measures as well as technique to prevent serious infection and technique-related complications (Dinwiddie, 2013). The following considerations apply:

1. Employ proper buttonhole cannulation procedure steps (skin prep, proper scab removal, re-prep of the skin, and proper use of blunt needles).
2. Use the needle wings to help guide the needle gently into the skin and vessel or conduit—excessive pressure prevents feedback to the cannulator's fingers to feel resistance.
3. Always cannulate the buttonhole under consistent conditions; if a tourniquet was used to establish the buttonhole, it should be used consistently, as otherwise, the tissues in the buttonhole tract may not align.
4. Consider the patient as a self-cannulation candidate. Benefits can include patient empowerment, less pain, and ease of cannulation, as the patient has to master cannulation of only their own specific access.

I. **Preventing and dealing with infiltration.** Infiltrations with cannulation can occur before dialysis, during dialysis with the blood pump running, or after dialysis in the course of needle removal. One should monitor closely for signs and symptoms of infiltration. A quick response to a needle infiltration can help minimize damage to the access.

1. If the infiltration occurs after the administration of heparin, care must be taken to properly clot the needle tract and not the fistula. In some cases, the decision to leave the needle in place and cannulate another site may be appropriate. The immediate application of ice can help decrease pain and the size of the infiltration and may decrease bleeding time.
2. Use caution when taping needles. Avoid lifting up the needle after it is in the vein. An improper needle flip or taping procedure can cause an infiltration.
3. If the fistula is infiltrated, it is best to rest the fistula for at least one treatment. If this is not possible, the next cannulation should be downstream to the site of the infiltration. If the patient still has a central venous catheter in place, one can restart the use of the fistula with one needle, returning blood via the venous catheter, and later advance to two needles, a larger needle size, and greater blood flow rates as the access allows.
4. Proper needle removal prevents postdialysis infiltrations. Prior to removing the needle, apply the gauze dressing over the needle site, but do not yet apply pressure. Next, carefully remove the needle at approximately the same angle as it was inserted. This prevents dragging the needle across the patient's skin. Using too steep of an angle during needle removal may cause the needle's cutting edge to puncture the vein wall.
5. Do not apply pressure to the puncture site until the needle has been completely removed.
6. Notify the nephrologist as soon as a cannulation injury has occurred. In some cases, fistula rest is adequate. In others, an intervention may be required.

J. **Hemostasis postdialysis.** Following needle removal, direct pressure over the site, usually with the tip of one or two fingers pushed firmly but not so hard as to occlude flow, is the best method for achieving hemostasis. One must prevent hematoma formation at the access site while controlling bleeding at the skin exit site. Pressure must

be held for at least 10 minutes before checking the needle site for bleeding. Adhesive bandages should not be applied until complete hemostasis has been achieved.

Prolonged bleeding (>20 minutes) may indicate increased intra-access pressure due to an unsuspected outflow stenosis. Bleeding also is common in patients receiving therapeutic doses of anticoagulants such as warfarin. Another cause of bleeding is heparin escape from a venous catheter lock in patients who are being transitioned from a venous catheter to an AV fistula, where the venous catheter is being used to return blood during initial fistula test use.

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7 Venous Catheter Access: The Basics

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I. OVERVIEW.

Patients being dialyzed with venous catheters do not do as well as those using an arteriovenous access. Patients dialyzing with catheters develop infections more often, have higher levels of inflammatory markers such as C-reactive protein, and die more frequently. It is unclear if these associative risks reflect a different patient population receiving catheters, if some risk factors occur when arteriovenous (AV) accesses fail and a catheter must be placed, or if the risks are due completely to some properties of catheter use per se. Probably all three are important. Two large, observational studies reported that among patients who initiated hemodialysis with a catheter, survival was higher in those who had undergone an AV fistula creation before needing dialysis, even if the AV fistula failed to mature. These findings suggest that the higher mortality among catheter-dependent patients is largely a reflection of the higher comorbidity of these patients. Survival rates for catheters are about 60% at 6 months and 40% at 1 year, if revisions are included. Inadequate blood flow through venous catheters remains a significant problem. Nominal blood flow of greater than 400 mL/min (actual flow 350 mL/min) can rarely be obtained, and usually flow is limited to a range closer to 300 mL/min. This limits use of venous catheters in larger patients and results in a lower than average urea reduction ratio (URR) or fractional urea clearance (Kt/V). In addition, the use of catheters may result in central vein stenosis in a subset of patients (Echefu, 2023). Central vein stenosis, in turn, is associated with shorter patency of an ipsilateral AV fistula.

In the chronic setting, venous catheters are utilized as a long-term vascular access for patients in whom an AV access cannot be readily created. Such patients include small children, some diabetic patients with severe vascular disease, patients who are morbidly obese, and patients who have undergone multiple AV access insertions and in whom additional sites for AV access insertion are not available. Additional indications include patients with cardiomyopathy unable to sustain adequate blood pressures or access flows. Whereas catheters were initially favored for more frequent dialysis, there has been good recent experience with nocturnal dialysis and short daily dialysis using AV fistulas or grafts. There has been renewed discussion about the potential acceptability of venous catheter access for chronic dialysis in some elderly patients, especially those with comorbidities and limited expected life span (Drew and Lok, 2014). Infection rates with venous catheters in elderly patients (>75 years) are relatively low, one-third of that in younger patients (Murea, 2014). Adherence to hand washing and catheter care protocols such as those suggested by the U.S. Centers for Disease control has resulted in marked overall reduction of dialysis catheter infection rates (Patel, 2013).

II. CATHETER TYPES AND DESIGN

A. Cuffed versus uncuffed.

Use of an uncuffed catheter for periods of time beyond

several weeks results in a relatively high rate of infection and is not recommended. Dacron or felt cuffs bonded to the catheter reduce the incidence of line-related infection and of catheter migration and must be used whenever a longer-term use of the catheter is anticipated, or when it is anticipated that a patient will be discharged from the hospital with a catheter remaining in place.

B. Design issues. Dual-lumen venous catheters are available in a "double-D" configuration or where the two lumens are in some related, side-by-side configuration. Coaxial catheters are now less frequently used. A side-by-side port design permits the intravenous portion of the catheter to be split into two parts close to the termination point. This results in a softer, more pliable catheter end, a greater separation of inlet and outlet ports, and perhaps a lower recirculation rate. The cuffed Tesio catheter system (used primarily for chronic dialysis) consists of two completely separate catheters, each made of soft silicone material, one for inflow and one for outflow.

C. Antiseptic impregnation. Some dialysis catheters or their cuffs are impregnated with antiseptic or silver-based coatings in an attempt to inhibit bacterial growth. At present there are no large studies that demonstrate improved outcomes with such catheters.

III. ACUTE DIALYSIS

A. Indications. Venous catheters are commonly used for acute angioaccess in the following patients: (a) those with acute kidney injury; (b) those requiring hemodialysis or hemoperfusion for overdose or intoxication; (c) those with late-stage chronic kidney disease needing urgent hemodialysis but without available mature access; (d) those on maintenance hemodialysis who have lost effective use of their permanent access and require temporary access until permanent access function can be reestablished; (e) patients requiring plasmapheresis; (f) peritoneal dialysis patients whose abdomens are being rested prior to new peritoneal catheter placement (usually for severe peritonitis that required peritoneal dialysis catheter removal); and (g) transplant recipients needing temporary hemodialysis during severe rejection episodes. The nascent interest in urgent start peritoneal dialysis, discussed in Chapter 22, and earlier referral of patients with chronic kidney disease for access placement should lower the need for urgent placement of central venous catheters for hemodialysis.

B. Insertion location. Available sites include the right and left internal jugular vein, the femoral veins, and the subclavian veins. One order of preference for these various sites is shown in Table 7.1. The optimal insertion site is the **right internal jugular vein** because the venous pathway to the right atrium is relatively short and straight. The subclavian site should generally be avoided because it is associated with a higher incidence of insertion-related complications (pneumothorax, hemothorax, subclavian artery perforation, brachial plexus injury) and a high incidence (up to 40%) of central venous stenosis. Use of the **left internal jugular vein** for acute dialysis is not optimal, as this represents a relatively long and twisty pathway to the right atrium; if subsequent chronic dialysis is needed, ideally one would like to leave the upper extremity central venous vessels alone to limit the rate of future stenosis. The **femoral vein** approach has several potential advantages. Placement tends to be simpler, especially for inexperienced operators. There is no risk of pneumothorax, hemothorax, or brachial plexus injury, although femoral arterial puncture and retroperitoneal bleed can occur. Originally, it was thought that the femoral approach had a higher risk of infection, but

recent experience from the Cathedia Study Group found comparable rates of infection and time to catheter tip colonization (14 days) with femoral and internal jugular catheters (Dugué, 2012). The femoral approach is useful for performing the initial hemodialysis treatment in patients who present with acute pulmonary edema because the patient's head and chest can remain elevated during insertion. The infection risk with femoral catheters is increased in obese patients (BMI > 28 kg/m^2), although the extent of this risk probably depends on the distribution of body fat. When femoral catheters are used, the length must be sufficient (usually at least 20 cm) so that the tip is in the inferior vena cava to permit better flow and to minimize recirculation. Another finding from the Cathedia Study was that URR and *Kt*/*V* delivered were similar with femoral and jugular catheters (Dugué, 2012). The European Best Practices Group does not agree with the order of preference of insertion sites listed in Table 7.1, and gives second preference to the left internal jugular vein, and recommends that femoral catheters be discouraged (Vanholder, 2010).

TABLE 7.1 Selected Factors Favoring Different Temporary (Nontunneled) Hemodialysis Catheter Insertion Sites

1. Right internal jugular
   - Critically ill and bed bound with body mass index >28
   - Postoperative aortic aneurysm repair
   - Ambulatory patient/mobility required for rehabilitation
2. Femoral
   - Critically ill and bed bound with body mass index <24
   - Tracheostomy present or planned in near-term
   - Need for long-term hemodialysis access present, highly likely or planned
   - Emergency dialysis required plus inexperienced operator and/or no access to ultrasound
3. Left internal jugular
   - Contraindications to right internal jugular and femoral sites
4. Subclavian
   - Contraindications to internal jugular
   - Right side to be used preferentially

Source: Reprinted with permission from Macmillan Publishers Ltd: Clark EG, Barsuk JH. Temporary hemodialysis catheters: recent advances. *Kidney Int*. 2014;86(5):888-895.

C. Uncuffed versus cuffed catheter use. The risk of infection of uncuffed catheters increases markedly after the first week. For this reason, the KDOQI 2019 vascular access guidelines recommend use of a cuffed catheter if the anticipated need for dialysis is longer than 1 week. They also recommend that femoral catheters in bed-bound patients not be left in place longer than 5 days. These recommendations, especially with regard to femoral catheters, may be a bit too stringent given the results of the Cathedia Study (Dugué, 2012), where median time to catheter tip colonization was 14 days. Once the likelihood of the need for prolonged dialysis is established, an uncuffed internal jugular catheter can be replaced with a cuffed catheter. In cases where a prolonged need for dialysis is likely at the outset, a cuffed catheter can be inserted initially, in the right internal jugular vein position if possible. Some success has been claimed using cuffed tunneled femoral catheters (Hingwala, 2014; Pokala, 2023). This has the advantage of locating the exit site away from overhanging skin folds, and easy removal, as long as

removal is done within several weeks of insertion. Placing a cuffed femoral catheter allows time for more definitive access site placement, whether it be for peritoneal dialysis or hemodialysis. Uncuffed dialysis catheters should be restricted to inpatient use. A cuffed dialysis catheters should always be placed prior to hospital discharge if continued need for dialysis is anticipated.

D. Anatomic variation and use of real-time ultrasound guidance. The central veins of the neck exhibit anatomic variability (Figure 7.1), and occasionally one of them may be absent. Atypical or ectatic carotid arteries are also a problem. With the use of ultrasound guidance, the rate of successful internal jugular puncture on first attempt increases markedly and the rate of carotid artery punctures and hematoma is greatly reduced (Rabindranath, 2011). In the femoral approach, the femoral vein is often behind the artery, and this overlap worsens as one proceeds down from the inguinal ligament (Beaudoin, 2011). Here, too, the use of ultrasound helps reduce complications (Clark and Barsuk, 2014).

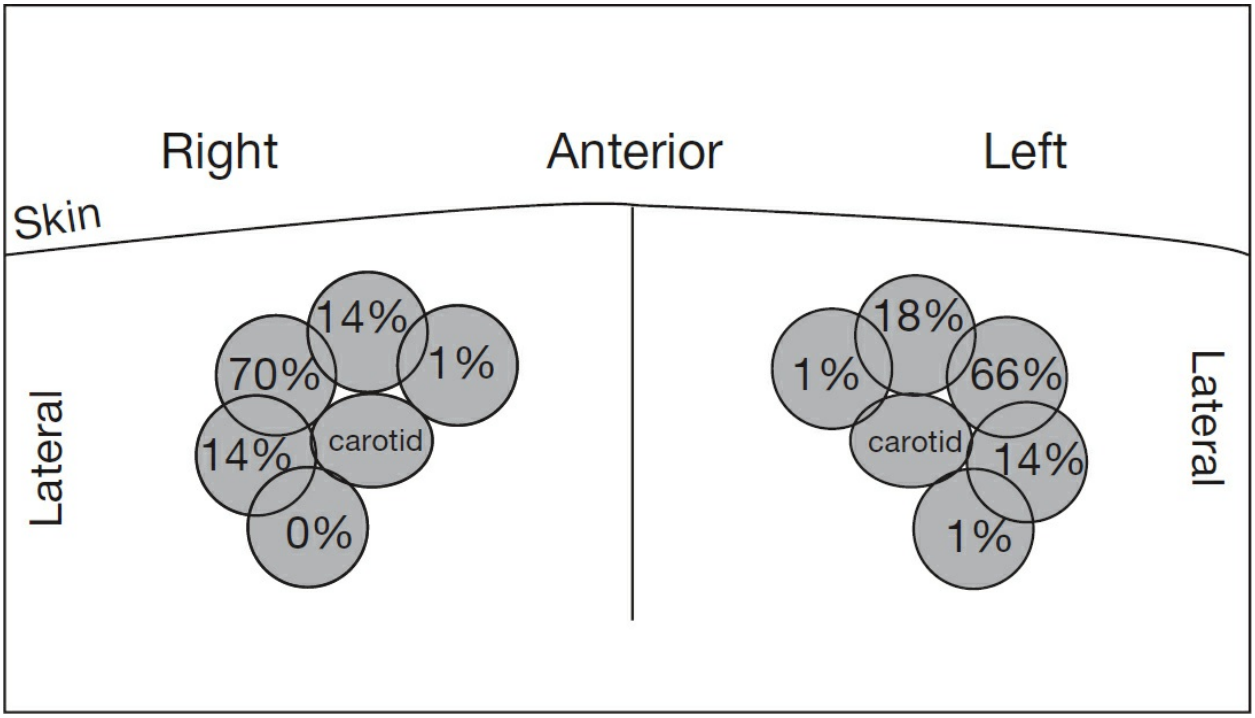


FIGURE 7.1: Anatomic variability of internal jugular vein as viewed using ultrasound localization. (Data from Caridi JG, et al. Sonographic guidance when using the right internal jugular vein for central vein access. *Am J Roentgenol.* 1998;171:1259-1263.)

E. Simulation-based training for catheter insertion. Venous catheter insertion for dialysis is a necessary skill for nephrology fellows to acquire, but many programs may not have resources to provide the required level of training. Simulation-based training has been proposed to remedy this, and provision of such intensive training has resulted in improved catheter-related outcomes (Clark and Barsuk, 2014).

IV. INSERTION TECHNIQUE

A. Initial site preparation. The catheter should be inserted using an aseptic technique,

with the operator wearing a sterile surgical gown and gloves in a maximum barrier protection environment. Prior to surgical scrub, it is helpful to examine the selected site using ultrasound to ensure that the patient has a suitable vein in the selected location. The insertion site and surrounding areas should be cleansed with surgical scrub and draped appropriately (include shoulder and chest wall if a cuffed tunneled catheter is to be inserted). The ultrasound probe should be covered with a sterile sheath.

B. Internal jugular approach. The ultrasound probe may be placed parallel to the long axis of the vessel and the cannulation needle inserted adjacent to the end or short axis of the probe. Alternatively, the probe may be placed perpendicular to the long axis of the vessel. This approach gives the vein the more typical appearance of a circle, but limits the visualization of the needle. The vein typically collapses with gentle pressure of the probe, whereas the artery does not. Additionally, the vein diameter increases with Valsalva maneuver; this can be easily observed with ultrasound. For internal jugular vein cannulation as an example, the ultrasound probe is placed parallel and superior to the clavicle, over the groove between the sternal and clavicular heads of the sternocleidomastoid muscle. It is important to avoid inserting the catheter through the muscle, as this is uncomfortable for the patient and leads to catheter dysfunction as the neck is rotated.

1. **Initial insertion of the guidewire through a 21G needle.** The site for insertion is infiltrated with local anesthesia. Using real-time ultrasound guidance, a 21G micropuncture needle with an attached syringe is inserted into the vein. The small needle limits potential complications if the carotid artery is inadvertently punctured compared to a larger 18G needle, which is usually included in commercially available dialysis catheter trays. Under direct visualization, the vein will be seen to gently push in before penetration of the anterior vein wall. The syringe is removed, and a 0.018″ guidewire is inserted through the needle. The guidewire is advanced. The position of the guidewire is confirmed using fluoroscopy.
2. **Insertion of the dilator over the guidewire.** The needle is then removed, and a coaxial 5-French dilator is then advanced over the guidewire. The guidewire and 3-French inner translational dilator are removed, leaving the 5-French outer dilator in place. A flow switch or stopcock is attached to the dilator to prevent the possibility of an air embolism.
3. **Uncuffed catheter insertion.** The next step depends on whether one is placing a non-cuffed temporary or cuffed tunneled catheter. For temporary catheter placement, a standard 0.035″ guidewire is advanced into the vein, and then the 5-French dilator is removed, leaving the guidewire. In a stepwise fashion, dilators of increasing size are passed over the guidewire to progressively dilate the soft tissue and venous tract; the dilator should move freely on the guidewire. The dilator should not be forcefully advanced, as it is possible for the dilator to get off axis and impinge on the guidewire and perforate the vein and/or the mediastinum. Consequently, one does not need to advance the entire length of the dilator as only the dilatation of the track from the skin to the vein is desired. If there is any doubt as to location of the dilator or if there is hesitancy or difficulty in dilating the tract, fluoroscopy should be used to assist in placement. The last dilator is then exchanged for the temporary catheter, which is advanced over the guidewire into position. After securing the catheter in

place, a chest radiograph should be obtained for confirmation of correct positioning and to check for any complications, if a fluoroscope was not available during insertion. At a later time point, if it becomes clear that the patient will require long-term dialysis support, a temporary non-cuffed catheter in the internal jugular vein may be safely converted to a cuffed tunneled catheter if there is no evidence of an exit-site infection.

4. **Cuffed catheter insertion**
    a. **Creating the skin exit site and tunnel.** For cuffed tunneled catheter insertion, a small skin incision is made from the 5-French dilator exit site extending laterally. The subcutaneous tissue is then exposed with blunt dissection, creating a subcutaneous pocket so that the catheter bend will be kink-free. Further dissection is made to ensure that the soft tissue around the 5-French dilator is free. The catheter exit site is then located. This may be accomplished by using the fourth rib interspace landmark technique, or the catheter length may be determined more precisely by using a guidewire to measure the distance from the insertion site to the mid-right atrium. Using this measurement as a guide, the length of tunnel may then be determined so that the cuff is within the tunnel approximately 1 to 2 cm from the exit site.
5. **Inserting the catheter through the skin exit site.** Once the exit site for the catheter is identified, the area is infiltrated with local anesthesia; a puncture is made through the skin using a number 11 knife blade inserted parallel to the skin. The knife is inserted to the widest point of the blade; this incision width accommodates most dual-lumen catheters. A long needle is used to infiltrate the tunnel tract, with local anesthesia extending from the exit site to the venotomy insertion site. The catheter is mounted on the end of the tunneling device, and the tunneling device is pulled from the exit site subcutaneously to the insertion site. The cuff of the catheter is pulled into the tunnel, and the tunneling device is then removed from the catheter.
6. **Dilating the deep tissues and venous tract.** A guidewire (Benson or angled glidewire) is now passed through the dilator into the inferior vena cava. Placement of the guidewire into the inferior vena cava decreases the likelihood of cardiac arrhythmias. The guidewire provided with most catheter trays may also be used. The 5-French dilator is then removed, and in a stepwise fashion, dilators of increasing size are passed over the guidewire in order to progressively dilate the soft tissue and venous tract. The dilator should move freely on the guidewire. It is possible for the dilator to get off axis and impinge on the guidewire and perforate the vein and/or the mediastinum. In this context, one does not need to advance the entire length of the dilator as only the dilatation of the track from the skin to the vein is required. If there is any doubt as to the location of the dilator or if there is hesitancy or difficulty in dilating the tract, the fluoroscope should be used to verify proper positioning.
7. **Completing catheter insertion.** After the final dilatation, the dilator is inserted with its peel-away sheath. As one inserts the sheath, a resistance is felt as the sheath goes through the soft tissue and then a final resistance as it enters the vein. The dilator and sheath are then removed and the catheter is threaded over the guidewire without using the sheath and advanced through the venous tract into final position (sheathless catheter insertion). One may need to slightly torque the catheter to advance it through the tract. This maneuver decreases the possibility of air embolism

and may result in both a smaller venotomy and in less postprocedure bleeding.

Alternatively, if the peel-away sheath is used, the sheath is advanced slightly and the dilator removed while occluding the sheath, leaving the guidewire in place to ensure access is available if there are any difficulties. The sheath should be grasped between the finger and thumb of one's hand to occlude the sheath. This prevents bleeding and/or aspiration of air while leaving enough length of the sheath to insert the catheter. Once the dilator and guidewire have been removed, the catheter is threaded over the wire and advanced into the opening of the sheath in such a way as to avoid twisting the catheter. The catheter is fed through the sheath. The catheter is pushed farther into the sheath, and the sheath is peeled downward toward the skin. As soon as the catheter is advanced maximally, the sheath is pulled out and then peeled down outside of the venotomy. This avoids the sheath creating a larger venous tract.

8. **Setting and securing the catheter cuff.** Once the sheath has been completely removed, the catheter is pulled back into the tunnel so that the cuff now is approximately 1 to 2 cm from the exit site. The catheter is now checked to ensure that it is functioning properly. A 10-mL syringe should be able to rapidly pull back blood without any shuttering if the catheter is to deliver a blood flow of greater than 300 mL/min.

   The venotomy insertion site at the neck is closed using appropriate suture after confirmation of adequate flow. Sutures should not be placed at the exit site as they serve as a nidus for infection. Additional suture is used to hold the catheter at the hub. Using "air knots" to secure the catheter hub increases patient comfort and decreases the likelihood of skin necrosis. The subcutaneous cuff will ultimately hold the catheter in position and anchor it to the subcutaneous tissue. Topical antibiotic ointment may be applied to the incisions and needle puncture sites, and a gauze dressing is applied.

C. Femoral approach. Uncuffed catheters normally are used, but as noted earlier, cuffed catheters may also be inserted. The patient is placed flat on his or her back, with the knee slightly flexed and leg abducted and rotated outward. The groin is shaved, cleansed, painted with antiseptic, and draped. The femoral vein should be located 2 to 4 cm below the inguinal ligament using a 21G needle filled with heparinized saline or with local anesthetic. As noted earlier, real-time ultrasound guidance improves the chance of a successful procedure. A small amount of local anesthetic can be infiltrated around the vein to prevent venous spasm. Once the vein is located, the small-gauge needle is withdrawn and replaced with an 18G needle. A guidewire is inserted through the needle into the vein. It is important for the guidewire to be freely movable back and forth after it is fully inserted. If the guidewire feels tight, chances are that it has entered a side branch of the iliofemoral vein. Under these circumstances, catheter insertion should not be attempted; rather, the guidewire should be withdrawn completely, the angle of the needle in the vein changed (sometimes the needle hub has to be lowered to the skin level to be almost parallel to the vein), and the guidewire reinserted. After free to-and-fro movement of the inserted guidewire is achieved, the 18G needle is removed and the cannula is inserted. The remainder of the procedure then generally follows the description for jugular vein insertion, above.

V. INSERTION-RELATED COMPLICATIONS.

These are listed in Table 7.2. Arterial puncture by the initial small-gauge probing needle should be treated by uninterrupted local pressure for 15 to 20 minutes. The cannula should never be inserted into an artery. In case of inadvertent arterial insertion of a dialysis catheter, dialysis should be postponed, and surgical opinion sought to avoid a major hematoma and tracheal compression. In the case of femoral insertions, retroperitoneal bleeding may be severe and life-threatening with either puncture of the artery or inadvertent puncture of the back wall of the vein. A large pneumothorax or hemothorax usually requires drainage using a surgically implanted chest tube. Perforation of the superior vena cava or cardiac chambers can be life-threatening. Diagnosis is suggested by unexplained chest pain, shortness of breath, or hypotension soon after commencing dialysis. Surgical intervention is sometimes needed for correction. Infection-related complications can be minimized at the time of catheter insertion by assuring adequate hand hygiene, use of sterile gown, mask, gloves and caps for the operator, and a large (full body) sterile drape to cover the patient, and application of chlorhexidine skin antisepsis prior to the procedure (O'Grady, 2011).

TABLE 7.2 Complications of Central Venous Catheterization

Immediate Complications
Arterial puncture (all)
Pneumothorax (IJ, SC)
Hemothorax (IJ, SC)
Arrhythmias (IJ, SC)
Air embolism (all IJ, SC>>F)
Perforation of cardiac chamber (IJ, SC)
Pericardial tamponade (IJ, SC)
Retroperitoneal hemorrhage (F)
Delayed Complications
Thrombosis (all)
Infection (all)
Central venous stenosis (SC>>IJ)
Arteriovenous fistula (all)
Injury to Adjacent Structures
Brachial plexus (IJ, SC)
Recurrent laryngeal nerve (IJ, SC)

F, femoral; IJ, internal jugular; SC, subclavian.

VI. CARE AND USE OF VENOUS CATHETERS

A. Dressings.

During catheter connect and disconnect procedures, both dialysis staff and patient should wear surgical masks. A face shield should not be used without a surgical mask because the shield tends to focus the wearer's breath directly on the exposed catheter hub. The lumen and catheter tips should never remain open to air. A cap or syringe should always be placed onto the catheter lumen while maintaining a clean field

under the catheter connectors. Catheter lumens must be kept sterile: Interdialytic infusions through the catheter are forbidden.

After each dialysis, catheter hubs or blood line connectors should be soaked in antiseptic for 3 to 5 minutes, and then dried prior to separation. Chlorhexidine-based antiseptic solutions (>0.5%) appear to give better results than povidone-iodine (Mimoz, 2007; Onder, 2009). However, in one study, a substantial percentage of patients and staff developed rash and other allergic symptoms associated with chlorhexidine use, and in one report, chlorhexidine was proposed as the cause of acute dialyzer reactions (Chan, 2019).

After disconnecting each line from the catheter, the threads of the catheter connector should be scrubbed with chlorhexidine (Table 7.3). The catheter should be covered with a sterile dry dressing. Nonbreathable or nonporous transparent film dressings should be avoided as they pose a greater threat of exit-site colonization than dry dressings. The best type of dressing to use is still a matter of controversy. The Centers for Disease Control and Prevention (CDC) recommendations are to "use either sterile gauze or sterile, transparent, semipermeable dressing to cover the catheter site" (O'Grady, 2011). The CDC has available resources, including videos to show best practice techniques of making such catheter dressing changes (CDC, 2014).

TABLE 7.3 The Centers for Disease Control Core Interventions for Dialysis Bloodstream Infection Prevention

1. Surveillance and feedback using National Healthcare Safety Network
   Conduct monthly surveillance for bloodstream infections and other dialysis events. Calculate facility rates and compare with rates in other facilities. Actively share results with front-line clinical staff
2. Hand hygiene observations
   Perform observations of hand hygiene opportunities monthly and share results with clinical staff
3. Catheter/vascular access care observations
   Perform observations of vascular access care and catheter accessing quarterly. Assess staff adherence to aseptic technique when connecting and disconnecting catheters and during dressing changes. Share results with clinical staff
4. Staff education and competency
   Train staff on infection control topics, including access care and aseptic technique. Perform competency evaluation for skills such as catheter care and accessing every 6-12 mo and upon hire
5. Patient education/engagement
   Provide standardized education to all patients on infection prevention topics, including vascular access care, hand hygiene, risks related to catheter use, recognizing signs of infection, and instructions for access management when away from the dialysis unit
6. Catheter reduction
   Incorporate efforts (eg, through patient education, vascular access coordinator) to reduce catheters by identifying and addressing barriers to permanent vascular access placement and catheter removal
7. Chlorhexidine for skin antisepsis
   Use an alcohol-based chlorhexidine (>0.5%) solution as the first-line skin antiseptic agent for central line insertion and during dressing changes[a]
8. Catheter hub disinfection
   Scrub catheter hubs with an appropriate antiseptic after cap is removed and before accessing. Perform every time catheter is accessed or disconnected[b]
9. Antimicrobial ointment
   Apply antibiotic ointment or povidone-iodine ointment to catheter exit sites during dressing change[c]

[a]Povidone-iodine (preferably with alcohol) or 70% alcohol by itself is alternative for patients with chlorhexidine

intolerance.

[b]If a closed needleless connector device is used, disinfect connector device as per manufacturer's instructions.

[c]CDC recommends using povidone-iodine ointment or bacitracin/gramicidin/polymyxin B ointment at the hemodialysis catheter exit site after catheter insertion and at each hemodialysis session. Bacitracin/gramicidin/polymyxin B ointment is not currently available in the United States. Triple antibiotic ointment (bacitracin/neomycin/polymyxin B) is available and might have a similar benefit but studies have not thoroughly evaluated its effect for prevention of bloodstream and exit-site infections. Other ointments that have been studied include single antibiotic ointments (eg, mupirocin). However, concerns exist about development of antimicrobial resistance and also their ability to cover the spectrum of potential pathogens (eg, gram-negative and gram-positive bacteria) that can cause bloodstream infections in dialysis patients. Another important consideration is that ingredients in antibiotic and povidone-iodine ointments may interact with the chemical composition of certain catheters. Therefore, before any product is applied to the catheter, first check with the catheter manufacturer to ensure that the selected ointment will not interact with the catheter material.

Reprinted from National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention. https://www.cdc.gov/dialysis-safety/media/pdfs/Hemodialysis-Central-Venous-Catheter-STH-Protocol-P.pdf

B. Risk of air embolism on removal of dialysis catheters from the neck. After removal of a jugular venous catheter, lethal air embolism has been reported (Boer and Hené, 1999). Because of this nonnegligible risk, specific protocols should be in place for removal of venous catheters from the neck. The protocol recommended by Boer and Hené (1999) is as follows:

1. No heparin on day of planned removal. Protamine given if heparin is already on board
2. Patient in head down position during catheter removal. Patient instructed not to cough or inhale deeply during removal
3. Air-occlusive dressing with generous amount of an inert ointment to provide an instantaneous air seal
4. Patient observed for 30 minutes before leaving dialysis facility
5. Air-occlusive dressing left in place for at least 24 hours

C. Catheter exchange over a guidewire (technique). The reasons for catheter exchange over a guidewire (dysfunction, infection) are discussed in detail in Chapter 9. The technique for exchange of a catheter in the internal jugular vein is as follows: The chest wall and the old catheter are prepped and draped in a sterile fashion. The operators should wear two sterile gloves on each hand. Local anesthesia is infiltrated at the old exit site and around the cuff of the existing catheter. Both catheter ports are aspirated to get rid of the heparin. Using a hemostat, blunt dissection is performed to free up the catheter cuff. At this point, a guidewire is introduced into the venous lumen of the catheter and navigated into the inferior vena cava. The catheter is gently pulled back so that it is situated at the brachiocephalic vein. A contrast injection is performed through the atrial port of the catheter to ascertain the presence of fibroepithelial sheath. If present, percutaneous balloon angioplasty should be considered and contrast injection repeated to evaluate the results of the sheath treatment. The old catheter should be removed while the wire is kept in place.

At this point, the operator(s) should remove the outer pair of gloves before handling the new catheter. This maneuver helps minimize the transfer of infectious organisms from the old catheter to the new catheter. The new catheter is then advanced over the wire and into the right atrium. The catheter function is assessed as described earlier.

D. Bathing and showering. The exit site should never be immersed in bath water. Showering is best avoided, but if the patient showers it should be done prior to coming

to the dialysis unit, where a new dressing and antibacterial ointment will be promptly applied. Showering should be done only after the exit-site sinus tract has become established. A recent quality assurance study suggested that in selected patients, showering in combination with a no-dressing technique for tunneled central venous catheters did not increase infection risk (Lawrence, 2014). Immersive swimming, as in a chlorinated pool, is generally discouraged for fear of infection.

E. Catheter locks

1. **Heparin.** After each dialysis session, the dead space of each lumen is filled with heparin (1,000 units/mL) through the catheter injection ports. A higher heparin lock concentration (5,000 vs 1,000 units/mL) was associated with lower need for tissue plasminogen activator use in one study (Maya, 2010). However, due to concerns about heparin leaking from the catheter into the systemic circulation and causing major bleeding complications, the higher concentration is rarely used. The dead space of each catheter lumen varies among manufacturers and length of catheter. The required volume of heparin is usually labeled on the catheter hub. It is important to record this information on the patient's chart, so it is readily available to the dialysis staff. Injection of a volume of heparin solution larger than necessary should be avoided, as it results in some degree of systemic anticoagulation that may be hazardous to patients at risk for bleeding. Prior to each dialysis, the heparin in each lumen is aspirated, the catheter flushed with heparinized saline (100 units/mL), and hemodialysis initiated.
2. **Citrate 4%.** Citrate can be used as an anticoagulant because it chelates calcium, which is essential for clotting to occur. A meta-analysis performed in 2014 concluded that citrate-based lock solutions containing antibiotics or antiseptics were better than their heparin-containing counterparts in reducing the rate of central line–associated bloodstream infections. Citrate alone was more effective than heparin, but primarily when a high concentration (30%) was used. At lower concentrations of citrate there seemed to be no advantage over heparin (Zhao, 2014). Citrate has been shown to leak out of catheter locks into the circulation fairly rapidly, quickly lowering its concentration to levels below those known to inhibit bacterial growth (Schilcher, 2014). In the United States, in the year 2000, use of very high concentrations of citrate in a dialysis catheter was associated with cardiac arrhythmia and death in one patient, presumably due to inadvertent injection of concentrated citrate into the left atrium, acutely lowering the ionized calcium level (Polaschegg and Sodemann, 2003). It is prudent to use the lowest concentration (4% citrate), recognizing that efficacy of citrate at this concentration alone may be no better than that of heparin. Citrate use at any concentration is problematic in countries (such as the United States) where it is not conveniently available in small volumes to be used for a locking solution.
3. **Other locks.** Other lock solutions have contained heparin, citrate, ethanol, or EDTA plus one or more antibiotics or antiseptics. At present, the use of prophylactic antibiotic-containing catheter locks has not been adopted at most dialysis centers, due to concerns about added cost, practical issues relating to compounding, and fear of promoting growth of resistant organisms. A locking solution containing vancomycin and gentamicin was found to increase the prevalence of *Staphylococcus* and antibiotic-resistant *Enterobacter*, for example (Dixon, 2012). Similarly,

prophylactic gentamicin locks increased the prevalence of gentamicin-resistant infections. At present, neither the CDC nor the US National Kidney Foundation recommend the routine use of lock solutions containing antibiotics (Camins, 2013), while the European Best Practices Group is somewhat equivocal (Vanholder, 2010). The 2019 KDOQI guidelines suggest that selective use of specific prophylactic antibiotic locks can be considered in patients in need of long-term central venous catheters who are at high risk of catheter-related bloodstream infections (eg, multiple prior episodes), especially in facilities with high rates of this complication (eg, >3.5/1,000 days).

Lock solution for prevention of infections in catheters is an active area of research. One goal is not only to sterilize the inside of the catheter but also to prevent the formation of biofilm. Locking solutions containing ethanol, citrate, or EDTA have a theoretical advantage of having some activity in affecting biofilm development. A solution containing glyceryl trinitrate, citrate, and ethanol has been reported to have some effects against not only common bacteria found in catheters but also biofilm (Rosenblatt, 2013). Other locking solutions have been developed and are in various stages of testing. A mixture of citrate, methylene blue, methylparaben, and propylparaben (C-MB-P) was reported to reduce the rate of central line–associated bloodstream infections by a substantial amount (Maki, 2011). There is some enthusiasm about locks containing a combination of taurolidine and citrate, although these are not commercially available in the United States. It is possible that the use of taurolidine, which tends to function as a disinfectant and which inhibits the formation of biofilm, may not be associated with emergence of resistant bacteria (Liu, 2014). A large randomized trial (LOCK IT-100) comparing heparin with heparin plus taurolidine locking solutions showed a substantially reduced rate of catheter-related bloodstream infections in the taurolidine plus heparin arm (Agarwal, 2023).

4. **Novel connection devices and catheter caps.** Use of certain needlefree catheter connection devices (Tego, ICU Medical, San Clemente, CA) and caps impregnated with chlorhexidine (ClearGuard, ICU Medical) have been shown to decrease the catheter-associated infection rate (Brunellli, 2014, 2018).

F. Prophylactic antibiotics. Systemic antibiotics are not given routinely prior to cuffed catheter insertion.

1. **Exit-site ointment.** Mupirocin ointment treatment of the catheter exit site to lower *Staphylococcus* colonization has been shown to reduce the catheter infection rate and to increase the catheter survival rate (McCann and Moore, 2010; O'Grady, 2011), but is not widely used for fear of long-term emergence of mupirocin-resistant organisms. One randomized controlled trial reported that polysporin exit site ointment reduced the risk of catheter-related bloodstream infections. The U.S. Centers for Disease Control recommends using exit-site ointments (Table 7.3), but is very concerned about the emergence of resistant organisms. The European Renal Best Practices group, in a 2010 commentary, recommends use of exit-site antibiotic ointment only until the insertion site has healed (Vanholder, 2010). As an intermediate strategy, use of exit-site ointments can be limited to those patients who evidence repeated episodes of infection. Prior to use of any ointment, one should check to make sure that the vehicle used to dissolve the ointment does not adversely

react with the plastics in the catheter material.

2. **Nasal decolonization.** In patients harboring *Staphylococcus* in the nose, nasal decolonization has been shown to reduce the rate of central line-associated bloodstream infections (Abad, 2013), but the specter of mupirocin resistance remains (Teo, 2011). This remains a more attractive treatment option in selected patients than for the unit as a whole, but nasal decolonization (of multidrug-resistant *S. aureus*, for example) has been applied to entire dialysis units with encouraging short-term results (Kang, 2012).

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8 Arteriovenous Vascular Access Monitoring and Complications

Tushar Vachharajani, Loay Salman, and Arif Asif

Once the arteriovenous (AV) access has been in use, the most important factors that limit its survival are stenosis, thrombosis, and infection. In general, complications occur more commonly in AV grafts than in AV fistulas.

I. **STENOSIS.** Vascular access stenosis is a harbinger of thrombosis, reduces access blood flow, and can lead to underdialysis. The most common cause of stenosis in AV grafts is neointimal hyperplasia, which usually occurs at or just distal to the graft-vein anastomosis. In AV fistulas, the location and cause of stenosis are more varied, with the juxta-anastomotic region being a frequent site in almost two-third of the cases. The common sites of stenosis in AV fistulas and grafts are shown in Figures 8.1 and 8.2. Because access patency is much worse after thrombectomy than after elective angioplasty, current Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend prospective monitoring and surveillance of AV fistulas and grafts for hemodynamically significant stenosis. KDOQI guidelines recommend routine monitoring with physical examination. However, the overall clinical benefit of routine surveillance for prolonging access patency remains controversial (Kumbar, 2012; Paulson, 2012). Randomized controlled trials have not consistently shown that surveillance improves outcomes in grafts; in fistulas, surveillance has been shown to reduce the rate of thrombosis, but may not prolong overall patency.

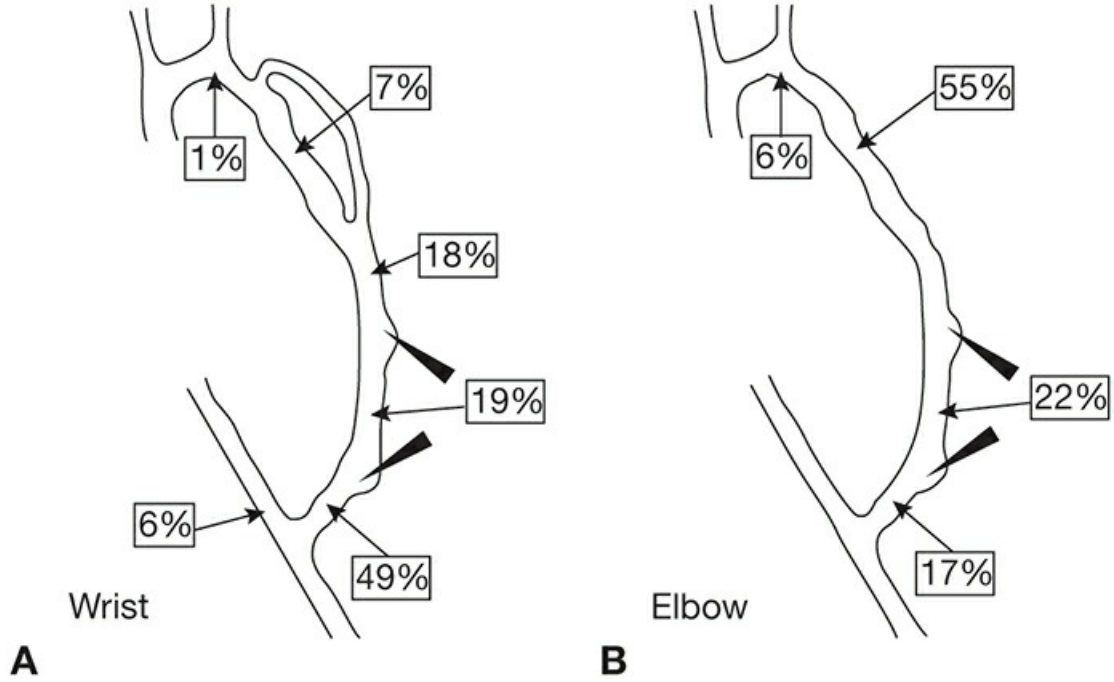


FIGURE 8.1: Common sites of stenosis in AV fistulas. Locations are shown in fistulas created at wrist (A) and fistulas created at elbow (B). AV, arteriovenous. (From Turmel-Rodrigues L, et al. Treatment of stenosis and thrombosis in haemodialysis fistulas and grafts by interventional radiology. *Nephrol Dial Transplant*. 2000;15:2032-2036, with permission.)

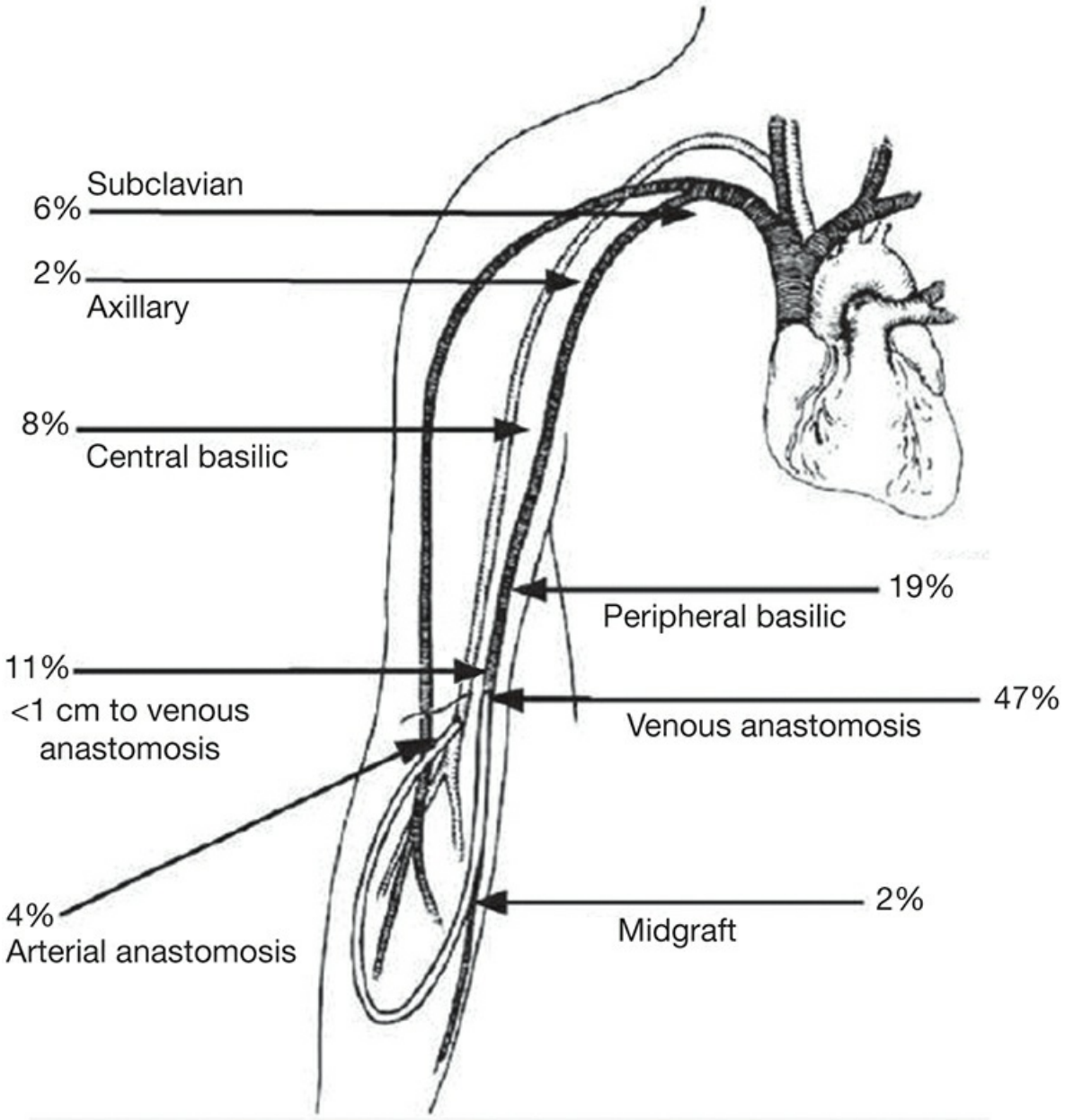


FIGURE 8.2: Common sites of stenosis in AV grafts. AV, arteriovenous. (Reproduced from Roy-Chaudhury P, et al. Vascular access in hemodialysis: issues, management, and emerging concepts. *Cardiol Clin*. 2005;23:249-273, with permission from Elsevier.)

There are several strategies to detect stenosis prior to definitive visualization of the access tract by Doppler ultrasound and, in the case of central vein stenosis, by venography. These early detection strategies depend on indirectly observing access pressure, flow, or recirculation during dialysis. The optimum early detection strategy differs somewhat for fistulas versus grafts and for forearm versus upper-arm locations. The basic principles are (a) recirculation of dialyzed blood across the access device immediately back through the dialysis circuit does not appear until access flow decreases to a level near to or less than flow in the extracorporeal circuit. Thus, barring inadvertent needle reversal or improper needle placement, access recirculation will not be present until access flow falls to the range

of 350 to 500 mL/min. At this range of flow, AV grafts are already at high risk for thrombosis, so if true recirculation is detected in an AV graft, it is an urgent indication to image the graft and correct the stenosis. On the other hand, in AV fistulas, continued patency is likely even when recirculation is present (flow in the 350-500 mL/min range). The benefits of screening AV fistulas for access recirculation are relatively small in terms of preventing thrombosis, but screening for recirculation is useful to prevent underdialysis. Access stenosis that occurs between the usual sites of needle insertion will not cause recirculation, but may markedly reduce access flow to thrombosis-prone levels. Stenosis in this location should be suspected when access flows are measured to be below the blood pump flow rate, but recirculation is not detectable. (b) Both grafts and fistulas commonly develop inflow stenosis, so strategies that detect inflow stenosis will be useful for both types of AV access. (c) Outflow stenosis occurs much more frequently in grafts than in forearm fistulas where the degree of neointimal hyperplasia is less and where accessory outflow veins often compensate for obstruction of a principal outflow channel. However, in upper-arm fistulas, outflow stenosis is not uncommon. Hence, strategies that detect outflow stenosis will be more useful in monitoring the function of AV grafts and of upper-arm fistulas.

A. Physical examination of an AV access was discussed in detail in Chapter 6. Table 8.1 shows the changes in physical findings with some common access complications. Physical examination is useful in detecting isolated inflow or outflow access stenosis, but is less effective in detecting combined inflow and outflow lesions. The accuracy of physical examination is substantially higher if the persons doing the examination have received special training (Coentrão, 2012). Physical examination techniques are available on a YouTube video released by Wake Forest University (Vachharajani, 2011).

TABLE 8.1 Physical Findings With Various Forms of Access Dysfunction

Parameter	Normal	Inflow Stenosis	Outflow Stenosis	Coexisting Inflow and Outflow Stenosis	Central Stenosis	Clotted Access
Pulse	Soft, easily compressible	Feeble pulse (hypopulsation)	Hyperpulsation (water-hammer pulse, angry pulse)	Soft, easily compressible pulse	Variable	Absent pulse
Thrill	Continuous	Discontinuous (In severe inflow stenosis, the thrill can be absent.)	Higher pitched, louder, then discontinuous (In severe outflow stenosis, the thrill can be absent.)	Discontinuous (usually absent)	Variable	Absent thrill
Augmentation test	Normal	Poor augmentation	Good augmentation	Poor augmentation	Good augmentation	
Arm elevation test (fistula only)	Normal collapse	Normal or accentuated collapse	No collapse	No collapse	No collapse	
Clinical features	No prolonged bleeding or difficulty in cannulation	Difficulty in cannulation and an increase in negative arterial pressure	Prolonged bleeding and high venous pressure		Edema of the arm and shoulder; breast, supraclavicular, neck and face swelling	Sometimes clots aspiration from the access
Access flow	Normal	Decreased	Decreased	Decreased	Variable	Absent

B. Access surveillance using information obtained routinely during every

dialysis session. Many dialysis machines have the option of measuring online ionic dialysance. In all dialysis machines, the outflow venous pressure is monitored. Trending the results of these measurements over time can help detect access stenosis.

1. **Trending ionic dialysance.** The ionic dialysance measured via conductivity includes any access recirculation component if present; as the degree of access recirculation increases, the online ionic dialysance will decrease, assuming that other features of the dialysis prescription (dialyzer K_0A, blood and dialysate flow rates, heparinization) are kept constant. Dialysis machines that measure ionic dialysance typically integrate the clearances measured during each treatment (K) to calculate a treatment Kt value (clearance × time) for that session. In one case series of six patients with AV fistulas, a sustained fall in Kt of 20% was associated with access recirculation (Fontseré, 2011). Another approach is to follow the ratio of ionic dialysance to blood flow. In one report, a ratio of less than or equal to 0.5 had high sensitivity and specificity for access recirculation (Mohan, 2010).
2. **Trending venous outflow pressures.** Venous pressures are measured continuously during routine hemodialysis. Venous pressures are a function of needle size, hematocrit (by its effect on blood viscosity), and blood flow rate. All other things being equal, a progressive rise in venous pressure over time (weeks to months) is often due to access outflow stenosis (Zasuwa, 2010). Some large dialysis organization data systems are able to remotely track such pressures and trend them over time (Vasc-Alert). One can also trend prepump arterial pressure, which will increase (in a negative direction) with worsening access inflow stenosis.

   The sensitivity of pressure measurements during dialysis to detect access stenosis can be increased by focusing on measurements taken at the beginning of dialysis with the blood flow rate set at a low value (200-225 mL/min), because at high blood flow rates, much of the resistance to flow is from the needle and not the vascular access. A baseline pressure value should be established when the access is first used. The threshold pressure that triggers further evaluation depends on the size of the needle, blood viscosity, and other factors; for 15G needles, a starting venous pressure threshold to use might be greater than 115 to 120 mm Hg; for 16G needles, the threshold might be more than 150 mm Hg. Such threshold pressures must be exceeded on three or more treatments in succession to be significant.

C. Periodic measurements of access blood flow rate. To what extent a low access flow rate reflects stenosis and an increased risk of thrombosis depends on the type of access. Flow through a forearm AV fistula commonly averages 500 to 800 mL/min, and in grafts, flow is somewhat higher, about 1,000 mL/min. Flow in upper-arm fistulas or grafts may be considerably higher. AV fistulas may maintain patency at flows as low as 200 mL/min, whereas AV grafts begin to clot at access flows between 600 and 800 mL/min—flows that often provide adequate dialysis but offer few clinical premonitory signs that the access is at risk for thrombosis. The current KDOQI (2019) recommendations are to have the patient referred for access visualization if the access flow is less than 500 to 600 mL/min or if the access flow is less than 1,000 mL/min and has decreased by more than 25% over the preceding 4 months. Although regular surveillance of vascular access for stenosis has been shown to decrease thrombosis rates when compared with historical controls, recent prospective studies have not shown conclusively that the detection of stenosis and correction with angioplasty improves

graft survival.

1. **Direct measurement of access flow by saline dilution.** This method for measuring access blood flow during hemodialysis treatments was pioneered by Krivitski (1995). The required equipment is made by Transonic Systems, Inc. and consists of a monitoring device and two matched flow/dilution sensors (Figure 8.3). The setup shown in Figure 8.3 is for the measurement of access recirculation; hence, the needles are not reversed. To measure access blood flow, one must deliberately cause access recirculation in the extracorporeal blood circuit by reversing the arterial and venous lines so that the dialyzer is fed from the downstream access needle (Figure 8.4). The degree of recirculation in such a system will depend on the ratio of the access blood flow rate to the rate of blood flow through the dialyzer. If the percentage recirculation and blood flow rate through the dialyzer are known, the access blood flow rate can then be calculated.

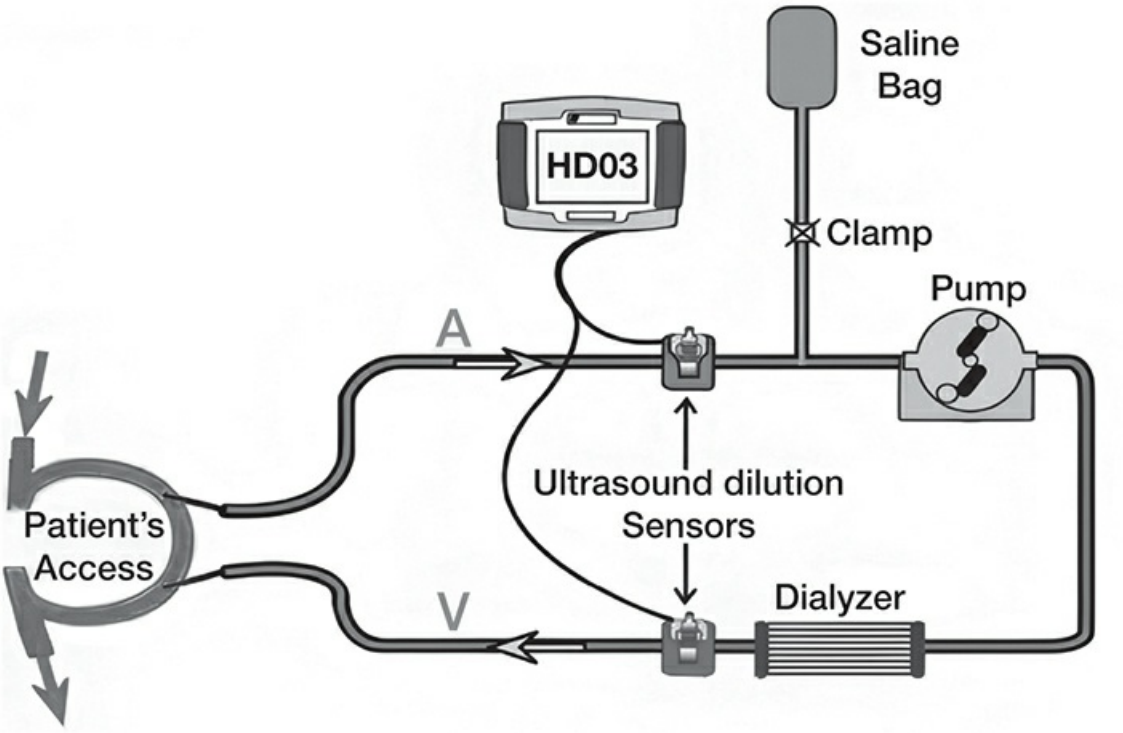


FIGURE 8.3: Setup to measure access recirculation by saline dilution and ultrasound detection. To measure access blood flow, the access needles need to be reversed (not shown). See text for description of the setup and method. (Image property of Transonic System Inc. Used with permission.)

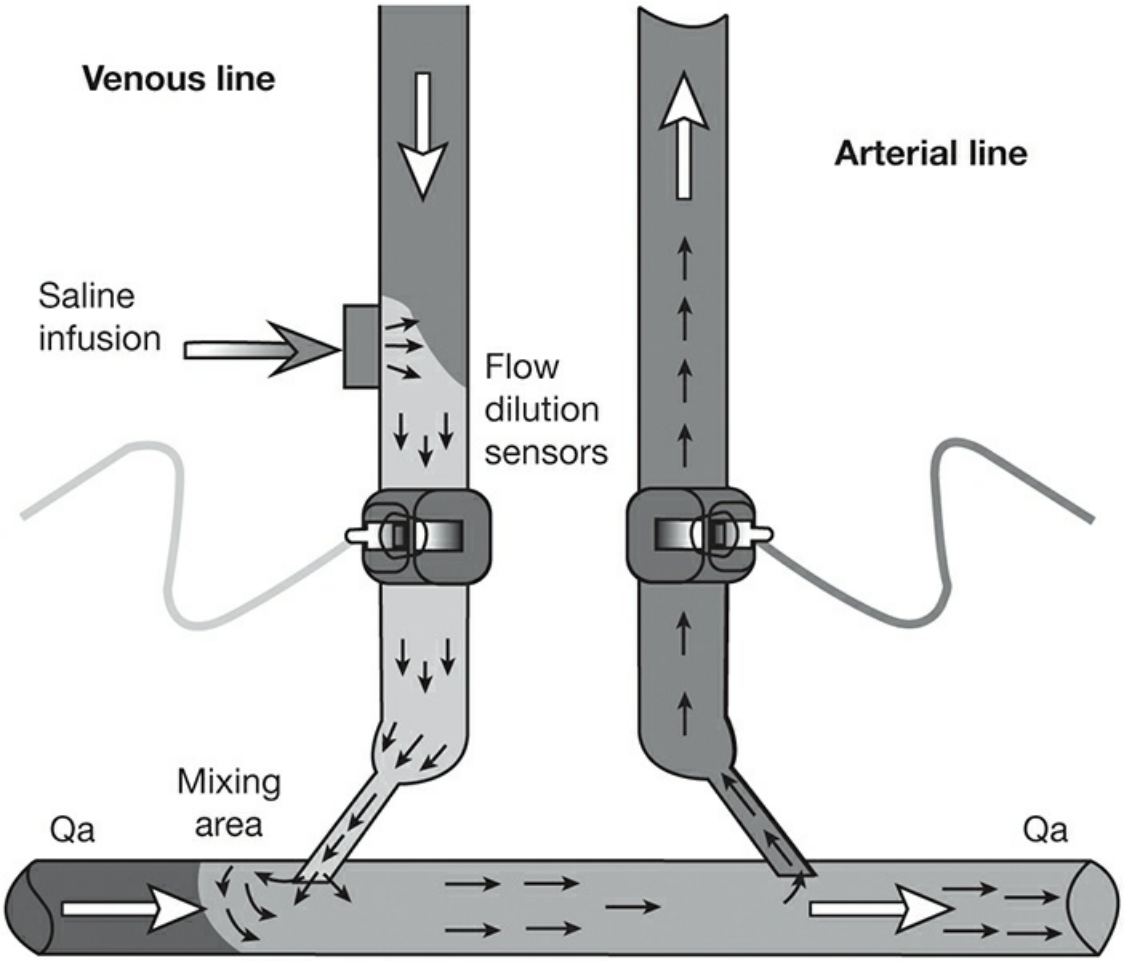


FIGURE 8.4: Measurement of access flow by saline dilution showing blood line reversal and position of blood line sensors. See text for details of the method. (Image property of Transonic System Inc. Used with permission.)

To measure the amount (percentage) of recirculation under needle-reversed conditions, a bolus of saline is injected into the blood leaving the dialyzer (Figure 8.4). The amount of dilution in the outlet blood line is measured by a downstream ultrasound sensor. The speed of sound through blood depends on the concentration of proteins in the plasma; accordingly, the dilution effect of the saline bolus in the outlet blood line can be quantified using this first sensor. Some of this saline-diluted blood will then traverse the vascular access segment between the two needles and reappear at the dialyzer inlet. The proportion of the saline-diluted blood that reappears at the dialyzer inlet depends on the ratio of access blood flow to the blood flow through the dialyzer. A second ultrasound sensor on the blood line leading to the dialyzer is then used to detect the proportion of saline-diluted blood that reappears at the dialyzer inlet (Figure 8.4). In practice, an additional measurement of recirculation is made with the blood lines not reversed, as the presence of any recirculation under nonreversed conditions will affect the calculations.

2. **Alternative measures of access flow using temperature, sodium, or hemoglobin changes.** The Fresenius Blood Temperature Module has the ability to acutely change the temperature of the blood leaving the dialyzer, and the ionic

conductivity module has the ability to acutely change the sodium concentration of blood leaving the dialyzer. This is done by abruptly altering the dialysis solution temperature or conductivity, respectively. This permits measurement of access blood flow rate in a similar method to saline dilution. The lines are reversed, the dialyzer blood outlet temperature or conductivity is altered, and the amount of this perturbation that gets transmitted to the dialyzer inlet via forced recirculation is calculated. The intervention is repeated without reversing the blood lines as a control. Hemoglobin dilution using an online hemoglobin monitor has been used to measure access blood flow in an analogous fashion (Jiang, 2011; Roca-Tey, 2012). Evidence suggests that these alternative methods are fairly accurate in measuring access blood flow, with the temperature method perhaps performing at a higher level (Badr, 2014). The advantage of using temperature or ionic dialysance is that the need for a separate ultrasound dilution sensor and monitoring device is no longer required.

D. Doppler ultrasonography to measure access flow. Doppler ultrasonography, though usually used to detect stenotic lesions directly, can also be used to measure the rate of flow through a vascular access. A variety of machines and several different flow velocity algorithms have been used. There is systematic underestimation or overestimation of flow by some machines. Flow measurement by Doppler depends on an accurate measurement of both velocity and vessel diameter. This may be difficult when the flow is turbulent in an access and when the vessel diameter is not uniform. Because of these confounders, flow is better measured at the brachial artery, where the vessel is a smooth cylinder of blood and flow is nonturbulent. Almost all of the flow in the brachial artery (apart from about 60-80 mL/min nutrient flow) passes through the vascular access, and brachial artery flow correlates very well with the access flow rate.

E. Intra-access pressure (P_{IA}) and access flow. Flow, pressure, and resistance are mathematically related. In an AV graft, the P_{IA} is usually less than 50% of MAP (mean arterial pressure). Most of this pressure drop occurs at the arterial anastomosis unless there is intragraft stenosis. When outflow stenosis develops (eg, due to neointimal hyperplasia at or downstream from the graft-vein anastomosis), P_{IA} rises and flow decreases. When P_{IA} rises above 50% of the MAP (P_{IA}/MAP > 0.50), graft flow commonly decreases into the thrombosis-prone range of 600 to 800 mL/min, and the presence of stenosis is likely. Details of how to compute this ratio based on an equivalent P_{IA} (EQP_{IA} = P_{IA} adjusted for the relative heights of the access measuring point and pressure transducer) are given in Table 8.2. In AV fistulas, blood entering the venous system returns via multiple collateral veins. As a consequence, P_{IA} in an AV fistula, which is on average lower than in an AV graft, may not increase with outlet stenosis and is therefore less reliable as a surveillance tool.

TABLE 8.2 Measuring the EQP_{IA}/MAP Ratio

Example:

1. Measure MAP: Assume that BP is 190/100. MAP is diastolic plus one-third of pulse pressure or 130 mm Hg.
2. Measure static intra-access pressure:
   a. With the blood pump off and the blood line upstream to the venous drip chamber clamped, the venous drip chamber pressure is 60 mm Hg.

b. Compute offset using equation: offset (mm Hg) = −1.6 + 0.74 × *H* (cm), where *H* is the height between the access and middle of the drip chamber. Assume *H* is 35 cm. Then offset = −1.6 + 25.9 = 24.3 mm Hg.

c. Add offset to compute EQP_{IA}: EQP_{IA} = 60 + 24.3 = 84.3 mm Hg.

d. Compute the EQP_{IA}/MAP ratio. In this case, 84/130 = 0.65, which is >0.5. This access is at risk for stenosis.

BP, blood pressure; EQP_{IA}, equivalent intra-access pressure; MAP, mean arterial pressure. Source: Besarab A, et al. Simplified measurement of intra-access pressure. *J Am Soc Nephrol*. 1998;9:284-289.

If a stenosis develops in the body of an AV graft between the areas used for arterial and venous limb cannulation, P_{IA} at the venous needle remains normal or can even decrease, despite increasing stenosis. Stenosis at the arterial anastomosis of both grafts and fistulas causes P_{IA} to decrease, and a widely patent arterial anastomosis causes high basal P_{IA} in the absence of stenosis.

F. Access recirculation. Both urea-based and non-urea-based (eg, ultrasound dilution) techniques have been used to detect recirculation. The urea-based methods depend on a comparison of inlet bloodline urea concentrations at full blood flow with those after a 15-second slow-flow period or after putting the dialysate flow into bypass. The ultrasound dilution technique described earlier can be used to measure recirculation. In this case, the blood lines are not reversed. If dialyzer outlet blood is recirculating through the access and diluting the dialyzer inlet, the bolus of saline injected into the outlet blood line will be detected by the sensor located on the inlet blood line soon after injection. Measurement of access recirculation by thermal dilution using a blood temperature module yields results similar to those obtained by the ultrasound dilution technique. Recirculation exceeding 10% should prompt investigation.

II. IMAGING THE VASCULAR ACCESS

A. Doppler ultrasonography. This noninvasive technique allows direct imaging of the flow pattern in AV grafts and fistulas. It has been useful for detecting stenoses and for evaluating aneurysms. Doppler flow measurements are prohibitively expensive for routine assessment. Their chief role is in the evaluation of flow and anatomy in accesses that have been screened by other techniques.

B. Access angiography. Most centers refer patients with a high probability of stenosis as determined by low-cost methods directly for angiography and balloon angioplasty, bypassing Doppler altogether. One should use the lowest possible dose of nonosmotic contrast agent, diluted, if possible. Angiography can be used for limited evaluation of the arterial tree as well.

C. Magnetic resonance angiography (MRA). The 2007 European Best Practice guidelines recommend the use of MRA to image the vascular access when there is the need to see both the venous and the arterial parts of the upper extremity circulation. A meta-analysis of studies comparing computed tomographic with magnetic resonance angiography found no major differences (Li, 2013). The incidence of nephrogenic systemic fibrosis with gadolinium is reduced with the newer contrast agents (Coca and Perazella, 2011), and per a recent Consensus Statement from the National Kidney Foundation and the American College of Radiology (2020), no confounded cases of nephrogenic systemic fibrosis have been reported for group III gadolinium-based contrast media (gadoxetate disodium) (Weinreb, 2020).

III. PERCUTANEOUS INTERVENTION AFTER ACCESS STENOSIS HAS BEEN IDENTIFIED.

Once a stenosis greater than 50% is detected, percutaneous transluminal catheter angioplasty or surgical revision of the lesion should be performed if one or more of the following are present: (a) abnormal physical examination, (b) previous history of thrombosis, (c) decreasing access flow, or (d) elevated or increasing measured static intra-access pressures (normalized to MAP). The expertise at each institution should determine which procedure is to be performed. If repeated angioplasties have been required within a short period for the same lesion, surgical revision should be considered.

In most institutions, vascular access–related procedures are performed by surgeons and interventionalists. Numerous centers in the United States now offer the nephrologist formal training in the techniques of percutaneous angioplasty and thrombectomy. Because nephrologists have a different clinical perspective of patients and their access-related problems, their direct involvement in interventional procedures may help minimize delays, decrease hospitalizations and costs, and increase overall patient satisfaction.

A. Treatment of early AV fistula dysfunction.

A significant number (20%-40%) of AV fistulas do not adequately develop and fail to sustain dialysis therapy. Vascular stenosis or the presence of a significant accessory vein (a side branch coming off the main venous channel that comprises the fistula) alone or in combination are the main culprits. Stenosis is present in over 70% of the cases of fistula nonmaturation. In most cases, the stenosis will be found close to the anastomosis (a juxta-anastomotic lesion). Percutaneous balloon angioplasty can successfully treat this lesion and salvage a great majority of otherwise failed fistulas. In cases of nonmaturation due to the presence of accessory veins, an obliteration procedure using one of three techniques (percutaneous ligation, venous cutdown, or coil insertion) can be used to salvage the failing fistula. The indications and benefits of using a drug-eluting balloon for angioplasty remain uncerain.

B. Flow measurements immediately after access revision.

Sometimes radiographic correction of an apparent stenosis does not result in improvement in the access blood flow rate. At other times, access blood flow initially increases, but then falls back to pretreatment levels within a day or two of the procedure. Measurement of access flow immediately after a revision or angioplasty is helpful in terms of determining the likelihood that the access will remain open for a clinically useful period.

C. Endovascular stents and vascular stenosis.

Endovascular stents have emerged as an important strategy to treat vascular access stenosis. Interventionalists use stents primarily to treat stenoses associated with AV grafts located at or just distal to the graft-vein anastomosis. Stents are also used in the management of pseudoaneurysms (see below). A stent graft is a metal stent with polytetrafluoroethylene (PTFE) covering its internal surface, external surface, or both. A large multicenter, randomized, controlled trial (Haskal, 2010) found better patency rates for stent graft versus simple angioplasty for the treatment of stenosis at the graft-vein anastomosis, a result confirmed by a subsequent meta-analysis (Hu, 2018).

It is not uncommon for dialysis access to be affected by several coexisting stenoses. The benefits of fixing one primary target lesion might be less important in the presence of such coexisting stenoses that might require the placement of additional stent grafts. The cost increment when using an endovascular stent must be balanced against the cost of an angioplasty alone or the alternative of primary surgical repair.

IV. THROMBOSIS.

Thrombosis is the most common complication of AV access and accounts for 80% to 85% of access loss. The primary patency rate of AV grafts is around 40% to 50% at 1 year and 25% at 2 years. Causes of thrombosis include stasis of flow, vascular endothelial injury, and altered blood coagulability, but other contributing factors include arterial stenosis, fistula compression, hematoma formation from cannulation injury, hypovolemia, hypotension, and hypercoagulable states. On physical examination, there is absence of thrill or bruit (Table 8.1). Both endovascular techniques (mechanical and/or pharmacologic) and surgical techniques are effective in declotting the access. In case of recurrent thrombosis, it is important to investigate for causes of thrombosis other than stenosis.

A. Predisposing factors.

An increasingly recognized number of patients undergoing dialysis have subtle accentuations of hemostasis, including high fibrinogen levels, reduced levels of protein S or C, factor V Leiden mutation, lupus anticoagulant, or elevated hematocrit levels due to erythropoietin therapy. Whether or not these conditions are associated with increased access thrombosis is controversial. Use of warfarin is problematic, because in patients with protein S or C deficiency, or even in the absence of these, warfarin may precipitate calciphylaxis with skin necrosis. Warfarin use is difficult to monitor in patients with lupus anticoagulant, as the prothrombin time is an unreliable measure of anticoagulation.

B. Prevention.

Anticoagulants and antiplatelet drugs may help prevent AV access thrombosis, but most studies published thus far do not support their routine use. Separate randomized clinical trials of both low-dose warfarin (with a target international normalized ratio of 1.4-1.9) and clopidogrel plus aspirin versus placebo in patients with PTFE grafts failed to demonstrate a reduction in thrombotic events or prolongation of graft survival. Both studies showed clinically and statistically significant bleeding complications in the treated patients. However, another randomized trial found a decrease in the relative risk of thrombosis in patients with new PTFE grafts treated with dipyridamole. A meta-analysis studying the usefulness of antiplatelet therapy to prevent vascular access failure that analyzed 21 eligible trials concluded that antiplatelet agents were useful to protect fistulas from thrombosis or loss of patency, but had little or no effect on the patency of AV grafts (Palmer, 2013).

C. Treatment

1. **In AV fistulas.** Thrombosis of the fistula occurs either soon after its construction or as a late event. Patients should be taught to monitor their fistula daily, when possible. Early thrombosis results from technical factors and almost always requires surgical or percutaneous intervention, although there may have been inadvertent compression while sleeping. Poor flow precedes late thrombosis in most cases, but hypotension or hypercoagulability may also precipitate thrombosis in the absence of downward flow trends. Treatment of thrombosis can be difficult but should be performed using either percutaneous methods or surgical thrombectomy, depending on the expertise of each institution. Techniques aiming to remove the bulk of the thrombus have been reported to have a higher success rate (Palmer, 2006).
2. **In AV grafts.** Thrombosis can be managed by surgical thrombectomy or by mechanical or pharmacomechanical thrombolysis, again depending on the expertise of the medical center. Treatment should be performed urgently to avoid the need for temporary access. The entire access circuit should be thoroughly evaluated during

the procedure by imaging. Residual stenosis exceeding 50% should be retreated by balloon angioplasty or surgical revision. The role of antiplatelet drugs or warfarin in patients with recurrent thrombosis is unknown. Patients who clot with intra-access flows greater than 1,000 mL/min should be educated to avoid external access compression, evaluated for hypercoagulability, and/or examined for the presence of delayed hypotension after dialysis. Routine monitoring and surveillance of the graft should resume shortly after successful treatment. For patients with failed thrombectomy and thrombolysis, surgical efforts should be focused on creating a secondary fistula from the venous drainage of the graft. Such fistulas are possible because of the venous enlargement and thickening caused by the previous graft and have the advantage of being usable much sooner after the creation of the fistula. KDOQI guidelines recommend that every patient should be evaluated for a secondary fistula after each episode of graft failure.

V. ISCHEMIA IN A LIMB BEARING AN AV ACCESS.

Dialysis access–associated hand ischemia, commonly known as "steal syndrome," complicates 1% to 20% of accesses and can lead to pain, loss of function, and, rarely, the loss of limb. One mechanism of hand ischemia is thought to be "arterial steal" from retrograde flow in the distal artery toward the access, but the presence of arterial stenosis or distal arteriopathy involving small vessels often is contributory. Risk factors include upper-arm access, peripheral arterial disease, and diabetes.

A. Detection.

Patients with an established fistula should be assessed monthly by interval history and physical examination. Clinically, there is pain, coldness, and paresthesias of the distal extremity, especially during dialysis, which can progress to cyanosis, pulselessness, ischemic ulcers, and dry gangrene over days to weeks to months. The onset can be immediately after access creation or insidiously over days to weeks. Examination requires comparison with the temperature, pulse, and function of the opposite hand.

Digital pressures, transcutaneous oxygen measurements, and arteriography (with access open and closed) are helpful in evaluation, but are not necessarily specific. The diagnosis is based on the clinical symptoms and signs as well as on the demonstration of poor circulation in the extremities. Differential diagnosis involves carpal tunnel syndrome, peripheral vascular disease, neuropathy, nerve trauma, or ischemic monomelic neuropathy due to the loss of blood supply to nerves.

B. Management.

Mild ischemia manifested by coldness or paresthesias but without sensory or motor loss can be managed expectantly. Pain of the hand on exercise due to a "steal" effect (or in extreme instances, pain at rest) or the appearance of nonhealing ulcers usually requires surgical intervention. Loss of motor function of the hand is a surgical emergency, and surgical evaluation for banding or ligation of the access should be done immediately.

1. **Distal revascularization interval ligation (DRIL) procedure.** With the usual radiocephalic side-to-side fistula, the radial artery anastomosis regularly steals blood flow from the ulnar artery system. Converting the side-of-artery to an end-of-artery anastomosis can sometimes be used to treat ischemia due to steal. Severe cases of steal syndrome require ligation of the AV fistula, but DRIL can be used to treat ischemia while preserving fistula patency. The DRIL technique requires ligation of

the artery immediately distal to the origin of the AV fistula and construction of a reversed saphenous vein bypass from the artery proximal to the origin of the fistula to the artery distal to the site of ligation. One report suggests that the success of the DRIL procedure is higher if the origin of the bypass graft is well upstream to the site of the fistula anastomosis to avoid a region of low pressure in the artery upstream to the fistula anastomotic site (Kopriva, 2014).

2. **Banding.** Steal due to high access flow can be treated by banding and can be achieved either using a minimally invasive procedure (Miller, 2010) or surgically.
3. **Other procedures.** Treatment of hand edema after placement of an AV fistula consists of converting the anastomosis from a side-of-vein to an end-of-vein opening or by selectively tying off affected veins. A small increase in circumference (2-3 cm) of the arm bearing the access is common after placement of an AV access, but larger increases indicate venous hypertension, usually due to stenosis of the central veins.

VI. PSEUDOANEURYSM.

Trauma to an AV access from repeated cannulation in the same area can cause damage to all layers of native vein or graft material. Large aneurysms can prevent adequate needle placement and limit potential puncture sites. These dilatations can further expand, especially if there is a downstream stenosis causing increased intra-access pressure. Aneurysms and pseudoaneurysms are prone to getting infected or can contribute to thrombosis. A major concern is rupture, that can lead to exsanguination and fatal hemorrhage. The signs of impending rupture include thin and shiny overlying skin, prolonged leaking or ulceration over the surface, and rapid enlargement of the aneurysm. Early intervention is essential to prevent such complications.

A. AV fistula.

Pseudoaneurysm is much more common than a true aneurysm. It results from failure to properly rotate access puncture sites, from inadequate hemostasis, and from extravasation of blood following dialysis needle removal. Most stable pseudoaneurysms and true aneurysms are treated by observation and by avoiding puncture of the fistula in the area of the aneurysm site. Rapid enlargement or skin changes are common indications to consider surgical revision.

B. AV graft.

In AV grafts, there is no true expansion of the vessel lumen; the wall of the "aneurysm," really a pseudoaneurysm, is formed by a layer of external soft tissue. These should be treated by resection and insertion of an interposition graft if they are rapidly expanding, greater than 12 mm in diameter, and/or threatening the viability of the overlying skin. The AV graft should be surgically revised if pseudoaneurysm formation limits the number of puncture sites available or is causing persistent symptoms such as pain or throbbing.

C. Use of stents.

Stents have been used for the percutaneous treatment of pseudoaneurysms (Fotiadis, 2014). Although these devices result in the immediate exclusion of pseudoaneurysm, recurrence of the pseudoaneurysm and stent-graft damage as a result of repeated cannulation remain major problems. Broken stent struts can sometimes protrude through the skin, posing a threat of injury to staff who place the patient on dialysis. Exclusion of a pseudoaneurysm using a stent graft represents an "off-label" use of the device. The risk of stent-graft infection is another consideration. Safety of cannulation through stent grafts used to treat pseudoaneurysms has not been conclusively established in a prospective manner. Similarly, the role of surgical

intervention in the treatment of pseudoaneurysms has not been directly compared with results using stent grafts. Stent grafts do provide rescue therapy in the event of angioplasty-induced vascular rupture. Complete rupture is one situation in which a stent graft is clearly indicated, as this stabilizes the access and avoids the need for an emergency surgical procedure.

VII. INFECTIONS. Infection of the access is usually manifested as erythema, pain, or purulent exudate from needle sites. Often, the first sign is fever with no other obvious source and positive blood cultures. The access should not be used if actively infected. Cultures (of blood and of any wound if present) should be taken and antibiotic therapy initiated. The possibility of endocarditis or other sources of infection should be investigated, depending on the pathogen found, especially if cultures fail to turn negative after antibiotic treatment. Ultrasound evaluation of the tissues around the access is sometimes useful in revealing localized fluid accumulation. An infected access usually requires surgical intervention for debridement or excision.

A. AV fistula. Infections are rare and usually caused by staphylococci; they should be treated in the same manner as subacute endocarditis with 6 weeks of antibiotics. Diagnosis is based on local signs of inflammation. Prompt therapy with antistaphylococcal antimicrobials after local and blood cultures have been obtained is often curative. Septic embolus during therapy warrants removal of the fistula.

B. AV graft. Graft infection occurs eventually in 5% to 20% of grafts placed, and thigh grafts have an even higher rate of infection. Prophylactic antimicrobials should be used when patients with vascular grafts undergo procedures capable of inducing bacteremia, such as dental extraction or genitourinary manipulation. Most graft infections are staphylococcal. Gram-negative organisms such as *Escherichia coli* may be cultured, especially from thigh grafts (Harish and Allon, 2011). Initial antibiotic treatment should include drugs active against gram-negative and gram-positive organisms as well as against *Enterococcus.* Local infection of a graft can be treated with antibiotics (based on culture results) and by incision/resection of the infected portion. Extensive infection requires complete excision/removal.

Septicemia may occur without local signs. In such cases, a technetium-labeled leukocyte scan may help reveal a graft infection, but care must be taken to remove any blood-soaked dressings prior to scanning, as they may lead to a falsely positive result. Hemorrhage may occur due to rupture of an infected graft. A graft that becomes infected within 30 days of placement probably should be removed.

1. **Silent infection in a thrombosed AV graft.** Old thrombosed grafts may become infected with few local signs, suggesting that perhaps such grafts should be electively removed soon after they are abandoned. This can be a cause of elevated serum C-reactive protein levels and erythropoiesis-stimulating agent (ESA) resistance. However, because surgical removal often requires extensive tissue dissection, this problem needs further study before a blanket recommendation can be made.

VIII. CONGESTIVE HEART FAILURE. Congestive heart failure is unusual with a forearm access but may occur in patients with upper-arm or femoral fistulas, particularly if there is coexistent heart disease. Although long-term cardiac function is thought to be generally

unaffected by the presence of an AV access, closure of access has been associated with a reduction of left ventricular mass and improvement in left ventricular eccentric and concentric hypertrophy (Movilli, 2010). Increased pulmonary arterial flow (which can be associated with a high-flow access) can aggravate pulmonary hypertension.

Some AV accesses can continue to increase their blood flow. There is a greater risk of high-output heart failure when the flow exceeds 20% of the cardiac output. Upper-arm access and access flow greater than 2,000 mL/min increase such risk. In these cases, banding of access to reduce access flow (Miller, 2010) should be considered. Despite theoretical benefits, surgical narrowing or banding should be considered primarily when cardiac studies have shown marked changes in cardiac output following transient occlusion of the access. In patients with unexplained high cardiac output states, one should first consider and correct any anemia that may be present. Use of vasodilators such as minoxidil or hydralazine without concomitant β-blockade is another common, correctable cause of high cardiac output. Finally, volume overload is common in patients undergoing dialysis and must be considered in individuals presenting with signs and symptoms of heart failure.

IX. COMPLICATION OF PERCUTANEOUS INTERVENTIONS.

The most frequent procedure-related complication seen in association with angioplasty is vessel rupture, as evidenced by contrast extravasation and/or bleeding. This complication is relatively infrequent (2%) and can range from clinically insignificant to severe. Subclinical extravasation of contrast at the site of angioplasty is not usually a cause for much concern. In mild cases of vessel rupture, there may be hematoma, but the patient is asymptomatic. Larger hematomas may affect access flow, and very large hematomas can result from total or near-total rupture of the access vein. In such instances, insertion of an endovascular stent can be very helpful to stem the bleeding.

Another complication that is associated with percutaneous angioplasty is pulmonary embolism, especially during thrombectomy. Clinically significant pulmonary embolism is infrequent. Distal embolization of thrombus into an artery can occur during thrombectomy, and in such cases, the thrombus should be immediately removed using an embolectomy catheter.

X. CLINICAL OUTCOME GOALS AND MONITORING

A. Establishment of a vascular access team and continuous quality improvement (CQI).

Establishment of a vascular access team that includes nephrologists, surgeons, interventionists, a vascular access coordinator, and dialysis personnel is essential to ensure good vascular access outcomes. Ideally, the vascular access team should meet regularly to review data and provide a measurement of performance based on established KDOQI guidelines. Data collected should include the number and type of vascular accesses, infection and thrombosis rates, number and type of interventions performed, and time to access failure. Centers should monitor outcome results after thrombosis and set minimum goals for both immediate- and long-term patency. Trends should be analyzed and feedback provided to all members of the team. This approach fosters preemptive action and salvage rather than replacement of AV accesses, helping to minimize the need for venous catheter access and ensure the delivery of an adequate dialysis dose.

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9 Venous Catheter Infections and Other Complications

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The main problems associated with venous catheters are infection, poor flow, thrombosis, and central venous stenosis.

I. VENOUS CATHETER INFECTION. Despite the best practices detailed in Chapter 7 (Table 7.3), infections do occur with venous catheters and at a rate substantially higher than with arteriovenous (AV) fistulas. Infection is the leading cause of catheter loss and increases morbidity and mortality. Most often, infection results from contamination of the catheter connectors, from lumen contamination during dialysis, or from infused solutions. Infection also may arise from the migration of the patient's own skin flora through the puncture site and onto the outer catheter surface. Catheters can sometimes become colonized from more remote sites during bacteremia.

A. Exit-site infection can be diagnosed when there is erythema, discharge, crusting, and tenderness at the skin exit site, but no tunnel tenderness or purulence. Treatment with topical antibiotic cream and oral antibiotics may be sufficient. These infections can be prevented by meticulous exit-site care. The patient should be investigated for nasal carriage of *Staphylococcus* and, if present, treated with intranasal mupirocin cream (half tube twice a day to each nostril for 5 days) to prevent future infections. With exit-site infection, the catheter must be removed if systemic signs of infection develop (leukocytosis or temperature >38 °C), if pus can be expressed from the track of the catheter, or if the infection persists or recurs after an initial course of antibiotics. If blood cultures are positive, then the catheter should be removed.

B. Tunnel infection is infection along the subcutaneous tunnel extending proximal to the cuff toward the insertion site and venotomy. Typically, there is marked tenderness, swelling, and erythema along the catheter tract in association with purulent drainage from the exit site. This can result in systemic bacteremia. In the presence of drainage or signs of systemic infection, the catheter should be removed immediately and antibiotic therapy prescribed.

C. Catheter-related bloodstream infection (CRBSI). Patients present with signs and symptoms of systemic infection, which may range from minimal to severe. Milder cases present with fever or chills, whereas more severe cases exhibit hemodynamic instability. Patients may develop septic symptoms after initiation of dialysis, suggesting systemic release of bacteria and/or endotoxin from the catheter. There can be signs of metastatic infection, including endocarditis, osteomyelitis, epidural abscess, and septic arthritis. Gram-positive organisms are the causative organisms in the majority of cases, but gram-negative infections occur in a very sizable minority. For details on how to treat CRBSI in patients undergoing dialysis, caregivers can refer to valuable information available on

the dialysis section of the U.S. Centers for Disease Control and Prevention (CDC) website (http://www.cdc.gov/dialysis), the National Kidney Foundation's (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) 2019 vascular access guidelines, the European Renal Best Practices (ERBP) access guidelines (Tordoir, 2007), the Infectious Disease Society of America (IDSA) guidelines update for management of CRBSI (Mermel, 2009), and the ERBP commentary on the IDSA guidelines (Vanholder, 2010). Treatment algorithms and tips from the IDSA are reproduced in Figure 9.1 and Tables 9.1 and 9.2, and key recommendations from the ERBP group are shown in Figure 9.2.

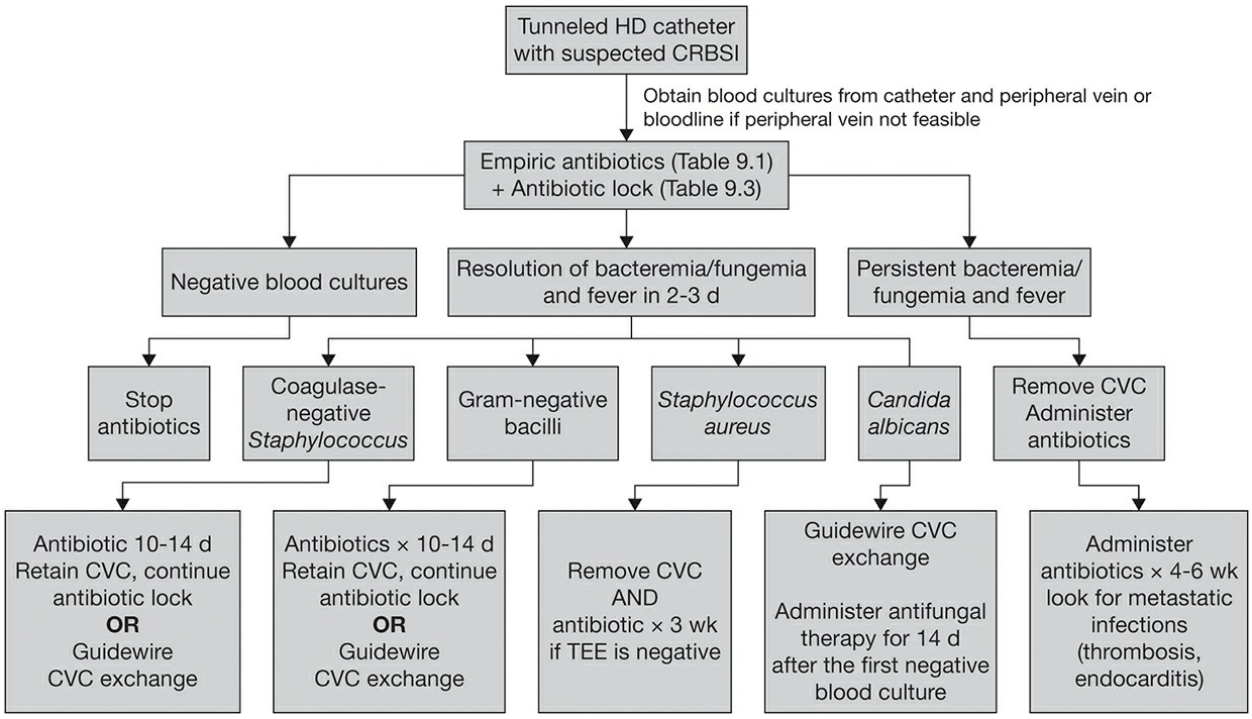


FIGURE 9.1: Pathway for treatment of cuffed hemodialysis catheter infections according to the Infectious Disease Society of America, 2009 Update. CRBSI, catheter-related bloodstream infection; CVC, central venous (dialysis) catheter; HD, hemodialysis; TEE, transesophageal echocardiography. (Reproduced with permission from Mermel LA, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;49:1-45.)

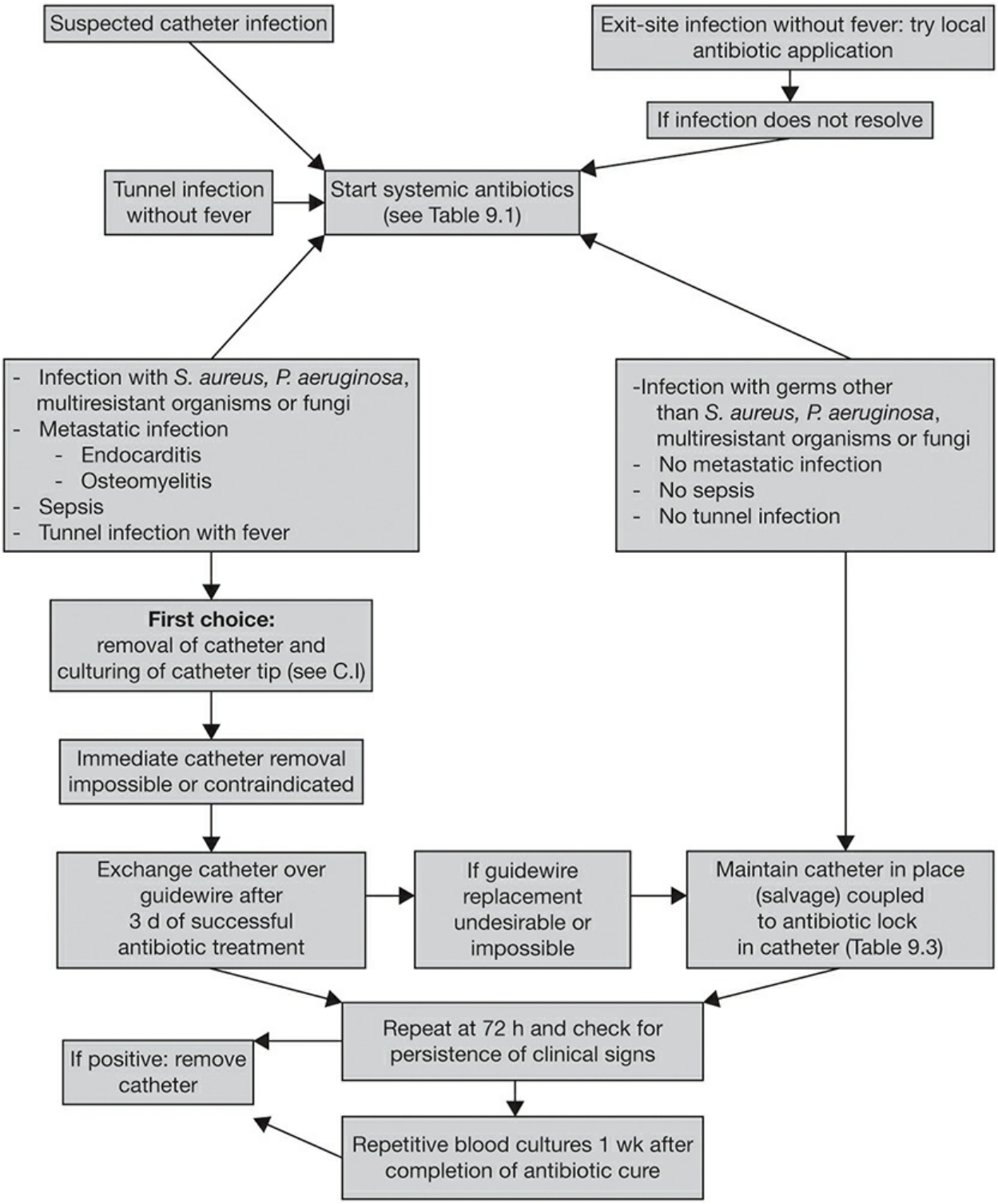


FIGURE 9.2: Pathway for treatment of cuffed hemodialysis catheter infections according to the European Best Practices Group, 2010 Update. (Adapted with permission from Vanholder R, et al. Catheter-related blood stream infections [CRBSI]: a European view. *Nephrol Dial Transplant*. 2010;25:1753-1756.)

TABLE

9.1 Antibiotic Dosing for Patients Who Are Undergoing Hemodialysis

Empirical Antibiotic Dosing Pending Culture Results
Vancomycin plus empirical gram-negative rod coverage based on local antibiogram data
OR
Vancomycin plus gentamicin
Typical Doses: (Doses need to be adjusted for residual renal function and for enhanced dialytic removal in case of frequent or extended dialysis, very high efficiency, high-flux treatments, or hemodiafiltration. Monitor predialysis trough levels if possible.)
(Cefazolin may be used in place of vancomycin in units with a low prevalence of methicillin-resistant staphylococci.)
Vancomycin: 20 mg/kg loading dose infused during the last hour of the dialysis session and then 500 mg during the last 30 min of each subsequent dialysis session
Gentamicin (or tobramycin): 1 mg/kg, not to exceed 100 mg after each dialysis session
Ceftazidime: 1 g IV after each dialysis session
Cefazolin: 20 mg/kg IV after each dialysis session
For Candida Infection
An echinocandin (caspofungin 70 mg IV loading dose followed by 50 mg IV daily; IV micafungin 100 mg IV daily; or anidulafungin 200 mg IV loading dose, followed by 100 mg IV daily); fluconazole (200 mg orally daily); or amphotericin B

IV, intravenous.

Adapted with permission from Vanholder R, et al. Diagnosis, prevention and treatment of haemodialysis catheter-related bloodstream infections (CRBSI): a position statement of European Renal Best Practice (ERBP). *NDT Plus.* 2010;3(3):234-246. doi:10.1093/ndtplus/sfq041

TABLE 9.2 Some Antimicrobial Concentrations in Lock Solutions[a]

Amikacin 25 mg/mL
Amphotericin B 2.5 mg/mL
Ampicillin 10 mg/mL
Cefazolin 5 mg/mL
Cefazolin 5 mg/mL plus gentamicin 1 mg/mL
Ceftazidime 5 mg/mL
Ciprofloxacin 0.2 mg/mL
Daptomycin 5 mg/mL
Linezolid 1 mg/mL
Gentamicin 1 mg/mL
Gentamicin 1 mg/mL plus vancomycin 2.5 mg/mL
Vancomycin 2.5-5.0 mg/mL[b]

[a]These can be mixed with heparin, 2,500 or 5,000 IU/mL, or with 4% citrate.

[b]Vancomycin at 20 mg/mL showed signs of incompatibility with 4% sodium citrate.

Mermel LA, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;49:1-45; Joshi AJ, Hart PD. Antibiotic catheter locks in the treatment of tunneled hemodialysis catheter-related blood stream infection. *Semin Dial*. 2013;26:223-226; Dotson B, et al. Physical compatibility of 4% sodium citrate with selected antimicrobial agents. *Am J Health Syst Pharm*. 2010;67:1195-1198.

The principles of CRBSI management in patients undergoing dialysis are different from the infectious disease guidelines for the treatment of infection in short-term central venous catheters. In hemodialysis, the venous catheter is a lifeline that sometimes can be replaced only with great difficulty. Thus, the guidelines include a variety of catheter salvage maneuvers, which involve the use of antibiotic-containing catheter locks or replacing the infected catheter with a new catheter in the same location over a guidewire. However, these catheter salvage techniques should be used only in limited, defined circumstances. If a patient's condition worsens after a relatively short trial of catheter salvage, the catheter must be removed to minimize the risk of spreading the infection to body organs.

1. **Blood and catheter tip cultures.** In working up a suspected CRBSI, cultures can be obtained from the catheter hub, from a peripheral vein, or from the blood lines during dialysis treatment. The IDSA recommendations are to take blood cultures from a catheter hub and from a peripheral vein and, when a catheter has been removed because of suspicion of infection, to also culture the distal 5 cm of its tip. One is looking for both blood cultures or for both the blood culture and a catheter tip culture to be positive with the same organism to confirm a diagnosis of CRBSI. When taking cultures from the skin or from a catheter hub, the IDSA recommends cleaning and sterilizing the area with chlorhexidine rather than povidone-iodine and allowing the antiseptic to dry before sampling; this avoids contamination of the cultured material with liquid antiseptic. The IDSA guidelines recognize that obtaining blood from the dialysis blood line is an acceptable substitute for peripheral blood cultures in many patients undergoing hemodialysis.

   The ERBP ad hoc advisory recommendations are similar to what the IDSA recommends. They too recognize the difficulties in obtaining cultures from peripheral veins in patients undergoing hemodialysis and believe that a practical alternative is to simply draw blood cultures from the dialysis circuit. Blood from the circuit during dialysis probably represents peripheral blood rather than localized catheter blood, so a positive blood culture drawn from the blood line may reflect a source of bacteremia other than at the catheter. The ERBP group suggests that the best way to deal with this possibility is by evaluating clinical history, examination, imaging, and targeted laboratory testing, including urine culture if possible.
2. **Indications for immediate catheter removal.** If there is evidence of septic thrombosis, endocarditis, osteomyelitis, or severe sepsis with hypotension, then the dialysis catheter needs to be removed immediately. The same recommendation generally holds for tunnel infection with fever. Dialysis should be continued with a temporary catheter inserted at a different location.
3. **Choice of antibiotic.** Gram-positive organisms, primarily *Staphylococcus* spp., are the most common, but gram-negative organisms may be isolated in up to 40% of cases. Broad-spectrum antibiotic therapy should be started immediately after drawing blood cultures. Dialysis units should keep a database of all CRBSI, including causative organisms, their susceptibility, and their response to therapy, as this information is extremely valuable in guiding antibiotic therapy for new cases. If methicillin-resistant *Staphylococcus* is known to be common in the local hemodialysis population, the initial therapy should include vancomycin rather than a first-generation cephalosporin. Adequate empiric gram-negative coverage can be

provided with either an aminoglycoside or a third-generation cephalosporin. Given that aminoglycosides may cause ototoxicity in up to 20% of patients undergoing hemodialysis, a third-generation cephalosporin may be a better choice. If treatment was begun for methicillin-resistant *Staphylococcus* and the culture shows a methicillin-sensitive organism, the treatment should be changed to cefazolin or a similar antibiotic.

4. **Dose of antibiotics.** It is practical to use antibiotics that can be given at the end of each dialysis session and maintain desired blood levels during the interdialytic interval. Some initial doses are given in Tables 9.1 and 9.2 (from the IDSA, Mermel, 2009). However, these doses may need to be increased in patients with substantial residual kidney function or those receiving intensive dialysis treatments such as frequent dialysis, high-intensity hemodiafiltration, or continuous renal replacement therapy. Where possible, predialysis trough drug levels should be monitored, but this is usually practical only in the inpatient setting. Helpful strategies for dosing antibiotics in patients undergoing hemodialysis or continuous kidney replacement therapy, as well as detailed dosing regimens, can be found in Mermel (2009).
5. **Duration of treatment and course.** Antibiotics should be discontinued promptly if the original blood cultures had no growth and the patient's symptoms are consistent with the absence of infection. In the event of positive cultures, the initially chosen antibiotic regimen should be adjusted once bacterial sensitivities are available. A 2- to 3-week course of systemic antibiotics is adequate in uncomplicated cases of catheter-related bacteremia. A longer course (4-8 weeks) is indicated if there is a metastatic infection such as endocarditis or osteomyelitis (see Figure 9.1 and Table 9.2).
6. **Catheter removal and exchange over a guidewire.** From an infectious disease perspective, the catheter is always best removed whenever a CRBSI occurs, regardless of the causal organism. However, since the patient will continue to require dialysis support, placement of a temporary catheter becomes necessary. Thus, the decision to remove the catheter should be individualized on the basis of the severity of sepsis and the availability of alternative venous access sites. If the patient is clinically septic and unstable despite the administration of systemic antibiotics, the catheter should be removed as soon as possible. Attempts to maintain the same catheter by treating through the infection have not been successful, with a success rate of less than 30% and the risk of metastatic infections. However, several studies support the use of guidewire exchange in patients whose symptoms resolve within 2 to 3 days of initiating intravenous antibiotics, reporting a 70% to 80% catheter salvage and cure. Thus, removing the infected catheter (and with it presumably the biofilm harboring the bacteria) and replacing it with a new catheter through the same venotomy preserves the venous access site while curing the infection. Guidewire replacement should be done only if the symptoms that prompted the initiation of antibiotic treatment have resolved over a period of 2 to 3 days of initial antibiotic therapy and there is no evidence of metastatic infection.
    a. **Catheter infection with *Staphylococcus aureus, Pseudomonas* sp., or *Candida* sp.** When the initial infection is with one of these organisms, both the IDSA and ERBP group recommend removal of the catheter as soon as this is known. Exchange of the catheter over a guidewire or attempts at catheter lock

salvage (see what follows) are not recommended with these infecting organisms unless extenuating circumstances are present.

7. **Antibiotic locks to treat established catheter infection.** Another approach to the treatment of patients with catheter-related bacteremia is to instill a concentrated antibiotic lock into the catheter lumen at the end of each dialysis session, as an adjunct to systemic antibiotics (Table 9.3). The antibiotic lock is used only for the duration of systemic antibiotics, after which a standard heparin or citrate lock is resumed. In about two-thirds of cases, the antibiotic lock successfully sterilizes the catheter biofilm, thereby permitting successful treatment of the bacteremia while salvaging the infected catheter. In the remaining one-third of cases, the patient has persistent fever or positive surveillance cultures, in which case prompt catheter replacement is indicated. The antibiotic lock protocol is most commonly successful in catheter-related bacteremia due to *Staphylococcus epidermidis* (75%) or gram-negative infections (87%), and less often successful in *S. aureus* infections (40%) (Allon, 2004; Poole, 2004), for which it is not recommended. There is a large amount of leakage from the solution instilled into a catheter lock over 24 hours (Schilcher, 2014; Sungur, 2007). For this reason, the concentration of antibiotic in the lock must be substantially higher than the minimal inhibitory concentration of the organism being targeted. Usually, the lock solution also contains either 2,500 or 5,000 IU/mL heparin or is mixed with 4% sodium citrate. Some commonly used antibiotic lock concentrations are shown in Table 9.2.

TABLE 9.3 Unique Aspects of Managing Patients Receiving Hemodialysis Through Catheters for Whom Catheter-Related Infection Is Suspected or Proven

Blood and Catheter Cultures

Peripheral blood samples should be obtained for culture from vessels that are not intended for future use in creating a dialysis fistula (eg, hand veins).

When a peripheral blood sample cannot be obtained, blood samples may be drawn during hemodialysis from blood lines connected to the dialysis catheter.

In patients with suspected CRBSI for whom blood cultures have been obtained and for whom antibiotic therapy has been initiated, antibiotic therapy can be discontinued if both sets of blood cultures have negative results and no other source of infection is identified.

When a peripheral blood sample cannot be obtained, no other catheter is in place from which to obtain an additional blood sample, there is no drainage from the insertion site available for culture, and there is no clinical evidence for an alternate source of infection, then positive results of culture performed on a blood sample obtained from a catheter should lead to continuation of antimicrobial therapy for possible CRBSI in a symptomatic patient undergoing hemodialysis.

Catheter Removal, Change, and Salvage With Antimicrobial Lock

The infected catheter should always be removed for patients with hemodialysis CRBSI due to *S. aureus, Pseudomonas* sp., or *Candida* sp. and a temporary (nontunneled) catheter should be inserted into another anatomic site. If absolutely no alternative sites are available for catheter insertion, then exchange the infected catheter over a guidewire.

When a hemodialysis catheter is removed for CRBSI, a long-term hemodialysis catheter can be placed once blood cultures with negative results are obtained.

For hemodialysis CRBSI due to other pathogens (eg, gram-negative bacilli other than *Pseudomonas* sp. or coagulase-negative staphylococci), a patient can initiate empirical intravenous antibiotic therapy without immediate catheter removal. If the symptoms persist or if there is evidence of a metastatic infection, the catheter should be removed. If the symptoms that prompted the initiation of antibiotic therapy (fever, chills, hemodynamic instability, or altered mental status) resolve within 2-3 d and there is no metastatic infection, then the infected catheter can be

exchanged over a guidewire for a new, long-term hemodialysis catheter.

Alternatively, for patients for whom catheter removal is not indicated (ie, those with the resolution of symptoms and bacteremia within 2-3 d after initiation of systemic antibiotics and an absence of metastatic infection), the catheter can be retained, and an antibiotic lock can be used as adjunctive therapy after each dialysis session for 10-14 d.

Antibiotic Therapy

Empirical antibiotic therapy should include vancomycin and coverage for gram-negative bacilli, based on the local antibiogram (eg, third-generation cephalosporin, carbapenem, or β-lactam/β-lactamase combination).

Patients who receive empirical vancomycin and who are found to have CRBSI due to methicillin-susceptible *S. aureus* should be switched to cefazolin. For cefazolin, use a dosage of 20 mg/kg (actual body weight), rounded to the nearest 500-mg increment, after dialysis.

A 4-6 wk, antibiotic course should be administered if there is persistent bacteremia or fungemia (ie, 172 h in duration) after hemodialysis catheter removal or for patients with endocarditis or suppurative thrombophlebitis, and 6-8 wk of therapy should be administered for the treatment of osteomyelitis in adults.

Patients receiving dialysis who have CRBSI due to vancomycin-resistant enterococci can be treated with either daptomycin (6 mg/kg after each dialysis session) or oral linezolid (600 mg every 12 h).

Antibiotic Locks

Antibiotic lock is indicated for patients with CRBSI involving long-term catheters with no signs of exit-site or tunnel infection for whom catheter salvage is the goal.

For CRBSI, antibiotic lock should not be used alone; instead, it should be used in conjunction with systemic antimicrobial therapy, with both regimens administered for 7-14 d.

Dwell times for antibiotic lock solutions should generally not exceed 48 h before reinstallation of lock solution; preferably, reinstallation should take place every 24 h for ambulatory patients with femoral catheters. However, for patients who are undergoing hemodialysis, the lock solution can be renewed after every dialysis session.

Catheter removal is recommended for CRBSI due to *S. aureus* and *Candida* sp., instead of treatment with antibiotic lock and catheter retention, unless there are unusual extenuating circumstances (eg, no alternative catheter insertion site).

For patients with multiple positive catheter-drawn blood cultures that grow coagulase-negative staphylococci or gram-negative bacilli and concurrent negative peripheral blood cultures, antibiotic lock therapy can be given without systemic therapy for 10-14 d.

For vancomycin, the concentration should be at least 1,000 times higher than the MIC of the microorganism involved.

At this time, there are insufficient data to recommend an ethanol lock for the treatment of CRBSI.

Follow-Up Cultures

It is not necessary to confirm negative culture results before guidewire exchange of a catheter for a patient with hemodialysis-related CRBSI if the patient is asymptomatic.

Surveillance blood cultures should be obtained 1 wk after completion of an antibiotic course for CRBSI if the catheter has been retained. If the blood cultures have positive results, the catheter should be removed, and a new, long-term dialysis catheter should be placed after additional blood cultures are obtained that have negative results.

CRBSI, catheter-related bloodstream infection; MIC, minimum inhibitory concentration.

8. **Follow-up blood cultures.** Surveillance blood cultures normally are obtained after 72 hours of treatment, depending on the patient's clinical course. Also, it is important to obtain follow-up blood cultures 1 week after the planned treatment course has finished to confirm that there has not been a recurrence of infection.

D. Complications of CRBSIs. Delay in therapy or prolonged attempts to salvage an infected cuffed catheter can lead to serious complications, including endocarditis, osteomyelitis, suppurative thrombophlebitis, and spinal epidural abscess. The last is a rare but serious neurologic complication in patients undergoing hemodialysis. In one series, 50% of cases of spinal epidural abscess were associated with attempted salvage

of an infected cuffed venous catheter (Kovalik, 1996). Presenting complaints are fever, backache, local spinal tenderness, leg pain and weakness, sphincter dysfunction, paresis, and/or paralysis. For diagnosis, magnetic resonance imaging appears to be less sensitive than computed tomography-myelography. Plain computed tomographic scanning without myelography has low sensitivity and can give misleading results (eg, disk protrusion). Early (immediate) decompressive surgery is usually advised, although rarely patients can be successfully treated with antibiotics only.

Endocarditis should be suspected in patients in whom fever and bacteremia persist despite appropriate antibiotics and catheter removal. This complication is seen most commonly in the setting of *S. aureus* bacteremia. Signs include the development of symptomatic heart failure and a new heart murmur. A transthoracic or transesophageal echocardiogram confirms the presence of valvular vegetations and insufficiency.

E. Aspirin. Aspirin treatment has been reported to be associated with a reduced incidence of *S. aureus*–related CRBSI (Sedlacek, 2007). Prior aspirin use also has been associated with reduced symptoms of infection and size of vegetations on cardiovascular implantable electronic devices (Habib, 2013). This finding needs to be confirmed, and the use of aspirin to limit infection incidence in tunneled venous catheters is not recommended by guideline groups at this time.

II. POOR CATHETER FLOW (CATHETER DYSFUNCTION).

Catheter dysfunction can be defined as a failure to deliver a blood flow rate of at least 300 mL/min at a prepump pressure that is less negative than −250 mm Hg. Associated problems are the inability to aspirate blood freely from the catheter lumens and frequent pressure alarms not responsive to patient repositioning or catheter flushing.

A. Initial (early) dysfunction. Recently placed catheters can have poor flow due to a kink, compression within the catheter tunnel from edema, malposition with the catheter having been inserted into the azygous or hemiazygous veins, or improper tip placement (Figure 9.3). A chest x-ray is valuable in evaluation. Tunnel edema usually subsides within 24 hours. Presence of a kink or a malpositioned tip requires the replacement of the catheter using a different tunnel or a different length of the catheter. It is also important to have an insertion site in the lower part of the neck close to the clavicle; a high insertion site in the neck can cause the catheter to become “positional,” with blood flow changing with the position of the neck. Eventually, the catheter tip moves up with neck movement, leading to poor blood flow. An exit site close to the breast tissue can also pull the tip of the catheter high into the superior vena cava. Exposed cuff or tunnel due to traction on the line or erosion of tissue increases the risk of malfunction and infection. These catheters require exchange. If the tunnel is eroded or infected, a new tunnel or new placement site is required. Left internal jugular catheters have a higher incidence of dysfunction than those inserted on the right side (Engstrom, 2013) for reasons not entirely clear but probably related to the twisty course required to reach the opening to the right atrium.

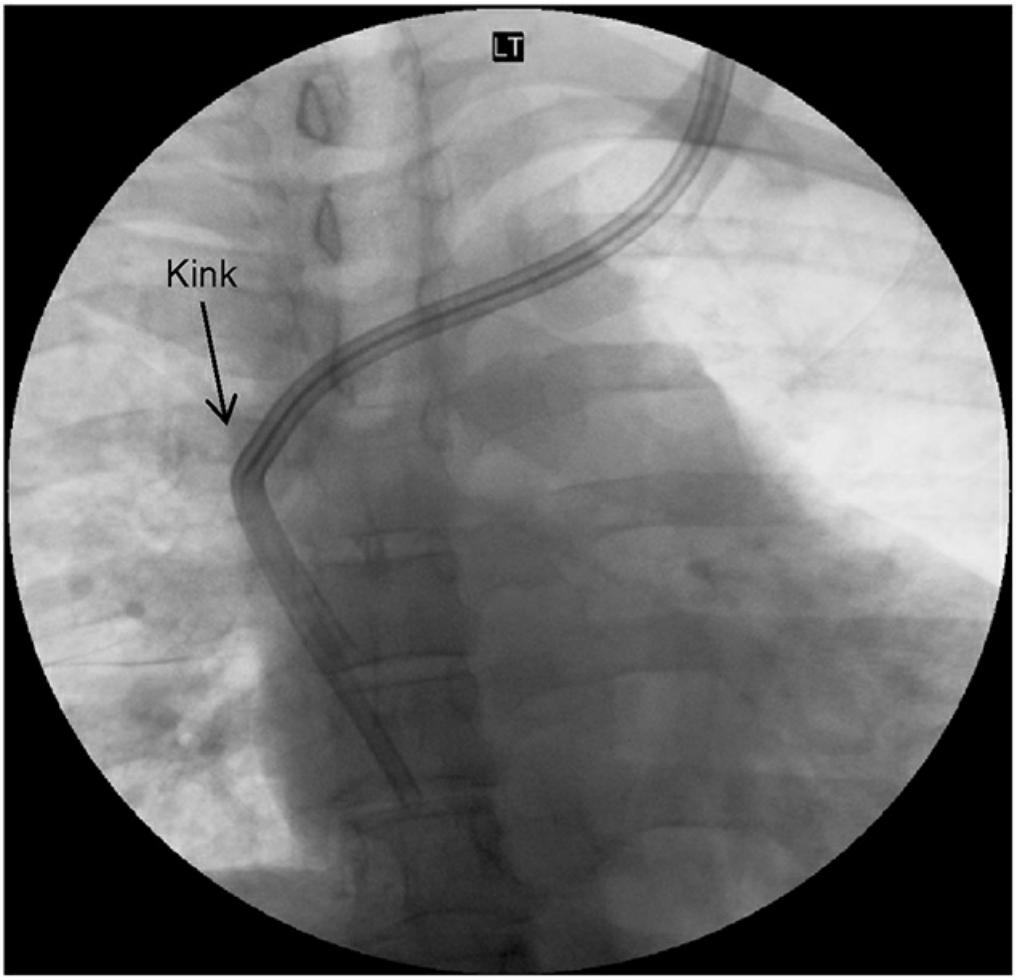


FIGURE 9.3: Kink: Left internal jugular venous catheter with a kink.

1. **Alteplase protocols.** Sometimes, early dysfunction can be due to intra-catheter thrombosis. A short (1 hour) or prolonged (overnight) instillation of tissue plasminogen activator (tPA) is usually effective in treating luminal thrombosis in the short term, although long-term catheter survival is not very good. Several tPA protocols have been described (Savader, 2001) (Table 9.4). Short protocols do not necessarily perform better than dwell protocols (Vercaigne, 2012). For a detailed description of various alteplase protocols, see BC Renal Agency (2011).

TABLE 9.4 Dosing of Tissue Plasminogen Activator (tPA) for Occluded Catheters

Catheter Lock and Aspirate Technique

Alteplase (1 mg/mL): Infuse 2 mg or volume of catheter into each catheter lumen as needed. For catheter lumen volumes >2 mL, after 2 mL of tPA is injected, inject sufficient normal saline to fill the catheter. For example, a 40-cm catheter with 2.6 mL volume per lumen: alteplase 2 mL injected (1 mg/mL), then 0.6 mL normal saline.

After initial administration, let the thrombolytic dwell for 30 min and then aspirate. If there is no blood return, let the thrombolytic dwell for another 30 min. If there is still no blood return, repeat the dose and aspirate again at 30 and 60 min.

If a catheter is “occluded” and the thrombolytic cannot be injected, connect a three-way stopcock to the occluded

catheter hub, and with a 20-mL nonfilled syringe aspirate on the catheter. The remaining port of the three-way stopcock should have the volume of thrombolytic in a syringe. With negative pressure on the catheter, turn the stopcock so it is now open to the catheter and the thrombolytic. The negative pressure will be transferred to the thrombolytic syringe, aspirating its contents into the catheter.

Infusion Technique

When the dwell technique is unsuccessful, attempt a short-term infusion.

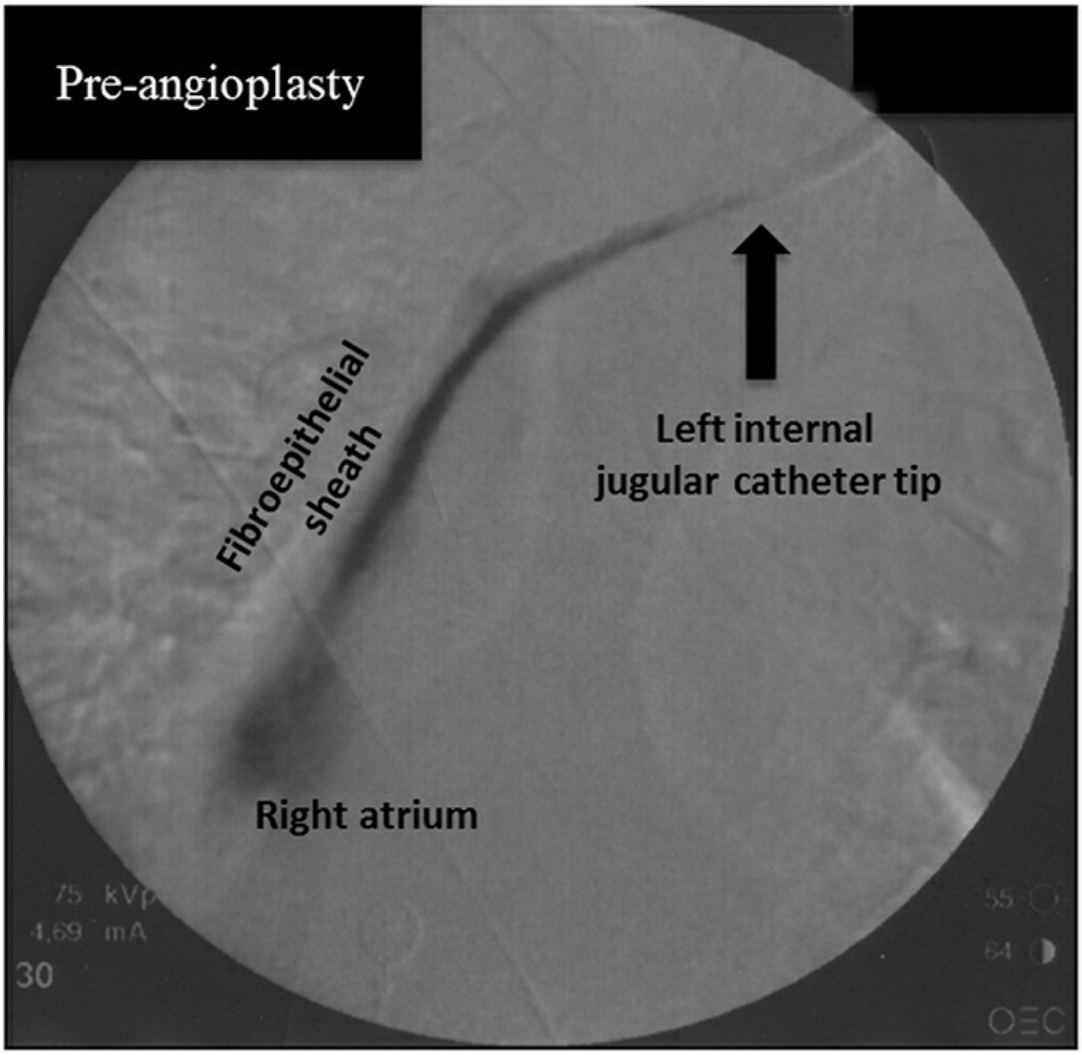
Begin by loading the catheter with tPA 2 mL per lumen. The concentration of tPA is 1 mg/mL. Once loaded, an infusion of tPA, 1 mg per lumen per hour, is run for 2-4 h and then rechecked.

The amount of thrombolytic utilized with infusion is probably not of sufficient amount to cause bleeding complications, but absolute and relative contraindications should be considered, and then risk vs benefit.

Locking catheters as well as biweekly or monthly instillations of thrombolytics have reportedly reduced catheter occlusions.

For additional thrombolytic protocols, see Lok (2006) and BC Renal Agency (2021).
Adapted with permission from www.venousaccess.com

B. Late dysfunction. Late dysfunction is due usually to the formation of a fibrin sleeve (Figure 9.4) or a mural thrombus. Almost all catheters inserted into a central vein develop a fibrin sleeve within a week or two of insertion. Such fibrin sleeves are initially clinically silent until they obstruct the ports at the distal end of the catheter. Generally, saline infuses into a port, but aspiration is difficult, producing a so-called ball-valve effect. Fibrin sleeves may serve as a nidus for infection. The use of warfarin or other anticoagulants on a chronic basis has not been shown to reduce fibrin sleeve or catheter thrombus formation (Mokrzycki, 2001).


Pre-angioplasty
Fibroepithelial sheath
Left internal jugular catheter tip
Right atrium
75 kVp
4.69 mA
30
55
64
OEC

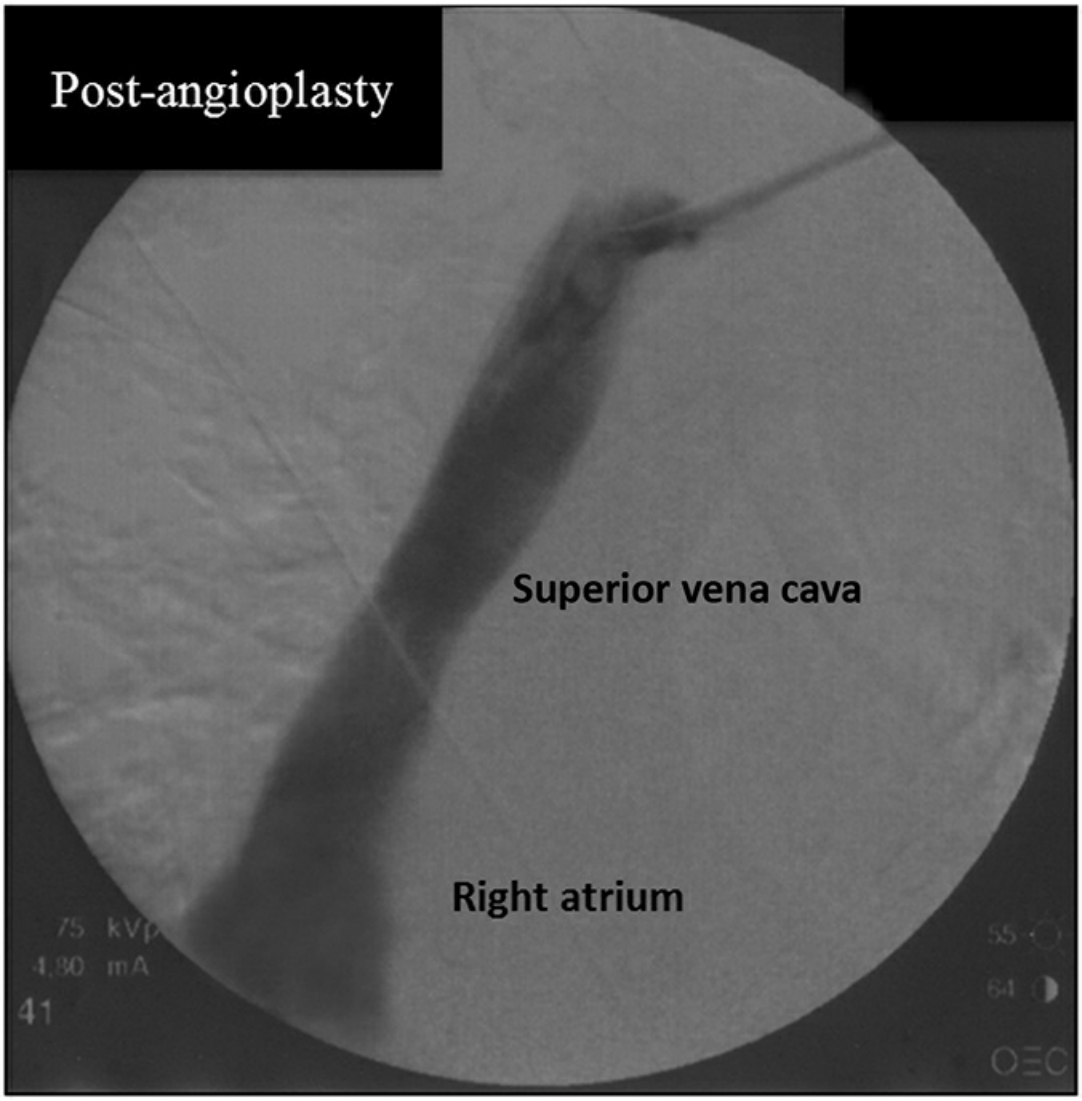


FIGURE 9.4: Fibrin sheath: left internal jugular venous catheter with fibrin sheath that extends beyond the catheter tip that has been retracted.

1. **Treatment of fibrin sheath.** The presence of a fibrin sheath is usually determined at the time of catheter exchange using radiocontrast material administered through the venous port of the old catheter (Figure 9.4). The condition is usually treated with an angioplasty balloon catheter inserted on a guidewire through the catheter tunnel. The balloon catheter is passed into the lumen of the fibrin sheath and is then inflated to disrupt the fibroepithelial sheath. An 8-mm diameter balloon usually is sufficient to accomplish this task. Disruption of the sheath is then confirmed by a repeat radiocontrast injection after the new catheter has been inserted. The balloon angioplasty technique results in the restoration of catheter blood flow rates sufficient for dialysis in the great majority of patients (Rasmussen, 2010; Shanaah, 2013).

C. Recurrent catheter dysfunction. A substantial minority of patients with dysfunctional catheters treated by catheter replacement and balloon angioplasty will develop recurrent catheter dysfunction. Such patients will require multiple catheter

replacements (Rasmussen, 2010). There is no ideal solution for such patients. Use of anticoagulants has not been shown to help, and the best resolution is conversion to an AV access where possible.

III. THROMBOSIS

A. Intraluminal thrombosis. Catheter thrombosis is commonly treated by instillation of tPA for 1 hour or longer. Some commonly used protocols are given in Table 9.4. Mechanical brushing of thrombus has been suggested, but is unpopular. Prophylactic oral anticoagulation with warfarin does not improve catheter patency unless therapeutic levels of anticoagulation with high international normalized ratio (INR) are achieved, and this can be associated with bleeding complications. Moreover, the fear of calciphylaxis and skin necrosis with warfarin therapy tends to limit its use in patients undergoing dialysis.

B. Central vein or intracardiac thrombosis can occur in association with large, indwelling catheters, and these can rarely result in embolic complications. Intra-atrial thrombi need prolonged systemic anticoagulation (for 6 months or longer) and follow-up for resolution.

C. Embolic complications. Large clots adherent to the end of the catheter or to the vessel wall can be clinically silent or can give rise to embolic events. Large mural thrombi can progress to stenosis and central vein thrombosis. Treatment options for a ball thrombus or a catheter-associated right atrial thrombus include simple catheter removal, systemic or catheter-assisted fibrinolytic therapy, and, rarely, thoracotomy with thrombectomy.

IV. CENTRAL VENOUS STENOSIS

A. Causes. Central venous stenosis arises from endothelial injury at the sites of catheter-endothelial contact through the release of a variety of growth factors. The incidence increases with the use of stiff, nonsilicone catheters; with the use of the subclavian approach (presumably because of higher angular stresses on the catheter in the subclavian position); and in patients with previous catheter-related infections. Risk factors include a history of multiple catheter insertions (including small and large venous catheters as well as peripherally inserted central catheters, so-called PICC lines) and prolonged duration of such catheters. Collateral vessels usually develop but may not be adequate to relieve extremity edema.

B. Presentation and diagnosis. Stenosis or occlusion of the subclavian vein, brachiocephalic vein, or superior vena cava usually presents with venous hypertension (ipsilateral swelling of the breast, shoulder, neck, and face) or vascular access dysfunction (high venous pressure on dialysis, inadequate dialysis, and prolonged bleeding). A stenosis may be asymptomatic and clinically silent until unmasked by the creation of an AV fistula. Asymptomatic central vein thrombosis is not uncommon in patients with a central vein dialysis catheter. Thrombosis of the AV access may result. Occlusion of multiple central veins in the chest can result in the development of superior vena cava syndrome. Careful history and examination will often reveal multiple central venous catheter scars in such patients. Multiple collateral blood vessels are visible on examination.

C. Treatment. Ligation of an AV access if present produces rapid improvement but

sacrifices the access. Initial anticoagulation (with heparin followed by warfarin) and elevation of the upper extremity on the involved side may ameliorate the symptoms and signs if thrombosis is present. More definitive therapy usually is required: Balloon angioplasty has been used for stenosis, but the lesion tends to recur. Stent placement combined with angioplasty (Figure 9.5) is indicated in elastic (easily distensible) central vein lesions or if a dilated stenosis recurs within a 3-month period. However, stent placement rarely solves the problem long term because stenosis can reoccur around the stent. Stenosis in the subclavian vein sometimes can be relieved by an axillary vein to internal jugular vein bypass.



FIGURE 9.5: Central vein stent: left brachiocephalic vein occlusion after angioplasty and stent placement.

V. CATHETER ADHESION. Over the long term, indwelling catheters can develop adhesions to venous or atrial endothelium. Adherence should be suspected when an attempt to remove the catheter induces severe pain or requires significant traction. The heart or mediastinum

may be pulled to one side when visualized under fluoroscopy. Removal of adhered catheters is a challenge and can require invasive techniques, including laser dissection or open surgical removal. Some novel closed maneuvers have been reported to be successful (Hong, 2011).

VI. PORT CLAMP FRACTURE. It is not uncommon to see a fractured port or clamp on a tunneled dialysis catheter. This can lead to the suction of air or the inability to double lock the port after dialysis, with an increased risk of bleeding. Often, one can replace one or both ports or clamps using replacement kits for specific catheters without having to change the entire catheter. If there has been port fracture with air suction, there is a higher risk of infection, and at the time of repair, prophylactic antibiotics should be given after drawing blood cultures.

VII. RISK OF AIR EMBOLISM AFTER CENTRAL VENOUS CATHETER REMOVAL. This is discussed in Chapter 7.

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10 Acute Hemodialysis Prescription

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I. THE HEMODIALYSIS PRESCRIPTION.

All patients are different, and the circumstances eventuating the need for acute hemodialysis vary widely. The prescription for hemodialysis will change accordingly. As a teaching tool only, we present a "typical" prescription for acute hemodialysis in a 70-kg adult.

Rx: Acute hemodialysis (NOT for initial treatment)
Session length: Perform hemodialysis for 4 hours
Blood flow rate: 350 mL/min
Dialyzer:
Dialyzer membrane: your choice
Dialyzer K_{UF}: your choice
Dialyzer efficiency: usually a dialyzer with an in vitro urea K_0A of 1,000 to 1,600 mL/min is used
Dialysis solution composition (variable):
Base: bicarbonate 25 mM
Sodium: 145 mM
Potassium: 3.5 mM
Calcium: 1.5 mM (3.0 mEq/L)
Magnesium: 0.375 mM (0.75 mEq/L)
Dextrose: 5.5 mM (100 mg/dL)
Phosphate: none
Dialysis solution flow rate: 500 mL/min
Dialysis solution temperature: 35 °C to 36 °C
Fluid removal orders:
Remove 2.2 L over 4 hours at a constant rate (550 mL/h)
Anticoagulation orders:
See Chapter 13

A. Determining dialysis session length and blood flow rate.

The dialysis session length together with the blood flow rate is the most important determinant of the amount of dialysis to be given (dialyzer efficiency is also a factor).

1. **Reduce the amount of dialysis for the initial one or two sessions.** For the initial treatment, especially when the predialysis serum urea nitrogen (SUN) level is very high (eg, >125 mg/dL [44 mmol/L]), both the dialysis session length and blood flow rate should be reduced. A urea reduction ratio (URR) of less than 30% to 40% should be targeted. This usually means for normal-sized (~75 kg) adults, using a 2-hour treatment time and a blood flow rate of 150 mL/min (to achieve a 30% URR) or 200 mL/min (to achieve a 40% URR). If longer sessions are needed to remove fluid, then isolated ultrafiltration should be performed during the extended treatment to limit rapid solute concentration changes. It may be best to avoid the use of large surface area, high-efficiency dialyzers, as these may be prone to clot at the low

blood flow rates required. A longer initial dialysis session or use of excessively high blood flow rates in the acute setting may result in the so-called **disequilibrium syndrome**, described more fully in Chapter 12. This neurologic syndrome, which includes the appearance of obtundation, or even seizures and coma, during or after dialysis, has been associated with excessively rapid removal of blood solutes. The risk of disequilibrium syndrome is increased when the predialysis SUN level is high. After the initial dialysis session, the patient can be reevaluated and should generally be dialyzed again the following day. After the first one or two dialysis treatments, the length of subsequent dialysis sessions can usually be increased to 3 hours, provided that the predialysis SUN level is less than 100 mg/dL (36 mmol/L). Subsequent dialysis sessions can be as long as needed. The length of a single dialysis treatment rarely exceeds 6 hours unless the purpose of dialysis is the treatment of drug overdose.

Slow low-efficiency hemodialysis (SLED) uses low blood and dialysis solution flow rates and longer treatment sessions in order to more safely remove fluid. SLED is described in Chapter 14.

2. **Dialysis frequency and dose for subsequent treatments and dialysis adequacy.** It is difficult to deliver a large amount of dialysis in the acute setting. Most intensive care unit patients are fluid overloaded, and urea distribution volume is often much greater than 50% to 60% of body weight. True delivered blood flow rate through a venous catheter rarely exceeds 350 mL/min and is often substantially lower. Some recirculation tends to occur in venous catheters and is greatest with catheters in the femoral position owing to the low pericatheter venous flow rate. Often, the treatment is interrupted owing to hypotension. Furthermore, the degree of urea sequestration in muscle may be increased, as such patients are often on pressors, reducing blood flow to muscle and skin, which contain a substantial portion of urea and other dissolved waste products. Concomitant intravenous (IV) infusions, which are often given to patients in an acute setting, dilute the urea level in the blood and reduce further the efficiency of dialysis.

   A typical 3- to 4-hour acute dialysis session will deliver a single-pool Kt/V of only 0.9, with an equilibrated Kt/V of 0.7. Dialysate-side urea removal may be even lower (Evanson, 1999). This low level of Kt/V, if given 3 times/wk, is associated with a high mortality in chronic, stable patients. One option is to dialyze sick patients with acute renal failure on a daily (6 or 7 times/wk) basis. Each treatment is then approximately 3 to 4 hours in length. The Kidney Disease Improving Global Outcomes (KDIGO) workgroup on acute kidney injury (2012) recommends that when attempting to maintain acute patients on a 3 times/wk schedule, each treatment should have a Kt/V of greater than or equal to 1.3. When there is a concern that there is inconsistent dialysis delivery (eg, catheter flow or hollow-fiber thrombosis problems), one can verify hemodialysis adequacy by assessing the URR using blood tests or devices that measure real-time solute clearance (ionic conductance or ultraviolet light absorption technologies).

   The amount of dialysis may need to be adjusted upward in hypercatabolic patients. A low predialysis SUN level should not be used as a justification to reduce the amount of dialysis unless substantial residual renal urea clearance is documented; many patients with acute renal failure tend to have decreased urea

generation rates due to lack of protein ingestion and/or to impairment of urea synthesis by the liver. Therefore, in such patients, a low SUN does not necessarily reflect low levels of other uremic toxins.

B. Choosing a dialyzer

1. **Membrane material.** A Cochrane report suggested that no firm conclusions could be drawn as of 2006 regarding the benefits of any one group of modern dialysis membranes over another for acute or chronic dialysis. The best dialyzer to select for acute dialysis, therefore, remained unclear, and there is still no evidence suggesting that a particular membrane material is superior. No recommendation favoring the use of high-flux membranes for acute dialysis can be made at this time, as membrane flux has not been studied as a separate factor in any randomized study of acute dialysis.
   a. **Anaphylactoid reactions.** These can occur and depend on both membrane material and sterilization mode. See Chapter 12 for details.
2. **Ultrafiltration coefficient (K_{UF}).** Ultrafiltration controllers are now available on all modern dialysis machines, and these accurately control the ultrafiltration rate by means of special pumps and circuits. Machines with volumetric ultrafiltration controllers are designed to use dialyzers of high water permeability (eg, $K_{UF} > 6.0$) and may lose accuracy if a high fluid removal rate is attempted using a dialyzer that is relatively impermeable to water.

   In the unlikely event that a dialysis machine with an ultrafiltration controller is not available, then a membrane with a relatively low water permeability (K_{UF}) should be chosen so that the transmembrane pressure (TMP) will have to be set at a relatively high level to remove the amount of fluid desired; then the inevitable errors in maintaining the desired TMP will have less impact on the rate of fluid removal. When close monitoring of the fluid removal rate is required and a machine with advanced ultrafiltration control circuitry is not available, the fluid removal rate can be monitored by placing the patient on an electronic bed or chair scale and continuously following the weight during dialysis.
3. **Dialyzer urea clearance.** As noted above, for the first couple of dialysis sessions, it is best to avoid using large surface area, very high-efficiency dialyzers, although they can be used as long as the blood flow is low (eg, 100-200 mL/min) and the session length does not exceed 2 hours. When heparin-free dialysis is used, there is less risk (theoretically) of clotting when a low blood flow rate is used with a smaller dialyzer, as the blood velocity through a small fiber bundle will be higher. After the initial one or two sessions, particularly if a high blood flow rate is being used, normal-sized dialyzers can be chosen.

C. Choosing the dialysis solution.

In our example, we have chosen a bicarbonate level of 25 mM with a sodium level of 145 mM, a potassium level of 3.5 mM, a calcium level of 1.5 mM (3.0 mEq/L), a magnesium level of 0.375 mM (0.75 mEq/L), a dextrose level of 5.5 mM (100 mg/dL), and no phosphate. Depending on the circumstances, this prescription may have to be altered in a given patient. It is important to recognize that for acute patients, the dialysis solution composition should be tailored. The “standard” composition designed for acidotic, hyperphosphatemic, hyperkalemic patients undergoing chronic dialysis is often inappropriate in an acute setting.

1. **Dialysis solution bicarbonate concentration.** In the sample prescription

mentioned earlier, we have chosen to use a 25-mM bicarbonate level. Intensive care unit patients are often relatively alkalotic for reasons described in what follows, and so prescriptions for "standard" bicarbonate dialysis solution, containing 35 to 38 mM, should not be used without first carefully evaluating the patient's acid-base status.

If the predialysis plasma bicarbonate level is 28 mM or higher or if the patient has respiratory alkalosis, a custom dialysis solution containing an appropriately lower bicarbonate level (eg, 20-28 mM, depending on the degree of alkalosis) should be used. One should remember that many dialysis solutions provide an additional 4 to 8 mEq/L of bicarbonate-generating base from acetate or citrate, as discussed in Chapter 5. In machines where the dialysate bicarbonate level can be adjusted by changing the proportioning ratio between the acid and base concentrates, final dialysate bicarbonate levels shown on the display screen often correspond to bicarbonate after mixing with the acid concentrate, and so the value shown may not include the added base content coming from acetate or citrate.

a. Dangers of metabolic alkalosis. A patient undergoing dialysis with even a mild metabolic alkalosis (eg, plasma bicarbonate level of 30 mmol/L) requires very little hyperventilation to increase blood pH to dangerous levels. Alkalemia (blood pH > 7.50) may be more dangerous than acidemia. Dangers of alkalemia include soft-tissue calcification and cardiac arrhythmia (sometimes with sudden death), although documentation of the latter risk in the literature is not easy to find. Alkalemia has also been associated with adverse symptoms such as nausea, lethargy, and headache.

In patients undergoing dialysis, the most common causes of metabolic alkalosis are a reduced intake of protein, intensive dialysis for any reason (eg, daily dialysis), and vomiting or nasogastric suction. Another common cause is administered lactate or acetate with total parenteral nutrition solutions or citrate due to citrate anticoagulation.

b. Predialysis respiratory alkalosis. Many patients who are candidates for acute dialysis have preexisting respiratory alkalosis. The causes of respiratory alkalosis are the same as in patients with normal renal function and include pulmonary disease (pneumonia, edema, embolus), hepatic failure, and central nervous system disorders. Normally, compensation for respiratory alkalosis is 2-fold. There is an acute decrease in the plasma bicarbonate level owing to the release of hydrogen ions from body buffer stores. In patients with normal renal function, there is a further delayed (2-3 days) compensatory fall in the plasma bicarbonate level because of the excretion of bicarbonate in the urine. Renal bicarbonate excretion obviously cannot occur in patients undergoing dialysis.

The therapeutic goal should always be to normalize the pH rather than the plasma bicarbonate level. In patients with respiratory alkalosis, the plasma bicarbonate level at which the blood pH will be normal may be as low as 17 to 20 mmol/L; the dialysis solution to use should contain less than the usual amount of bicarbonate to achieve a postdialysis plasma bicarbonate level in the desired subnormal range.

c. Achieving an appropriately low dialysis solution bicarbonate level. In certain machines, the proportioning ratio of concentrate-to-product water is

fixed, and as a result, the dialysis solution bicarbonate level can be reduced only by changing the concentrate bicarbonate level. With such machines, the bicarbonate cannot be reduced below approximately 32 mM. In machines where the concentrate-to-product water ratio can be changed, bicarbonate levels as low as 20 mM usually can be delivered, but not lower, and this does not include the 4 to 8 mEq/L from acetate or citrate. When attempting to provide a low-base-content dialysate, sodium diacetate-containing concentrate should not be used, as this will increase the base content by 8 mEq/L.

d. Patients with severe predialysis acidosis

1. **Dangers of excessive correction of metabolic acidosis.** Excessive correction of severe metabolic acidosis (starting plasma bicarbonate level <10 mmol/L) can have adverse consequences, including lowering of the ionized calcium level and a paradoxical acidification of the cerebrospinal fluid and an increase in the tissue production rate of lactic acid. Initial therapy should aim for only partial correction of the plasma bicarbonate level; a target postdialysis plasma bicarbonate value of 15 to 20 mmol/L is generally appropriate; and for such severely acidotic patients, a dialysis solution bicarbonate level of 20 to 25 mM is normally used.
2. **Respiratory acidosis.** The normal compensation to respiratory acidosis is an acute buffer response, which can increase the plasma bicarbonate level by 2 to 4 mmol/L, followed by a delayed (3-4 days) increase in renal bicarbonate generation. Because the second response is obviated in patients undergoing dialysis, respiratory acidosis will have a more pronounced effect on blood pH than in patients with normal renal function. One report has claimed benefit from using a lower than normal dialysate bicarbonate in one patient, with the thought of avoiding alkalemia and resultant respiratory depression (Palacios, 2011). However, there is little published information about the optimum dialysate bicarbonate to use, and the goal should usually be to normalize the blood pH.

2. **Dialysis solution sodium level.** The dialysis solution sodium level in the sample prescription is 145 mM. This level is generally acceptable for patients who have normal or slightly reduced predialysis serum sodium concentrations. If marked predialysis hypernatremia or hyponatremia is present, the dialysis solution sodium level will have to be adjusted accordingly.

a. Hyponatremia. Hyponatremia is common in seriously ill patients requiring acute dialysis, primarily because such patients have often received large amounts of hyponatremic IV solutions with their medications and parenteral nutrition. Hyponatremia is frequently seen accompanying severe hyperglycemia in patients with diabetes undergoing dialysis. For every increase of 100 mg/dL (5.5 mmol/L) in the serum glucose concentration, there is a corresponding initial decrease of 1.6 mmol/L in the serum sodium concentration as a result of the osmotic shift of water from the intracellular to the extracellular compartment. Because osmotic diuresis secondary to hyperglycemia does not occur, the excess plasma water is not excreted, and hyponatremia is maintained. Correction of hyperglycemia by insulin administration reverses the initial water shift and thereby corrects the hyponatremia.

1. **Predialysis serum sodium level greater than 130 mmol/L.** Intensive care patients often tend to be slightly hyponatremic, as they are often given various IV drugs in 5% dextrose and water. The goal should be to keep serum sodium at or above 140 mmol/L, and dialysis solution sodium should be in the range of 5 to 10 mM higher than the serum level. The potential benefits of keeping dialysis solution sodium up to 10 mM higher than the serum level in patients with possible brain edema and/or hypotension have been reviewed by Davenport (2008).
2. **Predialysis serum sodium level less than 130 mmol/L.** When the degree of predialysis hyponatremia is moderate to severe, and especially if the hyponatremia is of long duration, it is dangerous to achieve normonatremia quickly. Rapid correction of hyponatremia has been linked to a potentially fatal neurologic syndrome known as osmotic demyelination syndrome (Huang, 2007). The maximum safe rate of correction of the serum sodium concentration in severely hyponatremic patients is controversial but probably is in the range of 6 to 8 mmol/L per 24 hours. At this stage of incomplete knowledge, it seems prudent when treating patients with severe hyponatremia to set the dialysis solution sodium level as low as possible and to dialyze at a slow (50-100 mL/min) blood flow rate, and for not longer than 1 hour at a time, alternating with isolated ultrafiltration as needed for volume control. One can check the serum sodium after each 30 to 60 minutes of dialysis to ensure that the desired rate of sodium increase is not being exceeded. In one case report, use of a 50 mL/min blood flow over 3 hours resulted in the desired increase in the serum sodium of 6 mmol/L over the 3-hour dialysis period (Wendland and Kaplan, 2012). Another approach is to delay dialysis for a few days if possible and to treat hyponatremia with hypertonic saline, removing excess fluid by isolated ultrafiltration as needed. If continuous hemodialysis or hemofiltration is available, use of one of these modalities with an appropriate sodium-reduced dialysis solution/replacement fluid is another good option and allows for the greatest control of the rate of serum sodium increase (Yessayan, 2014).

b. Hypernatremia. Hypernatremia is less common than hyponatremia in a hemodialysis setting but does occur, usually in the context of dehydration, osmotic diuresis, and failure to give sufficient electrolyte-free water. It is somewhat dangerous to attempt to correct hypernatremia by hemodialyzing against a low-sodium dialysis solution. Whenever the dialysis solution sodium level is more than 3 to 5 mM lower than the plasma value, three complications of dialysis occur with increased incidence:

1. Osmotic contraction of the plasma volume occurs as water shifts from the dialyzed blood (containing less sodium than before) to the relatively hyperosmotic interstitium, causing hypotension.
2. The propensity to develop muscle cramps is increased.
3. Water from the dialyzed, relatively hyponatremic blood enters cells, causing cerebral edema and exacerbating the disequilibrium syndrome.

The risk of disequilibrium syndrome is the most important one; use of low-sodium dialysis solution should certainly be avoided in situations in

which the predialysis SUN level is high (eg, >100 mg/dL [36 mmol/L]). The safest approach is to first dialyze a patient with a dialysis solution sodium level close to that of plasma and then correct the hypernatremia by slow administration of slightly hyponatremic fluids.

3. **Dialysis solution potassium level.** The usual dialysis solution potassium concentration for acute dialysis ranges from 2.0 to 4.5 mM. An important number of patients requiring acute dialysis will have a plasma potassium value in the normal or even the subnormal range, especially in patients with nonoliguric acute renal failure and in oliguric patients if food intake is poor. Hypokalemia is also a complication of total parenteral nutrition. Correction of severe acidosis during dialysis causes a shift of potassium into cells, lowering the plasma potassium level further. Hypokalemia and arrhythmia can result.

   When the predialysis serum potassium level is less than 4.5 mmol/L, the dialysis solution potassium level can be greater than or equal to 4.0 mM, with special caution needed in cardiac patients prone to arrhythmias. In patients with a predialysis plasma potassium level greater than 5.5 mmol/L, a dialysis solution potassium level of 2.0 is usually appropriate in stable patients, but the dialysis solution potassium concentration should be raised to 2.5 to 3.5 in patients at risk for arrhythmia or in those receiving digitalis. If the potassium level is greater than 7.0, some nephrologists will use a dialysis solution potassium level below 2.0 mM. However, the plasma potassium level must be monitored hourly, and there is considerable danger of precipitating arrhythmia if the plasma potassium concentration is lowered too rapidly.

   a. **Potassium rebound.** There is a marked rebound increase in the serum potassium level within 1 to 2 hours after dialysis. One should resist the temptation to treat postdialysis hypokalemia with potassium supplements unless there are extenuating circumstances.
   b. **Acute hyperkalemia.** Patients with very severe hyperkalemia present with alterations on the electrocardiogram (low P waves, peaked T waves, widening of the QRS, cardiac standstill), along with weakness and lethargy. Such patients should be treated immediately with an IV infusion of calcium chloride or calcium gluconate and/or IV glucose plus insulin while arrangements for emergency hemodialysis are being made. The response to IV sodium bicarbonate in patients undergoing dialysis is suboptimal. Another therapy is IV or inhaled albuterol.
   c. **Subacute hyperkalemia.** Initial treatment should always be a careful review of the diet for high-potassium foods. The majority of patients respond to reduced alimentary potassium intake. If this fails, then oral administration of a compound such as sodium zirconium cyclosilicate (ZS-9) or patiromer, which binds potassium in the gut, can be tried. Older compounds such as sodium or calcium polystyrene sulfate combined with sorbitol to prevent constipation can also be used, but there have been reports of intestinal necrosis associated with sorbitol and oral sodium polystyrene sulfonate use (eg, Gardiner, 1997). Some reports have suggested a more rapid reduction in serum potassium with ZS-9 compared to patiromer, but comparable rates of reduction have also been reported.
   d. **Potassium removal and dialysis solution glucose.** Potassium removal

during dialysis using a glucose-free dialysis solution may be 30% greater than potassium removal using a 200 mg/dL (11 mmol/L) glucose solution because with glucose-free dialysis solution, there may be decreased intradialytic translocation of potassium into cells (Ward, 1987). However, glucose-free dialysis solution is not commonly used (see what follows), and dialysis solution containing 100 mg/dL (5.5 mmol/L) glucose may be the best option, and this concentration is becoming the industry standard.

4. **Dialysis solution calcium levels.** Our generally recommended level for acute dialysis is 1.5 to 1.75 mM (3.0-3.5 mEq/L). There is some evidence that dialysis solution calcium levels less than 1.5 mM (3.0 mEq/L) predispose to hypotension during dialysis (van der Sande, 1998). In patients with predialysis hypocalcemia, unless a sufficiently high dialysis solution calcium level is used, correction of acidosis can result in further lowering of the ionized plasma calcium level (with possible precipitation of seizures). One study showed that QTc dispersion increased (potentially promoting arrhythmias) when a low calcium dialysis solution was used (Nappi, 2000). Routine use of 1.25 mM (2.5 mEq/L) calcium dialysis solution (now standard for treatment of patients undergoing chronic dialysis taking calcium-containing phosphate binders) to treat patients with acute renal injury is not uncommon; however, there is little hard evidence to show that such a practice is harmful.
    a. **Dialytic treatment of acute hypercalcemia.** Hemodialysis can be effective in lowering the serum calcium concentration in hypercalcemic patients. In most commercially prepared hemodialysis solutions, the calcium concentration ranges from 1.25 to 1.75 mM (2.5-3.5 mEq/L). Under most circumstances, we prefer to add at least 1.25 mM (2.5 mEq/L) calcium to the hemodialysis solution to minimize the possibility of an overly rapid decrease in the serum ionized calcium (which can cause tetany or seizures). Frequent measurement of the serum ionized calcium concentration and physical examination of the patient should be performed during dialysis to avoid these complications.
5. **Dialysis solution magnesium levels.** The usual dialysis solution magnesium level ranges from 0.25 to 0.75 mM (0.5-1.5 mEq/L). Magnesium is a vasodilator, and in acute dialysis, one preliminary report suggests that blood pressure is better maintained when a dialysis solution magnesium level of 0.375 mM (0.75 mEq/L) is used versus a dialysis solution containing 0.75 mM (1.5 mEq/L) magnesium (Roy and Danziger, 1996). In another article (Kyriazis, 2004), a low dialysate magnesium level of 0.25 mM (0.50 mEq/L) was associated with intradialytic hypotension, especially when a low dialysate calcium was also used. So the best dialysis solution magnesium level to use for acute dialysis in terms of blood pressure maintenance remains unknown.
    a. **Hypomagnesemia.** Hypomagnesemia occurs in malnourished patients undergoing dialysis and in those receiving total parenteral nutrition during dialysis (owing to the shifting of magnesium into cells during anabolism). Hypomagnesemia can cause cardiac arrhythmia and can impair the release and action of parathyroid hormone. Cautious supplementation (eg, orally, intravenously) or increasing the concentration in the dialysate may be needed. Serum magnesium values should be carefully monitored in patients undergoing

dialysis during total parenteral nutrition, and total parenteral nutrition fluids should be supplemented routinely with magnesium unless the serum magnesium level is high.

   b. **Hypermagnesemia.** Hypermagnesemia is usually caused by accidental or covert use of magnesium-containing laxatives, enemas, or antacids. Manifestations of hypermagnesemia include hypotension, weakness, and bradyarrhythmias. Treatment is cessation of ingestion of magnesium-containing compounds. Hemodialysis also is effective in lowering the serum magnesium level.

6. **Dialysis solution dextrose level.** Dialysis solution for acute dialysis should always contain dextrose (100-200 mg/dL; 5.5-11 mmol/L). Septic patients, patients with diabetes, and those receiving β-blockers are at risk of developing severe hypoglycemia during dialysis. Addition of dextrose to the dialysis solution reduces the risk of hypoglycemia and may also result in a lower incidence of dialysis-related side effects. The interaction between dialysis solution glucose and potassium has already been discussed.
7. **Dialysis solution phosphate levels.** Phosphate is normally absent from the dialysis solution, and justifiably so, as patients in renal failure typically have elevated serum phosphate values. Use of a large surface-area dialyzer and the provision of a longer dialysis session increase the amount of phosphate removed during dialysis.

   a. **Hypophosphatemia.** Malnourished patients and patients receiving hyperalimentation may have low or low-normal predialysis serum phosphate levels. Predialysis hypophosphatemia may also be present in patients being intensively dialyzed for any purpose. In such patients, hypophosphatemia can be aggravated by dialysis against a conventional, zero-phosphate bath. Severe hypophosphatemia can cause respiratory muscle weakness and alterations in hemoglobin oxygen affinity. This can lead to respiratory arrest during dialysis. For patients at risk, phosphate can be added to the dialysis solution. Alternatively, phosphate can be given intravenously, although this must be done carefully to avoid overcorrection and hypocalcemia. Rapid correction of hypophosphatemia with IV phosphate has been associated with acute kidney injury (AKI). In one study, administration of 20 mmol over an average of 310 minutes was deemed generally safe, but was associated with a fall in ionized calcium in some patients, suggesting that a slower rate of replacement might be desirable (Agarwal, 2014).

   b. **Adding phosphate to bicarbonate-containing dialysis solutions.** For the prevention of hypophosphatemia, the phosphate concentration in the final dialysis solution should be about 1.3 mmol/L (4 mg/dL). Phosphate designed for IV use can be added to the bicarbonate component of the concentrate, which does not contain calcium or magnesium (Hussain, 2005). An alternative approach is to add sodium phosphate–containing enema preparations to either the bicarbonate or acid concentrate, as described in Chapter 15. The amount added can be set to achieve a final dialysis solution phosphate concentration of 1.3 mM (4.0 mg/dL); however, this practice is not Food and Drug Administration approved.

Of practical importance, adding phosphate or other supplements may be technically difficult or not feasible in facilities that rely on the dialysis machine to automatically mix the base solution from dry bicarbonate reagent.

D. Choosing the dialysis solution flow rates. For acute dialysis, the usual dialysis solution flow rate is 500 mL/min.

E. Dialysis solution temperature. This is usually 35 °C to 37 °C. The lower range should be used in hypotension-prone patients (see Chapter 12).

F. Ultrafiltration orders. Fluid removal needs can range from 0 to 5 kg per dialysis session.

1. Guidelines for ultrafiltration orders. Some guidelines to gauge the total amount of fluid that needs to be removed are as follows:

In patients with acute renal failure, it is extremely important to avoid hypotension at all times, including during dialysis. In a rat model of acute renal failure, Kelleher (1987) showed that the renal autoregulatory response to systemic hypotension is greatly impaired. They found that transient episodes of hypotension caused by blood withdrawal caused further renal damage and delay of functional renal recovery.

a. Even patients who are quite edematous and in pulmonary edema rarely need removal of more than 4 L of fluid during the initial session. The remaining excess fluid is best removed during a second session the following day.

b. If the patient does not have pedal edema or anasarca, in the absence of pulmonary congestion, it is unusual to need to remove greater than 2 to 3 L over the dialysis session. In fact, the fluid removal requirement may be zero in patients with little or no jugular venous distention. Fluid removal rates of 10 mL/kg/h are usually well tolerated in volume overloaded patients.

c. The fluid removal plan during dialysis should take into account the 0.2 L that the patient will receive at the end of dialysis in the form of saline to rinse the dialyzer and any other fluid ingested or administered during the hemodialysis session.

d. As already noted, if it is the initial dialysis, the length of the dialysis session should be limited to 2 hours. However, if a large amount of fluid (eg, 4.0 L) must be removed, it is impractical and dangerous to remove such an amount over a 2-hour period. In such instances, the dialysis solution flow can initially be shut off, and isolated ultrafiltration can be performed for 1 to 2 hours, removing some of the excess fluid as tolerated. Immediately thereafter, dialysis can be performed for 2 hours, removing the remainder of the desired fluid volume. (If severe electrolyte abnormalities, such as hyperkalemia, are present, dialysis may have to be performed prior to isolated ultrafiltration.)

e. In general, it is best to remove fluid at a constant rate throughout the dialysis treatment. If the dialysis solution sodium level has been set lower than the plasma value (eg, in the treatment of hypernatremia), the ultrafiltration rate can initially be reduced to compensate for the osmotic contraction of blood volume that will occur as the plasma sodium concentration is being lowered.

2. Impact of dialysis frequency on ultrafiltration needs. It is difficult in an acute setting to limit a patient's fluid gain to less than 2 L/d. Often 3 L/d is absorbed in patients receiving parenteral nutrition. Use of a frequent (4-7 times/wk) dialysis

schedule reduces the amount of fluid that needs to be removed with each dialysis, thereby lowering the risk of intradialytic hypotension and further ischemic damage to an already impaired set of kidneys. An alternative way to remove fluid relatively asymptomatically is to use SLED, a procedure described in Chapter 14.

II. HEMODIALYIS Procedure

A. Rinsing and priming the dialyzer (single-use setting).

Thorough rinsing of the dialyzer is important because it may reduce the incidence or severity of anaphylactic dialyzer reactions by virtue of the removal of leachable allergens (eg, ethylene oxide in ethylene oxide–sterilized dialyzers).

B. Obtaining vascular access

1. **Percutaneous venous cannula.** Clot or residual heparin is first aspirated from each catheter lumen. Patency of the catheter lumina is checked by irrigating with a saline-filled syringe. For acute dialysis, heparin-free dialysis is becoming more popular and is routinely used in some centers. If heparin is to be used, the heparin loading dose is administered into the venous catheter port and is flushed in with saline. After 3 minutes (to allow heparin to mix with the blood), blood flow is initiated.
2. **Arteriovenous (AV) fistula** (see also Chapter 6). Both needles are placed in the vein downstream to the anastomosis. Blood flow through the venous limb of the fistula is distal to proximal; hence, the arterial needle is placed distally. Some tips regarding needle placement are as follows:
   - **a.** In a patient with a poorly distended venous limb, brief application of a tourniquet may be helpful in defining its location. This tourniquet should be removed during dialysis, as its presence will encourage recirculation.
   - **b.** Choice of optimum needle size and use of ultrasound for access cannulation are discussed in Chapter 6. Larger needle sizes can be used when higher blood flow rates are desired.
   - **c.** Prepare the needle insertion sites with chlorhexidine or other suitable disinfectant.
   - **d. Arterial needle.** Insert it first, at least 3 cm away from the site of the AV anastomosis. The needle can be inserted bevel up or bevel down, pointing either upstream or downstream.
   - **e. Venous needle.** Insert bevel up or bevel down, pointing downstream (usually, this will be toward the heart). The insertion point customarily is inserted at least 3 to 5 cm downstream to the arterial needle to minimize entry of dialyzed blood into the arterial needle (recirculation), although one study suggests that closer needle placement does not result in recirculation (see Chapter 6).
   - **f. Angle of needle insertion.** This depends on the depth of the access from the surface of the skin and is usually 20–35° for AV fistulas and 45° for AV grafts (Brouwer, 2011).
3. **AV graft.** The anatomy of the graft should be known and preferably diagrammed in the patient's chart. The guidelines for placing needles are the same as for the AV fistula. Use of a tourniquet is never necessary.

   After the needles have been placed, if heparin is to be used, the heparin loading dose is given into the venous needle and flushed in with saline. After 3 minutes,

flow through the blood circuit is initiated.

C. Initiating dialysis. The blood flow rate is initially set at 50 mL/min, then 100 mL/min, until the entire blood circuit fills with blood. As the blood circuit fills, the priming fluid left in the dialyzer and tubing after rinsing can either be given to the patient or disposed of to drain. In the latter instance, the venous blood line is kept to drain until the blood column passes through the dialyzer and reaches the venous air trap. In unstable patients, the priming fluid is usually administered to the patient to help maintain the blood volume.

After the circuit is filled with blood and proper blood levels in the venous drip chamber are ensured, the blood flow rate should be increased promptly to the desired level. The pressure levels at the inflow (arterial) monitor, between the access site and the blood pump, and of the outflow (venous) monitor, between the dialyzer and the venous air trap, are noted, and the pressure limits are set slightly above and below the operating pressure to maximize the probability that the blood pump will stop and alarms will sound in the event of a line separation. If a line separation does occur, the pressure in the blood line will rapidly approach zero. As it does, it should trigger a properly set pressure limit switch. The lower pressure limit on the venous pressure gauge should be set within 10 to 20 mm Hg of the operating pressure; a larger gap can cause failure of the alarms to trigger with line separation. Unfortunately, even properly set venous pressure limits may not stop the pump if the venous needle dislodges or if there is a line separation. This issue is discussed in more detail in Chapter 4. For this reason, connections to the access should always be securely taped and kept visible to caregivers at all times (Ribitsch, 2014; Van Waeleghem, 2008). The dialysis solution flow can now be initiated. In machines with an ultrafiltration controller, the desired fluid removal rate is simply dialed in.

D. Beeps, buzzers, and alarms. As introduced in Chapter 4, the monitors on the dialysis solution machine include the following:

Blood Circuit	Dialysis Solution Circuit
Inflow pressure	Conductivity
Outflow pressure	Temperature
Air detector	Hemoglobin

1. Blood circuit (see Figure 10.1)

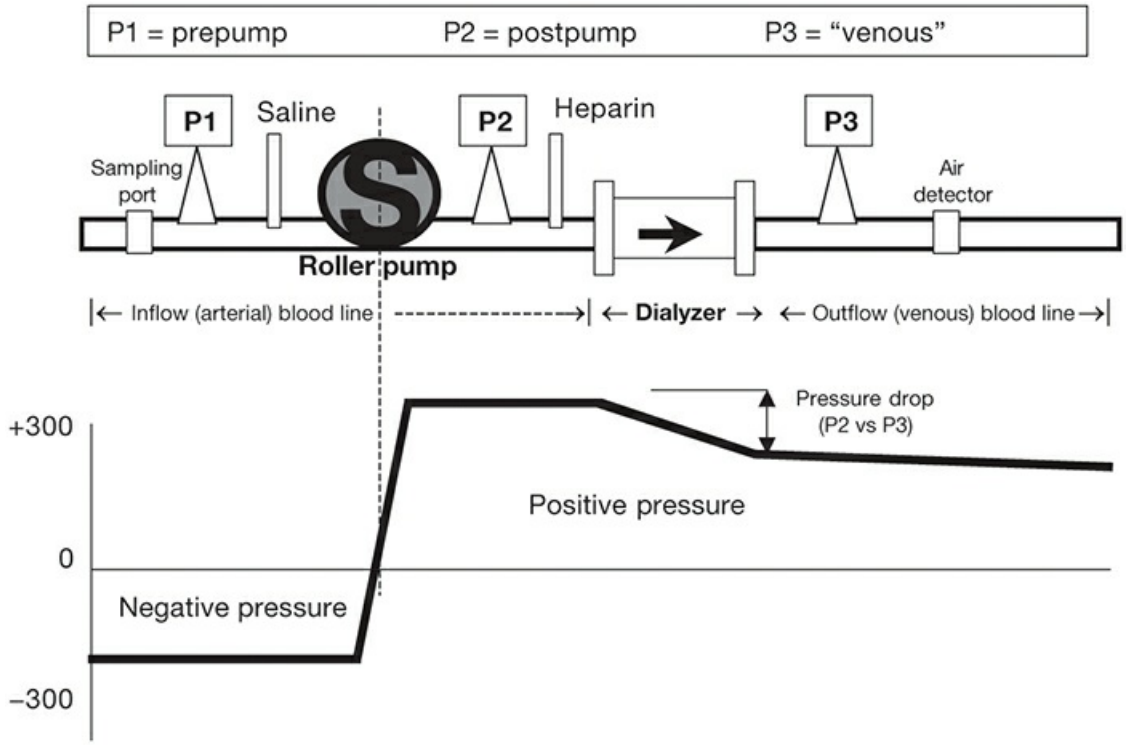


FIGURE 10.1: Pressure monitors and pressures on the blood side of the hemodialysis circuit.

a. Inflow (prepump) pressure monitor. Usually, the inflow pressure (proximal to the blood pump) is −80 to −200 mm Hg, with −250 mm Hg being considered the usual limit beyond which one does not go. If the access is not providing sufficient blood to the pump, the suction proximal to the blood pump will increase, and the alarm will sound, shutting off the blood pump.

1. **Causes of excessive inflow (prepump) suction**
   - **a. Venous catheter access. Usually, improper tip position or ball-valve thrombus or fibrin plug at the catheter tip.**
   - **b. AV access**
     - **i.** Improperly positioned arterial needle (needle not in vessel or up against vessel wall)
     - **ii.** Decrease in the patient's blood pressure (and hence flow through the access)
     - **iii.** Spasm of the access vessel (AV fistula only)
     - **iv.** Stenosis of the arterial anastomosis of an AV graft or fistula
     - **v.** Clotting of the arterial needle or of the access
     - **vi.** Kinking of the arterial line
     - **vii.** Collapse of the access due to elevation of the arm (if this is suspected, sit the patient up, blood pressure permitting, until the access site is below heart level)
     - **viii.** Use of too small a needle for the blood flow rate being used
2. **Management**
   - **a. Venous catheter.** Check lines for kinking. Sometimes, changing the arm or neck position or moving the catheter slightly makes the catheter

work. Reversing the catheter ports is another maneuver that sometimes works. If these initial steps do not work, subsequent steps include urokinase or tissue plasminogen activator infusion, checking catheter position in the radiology suite, or fibrin sleeve stripping, as described in Chapter 9.

b. AV access

i. Reduce blood flow rate to the point that inflow suction decreases and the alarm stays off.

ii. Verify that the patient's blood pressure is not unusually low. If the pressure is low, correct it by administering fluid or reducing the ultrafiltration rate.

iii. If a patient's pressure is not unusually low, untape the arterial needle, move it up or down slightly, or rotate it.

iv. Turn up the blood flow rate to the previous level. If inflow suction remains excessive, repeat step (iii).

v. If improvement is not obtained, continue dialysis for a longer time at a lower blood flow rate, or place a second arterial needle (leaving the original, flushed with heparinized saline, in place until the end of dialysis), and dialyze through the second needle.

vi. If excessive inflow suction persists despite needle change, the inflow to the vascular access may be stenosed. Occlude the access between the arterial and venous needles by transient pressure with two fingers. If the negative pressure at the prepump monitor increases markedly when the intraneedle segment is occluded, this is a sign that some of the inflow was coming from the downstream access limb and that blood flow through the upstream limb of the access is inadequate.

b. Outflow (venous) pressure monitor. Usually, the pressure here is +50 to +250 mm Hg, depending on needle size, blood flow rate, and hematocrit.

1. Causes of high venous pressure

a. The pressure may be as high as 200 mm Hg when using an AV graft because the high arterial pressure in the graft is often transmitted to the venous line.

b. High blood flow rate when using a relatively small (16G) venous needle

c. Clotting in the venous bloodline filter if one is being used. Clotting of the filter may be the first sign of inadequate heparinization and of incipient clotting of the entire dialyzer.

d. Stenosis (or spasm) at the venous limb of the vascular access

e. Improperly positioned venous needle or kinked venous line

f. Clotting of the venous needle or venous limb of the vascular access

2. Management of high venous pressure

a. If clotting of the venous blood line filter is at fault, the dialyzer should be rinsed with saline (by opening up the saline infusion line and briefly clamping the blood inlet line proximal to the saline infusion port). If the dialyzer is not clotted (fibers appear clear on saline rinse), then a new venous line can be rapidly primed with saline and substituted for the

partially clotted line, and dialysis can be resumed after adjusting the heparin dose.

b. The presence or absence of obstruction at the venous needle or in the venous limb of the access can be assessed by shutting off the blood pump, quickly clamping the venous blood line, disconnecting the venous blood line from the venous needle, and irrigating through the venous needle with saline and noting the amount of resistance.

c. Occlude the access between the arterial and venous needles by pressing down gently with two fingers. If stenosis downstream is causing outflow obstruction through the vascular access, the positive pressure measured at the venous monitor will increase further when the upstream access is occluded.

c. Air detector. The danger of inadvertent air entry is greatest between the vascular access site and the blood pump, where the pressure is negative. Common sites of air entry include the region around the arterial needle (especially if the inflow suction is very high), via leaky tubing connections, via broken blood tubing as it passes through the roller pump, or via the saline infusion set. Air can also enter the patient if air return is improperly performed at the end of dialysis. Many air emboli occur after the air detector has been turned off because of false alarms. This practice should be avoided. Air embolism can be fatal.

The creation of microbubbles during dialysis and their potential adverse effects is discussed in Chapter 4.

d. Blood line kinking and hemolysis. Severe hemolysis may occur because of kinking of the blood line between the pump and the dialyzer. This is a relatively common cause of dialysis machine/blood line malfunction causing patient injury. Blood lines configured for prepump pressure monitoring will not alarm if high pressures are encountered in the postpump segment between the pump and dialyzer. Even if a blood line with a postpump pressure monitor is being used, if the kink is upstream to the origin of the pressure monitoring line, high pressure due to the kink will not be detected.

2. Dialysis solution circuit monitors. The dangers of dialyzing against an excessively concentrated, dilute, or hot dialysis solution have been discussed in Chapter 4.

a. Conductivity. The most common cause of increased dialysis solution conductivity is either a kink in the tubing routing purified water to the dialysis machine or low water pressure, resulting in insufficient water delivery to the machine. The most common cause of reduced conductivity is an empty concentrate bottle. Otherwise, the cause is usually in the proportioning pump. The dialysis solution bypass valve is activated as soon as conductivity deviates from the specified limits, diverting the abnormal dialysis solution away from the dialyzer to the drain.

b. Temperature. Abnormal temperature is usually caused by some malfunction in the heating circuit that warms the dialysate. Again, a properly functioning bypass valve protects the patient.

c. Hemoglobin (blood leak). False alarms may be due to the presence of air

bubbles in the dialysis solution, to dialysate bilirubin in jaundiced patients, or to a dirty sensor. The dialysate may not appear to be discolored to the naked eye. A blood leak alarm should be confirmed by testing the effluent dialysate with a test strip of the sort used for detecting hemoglobin in the urine. If a leak is confirmed, blood should be returned and dialysis discontinued. Treatment of cyanide poisoning by IV high-dose hydroxocobalamin has been reported to generate a false blood leak alarm (Datar, 2019).

E. Patient monitoring and complications. The patient's blood pressure should be monitored as often as necessary, but at least every 15 minutes for an acute dialysis in an unstable patient. The manifestations and treatment of hypotension and other complications during dialysis are discussed in Chapter 12.

F. Termination of dialysis. The blood in the extracorporeal circuit can be returned using either saline or air. If saline is used, the patient usually receives 100 to 300 mL of this fluid during the rinse-back procedure, nullifying the corresponding amount of fluid removed by ultrafiltration. However, if the patient's blood pressure is low at the end of dialysis, the saline bolus will help to raise the blood pressure quickly. When air is used, the blood pump is first shut off, and the arterial blood line is clamped close to the patient. The arterial blood line is then disconnected just distal to the clamp, opening it to air. The blood pump is restarted at a reduced rate (20-50 mL/min), and the air is allowed to displace the blood in the dialyzer. When the air reaches the venous air trap, or when air bubbles are first seen in the venous blood line, the venous line is clamped, the blood pump shut off, and the return procedure terminated. Use of air to return the blood increases the risk of air embolism, and the termination procedure should be extremely carefully supervised when air return is employed.

G. Postdialysis evaluation

1. **Weight loss.** The patient should be weighed after dialysis whenever possible, and the postdialysis weight compared with the predialysis weight. It is not uncommon for the weight loss to be greater or less than that anticipated on the basis of the calculated ultrafiltration rate. Given the high accuracy of the volumetric ultrafiltration controllers in modern hemodialysis machines, unpredicted pre-to-post weight changes are usually due to the failure to take into account fluid administered to the patient during dialysis in the form of saline, medications, hyperalimentation, or oral fluid or food ingestion.
2. **Postdialysis blood values.** Blood can be sampled promptly after dialysis to confirm the adequacy of urea nitrogen removal and correction of acidosis. For urea nitrogen, sodium, and calcium, the postdialysis specimen is usually drawn 20 to 30 seconds to 2 minutes after dialysis. A postdialysis increase in the plasma urea level of 10% to 20% usually occurs within 30 minutes due to reequilibration of urea between various body compartments. The method of obtaining the postdialysis blood sample is quite important; if access recirculation is present, dilution of the inlet blood sample with dialyzed outlet blood can occur, yielding erroneously low plasma urea nitrogen values. The timing of the sampling is critically important in that it can help discern access recirculation, cardiopulmonary recirculation, and intercompartmental rebound effects. Reliable methods of obtaining the postdialysis sample are described in Chapters 3 and 11.
   a. **Urea nitrogen.** The methods described in Chapters 3 and 11 can be used to

estimate a predicted *Kt*/*V* and URR. If the serum urea nitrogen value has fallen to a lesser than expected extent, possible causes include partial clotting of the dialyzer, an error in setting of the blood flow rate, and recirculation at the vascular access site. Online machine methods of monitoring in vivo dialyzer clearance (ionic conductance) and *Kt*/*V* (ultraviolet light absorbance of the spent dialysate) are described in Chapter 11.

b. Potassium. The change in the plasma potassium level as a result of dialysis is difficult to predict because of the concomitant shifting of potassium into cells due to correction of acidosis or to cellular uptake of glucose. In acute patients, it is best to sample blood for potassium at least 1 hour after the end of dialysis.

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11 Chronic Hemodialysis Prescription

John T. Daugirdas

Please review Chapter 3 at this time. Many concepts developed in Chapter 3 will be only briefly touched on here.

I. UREA AS A MARKER SOLUTE. Although uremic toxicity is due to both small- and large-molecular-weight solutes, small toxins appear to be of greater importance. For this reason (and there are practical, laboratory measurement issues as well), the amount of dialysis prescribed is based on the removal of urea, which has a molecular weight of 60 Da. Urea is only slightly toxic per se, and so its plasma level is only reflecting concentrations of other, presumably more harmful, uremic toxins.

A. Urea removal versus serum level. Both removal and serum level should be monitored when checking dialysis adequacy. Monitoring of urea removal is more important. If removal is inadequate, then dialysis is inadequate, regardless of the serum level. On the other hand, a low serum urea level does not necessarily reflect adequate dialysis. The serum level depends not only on the rate of removal but also on the rate of urea generation. The generation rate is linked to the protein nitrogen appearance rate because most protein nitrogen is excreted as urea. A low serum urea level may be found in patients in whom removal is poor but in whom the generation rate is also low (eg, due to poor protein intake).

B. Measures of urea removal. These are the urea reduction ratio (URR), the single-pool *Kt*/*V* (sp*Kt*/*V*), the equilibrated *Kt*/*V* (e*Kt*/*V*), and the weekly standard *Kt*/*V* (std*Kt*/*V*) (see Chapter 3).

C. Dose of dialysis in terms of urea removal for thrice-weekly dialysis. In a secondary analysis of the randomized National Cooperative Dialysis Study (Gotch and Sargent, 1985), the rate of treatment failure increased dramatically in patients dialyzed 3 times/wk when sp*Kt*/*V* was less than 0.8, compared with when values were greater than 1.0. In large observational studies, similar results were found. For this reason, the Kidney Disease Outcomes Quality Initiative (KDOQI) Adequacy Workgroups have recommended a minimum sp*Kt*/*V* of 1.2 for patients undergoing dialysis, with a target value of at least 1.4 (National Kidney Foundation, 2015). This translates to a std*Kt*/*V* urea value of 2.1 when std*Kt*/*V* is calculated using modeling or by a method that takes volume contraction into account. The European Best Practice Guidelines (2002) recommend a slightly higher minimum amount of dialysis, defined as a minimum e*Kt*/*V* of 1.2. Values for e*Kt*/*V* tend to be about 0.15 units lower than sp*Kt*/*V*, the amount depending on the rate of dialysis. High-level evidence guideline recommendations depend on randomized studies, and in the field of dialysis adequacy, the only other larger randomized study that has been done is the HEMO study, where an sp*Kt*/*V* of 1.7 was compared with an sp*Kt*/*V* of 1.3 (the study doses were actually defined in terms of

e*Kt*/*V*). Patients assigned to the higher dose of dialysis did not live longer, were not hospitalized less frequently, and were not found to manifest nutritional or other benefits. Apart from these two studies, there is little high-quality evidence regarding dialysis dose and outcomes, and almost all recommendations and guidelines in this area are primarily opinion based.

1. **Effect of gender.** In the randomized analysis of the HEMO trial (Eknoyan, 2002), the women assigned to the higher dose of dialysis survived longer than the women assigned to the standard dose. Survival in the men assigned to the higher dialysis dose was slightly worse, so the overall effect of dose in the HEMO trial was negative, and it is not clear whether this dose-gender interaction was real or just a statistical fluke. If women need more dialysis, the reason is unclear. As detailed in Chapter 3, an alternative method of scaling dialysis dose might be to scale to body surface area (BSA) instead of to urea distribution volume (*V*). In healthy patients and in children, glomerular filtration rate (GFR) naturally scales to BSA, and an adult man and woman with similar values for BSA will have similar levels of GFR (Daugirdas, 2009). Because the ratio of *V*:BSA is about 12% to 15% different in men than in women, under current dosing guidelines, if a man and a woman have the same level of *V*, they will get the same dose of dialysis; however, BSA in the woman will be 12% to 15% higher, so theoretically one might argue that women need about 15% more dialysis than men. If one wishes to increase the dose of dialysis in terms of std*Kt*/*V*, the increase in sp*Kt*/*V* has to be increased by about twice as much. So this line of reasoning would suggest that the minimum sp*Kt*/*V* in women should be about 25% to 30% higher than that in men. However, the optimum method of scaling dialysis dose is not known, and there are no firm data other than the HEMO study and a few observational studies to suggest that BSA should be used to scale dialysis dose instead of *V*.
2. **Smaller patients.** One can come up with four reasons why smaller patients should get relatively more dialysis when dose is measured as sp*Kt*/*V*:
   - **a.** Small patients (those with small values for *V*) would get a larger amount of dialysis if the dose were scaled to BSA.
   - **b.** The KDOQI dose targets are in the form of sp*Kt*/*V* and not e*Kt*/*V*; postdialysis urea rebound tends to be larger in smaller patients.
   - **c.** It is fairly easy to deliver a high *Kt*/*V* to small patients (and also women) in a short session length (eg, 2.5 hours). Such short session lengths may not be sufficient to allow for the removal of middle molecules, nor for adequate removal of excess fluid, and this may result in a chronically overhydrated patient.
   - **d.** Short session length treatments may give a seemingly adequate *Kt*/*V* level, but in patients who gain large amounts of fluid between treatments, short session lengths may require a relatively high ultrafiltration rate to remove this fluid and high ultrafiltration rates are associated with a poor outcome.
3. **Malnourished patients.** When a patient's weight is substantially below the weight of their peers, or when a patient has lost a large amount of weight, one opinion is to scale dialysis to the patient's optimum "healthy" weight, and not the current reduced weight. The thinking is that the increased amount of dialysis will help return the patient to their healthier, premorbid condition.

4. **Residual renal urea clearance (Kru).** Whether patients with substantial residual kidney function can be managed with lower doses of dialysis is an unanswered question. In one large study, when patient urine volume was greater than 100 mL/d, the amount of dialysis delivered had little impact on survival (Termorshuizen, 2004). Methods of adjusting dialysis dose for residual kidney function are entirely opinion based. There are a variety of modeling-based adjustments that can be used. Readers can look to the European Best Practice recommendations (2002) and to the National Kidney Foundation's Kidney Dialysis Outcomes Quality Initiative (NKF-KDOQI) 2015 adequacy guidelines for some suggested guidance.

D. Adequacy targets for schedules other than 3 times/wk. There is no high-level evidence that can guide us in terms of dose titration when dialysis is given other than 3 times/wk. One approach is to maintain a minimum std*Kt/V* (calculated using modeling or the Frequent Hemodialysis Network [FHN] equation) of 2.1 across all dialysis schedules (Table 11.1). The value of 2.1 was chosen because it corresponds to a 3 times/wk schedule with an sp*Kt/V* of 1.2 (NKF-KDOQI, 2015).

TABLE 11.1 Minimum[a] sp*Kt/V* Values for Various Frequency Schedules of Dialysis (Achieving an Estimated std*Kt/V* = 2.1)

Schedule[b]	K_r, <2 mL/min/1.73 m^2	K_r, 2 mL/min/1.73 m^2 and higher
Two times/wk	Not recommended	2.0
Three times/wk	1.2	0.9
Four times/wk	0.8	0.6

Assumes session lengths of 3.5 to 4 hours.

K_r = residual kidney urea clearance.

[a]Target sp*Kt/V* values should be about 15% higher than the minimum values shown.

[b]Frequent dialysis (5 and 6 times/wk) is more completely discussed in Chapter 15.

Adapted from Hemodialysis Adequacy 2006 Work Group. Clinical practice guidelines for hemodialysis adequacy, update 2006. *Am J Kidney Dis*. 2006;48:(suppl1):S2-S90.

1. **Four to six sessions per week.** In one randomized trial that showed a benefit of more frequent dialysis, the FHN Daily Trial, the average delivered std*Kt*/*V* averaged 3.7, considerably higher than the 2.1 minimum dose suggested by NKF-KDOQI. The average number of treatments delivered per week was 5, and the average delivered session length was 154 minutes (FHN Trial Group, 2010).
2. **Twice-a-week dialysis.** In the developing world, many patients are dialyzed only twice a week for economic reasons, and in the United States, this was not unusual in the past. Kinetic modeling using an std*Kt*/*V* approach suggests that twice-a-week dialysis is not appropriate in patients without some modest degree of residual kidney function. There are preliminary data suggesting that starting incident patients out on twice-a-week dialysis may result in longer preservation of residual kidney function (Kalantar-Zadeh, 2014), but this has not been borne out in other studies. One observational study of twice-a-week dialysis done many years ago in the United States was unable to show an adverse association for this treatment strategy, and outcomes were actually a bit better than in patients dialyzed 3 times/wk. Lack of harm may have been due to preferential selection of patients with some residual

kidney function (Hanson, 1999), but there was no definitive evidence that this was the case.

E. Adequacy targets based on metrics other than urea removal

1. **Dialysis time.** Urea removal is only one measure of dialysis adequacy. For solutes such as phosphate and middle molecules, total weekly time on dialysis is the major determinant of removal. Short weekly time on dialysis also makes it difficult to remove excess salt and water from patients safely and effectively. The US KDOQI 2006 adequacy work group recommended a minimum session length of 3 hours for patients dialyzed 3 times/wk with little residual renal function. The European Best Practices Group (2002) recommends a minimum 4-hour treatment time. The benefits of dialysis sessions longer than 3.5 hours are not clear and seem to be greatest in Japan and intermediate in Europe; benefits are difficult to demonstrate in the United States (Tentori, 2012), perhaps because of the more intense dialysis given in the United States. In the United States, the average dialysis time is about 3.5 hours and is increasing toward 4 hours, similar to the practice in the rest of the world.

   One argument favoring longer dialysis sessions has to do with their effect on lowering the ultrafiltration rate. Lower ultrafiltration rates during dialysis are associated with improved survival (Mermelstein, 2023). Although the main cause of high ultrafiltration rates is large amounts of fluid ingestion between dialyses, for any given amount of weekly fluid ingestion, increasing weekly dialysis time will proportionately lower the ultrafiltration rate.

   Another argument against *Kt/V* is that a focus on urea removal tends to drive high-efficiency dialysis, with the use of large dialyzers and rapid blood flows; the high efficiency of such treatments may result in solute disequilibrium and intradialytic side effects. Also, high blood flow rates delivered using the requisite larger needle sizes may engender more blood turbulence and platelet activation, as well as access dysfunction. A related question is whether one should make "optimum" use of the dialysis time by prescribing the highest blood flow that is consistently achievable, and using the most efficient (high K_0A) dialyzer that one can afford. An alternative "slow and gentle" approach remains popular in Europe, according to which low blood flow rates and relatively small dialyzers are used. There are no randomized trials available to help choose between these two options. The best approach may be to set targets on the basis of both *Kt/V* (perhaps with higher minimum targets for women and smaller patients) and dialysis time. Changing the *Kt/V* target to a body surface area–adjusted value by itself solves the problem of short dialysis time given to smaller patients and women, as the amount of dialysis given to such patients based on body surface area needs to be considerably larger, and this takes more time to deliver.

   The association between surface area–normalized std*Kt/V* and outcomes is more monotonic compared to the association of outcomes with treatment *Kt/V* or std*Kt/V* (Pattharanitima, 2020).

2. **Removal of high-molecular-weight solutes.** Many higher-molecular-weight solutes accumulate in uremia, ranging in weight from 500 to 40,000 Da. As detailed in Chapter 3, their removal is impaired during hemodialysis for a number of reasons. Because they are large, they diffuse slowly through a dialysis membrane. The pore size of so-called low-flux dialyzer membranes does not allow for the passage of

molecules above 10,000 Da in weight. The so-called high-flux dialyzer membranes that now are almost uniformly used do allow the passage of such larger molecules. One molecule in this category is β-2-microglobulin, which has a molecular weight of 11,800 Da. Accumulation of β-2-microglobulin has been associated with β-2-microglobulin amyloidosis, which can manifest as carpal tunnel syndrome (hand pain, paresthesia), tendinitis, shoulder pain, spinal cord compression, and gastrointestinal problems (pseudo-obstruction, bleeding, ischemia). Although removal of β-2-microglobulin is increased with high-flux membranes, predialysis serum levels remain 15 to 20 higher than those found in nonuremic individuals, and β-2-microglobulin–related complications remain of concern, especially in patients on hemodialysis for longer than 5 years (Portales-Castillo, 2020).

II. WRITING THE INITIAL PRESCRIPTION

A. The dialysis dose: *K* × *t*.

A dialysis prescription involves two main components: *K*, the dialyzer clearance, and *t*, the dialysis session length. *K*, in turn, depends on the dialyzer size used and the blood flow rate. The dialysate flow rate also plays a small role, as discussed in Chapter 3.

1. ***K* usually ranges from 200 to 260 mL/min.** For adult patients dialyzed using a blood flow rate of 400 mL/min, dialyzer clearance *K* will usually be about 230 ± 30 mL/min. One can use a urea kinetics calculator or a nomogram such as Figure 13.6, to get a reasonable estimate of dialyzer clearance from the blood flow rate and the efficiency of the dialyzer (K_0A) being used. If we assume that *K* will be 250 mL/min for a dialysis session length of 4 hours, $K \times t$ will be 250 × 240 = 60,000 mL or 60 L. This represents the total volume of blood water cleared of urea during the dialysis session.
2. **Targeting *K* × t on the basis of patient size and desired *Kt/V*.** Assume that we have a clearance of 250 mL/min and a session length of 4 hours. How large a patient could we dialyze and still meet KDOQI guidelines? Remember that the guidelines suggest using a prescribed $(K \times t)/V$ of 1.4 to ensure that the delivered dose stays above 1.2. Over the 4-hour session, we are delivering 60 L of $K \times t$, and if we want a prescribed Kt/V of 1.4, V must be 60/1.4 = 43 L, corresponding to a weight of about 86 kg. See Tables 11.2 and 11.3 for some additional examples.

TABLE 11.2 The Initial Prescription for a Specific Patient to Achieve a Desired sp*Kt/V*

Step 1: Estimate the patient's *V*. Use 90% of the Watson total body water estimate or 50% of the postdialysis body weight.

Step 2: Multiply *V* by the desired *Kt/V* to get the required $K \times t$.

Step 3: Compute required *K* for a given *t*, or the required *t* for a given *K*.

Step 1. Estimate *V*. This is best done from anthropometric equations incorporating height, weight, age, and gender as devised by Watson (Appendix B). Alternatively, one can use the Hume-Weyers equations or the nomogram (Appendix B). Use 90% of the estimated Watson volume to estimate the urea distribution volume (*V*). Assume that, in this case, the estimated *V* is 40 L.

Step 2. Compute the required *K* × *t*. If the desired *Kt/V* is 1.5 and the estimated *V* is 40 L, then the required $K \times t$ is 1.5 times *V*, or 1.5 × 40 = 60 L.

Step 3. Compute the required t or *K*. The required $K \times t$ can be achieved with a variety of different combinations

of K (which depends on K_0A, Q_B, and Q_D) and t. A variety of urea modeling programs are available that will do a computer simulation of various scenarios and come up with many possible combinations of K and t. Internet-based calculators can be accessed via the Web References cited at the end of this chapter.

Given a desired session length t, how to compute the required K?

One approach is to input a session length t and then ask: What kind of dialyzer, blood flow rate, and dialysate flow rate would I then need to achieve the required $K \times t$? Again, simple algebra is sufficient. From the previous example:

Desired spKt/V = 1.5; Estimated V = 40 L, $K \times t$ = 60 L

First, convert $K \times t$ to milliliters to get 60,000 mL. If the desired session length is 4 h or 240 min:

Desired t = 240 min

Required $K = (K \times t)/t$ = 60,000/240 = 250 mL/min

Now that we know the required K, how to choose K_0A, Q_B, and Q_D.

How does one now choose K_0A, Q_B, and Q_D? A simple way is to select the most rapid value of Q_B that can be reliably and consistently delivered. Assume in this patient that a blood pump speed of 400 mL/min will be possible. One can then go to the K-K_0A-Q_B nomogram (Figure 3.6) to find the approximate dialyzer K_0A value that will be required to achieve a K of 250 mL/min at a blood flow rate of 400 mL/min.

To find the required dialyzer K_0A, find 400 (which is Q_B) on the horizontal axis, then go up until you find 250 (desired K) on the vertical axis. At this point, you are on a K_0A line of about 900, so a dialyzer with a K_0A value of at least 900 mL/min will be needed. Some 5%-10% improvement in K can be obtained by increasing the dialysate flow rate to 800 mL/min when the blood flow rate is relatively high. However, with some modern dialyzers that include spacer yarns to optimize dialysate flow around the fibers, increasing dialysate flow from 600 to 800 mL/min was shown to have very little impact (Ward, 2011).

TABLE 11.3

Given an Actual Blood Flow Rate (Q_B), How to Compute Required Session Length Given Two Possible Choices of Dialyzers

A common situation occurs when the maximum blood flow rate that can be reliably delivered is known. Often, one has a choice between using a larger (more expensive) or a smaller (slightly cheaper) dialyzer. Let us assume that one is constrained to use a dialysate flow rate of 500 mL/min. What would the dialysis session length then need to be to achieve a target spKt/V of 1.5? Let us assume that we are prescribing for the same patient, with an estimated V of 40 L, which means that $K \times t$ again must be 60 L or 60,000 mL. Assume that the projected blood flow rate is 400 mL/min. Of the two dialyzers available, we looked up their K_0A (maximum clearance) values and found they are 1,400 mL/min for the larger one and 800 mL/min for the smaller one. So how long do we need to dialyze this patient with each of the two dialyzers?

Step 1: From Figure 3.6 (which we can use because Q_D = 500 mL/min), find the K corresponding to Q_B of 400 mL/min (x-axis value) for each of the two dialyzers. K will be the value on the vertical axis that corresponds to the intersection of the 1,400- and 800-K_0A lines with a perpendicular rising from the horizontal axis (Q_B) at a point representing 400 mL/min. We find that the K values are about 270 mL/min for the bigger (K_0A = 1,400) dialyzer and 220 mL/min for the smaller (K_0A = 800) dialyzer.

Step 2: We know that spKt/V = 1.5 and estimated V = 40 L. Our desired $K \times t$ is 60 L or 60,000 mL. By algebra:

$$800\text{-}K_0A \text{ dialyzer}, K = 220: \quad t = \frac{(K \times t)}{K} = \frac{60{,}000}{220} = 273\text{min}$$

$$1{,}400\text{-}K_0A \text{ dialyzer}, K = 270: \quad t = \frac{(K \times t)}{K} = \frac{60{,}000}{270} = 222\text{min}$$

Our calculations thus suggest that we will need to dialyze for 50 min longer using the smaller (K_0A = 800) dialyzer to achieve the same spKt/V of 1.5.

B. How weight change during dialysis affects the dialysis prescription. In patients who have large weight gains, one will need a higher *Kt/V* to get a given URR than in patients with minimal weight gain (see Figure 3.14 in Chapter 3). For example, to get a URR of 70%, one needs to prescribe a *Kt/V* of only 1.3 if no fluid is removed, but one needs a *Kt/V* of 1.5 if the weight loss during dialysis (UF/*W*) is 6% of the body weight (see the 0.06 UF/*W* line in Figure 3.14).

III. CHECKING THE DELIVERED DOSE OF DIALYSIS.

The dialysis dose is usually monitored on a monthly basis, according to KDOQI guidelines, by drawing a predialysis and postdialysis serum urea nitrogen (SUN). Alternatively and/or additionally, in vivo dialyzer clearance can be monitored during each treatment by checking the dialyzer sodium (conductivity) clearance, or the delivered dialysis dose can be followed by tracking the ultraviolet (UV) absorbance of the spent dialysate, as described in Chapter 3.

The pre- and post-SUN values are used to compute the URR, which is then combined with information concerning UF/*W* and with some other adjustments to compute the delivered sp*Kt/V*. One caveat: When checking the URR, one must be sure to use a properly drawn postdialysis blood specimen. In the presence of access recirculation, the postdialysis blood may be low due to admixture of dialyzer inlet blood with dialyzer outlet blood unless a slow-blood-flow or a stop-dialysate-flow technique is used. Two KDOQI-suggested techniques for blood drawing are described in Table 11.4, and the reasons behind them are explained in detail in Chapter 3.

TABLE 11.4 Guidelines for Obtaining the Postdialysis Serum Urea Nitrogen Sample

Principles

The effect of access recirculation will reverse quickly. When blood flow is slowed to 100 mL/min, the inflow urea concentration will rise in about 10-20 s (depending on the amount of dead space in the arterial line, usually about 10 mL).

Method

1. Set the ultrafiltration rate to 0.
2. Slow the blood pump to 100 mL/min for 10-20 s.
3. Stop the pump.
4. Draw a sample, either from the arterial blood line sampling port or from the tubing attached to the arterial needle.

Alternate Method

1. Set the ultrafiltration rate to 0.
2. Put dialysate into bypass.
3. Keep blood flow going at the usual rate; wait 3 min.
4. Draw the sample.

A. Methods of computing spKt/V from the pre- and post-SUN

1. **Nomogram method.** One uses Figure 3.14 as described before. Assume that a URR of 0.70 or 70% is measured. Depending on whether 0%, 3%, or 6% of the body weight was removed during the dialysis treatment, the delivered sp*Kt*/*V* for that treatment will be 1.3, 1.4, or 1.5, respectively.

2. **More exact methods.** The optimal method recommended by the KDOQI guidelines to calculate *Kt/V* is to use a urea kinetic modeling program. The basic principles of how such programs work are described in Chapter 3. These programs are available commercially, and one, Solute Solver, is available on the Internet (http://www.ureakinetics.org). An alternative method that is approved by KDOQI is to use the following equation (Daugirdas, 1993):

   $$spKt/V = -\ln(R - 0.008 \times t) + (4 - 3.5 \times R) \times UF/W$$

   where R is (1 − URR), or simply post-SUN/pre-SUN, t is the session length in hours, −ln is the negative natural logarithm, UF (volume of ultrafiltration) is the weight loss in kilograms, and W is the postdialysis weight. See Chapter 3 for a more complete discussion of this formula.

IV. ADJUSTING THE INITIAL DIALYSIS PRESCRIPTION.

When patients are put on a particular dialysis prescription, even when there are no apparent changes in therapy, the delivered sp*Kt/V* derived from the measured URR often will vary considerably from month to month. The reasons are not completely clear, but laboratory error in measuring the SUN values in the samples, possible variations in how the postdialysis blood is drawn and variations in actual session length, time-averaged blood flow rate, and dialyzer clearance may all have a role (Raimann, 2020). It may be useful to average the sp*Kt/V* value from three monthly treatments to determine whether the standard minimum sp*Kt/V* of 1.2 is being delivered.

Example: Assume that we want to target an sp*Kt/V* of 1.5. The patient is monitored monthly, and from the URR, the following sp*Kt/V* values are obtained:

Month	sp*KtlV*
Jan	1.40
Feb	1.35
Mar	1.54
Apr	1.30

The average of these values is 1.40. Although this is well within KDOQI targets for dialysis adequacy, if one wishes to achieve the original sp*Kt/V* goal of 1.5, one needs to increase the numerator ($K \times t$) in *Kt/V* by a factor of 1.5/1.4 or 1.07 (7%).

One now has a choice in that either the K or the t term can be increased by 7% (or each one can be increased so that their product increases by 7%). The simplest way to increase *Kt/V* from 1.4 to 1.5 is to increase dialysis session length by 7%. This would mean adding 17 minutes to a 4-hour treatment (1.07 × 240 = 257 minutes). Another option is to try to increase the K term by going to a higher blood flow rate, going to a larger dialyzer, or increasing the dialysate flow rate. However, it is often difficult to increase the blood flow rate further. The impact of changing to a more efficient dialyzer can be estimated from the K_0A versus clearance nomogram shown in Figure 3.6. Increasing the dialysate flow rate to 800 mL/min, which typically results in about a 5% to 10% increase in clearance as long as the blood flow rate is greater than 400 mL/min, might also do the trick, but is not always helpful with some advanced dialyzers where the dialysate flow path is already optimized (Ward, 2011).

V. THE CONCEPT OF MODELED V.

One of the advantages of using a modeling program is that the computer calculates how much urea was removed, and then, on the basis of the URR, weight change, and session length, calculates the size of the volume from which the urea appears to have been removed. To do this, the computer uses a "marbles in the box" approach described in Chapter 3. It is important to recognize that *V* is a tool that is used to assess dialysis adequacy. It does not always reflect the true urea distribution volume. Computers are not very smart, in the sense that they use only the information given to them. For example, if the URR and hence sp*Kt/V* suddenly decrease owing to a batch of bad dialyzers, all the computer knows is that the sp*Kt/V* has suddenly fallen, but it is not told that the dialyzer clearance (*K*) has changed. Also, the session length (*t*) has not changed. How, then, can the computer explain the sudden decrease in sp*Kt/V* if $K \times t$ is unchanged? All it knows is that $(K \times t)/V$ is lower than it was and that $(K \times t)$ is unchanged. The only way the computer can explain this scenario is to assume that the patient's urea distribution volume (*V*) must have increased. A marked change in a patient's true volume happens only rarely, so a rise in modeled *V* usually means that for some reason, less dialysis was given than was ordered or anticipated.

A. Monitoring modeled V in individual patients

Example 1. In a different patient, in May, an sp*Kt/V* of 1.5 is delivered, and the computer models the size of the patient's urea volume (modeled *V*) as 43 L. Values for the subsequent 4 months are as shown.

Month	sp*Kt/V*	Modeled *V*
May	1.5	43
Jun	1.43	45
Jul	1.7	38
Aug	1.8	36
Sep	1.1	58

A transient increase in the value for *V* was found in September owing to an unexpectedly low value for the sp*Kt/V*. What should be done at this point?

Step 1: Review the dialysis run sheet for the September treatment. The low sp*Kt/V* and the apparent rise in *V* most probably reflect an unrecorded decrease in *K* or *t*. Was the treatment shortened? Was the blood flow rate reduced during all or part of the treatment? Did the dialysate concentrate run out? Were there problems with access during the treatment? If the answer to these questions is no, it can be assumed that the aberrant result was most likely due to measurement error.

Step 2: The prescription should not be changed at this point. One approach is to obtain one or more additional pre-/post-SUN measurements to determine whether the low sp*Kt/V* value was a fluke or something about which to be concerned. The September sp*Kt/V* measure is still 1.1, which is close to the minimum KDOQI guideline of 1.2, so one could justify waiting for the next regular monthly blood draw. This situation shows why having some sort of machine-generated clearance, from either dialyzer sodium clearance or UV dialysate absorbance, would be of great help, as these clearances are measured every treatment, and they would show whether the low September value is an anomaly or some form of laboratory error.

A repeat sp*Kt/V* should be measured, and if the repeat value is still low, this means

that some major problem has developed in delivering either the prescribed *K* or *t*. The most likely explanation that would cause a decrease in sp*Kt/V* of this magnitude would be the development of access recirculation. Other potential causes are discussed in Table 11.5.

TABLE 11.5 Reasons Why the Urea Reduction Ratio-Based Delivered sp*Kt/V* May Be Different Than Prescribed *Kt/V*

Reasons why delivered *Kt/V* may be less than prescribed (in this case, modeled *V* will be increased)
Patient's *V* greater than initial estimate (initial R_X only)
Actual blood flow less than that marked on the blood pump (very common when prepump negative pressure is high)
Blood flow temporarily lowered (symptoms or other reasons)
Actual dialysis session length shorter than prescribed
Dialyzer K_0A less than expected (manufacturer's specifications incorrect, decreased due to reuse, partial clotting, etc)
Access recirculation or inadvertent needle reversal (when postdialysis SUN is drawn properly using a slow-flow period prior to the draw)
Rebound (use of delayed postdialysis SUN to compute sp*Kt*/*V* and *V*) Lab error in measuring the predialysis SUN (predialysis SUN artefactually low; one should compare to values from previous months).
Reasons why delivered *Kt/V* may be greater than prescribed (in this case, modeled *V* will be decreased)
Patient's *V* less than initial estimate (initial R_X only) or recent, severe weight loss
Postdialysis SUN specimen artifactually low
a) Access recirculation or inadvertent needle reversal, and postdialysis blood contaminated with dialyzer outlet blood (slow-flow method not used)
b) Specimen drawn from dialyzer outlet blood line
Session length longer than the time recorded
Recent correction of access recirculation or inadvertent needle reversal

SUN, serum urea nitrogen. See also Raimann, 2020.

Example 2 (sustained fall in *V*). Suppose that in another patient we have a sustained increase in sp*Kt/V* for no apparent reason, causing a decrease in modeled *V*:

Month	sp*Kt/V*	Modeled *V*
Jul	1.2	54
Aug	1.15	56
Sep	1.43	45
Oct	1.70	38
Nov	1.47	43

Here we have a patient whose *V* was initially about 54 L, and then, sometime around September, the *V* appeared to decrease suddenly to about 44 L. The treatment was unchanged. The sp*Kt/V* value jumped from 1.2 to 1.5, so the computer interprets this as a patient who has shrunk. What could cause this (Table 11.5)?

Step 1: The first possibility to rule out is a true decrease in *V*, which can occur either because of better removal of chronic overhydration or because of loss of lean

body mass due to intercurrent illness. Such a massive change is unlikely and can easily be ruled out by checking the patient's weight.

Step 2: Review the dialysis run sheets. Assuming that the patient's weight has not markedly decreased, true V has not decreased. Rather, the $K \times t$ must have increased in some manner relative to that delivered in October. The goal is to explain how this could have occurred. One needs to compare the run sheets before and after October. It is possible that a preexisting problem in delivering the entire session length or prescribed blood flow rate that was active prior to October was corrected in October and the months that followed.

Step 3: Access recirculation/needle placement. If there was a change in access in October, then this might have resulted in cessation of access recirculation, or perhaps prior to October the needles were being reversed and after October the problem was found and corrected.

Step 4: Check to see whether there was a systematic change in how the blood samples were collected. Consider the following scenario: This patient always had access recirculation; however, prior to October, the postdialysis sample was drawn using a proper slow-flow method. Then, in October, a new technician arrived, who drew the postdialysis samples after simply stopping the blood pump, without any antecedent slow-flow period to clear the blood line of recirculated blood. This would result in a sudden, unexplained drop in the postdialysis SUN, which would translate into a factitious rise in the URR and spKt/V, with a concomitant fall in modeled V.

VI. MONITORING CHANGES IN V FOR THE ENTIRE UNIT AS A QUALITY ASSURANCE TOOL.

Whereas large fluctuations in V can occur in individual patients, averaging the modeled V for the entire unit is useful as a quality assurance tool and can identify several problems associated with dialysis delivery. Here, a small change in V for the unit over time can often be detected. It is useful to compute both an anthropometric V (V_{ant}) and the modeled V for each patient and to follow the ratio of the two. Unit wide, V/V_{ant} should average close to 0.90 to 1.0. An average unit-wide ratio greater than 1.0 suggests that one or both components of $K \times t$ are being overestimated.

VII. INABILITY TO REACH THE DESIRED SP*KT/V*.

Patients in whom it is difficult to reach an spKt/V of at least 1.2 fall into three categories: (a) patients with poor access, resulting in either limitation of blood flow and/or access recirculation; (b) very large patients; and (c) patients with frequent hypotension, angina, or other side effects, resulting in frequent reductions in blood flow during dialysis.

A. Therapy 4 times/wk.

Four-sessions-per-week schedules are becoming increasingly popular for treating larger patients as well as patients with hypertension and problems with removing excess fluid. The 2006 version of the KDOQI clinical practice recommendations suggests that with such schedules, when residual renal urea clearance is below 2.0 mL/min/1.73 m^2, the minimum spKt/V value can be reduced from 1.2 to about 0.8 (Table 11.1). One additional advantage of a four-per-week schedule is that it avoids the long, weekend interdialytic interval, around which adverse events and deaths are more common (Foley, 2011).

VIII. COMPUTING AND MONITORING THE NORMALIZED PROTEIN NITROGEN APPEARANCE RATE (nPNA).

This is described in Chapter 3, and monitoring of nutritional status is discussed in Chapter 29.

IX. CHOICE OF DIALYZER

A. Membrane material. Issues pertaining to biocompatibility and acute dialyzer reactions are discussed in Chapters 3, 10, and 12.

B. Should a high-flux dialyzer be used? This question was partially answered by the National Institutes of Health (NIH) HEMO trial. Although randomization to high-flux membranes was associated with about an 8% increased survival, this did not attain statistical significance. Significant benefits in survival were measured in the predefined subgroup of patients who were on dialysis longer than 3.7 years (the median level for the HEMO patients). Also, cardiovascular mortality appeared to be reduced in all patients assigned to high-flux dialysis. These data are generally in accord with the European Membrane Permeability Outcomes (MPO) trial (Locatelli, 2009). On the basis of these results, both the KDOQI Adequacy Workgroup in 2006 (reiterated in 2015) and the European Best Practices Group recommend the use of a high-flux membrane where proper water treatment is available. Use of high-flux membranes may also reduce the incidence of β-2 microglobulin amyloidosis in patients dialyzed for many years. It is not clear whether this benefit is due to the enhanced removal of β-2 microglobulin or whether the use of more advanced dialysis technology associated with high-flux dialysis results in less procedure-related inflammation. However, even with the use of high-flux dialyzers, β-2-microglobulin amyloidosis remains a problem in patients on dialysis for many years (Portales-Castillo, 2020).

X. FLUID REMOVAL ORDERS

A. Concept of "dry weight" or optimum postdialysis weight. The so-called dry weight (optimum postdialysis weight is a better term) is the postdialysis weight at which all or most excess body fluid has been removed. If the dry weight is set too high, the patient will remain in a fluid-overloaded state at the end of the dialysis session. Fluid ingestion during the interdialysis interval might then result in edema or pulmonary congestion. If the dry weight is set too low, the patient may suffer frequent hypotensive episodes during the latter part of the dialysis session. Patients who have been ultrafiltered to below their optimum postdialysis weight often experience malaise, a washed-out feeling, cramps, and dizziness after dialysis. The postdialysis recovery is extremely stressful and unpleasant. Also, the risk of arteriovenous (AV) access clotting is increased.

In practice, the optimum postdialysis weight of each patient must be determined on a trial-and-error basis. When setting the ultrafiltration rate, allow for the 0.2 L of saline that the patient will receive at the end of dialysis during the blood return procedure. Also, compensate for any fluid ingestion or parenteral fluid administration during the treatment session.

1. **Frequent resetting of the optimum postdialysis weight.** A common error in dialysis units is the failure to reevaluate the optimum postdialysis weight often enough. If a patient loses flesh weight, the previously set dry weight becomes too high, and if maintained, can result in patient overhydration and hospitalization for

fluid overload. The optimum postdialysis weight should therefore be reevaluated at least every 2 to 4 weeks. A progressive decrease in the optimum postdialysis weight can be a clue to an underlying nutritional disturbance or disease process. Reevaluation of the dry weight is mandatory whenever a patient returns to the dialysis unit after being hospitalized or after any severe intercurrent illness (flesh weight will have been lost, and the previously set target postdialysis weight will now likely be too high).

As discussed in Chapter 31, clinical determination of optimum postdialysis weight based on signs of edema or lung râles is unreliable. Bioimpedance devices identify an important subset of patients who appear to be markedly fluid-overloaded despite no outward signs of edema. A different subset of patients is made up of those who have been taken below their optimum postdialysis weight (Hecking, 2013). This can result in large interdialytic weight gains and heightened sodium intake as patients struggle to return to a more optimum weight and can also result in accelerated loss of residual kidney function.

The use of bioimpedance to help identify optimum postdialysis weight, along with other technology such as lung ultrasound ("comets"), is discussed more completely in Chapter 31. Although the new technology is helpful, experience with these devices is just beginning, and with whole-body bioimpedance, for example, it is not clear to what extent the bioimpedance estimate of fluid overload is applicable to patients with markedly high or low levels of body mass index.

B. Fluid removal rate. Usually, fluid is removed at a constant rate during dialysis. There has been interest in restricting the maximum ultrafiltration rate as a quality assurance tool. Evidence suggests survival is increased in patients undergoing hemodialysis with a lower ultrafiltration rate. There appears to be no threshold value. The ultrafiltration rate in patients undergoing hemodialysis in the United States has been decreasing and now averages about 7.5 mL/kg/h (about 550 mL/h for an average-sized patient). Various ultrafiltration rate "warning levels" can be set in the hope of avoiding higher mortality rates associated with those levels as derived from observational studies (Mermelstein, 2023).

There are several approaches by which the fluid removal rate can be reduced. The most obvious is to extend the dialysis time, but this is not the only approach: reducing interdialytic weight gain by limiting sodium intake often is more acceptable to the patient and easier to implement (Lew, 2023; Pirkle, 2018). In patients with substantial urine volume, use of diuretics will reduce the ultrafiltration rate by virtue of increasing daily urine volume unless the patient reacts by taking in more fluid.

There is some interest in using a nonconstant fluid removal rate during a dialysis session. In one approach, the fluid removal rate is increased during the initial 1 to 2 hours of dialysis and reduced toward the end of dialysis. The dialysis solution sodium level also may be increased during the initial phase of dialysis to help maintain the blood volume osmotically. The benefits of this approach remain controversial.

XI. DIALYSIS SOLUTIONS (TABLE 11.6)

TABLE 11.6 Dialysis Solution Orders

Flow rate:
500 mL/min
Base:
Bicarbonate (32 mM)/plus acetate (4 mM); or bicarbonate 28 mM/plus acetate 8 mM[a]
Electrolytes and dextrose:
Potassium = 2.0 mM (3.0 mM for patients taking digitalis or patients with a low-normal potassium predialysis)
Sodium = 135-145 mM (138 mM)
Dextrose = 100 mg/dL (5.5 mmol/L)
Calcium = 1.25-1.5 mM (2.5-3.0 mEq/L; depends on the type of phosphate binder used)
Magnesium = 0.50 mM (1.0 mEq/L)

[a]For example, when using sodium diacetate (Granuflo) dry acid concentrate.

A. Flow rate. The standard dialysis solution flow rate is 500 mL/min. When the blood flow rate is high (eg, >400 mL/min) and when a high-K_0A dialyzer is used, increasing the dialysis solution flow rate to 800 mL/min will increase dialyzer clearance (K) by about 5% to 10%. The optimum value for the dialysis solution flow rate is 1.5 to 2.0 times the blood flow rate, and using high dialysate flow rates when the blood flow rate is relatively low will not increase dialysis efficiency and still increase the cost.

B. Composition

1. Bicarbonate concentration. Bicarbonate dialysis solution is the fluid of choice, and the use of dialysis solution containing only high concentrations of acetate (and no bicarbonate) is now considered obsolete.

The concentration of base should be adjusted to achieve a predialysis plasma bicarbonate concentration of 20 to 23 mmol/L. There has been some interest in increasing dialysis solution bicarbonate level or giving supplementary oral bicarbonate to increase the predialysis HCO_3 level. A definite clinical benefit of raising predialysis HCO_3 beyond 20 to 23 has not been shown. Metabolic alkalosis may result during the early postdialysis period in such patients, with a theoretically increased risk of calcium-phosphate precipitation and of cardiac arrhythmia.

As discussed in Chapter 4, in dialysis machines that are capable of adjusting the dialysis solution bicarbonate level, the machine readout usually gives the bicarbonate level of the product dialysate not taking into account the presence of any bicarbonate-generating anions such as acetate or citrate. Acetate, especially when sodium diacetate is used in the concentrate, can add as much as 8 mM of bicarbonate-generating base to the dialysate. This added base content should be kept in mind when titrating dialysis solution to bicarbonate to the serum level.

The average dialysis solution bicarbonate level tends to be higher in the United States than in some European countries, and high dialysis bicarbonate values have been associated with increased mortality (Tentori, 2013). The increased mortality was due primarily to infectious, rather than cardiovascular, causes. It is not at all clear whether this association is causal or mediated by some sort of confounding. Mortality is increased in patients with both low and high predialysis serum bicarbonate, but the mortality at the high end is confounded by malnutrition, as patients with high predialysis serum bicarbonate levels are not uncommonly malnourished (due to lower ingested acid load associated with food intake).

High dialysis solution bicarbonate has been shown to act synergistically with low dialysis solution calcium and potassium (Di Iorio, 2012) to prolong the QTc interval on the electrocardiogram, a change associated with increased risk of arrhythmia.

2. **Potassium.** The usual dialysis solution potassium level is 2.0 mM unless the patient's usual predialysis plasma potassium concentration is less than 4.5 or unless the patient is receiving digitalis. In the latter two instances, the dialysis solution potassium level should usually be 3.0 mM. Should the interdialytic serum potassium levels be high because of the use of this 3-mM dialysis solution, chronic administration of potassium-binding compounds such as sodium zirconium cyclosilicate (ZS-9) or patiromer may be helpful (Fishbane, 2019; Jaques, 2022). Malnourished patients may have low predialysis serum potassium levels, and in these patients, the dialysate potassium level can and should be increased to avoid hypokalemia. Use of 1.0-mM potassium dialysate on a chronic basis to control hyperkalemia has been associated with an increased incidence of cardiac arrest (Lafrance, 2006). If a low dialysis solution potassium level is used at all, it should be used on a relatively short-term basis. If the patient stops ingesting a high-potassium diet for whatever reason, continued use of a low-potassium dialysis solution can then result in adverse consequences. Survival is highest in patients being dialyzed against a 3 K bath or higher (Jadoul, 2012).
3. **Sodium.** The usual dialysis solution sodium level is between 135 and 145 mM. Levels above 138 mM are associated with increased thirst and weight gain between dialyses, although the extra fluid often can be removed during dialysis with fewer symptoms. The blood pressure may increase. Dialysis solution sodium levels lower than 135 mM predispose to hypotension and cramps.

   One study suggests that patients may have individual "set points" for sodium (Keen, 1997). Little is known about why some patients undergoing dialysis have low predialysis sodium values. Predialysis hyponatremia has been linked to overhydration and increased interdialytic weight gain. In nondialysis populations, as well as in patients undergoing dialysis, hyponatremia is associated with an increased mortality risk. These patients may have cardiac dysfunction with nonosmotic release of vasopressin or some sort of "sick cell" syndrome with impairment of the Na-K exchanger, reflecting overall poor health. In patients with a low sodium set point, a lower dialysis sodium level can logically be used, which should minimize postdialysis thirst and weight gain. However, a cross-sectional study found slightly better survival when hyponatremic patients were dialyzed against a higher sodium dialysis solution (Hecking, 2012). Also, in a large observational trial, use of dialysate sodium values less than 138 mM was associated with higher mortality (Pinter, 2024).
4. **Dextrose.** A dextrose concentration of 100 mg/dL or 5.5 mmol/L is most commonly used. Lower dialysate glucose concentrations are associated with better potassium removal, but may increase the risk of hypoglycemia.
5. **Calcium.** Dialysis solution calcium levels in chronic patients normally range from 1.25 to 1.5 mM (2.5-3.0 mEq/L). The usual level in patients taking calcium-containing phosphate binders is 1.25 mM (2.5 mEq/L), but the level may have to be adjusted upward or downward depending on clinical response and parathyroid

hormone status. In patients taking the newer resin-based phosphate binders, which do not contain calcium, the dialysis solution calcium level may need to be increased to avoid negative calcium balance. Dialysis solution calcium levels lower than 1.25 mM (2.5 mEq/L) have been advocated by some when calcium-containing phosphate binders are used, in order to prevent calcium overload. However, the use of such low dialysate calcium solutions has been associated with an increased risk of sudden cardiac arrest (Pun, 2013). A 1.25-mM dialysate calcium solution has been advocated for use in patients with adynamic bone disease, as it may stimulate the release of parathyroid hormone (Sethi, 2023).

6. **Magnesium.** The usual dialysis solution magnesium level is 0.25 to 0.5 mM (0.5-1.0 mEq/L). In general, survival of patients undergoing dialysis is better when such patients are not hypomagnesemic. Also, frequent use of protein pump inhibitors in this population may reduce oral magnesium absorption and increase the risk of hypomagnesemia (Alhosaini, 2014). The trend is to use 0.5 mM (1.0 mEq/L) solution, at the higher end of this range. Use of citric acid to acidify bicarbonate dialysate will result in some complexing of both dialysate calcium and magnesium, and the impact of a high magnesium dialysis solution may be somewhat attenuated when such solutions contain citric acid.

C. Temperature.

The dialysate temperature should be set as low as possible without engendering patient discomfort, generally in the range of 34.5 °C to 36.5 °C. As discussed in Chapter 12, individualization of cool dialysate, effected by measuring patient tympanic membrane temperature and setting dialysis solution temperature 0.5 °C lower, may retain the benefits of cool dialysis solution in terms of protection from intradialytic hypotension and shortening of postdialysis recovery time, while avoiding the discomfort of feeling cold and shivering. Another approach is to lower the dialysate temperature during the latter half of the dialysis session. Individualized cool dialysate also may reduce the incidence of myocardial stunning and dialysis-associated ischemic damage to brain white matter. In one study from China, the use of cool temperature dialysis solution chronically was associated with reduced cardiovascular morbidity and mortality (Hsu, 2012). One large randomized study, however, has called into question the benefits of individualized cool dialysate (Hull, 2023).

XII. ANTICOAGULATION ORDERS.

See Chapter 13.

XIII. STANDING ORDERS FOR COMPLICATIONS.

Complications are discussed in depth in Chapter 12. Frequently occurring complications, such as hypotension, cramps, restlessness, nausea, vomiting, itching, and chest pain, can be managed with a set of standing orders. However, symptoms during dialysis may be the result of a more serious disease process that can require immediate diagnosis and specific treatment.

XIV. PATIENT MONITORING

A. Prior to and during the treatment session

1. Prior to dialysis

a. **Weight.** The predialysis weight should be compared with the patient's last postdialysis weight and with the target optimum weight to obtain some idea of interdialysis weight gain. A large interdialysis weight gain, especially when

coupled with symptoms of orthopnea or dyspnea, should prompt a complete cardiovascular examination and reassessment of the target weight (it may be too high). Patients should strive to keep their interdialysis weight gain below 1.0 kg/d, although the average weight gain tends to be higher. They also need to be counseled about limiting sodium rather than fluid intake, as the water intake generally follows that of salt. Excessive thirst may be due to a high dialysis solution sodium level. Complaints of a washed-out feeling or of persistent muscle cramps after dialysis suggest that the target postdialysis weight is too low.

b. Blood pressure. The optimum blood pressure to monitor is controversial, and either average intradialytic pressure or postdialysis pressure may be more predictive of volume overload than predialysis pressure (see Chapter 31). In some patients, blood pressure can increase during dialysis despite fluid removal. The causes are speculative, but this has been associated with poor survival. Volume-resistant hypertensive patients sometimes benefit from further fluid removal, and blood pressure may decrease only after a lag period of several months (Fishbane, 1996).

Patients with hypertension are routinely counseled to withhold their blood pressure medication on the day of dialysis to limit the incidence of dialysis hypotension. This is not absolutely necessary, especially for patients who will be dialyzed in the afternoon. Management of high blood pressure is described in Chapter 31, but basically focuses on sodium restriction, lengthening the weekly dialysis time, and, if available, moving to a more frequent dialysis schedule. Use of whole-body bioimpedance to guide fluid removal has been shown to lower blood pressure. Abiding by a maximum ultrafiltration rate and using this as an incentive to get patients to reduce interdialytic weight gain can also reduce blood pressure (Pirkle, 2018).

Although it is important to investigate and perhaps treat patients with very high levels of predialysis blood pressure, very aggressive approaches to reduce predialysis blood pressure have been associated with an increased rate of dialysis hypotension and access failure (see Chapter 31).

c. Temperature. The patient's temperature should be measured. The presence of a fever prior to dialysis is a serious finding and should be investigated diligently. The manifestations of infection in a patient undergoing dialysis may be subtle. On the other hand, a rise in body temperature of about 0.5 °C during dialysis is normal and not necessarily a sign of infection or pyrogen reaction.

d. Access site. Whether or not fever is present, the vascular access site should always be examined for signs of infection before each dialysis.

2. During the dialysis session. Blood pressure and pulse rate are usually measured every 30 to 60 minutes. Any complaints of dizziness or of a washed-out feeling are suggestive of hypotension and should prompt immediate measurement of the blood pressure. Symptoms of hypotension may be quite subtle, and patients sometimes remain asymptomatic until the blood pressure has fallen to dangerously low levels.

B. Laboratory tests (predialysis values)

1. Serun urea nitrogen (SUN). This should be measured monthly as part of the URR. Whether the monthly postdialysis SUN measurement can be dispensed with in

units where in vivo dialyzer clearance is monitored using conductivity, or patient *Kt/V* is monitored via UV dialysate absorbance, is an open question, but data suggest that using urea modeling to establish a value for urea distribution volume and then using the $K \times t$ value obtainable from hemodialysis machines that monitor intradialytic conductivity-based sodium clearance can be useful to limit the need for monthly postdialysis serum urea measurement (Raimann, 2020). Use of the predialysis urea nitrogen would continue to be useful, as it allows for computation of the nPNA.

2. **Serum albumin.** The predialysis serum albumin level should be measured every 3 months. The serum albumin concentration is an important indicator of nutritional state. A low serum albumin level is a very strong predictor of subsequent illness or death in patients undergoing dialysis. The increased mortality risk begins at serum albumin levels less than 4.0 g/dL (40 g/L). Patients with serum albumin levels less than 3.0 g/dL (30 g/L) are at high risk of morbid events, and every effort should be made to find the cause of the low albumin value and correct it.
3. **Serum creatinine.** The predialysis serum creatinine level is measured monthly. The usual mean value in patients undergoing hemodialysis is about 10 mg/dL (884 *mc*mol/L), with a common range of 5 to 15 mg/dL (440-1,330 *mc*mol/L). Paradoxically, in patients undergoing dialysis, high serum creatinine levels are associated with a low risk of mortality, probably because the relatively high serum creatinine value is an indicator of maintained muscle mass.

   The serum creatinine and urea nitrogen levels should be examined in tandem. If parallel changes in both occur, then alteration in the dialysis prescription or degree of residual renal function should be suspected. If the serum creatinine level remains constant but a marked change occurs in the SUN value, the change in the latter is most likely due to altered dietary protein intake or altered catabolic rate of endogenous body proteins.
4. **Serum total cholesterol.** The serum total cholesterol level is an indicator of nutritional status. A predialysis value of 200 to 250 mg/dL (5.2-6.5 mmol/L) is associated with the lowest mortality risk in patients undergoing dialysis. Low serum total cholesterol values, especially less than 150 mg/dL (3.9 mmol/L), are associated with an elevated mortality risk in patients undergoing dialysis, probably because they reflect poor nutritional status.
5. **Serum potassium.** Patients undergoing dialysis with a predialysis serum potassium level of 5.0 to 5.5 mmol/L have the lowest mortality risk. The mortality risk increases greatly for values over 6.5 and under 4.0 mmol/L.
6. **Serum phosphate.** Measure monthly. The predialysis value associated with the lowest mortality is below 5.5 mg/dL (1.8 mmol/L). Mortality rates increase for values over 9.0 mg/dL (2.9 mmol/L) and under 3.0 mg/dL (1.0 mmol/L). Current Kidney Disease: Improving Global Outcomes (KDIGO) targets are to “lower serum phosphate toward the normal range.” Serum phosphate values tend to be slightly higher on Monday/Tuesday, that is, after the 3-day interdialytic interval.
7. **Serum calcium.** Measure monthly (more often when changing the dose of vitamin D). The lowest mortality is associated with values of 9 to 12 mg/dL (2.25-3.0 mmol/L). Mortality rates increase markedly at values over 12 mg/dL (3.0 mmol/L) and under 7 mg/dL (1.75 mmol/L). The target value should be calcium within the

normal range. Targeting the upper range of normal serum calcium is no longer recommended, for fear of precipitating vascular calcification.

8. **Serum magnesium.** This is not routinely monitored in patients undergoing hemodialysis. However, hypomagnesemia is common in patients undergoing hemodialysis receiving proton pump inhibitors (Alhosaini, 2014), and low serum magnesium is associated with atrial fibrillation and poor cardiovascular outcomes in many populations. The cost-benefits of routine periodic monitoring of serum magnesium have not been studied.
9. **Serum alkaline phosphatase.** Measure every 3 months. High values are a sign of hyperparathyroidism or liver disease. High levels are associated with elevated mortality risk.
10. **Serum bicarbonate.** Measure monthly. The lowest mortality is for values between 20 and 22.5 mmol/L. Mortality increases for both lower and higher values. Marked increases in mortality are noted when the predialysis value is under 15 mmol/L. Predialysis acidosis can be corrected by the administration of alkali between dialyses.
11. **Hemoglobin.** This is checked at least monthly and in many cases every 2 weeks. Machine measurement of hemoglobin using optical sensors is becoming popular. Optimal management of chronic kidney disease–related anemia is discussed in Chapter 32. Spontaneously high hemoglobin levels (without erythropoietin therapy) may be a sign of polycystic kidney disease, acquired renal cystic disease, hydronephrosis, or renal carcinoma. Serum ferritin levels, iron levels, and iron-binding capacity, as well as erythrocyte indexes, should be checked every 3 months.
12. **Serum aminotransferase values are usually checked monthly.** High or even high-normal values may unmask silent liver disease, especially hepatitis or hemosiderosis. The blood should be screened for the presence of hepatitis B surface antigen and for hepatitis C (see Chapter 33).
13. **Serum parathyroid hormone levels** should be checked every 3 to 6 months, as detailed in Chapter 34.

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12 Complications During Hemodialysis

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The most common complications during hemodialysis are, in descending order of frequency, hypotension, cramps, nausea and vomiting, headache, chest pain, back pain, and itching.

I. INTRADIALYTIC HYPOTENSION. Intradialytic hypotension (IDH) is important not only because it can cause distressing symptoms, but because it is associated with poor long-term outcomes. Patients with IDH show increased mortality (Flythe, 2015) and also increased rates of cardiac wall motion abnormalities during dialysis (myocardial stunning) (McIntyre and Odudu, 2014) and eventually a fixed cardiac defect with decreased ejection fraction. They also develop more ischemic injury to the brain (frontal lobe atrophy), gut (mesenteric ischemia), and kidneys (loss of residual renal function). There are various definitions for IDH, including a nadir (lowest) systolic BP less than 90 mm Hg (or <100 mm Hg if baseline systolic blood pressure is greater than 160), a fall in systolic BP of 20 or 30 mm Hg associated with symptoms or intervention, or a fall by some percentage of the starting blood pressure. For quality assurance purposes, a definition of nadir systolic BP less than 90 or 100 mm Hg might be most useful, as this has the strongest association with increased mortality (Flythe, 2015). The incidence of IDH is highest in patients with low predialysis blood pressure. Not surprisingly, a low predialysis blood pressure may be a marker of cardiac disease, and hearts with functional or structural abnormalities may be less able to compensate hemodynamically for fluid removal. IDH is also associated with an increased risk of AV access thrombosis (Chang, 2011), particularly when a central venous access is being used for dialysis (eg, during fistula maturation). Mechanistic causes of IDH are detailed in Table 12.1.

TABLE 12.1 Causes of Intradialytic Hypotension

1. Volume-related
   - a. Large weight gain (high ultrafiltration rate)
   - b. Short weekly dialysis time (high ultrafiltration rate)
   - c. Excessively low target (“dry”) weight
2. Inadequate vasoconstriction
   - a. High dialysis solution temperature
   - b. Autonomic neuropathy
   - c. Antihypertensive medications
   - d. Eating during treatment
   - e. Anemia
3. Cardiac factors
   - a. Diastolic dysfunction
4. Uncommon causes

a. Pericardial tamponade
b. Myocardial infarction
c. Occult hemorrhage
d. Septicemia
e. Dialyzer reaction
f. Hemolysis
g. Air embolism

There may be **two general categories of IDH**, as first suggested by Maeda (1988). In some episodes, the fall in blood pressure is sudden and is not preceded by an acute change in blood volume, while in other cases the fall in blood pressure occurs more gradually and appears to be linked to changes in blood volume. Keane (2021) found that IDH occurring during the first half of a dialysis session was not related to the rate of fluid removal and that IDH episodes occurring during the first half of a dialysis treatment were more strongly associated with mortality than IDH episodes that occurred during the last half of a dialysis session.

A. IDH related to blood volume changes. Volume-related causes of IDH are most important in that the blood pressure during hemodialysis normally does not decrease (beyond an initial, trivial amount) if fluid is not removed. Thus, any maneuver that slows the ultrafiltration rate (UFR), whether it be extending the weekly time on dialysis, reducing the weekly volume of fluid ingestion, or increasing the volume of urine excreted, should reduce the rate of IDH.

1. **Avoid large interdialytic weight gains.** Emphasizing salt restriction is far more effective in decreasing interdialytic weight gain than focusing on fluid restriction (Tomson, 2001). Observational data find an association between a higher sodium intake and poor outcome (Mc Causland, 2012).
2. **Increasing weekly treatment time.** Increasing weekly treatment time will decrease the required UFR, and this will decrease the frequency of IDH. The weekend-long interdialytic interval is associated with a higher interdialytic weight gain; if the same postdialysis weight is targeted after the weekend, a higher UFR will need to be used to achieve it. Patients undergoing in-center dialysis with fluid removal problems are often treated on a Mon-Wed-Fri-Sat schedule. The additional Saturday treatment cuts out the long-weekend interdialytic interval and also increases the weekly dialysis time. A maximum UFR of 13 mL/kg per hour has been recommended to minimize IDH; use of this standard requires that both the dialysis center and patients are amenable to added treatment time to achieve ultrafiltration goals. The logic of scaling of a maximum desirable UFR value to body weight in a 1:1 ratio (eg, as mL per kg) has been questioned, and UFR warning levels associated with a given level of increased mortality risk for patients with different body weights have been proposed as an alternative (Mermelstein, 2023).

   The Kidney Disease Outcome Quality Initiative (KDOQI) 2006 adequacy guidelines recommend that treatment time not be reduced below 3 hours (for thrice-weekly dialysis) in patients with little or no residual urine output, regardless of how high their *Kt/V* may be. The European Best Practice Guidelines recommend that 4 hours of therapy should be provided for all patients dialyzed on a three-per-week schedule, regardless of body size. Increasing dialysis frequency without increasing weekly dialysis time does not always reduce IDH, although in one study, the degree of myocardial stunning was reduced with short daily hemodialysis (Jeffries, 2011).

3. **Maintaining and increasing urinary volume.** In patients with residual kidney function, the volume of urine output reduces the fluid removal requirement during dialysis. Urine volume can be increased using diuretic therapy (Lemes, 2011).
4. **Choose target weight carefully.** A patient's target or dry (euvolemic) weight is usually chosen primarily on a clinical basis, taking into account a patient's blood pressure, presence of edema, and tolerance of ultrafiltration to the chosen weight. The decision can be aided with the results of testing that is slowly making its way into the clinic (eg, bioimpedance devices, measurement of serum atrial natriuretic factor levels, relative blood volume monitors, and pulmonary ultrasound). The term "target weight" may be more appropriate than "dry weight," because some level of volume overload is required in many patients to prevent IDH. This is because as the patient's dry weight is approached, the rate at which the blood compartment refills from surrounding tissue spaces is diminished. Patients who require high UFRs may be unable to reach their true dry weight because the progressively slower refill rate as dialysis proceeds provokes transient hypovolemia at the end of treatment, often accompanied by IDH cramps, dizziness, and postdialysis malaise. More ominously, hypoperfusion of the heart, brain, and gut may have cumulative adverse consequences, suggesting that targeting a euvolemic weight may not always be advisable (Huang, 2015).

   Intradialytic hematocrit monitors may help recognize a dry weight that is too high. A "flat-line" hematocrit response (eg, lack of an increase during dialysis) despite fluid removal indicates extremely rapid blood compartment refilling and suggests fluid overload. However, a randomized trial in which such monitors were utilized clinically resulted (paradoxically) in an increased, rather than a decreased, hospitalization rate (Reddan, 2005). Attempts to identify of a specific level of hemoconcentration ("crash-crit") at which IDH occurs does not appear to be useful in avoiding IDH. One newer method attempts to calculate the total blood volume at the start of dialysis by measuring the amount of hemodilution after injection of a known volume of saline. Then attempts are made to identify a level of absolute blood volume that is associated with IDH, with the goal of slowing the ultrafiltration rate as this level of blood volume is approached (Jongejan, 2024).

   The use of multifrequency bioimpedance devices to adjust target postdialysis weight is growing in popularity. Reduction of fluid overload results in a lower prevalence of left ventricular hypertrophy, a finding that is strongly associated with poor outcome. Trying to treat hypertension via aggressive fluid removal without technologic guidance has been associated with increased IDH (Davenport, 2008) and with an increased rate of access failure and cardiovascular hospitalization (Curatola, 2011). Use of a multifrequency impedance monitor was associated with less hypertension and reduced left ventricular mass (Hur, 2013) without apparent side effects, although the rate of loss of urine volume was accelerated in the group using bioimpedance to lower target weight. While there was no benefit in terms of IDH, the incidence of IDH was not worsened in the group subjected to boimpedance-guided volume optimization.
5. **Use an appropriate dialysis solution sodium level.** When the dialysis solution sodium level is markedly below that of plasma, the blood returning from the dialyzer is hypotonic with respect to the fluid in the surrounding tissue spaces. To

maintain osmotic equilibrium, water leaves the blood compartment, causing an acute reduction in the blood volume. Higher dialysis solution sodium levels limit the reduction in blood volume accompanying ultrafiltration, but they also increase interdialytic weight gain, blood pressure, and postdialysis thirst.

Sodium modeling (or sodium gradient dialysis) involves the use of a high dialysis solution sodium early in treatment (145-155 mM), with a progressive fall (linear, step, or logarithmic) to lower levels (135-140 mM) at the end of treatment seeking to obtain the benefits of high-sodium dialysis solution without its complications. Review of the large literature on this subject shows that sodium modeling is of uncertain benefit (Stiller, 2001). It should also be noted that a patient's postdialysis serum sodium is a function of a treatment's time-averaged concentration of dialysis solution sodium, not the terminal level of dialysis solution sodium.

Instead of a "one-size-fits-all" level of dialysis solution sodium for the entire dialysis unit, using a sodium level that is close to the patient's average predialysis serum value—an "individualized" dialysis solution sodium—may reduce symptoms as well as interdialytic thirst (Santos and Peixoto, 2010). Using a relatively high dialysis solution sodium (>142 mmol/L) may benefit frail patients at high risk for IDH, likely because the consequences of recurrent IDH are more dire than those from using a high-sodium dialysis solution (Marshall and Dunlop, 2012). On the other hand, use of a relatively low dialysate sodium level might reduce IDH because it tends to lower interdialytic weight gain and the need for ultrafiltration (Shah and Davenport, 2012). An increasing concern about hypervolemia has led to a "volume first" approach to the dialysis prescription (Weiner, 2014), which, in turn, led to recommendations for a lower than is customary dialysate sodium (134-138 mmol/L). The current practice in the United States is to use a dialysate sodium of 138 mmol/L. Of some concern is a recent international observational study that suggested mortality was increased in patients being dialyzed against a dialysate sodium of less than 138 mmol/L (Pinter, 2024), and the increased mortality association was unrelated to the level of predialysis serum sodium. However, there was confounding between country of origin and dialylsate sodium level.

6. **Blood volume control devices with a feedback loop.** For a number of years now, software has been allowing improved feedback control of UFR based on monitoring of blood volume during dialysis. Some randomized trials suggest that such feedback devices can reduce the incidence of dialysis-induced hypotension while avoiding a positive sodium balance (Davenport, 2011), though other studies are not supportive (Leung, 2017).

B. Hypotension related to lack of vasoconstriction. In the hypovolemic state, cardiac output is limited by cardiac filling; a reduction in either peripheral vascular resistance or cardiac filling in this setting can precipitate hypotension. Under conditions of decreased cardiac filling, increases in heart rate have little effect on cardiac output. Because more than 80% of the total blood volume circulates in veins, changes in venous capacity can have important effects on a patient's effective circulating blood volume and cardiac output. When arteriolar resistance decreases, more arterial pressure is transmitted to veins, causing passive stretching and distension, and an increased sequestration of blood in veins away from the heart. Although not important in

euvolemic patients given a vasodilator (because cardiac filling is more than adequate), this mechanism can result in hypotension when hypovolemia is present (Daugirdas, 1991). The degree of arteriolar constriction, or total peripheral resistance, is also important because total peripheral resistance will determine the blood pressure for any level of cardiac output.

1. **Lower dialysis solution temperature.** Ideally, the dialysis solution temperature should be one that maintains a patient's arterial blood temperature at its initial level throughout dialysis. When the dialysis solution temperature is higher than this ideal level, the patient receives a heat load from the warm dialysate and cutaneous vasodilation occurs to allow heat to be dissipated. This vasodilation reduces vascular resistance and predisposes the patient to hypotension. Blood temperature modules are available for dialysis machines, which can provide patients with a euthermic treatment. Without such a device, the choice of dialysis solution temperature is problematic, with even small (1.1 °C) differences in temperature having a notable impact on blood pressure (Sherman, 1984). The widely used dialysis solution temperature of 37 °C is almost always in excess of euthermic values. Levels of 35.5 °C to 36.0 °C are better initial choices, with adjustment made up or down depending on tolerance (chills) and effectiveness (blood pressure). There is no single temperature level that is optimal for all patients. Further, over the course of a treatment, the optimal dialysate temperature declines due to the thermal consequences of the progressive vasoconstriction that occurs. Cool dialysis solutions cause patient discomfort only when the dialysate temperature is below the optimal (usually unknown) level; euthermic dialysis is not associated with shivering and only rarely with chills (Maggiore, 2002). In patients who complain of cold discomfort, the dialysate temperature can be reduced only during the second half of a dialysis treatment. When cooled dialysate is individualized, a shorter postdialysis recovery time, better maintenance of blood pressure, reduced myocardial stunning, and less evidence of progressive ischemia-related brain white matter damage is seen (McIntyre, 2014). Despite a large body of evidence supporting the use of lower dialysate temperatures to reduce the incidence of IDH, a large, multicenter study from Canada showed no benefit of use of individualized dialysate temperature based on tympanic membrane temperature measurements. However, this was a cluster randomized study where treatments were applied to entire dialysis units as opposed to patients with frequent IDH (Mytemp writing committee, 2022).
2. **Avoid intradialytic food ingestion in hypotension-prone patients.** Eating during hemodialysis can precipitate or accentuate a fall in blood pressure (Fotiadou, 2020; Sherman, 1988). The effect is probably a result of dilation of resistance vessels in the splanchnic bed, which reduces total peripheral reistance and increases splanchnic venous capacity. The "food effect" on blood pressure probably lasts at least 2 hours. Patients who are prone to hypotension during dialysis should avoid eating just before or during a dialysis session.
3. **Minimize tissue ischemia during dialysis.** During any type of hypotensive stress, the resulting tissue ischemia causes the release of adenosine. Adenosine blocks the release of norepinephrine from sympathetic nerve terminals and also has intrinsic vasodilator properties. Severe hypotension can therefore amplify itself: Hypotension → ischemia → adenosine release → impaired norepinephrine release

→ vasodilation → hypotension.

This may be one reason for the clinical observation that patients with low hematocrit levels (eg, <20%-25%) are very susceptible to dialysis hypotension (Sherman, 1986). Few patients currently have levels of anemia severe enough to cause hypotension. Such patients may benefit from transfusion, although the current trend is to strongly discourage transfusion of acutely ill patients in an intensive care setting. Use of nasal oxygen in hypotension-prone patients may be another way of limiting tissue ischemia and IDH (Jhawar, 2011).

4. **Midodrine.** Midodrine, an orally acting α-adrenergic agonist, reduces the frequency of IDH. A dose of 10 mg orally 1.5 to 2 hours before a dialysis session is typical, though use of as much as 40 mg has been reported. Supine hypertension is the major dose-limiting factor. Active cardiac ischemia (but not simply coronary artery disease) is a contraindication. Concomitant use of α-adrenergic blockers renders midodrine ineffective. No data exist as to whether the drug is especially useful in patients with autonomic insufficiency (half of the population undergoing dialysis), as might theoretically be the case. The effect of midodrine does not seem additive to that of using cool dialysate (Cruz, 1999). Giving midodrine during dialysis may be ineffective because of the high prevalence of intradialytic (as well as chronic) gastroparesis in patients; increased predialysis dosing may be wiser. Several studies have been published suggesting increased mortality in dialysis patients treated with midodrine for IDH, but confounding by indication was a possible (likely) explanation for the findings.
5. **Sertraline.** The selective serotonin reuptake inhibitor sertraline appears to reduce the frequency of IDH. Some evidence suggests that the drug improves autonomic function. Four to 6 weeks of therapy may be required to observe an effect. As with midodrine, sertraline was not shown to give added protection against IDH when cool dialysate was used (Brewster, 2003). The benefits of sertraline for IDH prevention are not universally accepted (Georgianos, 2019).
6. **Antihypertensive medication.** Antihypertensive medications administered prior to dialysis adversely impact the ability of the cardiovascular system to adjust to volume removal. One large study suggested that the risk of IDH is increased with use of most classes of antihypertensive medications, with the sole exception of calcium channel blockers (Zoccali, 2024).
7. **Dialysis fluid potassium level.** A low concentration (1 mEq/L) of dialysis fluid potassium is associated with more frequent IDH, perhaps via autonomic effects. If otherwise possible, using higher potassium levels is advisable for hemodynamic benefits as well as reduced arrhythmogenic effect.
8. **Fludrocortisone.** Although there is some physiologic basis for anticipating benefits from fludrocortisone in ameliorating IDH, the documentation of this is limited to case reports and a small, randomized trial failed to show a benefit (Vongchaiudomchoke, 2023).
9. **Vasopressin.** Vasopressin levels normally increase with hypotension, but in patients undergoing dialysis, the increase is often suboptimal. Vasopressin preferentially constricts splanchnic vessels, and such constriction may help to redistribute blood volume centrally during fluid removal. Vasopressin infusion can reduce the incidence of IDH (van der Zee, 2007). Intranasal deamino arginine

vasopressin (DDAVP) 30 minutes before dialysis also was effective in a 17-patient blinded placebo crossover study; IDH occurred only 18 times in 204 dialysis treatments compared with 125 times in the placebo group (Beladi-Mousavi, 2012).

C. Hypotension related to cardiac factors

1. **Diastolic dysfunction.** A stiff, hypertrophied heart is especially prone to a reduction in output when there is even a minor reduction in filling pressure. Diastolic dysfunction is common in patients undergoing dialysis owing to the effects of hypertension, coronary artery disease, and probably uremia itself. Atrial fibrillation impairs ventricular filling and increases the risk of IDH. Some limited data suggest that using calcium channel blockers as antihypertensive agents may reduce the frequency of IDH (Lefranc, 2024).
2. **Heart rate and contractility.** Most, but not all, dialysis hypotension is associated with decreased cardiac filling, a setting in which cardiac compensatory mechanisms can do little to increase output. In some patients, total peripheral resistance may fall (owing to temperature effects, food ingestion, or tissue ischemia) without a fall in cardiac filling. In this setting, impairment of cardiac compensatory mechanisms can play a direct role in the development of hypotension.
3. **Dialysis solution calcium and magnesium.** A higher dialysis solution calcium concentration (1.75 vs 1.25 mM) increases cardiac contractility and intradialytic blood pressure, especially in patients with cardiac disease (van der Sande, 1998). However, in the chronic outpatient setting (as opposed to an intensive care unit), the frequency of symptomatic IDH is not reduced with a higher-calcium dialysis solution (Sherman, 1986). Since high dialysis solution calcium levels may contribute to vascular calcification, their use for prolonged periods is not advisable. Dialysis solution magnesium levels may impact dialysis hypotension, but whether a higher or a lower level should be used is controversial.

D. Unusual causes of hypotension during dialysis.

Rarely, hypotension during dialysis may be a sign of an underlying, serious event. Causes are listed in Table 12.1.

E. Detection of hypotension.

Most patients complain of feeling dizzy, light-headed, or nauseated when hypotension occurs. Some experience muscle cramps. Others may experience very subtle symptoms, which may be recognizable only to dialysis staff familiar with the patient (eg, lack of alertness, darkening of vision); patients themselves are frequently quite aware of symptoms portending IDH. In some patients, there are no symptoms whatsoever until the blood pressure falls to extremely low (and dangerous) levels. For this reason, regular blood pressure monitoring is required throughout the hemodialysis session, with its frequency depending on the individual case.

F. Management of IDH.

Management of the acute hypotensive episode is straightforward. The patient should be placed in the Trendelenburg position (if respiratory status allows this), and a bolus of 0.9% saline (100 mL or more, as necessary) should be rapidly administered through the blood line. The UFR should be reduced to as near zero as possible. The patient should then be observed carefully. Ultrafiltration can be resumed (initially at a slower rate) once vital signs have stabilized. An alternative to saline for treating the hypotensive episode includes glucose, mannitol, and albumin solutions. However, albumin is costly and offers little benefit over other approaches (Fortin, 2010; Knoll, 2004) while mannitol accumulates, reducing its benefit on subsequent treatments. IDH may respond better to rapid administration of hypertonic

saline (over 2 minutes) than to slower administration (5 minutes) of (probably) an equivalent sodium load administered as 0.9% saline; the tonicity-induced increase in vasopressin levels is the likely basis for the differential effects (Shimizu, 2012). However, caution is advised if a high dialysis solution sodium is being used. Nasal oxygen administration is not generally of benefit during hypotensive episodes, though it may have value in selected patients (Jhawar, 2011).

1. **Slowing the blood flow rate.** The benefits of slowing the blood flow rate to treat IDH are no longer applicable to current dialysis practice (Sherman, 2016). It is, however, still utilized if hypotension is severe or unresponsive to stopping ultrafiltration and infusion of volume expanders, though without objective evidence of its value. Repeated slowing of the blood flow rate will reduce solute removal and cause underdialysis.

G. Prevention. One strategy to help prevent hypotension during dialysis is given in Table 12.2.

TABLE 12.2 Strategy to Help Prevent Hypotension During Dialysis

1. Use a dialysis solution temperature of 35.5°C or individualize as per patient tolerance.
2. Review dietary sodium intake and any other reasons for excess fluid intake. Fluid intake should ideally be <1 L per day in anuric patients. If predialysis serum sodium is low, consider the level of dialysis solution sodium versus serum sodium.
3. If substantial residual kidney function exists, consider increasing urine volume using diuretics.
4. Extend weekly dialysis time to lower ultrafiltration rate.
5. Consider raising the patient's target weight.
6. In refractory cases, consider a trial of higher (140–145 mM) dialysis sodium, as tolerated, especially if a high interdialytic weight gain is not a problem. If a high interdialytic weight gain is present, consider cautiously lowering dialysis solution sodium level.
7. Give daily dose of antihypertensive medications after, not before, dialysis; consider changing therapy to the calcium channel blocker class of drugs.
8. Assess the benefits of a predialysis hemoglobin level consistently = 10–11 g/dL (100–110 g/L).
9. Do not give food or glucose orally during, or immediately preceding, dialysis to hypotension-prone patients.
10. Consider use of a blood volume monitor.
11. Consider a trial of midodrine
12. Consider use of a higher (e.g., 3.0 mM) potassium dialysis solution if predialysis levels allow.

II. MUSCLE CRAMPS

A. Etiology. The pathogenesis of muscle cramps during dialysis is unknown. The four most important predisposing factors are hypotension, hypovolemia (patient below dry weight), high UFR (large weight gain), and use of low-sodium dialysis solution. These factors all tend to favor vasoconstriction, resulting in muscle hypoperfusion, leading to secondary impairment of muscle relaxation. Muscle cramps most commonly occur in association with hypotension, although cramps often persist after seemingly adequate blood pressure has been restored. The frequency of cramping increases logarithmically with the weight loss requirements; weight losses of 2%, 4%, and 6% have been associated with cramping frequencies of 2%, 26%, and 49%, respectively.

Cramping is more common during the first month of dialysis than in subsequent periods. It is more common in patients with a low cardiac index. Diagnostically obscure elevations in serum creatinine phosphokinase levels on routine monthly laboratory tests

may result from intradialytic muscle cramping. Hypomagnesemia may cause treatment-resistant muscle cramping during dialysis. Hypocalcemia should also be considered as a potential cause, especially in patients treated with relatively low-calcium dialysis solution (1.25 mM) and calcium-free phosphate binders and/or calcimimetics. Predialysis hypokalemia, exacerbated by the usual level of dialysis solution potassium (2 mM), may precipitate cramping as well.

B. Management. When hypotension and muscle cramps occur concomitantly, both may respond to treatment with 0.9% saline; however, it is not unusual for muscle cramps to persist. Hypertonic solutions (saline, glucose, mannitol) may dilate muscle blood vessels and are more effective in the acute management of muscle cramps. Because the concentrated sodium load associated with hypertonic saline administration can be problematic, hypertonic glucose administration is preferred for the treatment of cramps in patients without diabetes. Mannitol may accumulate in patients undergoing dialysis, particularly when administered late in treatment—the usual time for the occurrence of cramps. Nifedipine (10 mg) sometimes can reverse cramping. Though reportedly not causing a notable fall in blood pressure, nifedipine should be reserved for cramping in hemodynamically stable patients. Forced stretching of the muscle involved (eg, ankle flexion for calf cramping) may provide relief. Massage varies in its utility on an individual basis.

C. Prevention. Prevention of hypotensive episodes will eliminate most cramping.

1. **Stretching exercises.** A program of stretching exercises targeted at the affected muscle groups may be useful and should be the first-line treatment for both dialysis-related cramps and nocturnal cramps (Evans, 2013).
2. **Massage.** In one small, randomized study (Mastnardo, 2016), massaging the legs for 20 min during each dialysis reduced the incidence of cramps both during dialysis and at home during the interdialytic interval. A second randomized trial was in agreement with these results (Parlak, 2024).
3. **Dialysate sodium.** The frequency of cramping is inversely related to the dialysis solution sodium level. Raising sodium levels to just below the threshold for induction of postdialysis thirst will be beneficial, as will the use of sodium gradient dialysis, although the latter may be at the expense of increasing interdialytic weight gain and blood pressure.
4. **Dialysate magnesium.** Avoiding low predialysis levels of magnesium, calcium, and potassium may also be helpful. In one study, use of 0.5 mM (1 mEq/L) dialysis solution magnesium was associated with both less frequent and less intense cramping than when 0.375 mM (0.75 mEq/L) solution was used (Lynch, 2014). Magnesium supplements have not been shown to be useful in nonuremic subjects, and magnesium should be given with great caution to patients undergoing dialysis. The use of Osvaren (calcium acetate/magnesium carbonate) as a phosphate binder compared with sevelamer showed no change in the incidence of cramps.
5. **Biotin.** Biotin, in a dose of 1 mg/d, has been reported to improve intradialytic cramps, despite baseline serum levels being higher than in control subjects (Oguma, 2012). This study needs to be confirmed before biotin use can be more widely recommended.
6. **Vitamin K.** A 39-patient randomized, blinded, placebo-controlled crossover study found that vitamin K2 (menaquinone, 360 mcg/d) reduced cramping by over 60%

(Xu, 2022).

7. **Carnitine, oxazepam, and vitamin E.** Carnitine supplementation of patients undergoing dialysis may reduce intradialytic muscle cramps (Ahmad, 1990) as may oxazepam (5-10 mg, given 2 hours prior to dialysis) and vitamin E. See Evans (2013) for a review.
8. **Compression devices.** A type of sequential compression device may be of benefit (Ahsan, 2004).
9. **Quinine.** Quinine sulfate before dialysis, though effective in preventing intradialytic cramps, is inadvisable because of its association with thrombocytopenia, hypersensitivity reactions, and QT prolongation. The U.S. Food and Drug Administration (FDA) has issued a number of guidance documents aimed at counseling health professionals against the use of quinine for leg cramps.

III. NAUSEA AND VOMITING

A. Etiology. Nausea or vomiting occurs in up to 10% of routine dialysis treatments. The cause is multifactorial. Most episodes in stable patients are probably related to hypotension. Nausea or vomiting can also be an early manifestation of the disequilibrium syndrome described below. Both type A and type B varieties of dialyzer reactions can cause nausea and vomiting. Gastroparesis, very common in diabetes but also seen in patients without diabetes, is exacerbated by hemodialysis and may play a role in some patients. Contaminated or incorrectly formulated dialysis solution (high sodium, calcium) may cause nausea and vomiting as part of a constellation of symptoms. Patients undergoing dialysis appear to develop nausea and vomiting more readily than other patients (eg, with an upper respiratory infection, narcotic usage, hypercalcemia); dialysis may precipitate these symptoms in such a predisposing setting.

B. Management. The first step is to treat any associated hypotension. Vomiting may be particularly problematic when associated with a hypotension-induced reduction in the level of consciousness owing to the risk of aspiration. Antiemetics can be administered as needed.

C. Prevention. Avoidance of hypotension during dialysis is of prime importance. Persistent symptoms unrelated to hemodynamics may benefit from metoclopramide. Sometimes a single predialysis dose of 5 to 10 mg is sufficient.

IV. HEADACHE

A. Etiology. Headache occurs in as many as 70% of patients during dialysis; its cause is largely unknown though is more likely in patients with higher predialysis blood urea nitrogen (BUN) and blood pressure (Gozubatik-Celik, 2019). It may be a subtle manifestation of the disequilibrium syndrome (see section VII, below). Dialysis may precipitate migraine headaches in those with a history of the disorder. With atypical or particularly severe headache, a neurologic cause (particularly a bleeding event precipitated by anticoagulation) should be considered. In one refractory case, administration of intradialytic nasal oxygen was helpful (Gianneschi and Michaud, 2024).

B. Management. Acetaminophen can be given during dialysis.

C. Prevention. Decreasing dialysis solution sodium may also be helpful in patients being treated with high sodium levels. A cup of strong coffee may help prevent (or treat)

caffeine withdrawal symptoms, though its use (with 200 mg of caffeine) does not reduce the frequency of IDH (Aoun, 2021). Patients suffering from headache during dialysis may be magnesium deficient (Goksel, 2006). A cautious trial of magnesium supplementation may be indicated, keeping in mind the risks of giving magnesium to patients with renal failure.

V. CHEST PAIN AND BACK PAIN. Mild chest pain or discomfort (often associated with some back pain) occurs in 1% to 4% of dialysis treatments. The cause is unknown. There is no specific management or prevention strategy, though switching to a different variety of dialyzer membrane may be of benefit. The occurrence of angina during dialysis is common and must be considered in the differential diagnosis, along with numerous other potential causes of chest pain (eg, hemolysis, air embolism, pericarditis). The management and prevention of angina are discussed in Chapter 36.

VI. ITCHING. Itching, a common problem in patients undergoing dialysis, is sometimes precipitated or exacerbated by dialysis. Itching appearing only during the treatment, especially if accompanied by other minor allergic symptoms, may be a manifestation of low-grade hypersensitivity to the dialyzer or blood circuit components. More often than not, however, itching is simply present chronically and is noticed in the course of the treatment while the patient is forced to sit still for a prolonged period of time. Viral (or drug-induced) hepatitis, hypercalcemia, and scabies should not be overlooked as potential causes of such itching.

Chronically, general moisturizing and lubrication of the skin using emollients is recommended, and this should be the first line of therapy. One should make sure that dialysis is adequate and that a *Kt/V* of at least 1.2 and possibly higher is being delivered, though the evidence that higher *Kt/V* improves pruritus is not strong. Pruritus is often found in patients with elevated serum calcium or phosphate levels and/or substantially elevated parathyroid hormone (PTH) level; in such patients, reductions in phosphate, calcium (to the lower end of the normal range), and PTH levels are indicated. Standard symptomatic treatment using antihistamines is common practice but has not been shown to be effective; studies suggest that pruritus in patients undergoing dialysis is mediated via a nonhistaminergic neural pathway (Papoiu, 2014). Gabapentin (or pregabalin), UVB (ultraviolet light B) therapy, oral charcoal, or nalfurafine might be the next line of therapy, followed by naltrexone, sertraline, doxepin, or tacrolimus ointment (Figure 12.1) (Mettang and Kremer, 2015). Acupuncture may be of benefit, with six studies (all potentially biased) evaluating and supporting its use (Kim, 2010). Recently, difelikefalin, an IV selective κ-opioid receptor (KOR) agonist, was approved in the United States for the treatment of pruritus in patients undergoing hemodialysis. It is significantly, though modestly effective for this indication (Fishbane, 2020).

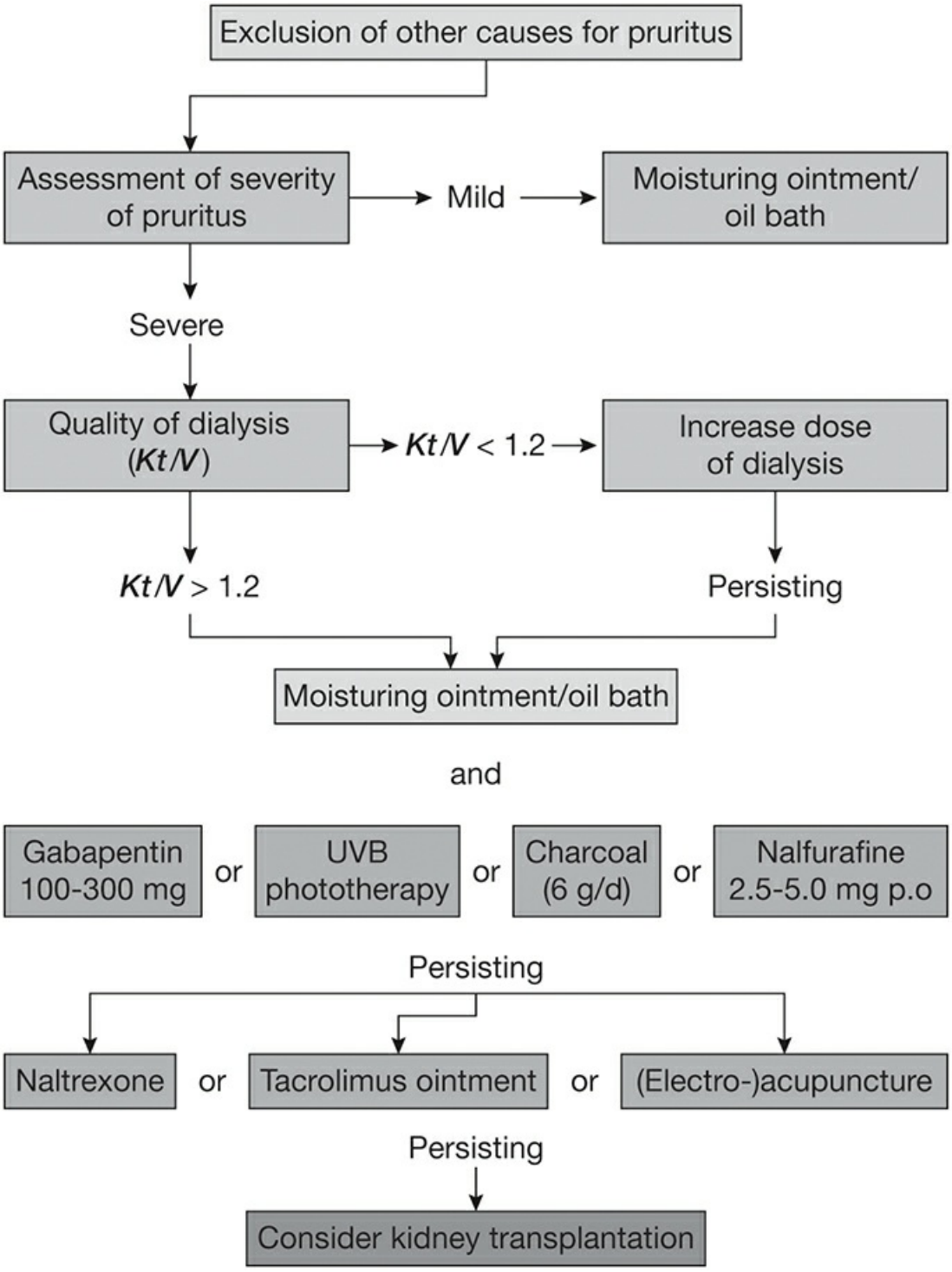


FIGURE 12.1: Algorithm to manage pruritus. UVB, ultraviolet light B. (Reproduced with permission from Mettang T, Kremer AE. Uremic pruritus. *Kidney Int*. 2015;87[4]:685-691.)

VII. DISEQUILIBRIUM SYNDROME

A. Definition. The disequilibrium syndrome is a set of systemic and neurologic symptoms often associated with characteristic electroencephalographic findings that can occur

either during or following dialysis. Early manifestations include nausea, vomiting, restlessness, and headache. More serious manifestations include seizures, obtundation, and coma (see also Chapter 38).

B. Etiology. The cause of the disequilibrium syndrome is controversial. Most believe it is related to an acute increase in brain water content. When the plasma solute level is rapidly lowered during dialysis, the plasma becomes hypotonic with respect to the brain cells, and water shifts from the plasma into brain tissue. Others incriminate acute changes in the pH of the cerebrospinal fluid during dialysis as the cause of this disorder.

The disequilibrium syndrome was a much larger problem four or more decades ago when acutely uremic patients with very high serum urea nitrogen values were commonly subjected to prolonged dialysis. However, milder forms of the syndrome may still occur in patients undergoing long-term dialysis, manifesting as nausea, vomiting, or headache. The full-blown disequilibrium syndrome, including coma and/or seizures, can still be precipitated when an acutely uremic patient is dialyzed too energetically.

C. Management

1. **Mild disequilibrium.** Symptoms of nausea, vomiting, restlessness, and headache are nonspecific; when they occur, it is difficult to be certain that they are due to disequilibrium. Treatment is symptomatic. If mild symptoms of disequilibrium develop in an acutely uremic patient during dialysis, the blood flow rate should be reduced to decrease the efficiency of solute removal and pH change, and consideration should be given to terminating the dialysis session earlier than planned. Hypertonic sodium chloride or glucose solutions can be administered for the treatment of muscle cramps.
2. **Severe disequilibrium.** If seizures, obtundation, or coma occur in the course of a dialysis session, dialysis should be stopped. The differential diagnosis of severe disequilibrium syndrome should be considered (see Chapter 38). Treatment of seizures is discussed in Chapter 38. The management of coma is supportive. The airway should be controlled and the patient ventilated if necessary. Intravenous mannitol may be of benefit. If coma is due to disequilibrium, then the patient should improve within 24 hours.

D. Prevention

1. **In an acute dialysis setting.** When planning dialysis for an acutely uremic patient, one should not prescribe an overly aggressive treatment session (see Chapter 10 and Appendix C). The target reduction in the plasma urea nitrogen level should initially be limited to 30-40%. Use of a low-sodium dialysis solution (more than 2-3 mM less than the plasma sodium level) may exacerbate cerebral edema and should be avoided. In hypernatremic patients, one should not attempt to correct the plasma sodium concentration and the uremia at the same time. It is safest to dialyze a hypernatremic patient initially with a dialysis solution sodium value close to the plasma level and then to correct the hypernatremia slowly postdialysis by administering 5% dextrose.
2. **In a chronic dialysis setting.** The incidence of disequilibrium syndrome can be minimized by the use of a dialysis solution with a sodium concentration of at least 140 mM. Intradialytic symptom frequency is similar with a dialysate glucose concentration of 200 mg/dL and with a glucose level of 100 mg/dL (11 vs 5.5 mM)

(Raimann, 2012). Using a high dialysis solution sodium concentration (145-150 mM) that declines over the course of treatment for patients has been advocated in this setting: the initially high dialysis solution sodium results in a rising plasma sodium that may counteract the osmotic effects of the initially rapid removal of urea and other solutes from plasma. There is evidence that use of this approach reduces the incidence of disequilibrium-type intradialytic symptoms, but it may increase interdialytic weight gain and blood pressure because of diffusive entry of sodium from dialysis solution to blood during the treatment session.

VIII. DIALYZER REACTIONS.

This is a broad group of events that includes both anaphylactic and less well-defined adverse reactions of unknown cause (Jaber and Pereira, 1997). In the past, many of these reactions were grouped under the term "first-use" syndrome because they presented much more often when new (as opposed to reused) dialyzers were employed. However, similar reactions occur with reused dialyzers, and we now discuss them under the more general category used here. There appear to be two varieties: an anaphylactic type (type A) and a nonspecific type (type B). The occurrence of type B reactions appears to have diminished considerably during the past several decades and this A vs. B classification is now of limited clinical utility.

A. Type A (anaphylactic type)

1. **Manifestations.** When a full-blown, severe reaction occurs, the manifestations are those of anaphylaxis. Dyspnea, a sense of impending doom, and a feeling of warmth at the fistula site or throughout the body are common presenting symptoms. Cardiac arrest and even death may supervene. Milder cases may present only with itching, urticaria, cough, sneezing, coryza, or watery eyes. Gastrointestinal manifestations, such as abdominal cramping or diarrhea, may also occur. Patients with a history of atopy and/or with eosinophilia are prone to develop these reactions. Symptoms usually begin during the first few minutes of dialysis, but onset may occasionally be delayed for up to 30 minutes or more.
2. **Etiology**
   a. **Ethylene oxide.** Most type A (anaphylactic) reactions in the past were due to hypersensitivity reactions to ethylene oxide, which was widely used by manufacturers to sterilize dialyzers. Currently, manufacturers more often use other methods of sterilization (γ-radiation, steam, electron beam), and when ethylene oxide is used, little residual compound is left in the dialyzers. As a result, ethylene oxide reactions are now uncommon. Some reactions attributed to ethylene oxide have been linked to use of ethylene-oxide-sterilized blood tubings, even when the sterilization method of the dialyzer did not use ethylene oxide (Crane, 2023).
   b. **Dialysis membrane reactions.** These were initially reported in patients dialyzed with the AN69 (acrylonitrile-sodium methallyl sulfonate) membrane who were also taking angiotensin converting enzyme (ACE) inhibitors (but not angiotensin receptor blockers). The reactions are thought to be activation of the bradykinin system by the negatively charged AN69 membrane with the effects magnified because ACE inhibitors block bradykinin inactivation. The AN69 membrane has, in recent years, been modified by the addition of polyethyleneimine, a polymer that neutralizes the problematic negative surface

charge and sharply reduces bradykinin activation. The risk of ACE inhibitor–associated reactions with other PAN (polyacrylonitrile)- or non–PAN-based membranes has not been well assessed but is likely quite low.

There have been a substantial number of case reports of type A reactions to dialyzers with polysulfone membranes made by a variety of manufacturers; about half occurred on the first exposure to the dialyzer (Boer, 2017). Switching to an alternative membrane was almost always a successful intervention.

c. **Contaminated dialysis solution.** Type A dialyzer reactions may be accounted for in some instances by dialysis solution contamination with high levels of bacteria and endotoxin, particularly with the use of high-flux dialyzers. Such reactions are likely to occur promptly (within 2 minutes) of initiating dialysis; complement-mediated reactions are more delayed (15-30 minutes) in onset. Fever and chills are particularly common symptoms with these reactions. The higher the bacteria and endotoxin levels are, the greater the risk of a reaction.

d. **Reuse.** Clusters of anaphylactic-type dialyzer reactions have occurred in a reuse setting. The problem has often been linked to inadequate dialyzer disinfection during the reuse procedure, but in many cases, the cause is unknown. Prior to the year 2000, half of Centers for Disease Control and Prevention (CDC) investigations of outbreaks of bacteremia or pyrogenic reactions in patients undergoing dialysis over a 20-year period were ascribed to dialyzer reuse problems (Roth and Jarvis, 2000).

e. **Heparin.** Heparin has occasionally been associated with allergic reactions, including urticaria, nasal congestion, wheezing, and even anaphylaxis. When a patient seems to be allergic to a variety of different dialyzers regardless of the sterilization mode, and dialysis solution contamination also has been reasonably excluded, a trial of heparin-free dialysis or citrate anticoagulation should be considered. Low-molecular-weight heparins are not a safe substitute in such patients owing to cross-reactivity with heparin, which may result in anaphylactic reactions.

f. **Complement fragment release.** Acute increases in pulmonary artery pressure have been documented in both animals and humans during dialysis with unsubstituted cellulose membranes. However, there is no good evidence that complement activation causes type A dialyzer reactions. Several studies have found no difference in type A reaction rates between membranes that readily activate complement (cuprophane) and those that do not (polysulfone, AN69).

g. **Eosinophilia.** Type A reactions tend to occur more readily in patients with mild to moderate eosinophilia. Very severe reactions to dialysis or plasmapheresis were reported in patients with very high eosinophil counts; these were thought to be due to sudden eosinophil degranulation with the release of bronchoconstrictive and other mediators.

h. **Thrombocytopenia.** Thrombocytopenia has been reported with or without dialyzer reaction symptoms in association with use of dialyzers made of polysulfone. Heparin antibodies apparently were not involved. The platelet count often was restored to normal and symptoms abated on changing to a dialyzer membrane made of cellulose triacetate (Claudio-Gonzalez, 2021).

3. **Management.** Identifying the actual cause of a dialyzer reaction frequently is not possible. It is safest to stop dialysis immediately, clamp the blood lines, and discard the dialyzer and blood lines without returning the contained blood. Immediate cardiorespiratory support may be required. According to the severity of the reaction, treatment with intravenous antihistamines, steroids, and epinephrine can be given.
4. **Prevention.** In a patient with a type A reaction to an ethylene oxide–sterilized dialyzer that persists despite extensive rinsing of the dialyzer prior to use, the dialyzer type can be changed to a γ-irradiated, steam-sterilized, or electron beam–sterilized dialyzer (see Appendix D). Changing or stopping heparin, trying a less complement-activating membrane, and substituting an angiotensin receptor–blocking agent for an ACE inhibitor may also be tried. A role for latex exposure during dialysis initiation in a sensitized patient should be considered as well. For patients with mild type A symptoms unresolved by these interventions, predialysis administration of antihistamines may be of benefit.

B. Nonspecific type B dialyzer reactions

1. **Symptoms.** The principal manifestations of a type B reaction are chest pain, sometimes accompanied by back pain. Symptom onset is usually 20 to 40 minutes after starting dialysis. Typically, type B reactions are much less severe than type A reactions.
2. **Etiology.** The cause is unknown. Complement activation has been suggested to be a culprit, but its etiologic role in the development of these symptoms is uncertain. The observation that chest and back pain may occur less frequently with reused dialyzers than with new dialyzers suggests that washout of potentially toxic substances during dialyzer reprocessing or membrane bioincompatibility (reduced by residual protein coating of the membrane) may play a role. Other causes of chest and back pain must be excluded, and the diagnosis of a type B dialyzer reaction is one of exclusion. In particular, subclinical hemolysis must be ruled out. A syndrome of acute respiratory distress associated with heparin-induced thrombocytopenia has been described (Popov, 1997), which may superficially resemble a type B dialyzer reaction.
3. **Management.** Management is supportive. Nasal oxygen should be given. Myocardial ischemia should be considered, and angina pectoris, if suspected, can be treated as discussed in Chapter 36. Dialysis can usually be continued, as symptoms invariably abate after the first hour.
4. **Prevention.** Trying a different dialyzer membrane may be of value.

IX. HEMOLYSIS.

Acute hemolysis during dialysis may be a medical emergency.

A. Manifestations.

The symptoms of hemolysis are back pain, tightness in the chest, and shortness of breath. A dramatic deepening of skin pigmentation may occur. Common are a port-wine appearance of blood in the venous blood line, a pink discoloration of the plasma in centrifuged blood samples, and a marked fall in the hematocrit. If massive hemolysis is not detected early, then hyperkalemia can result owing to the release of potassium from the hemolyzed erythrocytes, leading to muscle weakness, electrocardiographic abnormalities, and, ultimately, cardiac arrest.

B. Etiology.

Acute hemolysis has been reported in two primary settings: (a) an obstruction or narrowing in the blood line, catheter, or needle or (b) a problem with the

dialysis solution. The possibility of hemolysis induced by the combination of G6PD deficiency and sulfamethoxazole, glimepiride, or any of the fluoroquinolone antibiotics; quinine ingestion (even tonic water) should also be considered.

1. **Blood line obstruction/narrowing.** Kinks may develop in the arterial blood line (Sweet, 1996). An epidemic of hemolysis also has been reported owing to manufacturing defects in the link between the dialyzer outlet blood line and the venous air trap chamber (CDC, 1998). Hemolysis (usually subclinical) may also appear when blood flow rate is high, and relatively small needle sizes are used, resulting in an excessively negative prepump (arterial) pressure (De Wachter, 1997). Routine blood line pressure monitoring will call attention to many, but not all, such problems.
2. **Problems with dialysis solution.** These are as follows:
   a. Overheated dialysis solution
   b. Hypotonic dialysis solution (insufficient concentrate-to-water ratio)
   c. Dialysis solution contaminated with formaldehyde, bleach, chloramine (from city water supply), copper (from copper piping), fluoride, nitrates (from water supply), zinc, or hydrogen peroxide (see Chapter 5).

C. Management. The blood pump should be stopped immediately and the blood lines clamped. Hemolyzed blood has a very high potassium content and should not be reinfused. One should be prepared to treat the resultant hyperkalemia and possible drop in hematocrit. The patient should be observed carefully, and hospitalization should be considered. Delayed hemolysis of injured erythrocytes may continue for some time after the dialysis session. Severe hyperkalemia may occur, and this may require additional dialysis or other measures (eg, administration of an Na/K ion exchange resin by mouth or rectum) to control. A complete blood count, reticulocyte count, and levels of haptoglobin, free hemoglobin, lactate dehydrogenase, and methemoglobin should be obtained. Dialysis solution water (chloramine, nitrates, metals) and, if reprocessed, the dialyzer (residual sterilant) need to be assessed as well.

D. Prevention. Unless the problem is an obstruction in the blood path or a faulty roller pump causing excessive blood trauma, the cause of the hemolysis must be assumed to be in the dialysis solution, and samples of dialysis solution must be investigated to determine the cause.

X. AIR EMBOLISM.

Air embolism is a potential catastrophe that can lead to death unless detected and treated quickly.

A. Manifestations

1. **Symptoms.** These depend to an extent on the position of the patient. In seated patients, infused air tends to migrate into the cerebral venous system without entering the heart, causing obstruction to cerebral venous return, loss of consciousness, convulsions, and even death. In recumbent patients, the air tends to enter the heart, generate foam in the right ventricle, and pass into the lungs, producing dyspnea, cough, chest tightness, and arrhythmias. Further passage of air across the pulmonary capillary bed into the left ventricle can result in air embolization to the arteries of the brain and heart, with acute neurologic and cardiac dysfunction.
2. **Signs.** Foam is often seen in the venous blood line of the dialyzer. If air has gone

into the heart, a peculiar churning sound may be heard on auscultation.

B. Etiology. The predisposing factors and possible sites of air entry have been discussed in Chapter 4. The most common sites of air entry are the arterial needle, the prepump arterial tubing segment, and an inadvertently opened end of a central venous catheter.

C. Management. The first step is to clamp the venous blood line and stop the blood pump. The patient is immediately placed in a recumbent position on the left side with the chest and head tilted downward. Further treatment includes cardiorespiratory support, including administration of 100% oxygen by mask or endotracheal tube. Aspiration of air from the atrium or ventricle with a percutaneously inserted needle or cardiac catheterization may be needed if the volume of air warrants it.

D. Prevention. See Chapters 4 and 10.

XI. OTHER COMPLICATIONS. Arrhythmia and cardiac tamponade are discussed in Chapter 36. Severe disequilibrium syndrome, seizures, and intracerebral bleeding are discussed in Chapter 38.

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13 Anticoagulation

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I. BLOOD CLOTTING IN THE EXTRACORPOREAL CIRCUIT. The patient's blood is exposed to intravenous cannulas, tubing, drip chambers, headers, potting compound, and dialysis membranes during the dialysis procedure. These surfaces exhibit a variable degree of thrombogenicity and may initiate clotting of blood, especially in conjunction with exposure of blood to air in drip chambers. The resulting thrombus formation may be significant enough to cause occlusion and malfunction of the extracorporeal circuit. Clot formation in the extracorporeal circuit begins with the activation of leukocytes and platelets, leading to surface blebbing and shedding of surface membrane lipid–rich microparticles, which initiate thrombin generation, activation of coagulation cascades, further thrombin formation, and fibrin deposition. New advances in the production of blood lines for the dialysis circuit designed to utilize less tubing and fewer connections, along with eliminating the traditional drip chamber, so reducing both turbulent blood flow, air-blood interfaces and microbubble generation, reduce the requirements for extracorporeal anticoaguation. Factors favoring clotting are listed in Table 13.1.

TABLE 13.1 Factors Favoring Clotting of the Extracorporeal Circuit

Low blood flow rate, especially through a large surface area dialyzer with a high filling volume
High hematocrit
High ultrafiltration rate
Dialysis access recirculation
Intradialytic blood and blood product transfusion
Intradialytic lipid infusion
Use of drip chambers (air exposure, foam formation, turbulence)

A. Assessing coagulation during dialysis

1. **Visual inspection.** Signs of extracorporeal circuit clotting are listed in Table 13.2. Visualization of the circuit can be best accomplished by rinsing the system with a saline solution while temporarily occluding the blood inlet.

TABLE 13.2 Signs of Clotting in the Extracorporeal Circuit

Extremely dark blood
Shadows or black streaks in the dialyzer
Foaming with subsequent clot formation in drip chambers and venous trap
Rapid filling of transducer monitors with blood
"Teetering" (blood in the postdialyzer venous line segment that is unable to continue into the venous chamber but falls back into the line segment)
Presence of clots at the inflow dialyzer header

2. **Extracorporeal circuit pressures.** Arterial and venous pressure readings may change due to clotting in the extracorporeal circuit, depending on the location of thrombus formation. An advantage of using blood lines with a postpump arterial pressure monitor is that the difference between the postpump and venous pressure readings can serve as an indicator to the location of the clotting. An increased pressure difference is seen when the clotting is confined to the dialyzer itself (increased postpump pressure, decreased venous pressure). If clotting occurs in or distal to the venous blood chamber, then the postpump and venous pressure readings increase in tandem. If clotting is extensive, then the rise in pressure readings will be precipitous. A clotted or malpositioned venous needle can also increase pressure readings.
3. **Dialyzer appearance after dialysis.** The presence of a few clotted fibers is not unusual, and the headers often collect small blood clots or whitish deposits (especially in patients with hyperlipidemia). More significant dialyzer clotting should be recorded by the dialysis staff to serve as a clinical parameter for adjustment of anticoagulant dosing. It is useful to classify the amount of clotting on the basis of the visually estimated percentage of clotted fibers in order to standardize documentation (eg, <10% of fibers clotted, grade 1; 10% to 50% clotted, grade 2; >50% clotted, grade 3).
4. **Measurement of residual dialyzer volume.** In units practicing dialyzer reuse, automated or manual methods are used to determine the clotting-associated fiber loss during each treatment. This is done by comparing the predialysis and postdialysis fiber bundle volumes. Dialyzers suitable for reuse characteristically have less than 1% fiber loss over each of the first 5 to 10 reuses.

II. USE OF ANTICOAGULANTS DURING DIALYSIS.

When no anticoagulant is used, dialyzer clotting rate during a 3- to 4-hour dialysis session is substantial (5%-10%), and when this occurs, it results in loss of the dialyzer and blood tubings, plus loss of approximately 100 to 180 mL of blood (the combined fill volume of the dialyzer and blood line in the extracorporeal circuit). This is an acceptable risk for many adult patients judged to be at high risk of anticoagulant-induced bleeding, as bleeding in such patients may result in catastrophic consequences, and for such patients, anticoagulation-free dialysis (described below) is appropriate. However, for the great majority of patients, who are judged not to be at a markedly increased bleeding risk, some form of anticoagulation is usually employed. In programs reusing dialyzers, therapeutic levels of anticoagulation during dialysis are key to obtaining reasonable reuse numbers.

There is considerable variability as to the type of anticoagulation used for intermittent hemodialysis. Worldwide, heparin remains the most common anticoagulant used. In the United States, unfractionated heparin (UFH) is mostly used, whereas in the European Union, low-molecular-weight heparin (LMWH) is the anticoagulant of choice recommended by the European Best Practice Guidelines (2002). A small number of dialysis units anticoagulate the blood circuit using trisodium citrate, and in special circumstances, direct thrombin inhibitors such as argatroban, heparinoids (danaparoid, fondaparinux), prostanoids, and nafamostat mesylate may be used as alternative anticoagulants.

III. MEASURING BLOOD CLOTTING DURING DIALYSIS.

Due to economic constraints,

the relatively low risk of bleeding complications from heparin usage during dialysis, and regulatory issues (the requirement for local laboratory certification), heparin therapy is typically prescribed empirically, without laboratory monitoring. In patients with an increased risk of bleeding, the need to monitor anticoagulation is often circumvented by using heparin-free dialysis.

When monitoring clotting, blood should be drawn from the arterial blood line, proximal to any heparin infusion site, to reflect the clotting status of the patient rather than that of the extracorporeal circuit. Baseline clotting studies taken from a venous catheter may be confounded by residual heparin present within the catheter (Pepper, 2007).

A. Clotting tests used to monitor heparin therapy

1. **Activated partial thromboplastin time (APTT).** This is the most commonly used test in a hospital setting, but is only for UFH. APTT results vary with individual assays, so many centers report a ratio compared to control (APPTr). Heparin resistance states can be falsely suggested owing to elevated levels of factor VIII. Baseline levels may be prolonged because of lupus anticoagulant, depending upon the kit used (Naito, 2008).
2. **Whole-blood partial thromboplastin time (WBPTT).** This is similar to the above, but a bedside test. The WBPTT test accelerates clotting by the addition of 0.2 mL of actin FS reagent (Thrombofax, purified soy phosphatides with plasma activator) to 0.4 mL of blood, which is then placed in a heating block at 37 °C for 30 seconds and then tilted every 5 seconds until a clot forms. The prolongation of the WBPTT is linearly related to the blood heparin concentration (in the range applicable to dialysis). It should only be used to monitor UFH.
3. **Activated clotting time (ACT).** The ACT test uses siliceous earth to accelerate clotting. The ACT is less reproducible than WBPTT, especially at low blood UFH levels. Devices that automatically tilt the tube and detect clot formation facilitate standardization and reproducibility of both WBPTT and ACT for UFH monitoring.
4. **Lee-White clotting time (LWCT).** The Lee-White test requires 0.4 mL of blood placed into a glass tube, which is then inverted every 30 seconds, usually at room temperature, until the blood clots. The LWCT is rarely used, as disadvantages include the long period of time required before clotting occurs, extensive use of technician time required, and the relatively poor standardization and reproducibility of the test.
5. **Activated Factor Xa.** Factor Xa can be measured by chromogenic or functional clotting assays. Laboratory assays of anti-Xa activity differ, as some contain exogenous purified antithrombin (AT), and anti-Xa activity measured using these assays may not necessarily correlate with the biologic effect (Hutt Centeno, 2019). Although UFH can be monitored by Xa activity, this is typically reserved for LMWHs and heparinoids, typically aiming for a peak anti-Xa activity of 0.4 to 0.6 IU/mL and less than 0.2 IU/mL at the end or shortly after completion of dialysis.
6. **Factor Xa–activated ACT.** This test has been proposed as a more sensitive test for monitoring anticoagulation with LMWH (Frank, 2004), but is not widely used in clinical practice.

IV. ANTICOAGULATION TECHNIQUES

A. Unfractionated heparin

1. **Mechanisms of action.** Heparin changes the conformation of AT, leading to rapid inactivation of coagulation factors, in particular, factor IIa. Unfortunately, heparin also stimulates platelet aggregation and activation, but these undesirable effects are counterbalanced by interference with binding and activation of coagulation factors at the platelet membrane. Undesired side effects of heparin include pruritus, allergy including anaphylactoid reactions, alopecia, osteoporosis, hyperlipidemia, thrombocytopenia, and excessive bleeding.
2. **Target clotting times.** UFH can usually be given liberally during dialysis without fear of precipitating a bleeding episode in patients without an abnormal bleeding risk. The effect of two routine UFH regimens on clotting times is shown in Figure 13.1. The goal is to maintain WBPTT or ACT at 180% of the baseline during most of the dialysis session (Table 13.3). However, at the end of the session, the clotting time should be shorter (140% baseline for WBPTT or ACT) to minimize the risk of bleeding after withdrawal of the access needles.

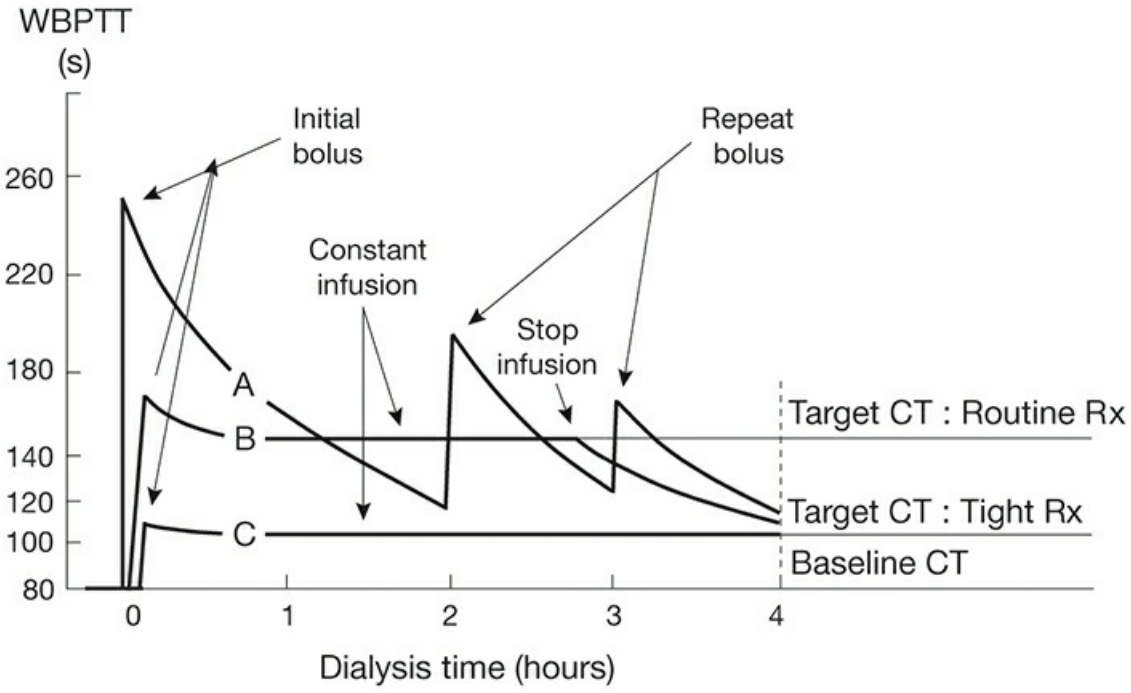


FIGURE 13.1: Effect of various heparin regimens on clotting time as reflected by the WBPTT. Clotting time (CT) using the WBPTT test. A. Routine regimen, repeated bolus method. B. Routine regimen, constant-infusion method. C. Tight regimen, constant-infusion method. WBPTT, whole-blood partial thromboplastin time.

TABLE 13.3 Target Clotting Times During Dialysis

			Routine Heparin		Tight Heparin	
			Desired Range		Desired Range	
Test	Reagent	Baseline Value	During Dialysis	At the End of Dialysis	During Dialysis	At the End of Dialysis
APPTr		1.0	2.0-2.5	1.5-2.0	1.5-2.0	1.5-2.0
WBPTT	Actin FS	60-85 s	+80% (120-140)	+40% (85-105)	+40% (85-105)	+40% (85-105)
ACT[a]	Siliceous earth	120-150 s (200-250)	+80% (170-190)	+40% (170-190)	+40% (170-190)	+40%
LWCT[b]	None	4-8 min	20-30	9-16	9-16	9-16

ACT, activated clotting time; APPTr, activated partial thromboplastin time ratio; LWCT, Lee-White clotting time; WBPTT, whole-blood partial thromboplastin time.

[a]There are various methods of performing the ACT, and the baseline value with some methods is much lower (eg, 90-120 seconds).

[b]Baseline values of the LWCT vary greatly, depending on how the test is performed.

The target clotting times using the LWCT are also listed in Table 13.3. In contrast to WBPTT or ACT, the target clotting times during dialysis are considerably greater than 180% baseline during and greater than 140% baseline at the session end.

3. **Routine heparin prescriptions.** There are two basic techniques for administering UFH. First, a heparin bolus is followed by a constant heparin infusion, or second, a heparin bolus is followed by repeated bolus doses as necessary. For the purpose of discussion, we present a typical prescription in each category.

Rx: Routine heparin, constant-infusion method

Administer the initial bolus dose (eg, 2,000 IU). The initial UFH dose is best administered into the venous access tubing (downstream to the dialyzer) and flushed in with saline (rather than being infused into the arterial blood line upstream to the dialyzer). Introducing UFH into the arterial blood line risks possible loss of the smaller heparin molecules during passage through the dialyzer, and nonheparinized blood to circulate until the loading dose is recirculated through the body. Wait 3 to 5 minutes to allow heparin dispersion before initiating dialysis. Start UFH infusion into the arterial blood line (eg, at a rate of 1,200 IU/h).

Rx: Routine UFH single-dose-only or repeated bolus method

Administer the initial bolus dose (eg, 4,000 IU). Then give an additional 1,000 to 2,000 IU bolus if necessary. The prescriptions used in the United States, however, vary quite widely. Those centers that reuse dialyzers tend to use more UFH in order to maximize reuse number. Some centers give only a single initial dose (eg, 2,000 IU) of UFH, with no subsequent infusion or boluses. Some centers give a fairly large (75-100 IU/kg) initial bolus followed by a 500 to 750 IU/h infusion. Laboratory clotting studies suggest a benefit for the intermittent bolus approach (Nasiri, 2016).

a. **Effect of body weight on the size of the UFH dose.** Although the volume of distribution of heparin has been found to increase as body weight rises (Smith,

1998), many dialysis centers do not regularly adjust heparin dosage in accordance with body weights ranging between 50 and 90 kg. Some centers adjust both the loading and maintenance doses according to body weight.

b. **Effect of prescription of oral anticoagulants on the size of the heparin dose.** Increasing numbers of older patients are prescribed coumarin oral anticoagulants, and newer oral anti-Xa inhibitors (apixaban, rivaroxaban) and direct thrombin inhibitors (dabigatran) are entering medical practice. Hemodialysis reduces the plasma concentration of dabigatran, while rivaroxaban and apixaban cannot be eliminated by dialysis, so are likely to accumulate in dialysis patients and thus increase the risk of bleeding. Most patients on coumarin anticoagulants with an international normalized ratio (INR) of less than 2.5 still require anticoagulation for dialysis, but those with metallic heart valves who have INR values greater than 3.0 typically do not require heparin. Similarly, patients prescribed aspirin and other antiplatelet agents also require standard heparin dosages, but heparin doses should be reduced or withheld in patients with thrombocytopenia (<50,000 × 106/L). There is little clinical data currently on the newer generations of oral anticoagulants, but caution is advised, particularly with the direct thrombin and anti-Xa inhibitors, as the majority of patients anticoagulated with apixaban do not require heparin for dialysis treatments.

c. **When to terminate the heparin infusion.** The UFH half-life in dialysis patients averages 50 minutes but ranges from 30 to 120 minutes. For a patient with an average UFH half-life of 1 hour, if the infusion during dialysis is prolonging WBPTT or ACT to 180% baseline value, then stopping the infusion approximately 1 hour prior to the end of dialysis will result in the desired WBPTT or ACT value of 140% baseline at session termination. When venous catheters are used, heparin infusions are commonly continued up to the end of dialysis.

d. **Posttherapy needle puncture site bleeding.** When this occurs, in addition to reevaluation of the UFH dose, the vascular access (graft or fistula) should be reviewed for the presence of outflow stenosis, as the increased intra-access pressure may be predisposing to posttreatment bleeding. There should also be an evaluation of the needle insertion technique. Poor technique and failure to rotate puncture sites can lead to shredding of the wall of a graft so that it leaks following needle removal, no matter how well anticoagulation is controlled.

4. **Evaluation of clotting during routine heparinization.** A small amount of inadvertent clotting of the extracorporeal system is expected and generally does not necessitate a change in UFH prescription. When clotting occurs, it is useful to evaluate the likely cause. Often, the underlying cause may be correctable (eg, access revision). Operator-induced errors, as listed in Table 13.4, must be considered and managed through education. Recurrent clotting warrants individual reevaluation and adjustments in UFH dosing.

TABLE 13.4 Technical or Operator-Induced Factors That May Result in Clotting

Dialyzer Priming

Retained air in dialyzer (due to inadequate priming or poor priming technique)
Inadequate priming of the heparin infusion line
Heparin Administration
Incorrect heparin pump flow rate setting
Incorrect loading dose
Delayed starting of heparin pump
Failure to release the heparin line clamp
Insufficient time delay after loading dose for systemic heparinization to occur
Dialysis Circuit
Kinking of dialyzer outlet blood line
Vascular Access
Inadequate blood flow due to needle/catheter positioning or clotting
Excessive access recirculation due to needle/tourniquet position
Frequent interruption of blood flow due to machine alarms

5. **Bleeding complications of routine heparinization.** The risk of increased bleeding due to systemic anticoagulation is 25% to 50% in high-risk patients with bleeding gastrointestinal lesions (gastritis, peptic ulcer, angiodysplasia), recent surgery, pericarditis, or thrombocytopenia. De novo bleeding can involve the central nervous system, retroperitoneum, and mediastinum. The tendency to bleed is potentiated by uremia-associated defects in platelet function and possibly by endothelial abnormalities (Krishnaswamy, 2011).

B. Tight heparin

1. **General comments.** Tight heparinization schemes are recommended for patients who are at slight risk for bleeding, when the risk of bleeding is chronic and prolonged, and where use of heparin-free dialysis has been unsuccessful because of frequent clotting. When using WBPTT or ACT to monitor therapy, the target clotting time (see Table 13.3 and curve C in Figure 13.1) is equal to the 140% baseline. Target clotting times using the Lee-White method are given in Table 13.3. If the baseline WBPTT or ACT value is greater than 140% of the average baseline value for patients in the dialysis unit, it is best not to use heparin and to proceed with a heparin-free or regional citrate technique.
2. **The tight heparin prescription.** A bolus dose followed by a constant infusion of heparin is the best technique for administering a tight heparin prescription because constant infusion avoids the rising and falling clotting times that are inevitable with repeated bolus therapy. A typical tight heparin prescription is as follows:

   Rx: Tight heparin, constant-infusion method

   Obtain baseline clotting time (WBPTT or ACT).

   Initial bolus dose = 750 IU UFH.

   Recheck WBPTT or ACT after 3 minutes.

   Administer a supplemental bolus dose if needed to prolong WBPTT or ACT to 140% baseline.

   Start dialysis and UFH infusion at a rate of 600 IU/h.

   Monitor clotting times every 30 minutes.

Adjust the UFH infusion rate to keep WBPTT or ACT at 140% baseline.
Continue UFH infusion until the end of the dialysis session.

C. Heparin-associated complications. Apart from bleeding, complications of note are an increase in blood lipids, thrombocytopenia, and the potential for hypoaldosteronism and exacerbation of hyperkalemia, especially in patients with substantial residual renal function. Some patients may complain of alopecia.

1. **Lipids.** Heparin activates lipoprotein lipase, and in this way can increase the serum triglyceride concentration. Lower levels of high-density lipoprotein (HDL) cholesterol are associated with higher doses of heparin (Näsström, 2001).
2. **Heparin-induced thrombocytopenia (HIT).** There are two types of HIT. In type 1 HIT, the reduction in platelet count occurs in a time- and dose-dependent manner and responds to a reduction in heparin dose. In type 2 HIT, there is agglutination of platelets and paradoxical arterial and/or venous thrombosis. Type 2 HIT, which is attributable to the development of immunoglobulin G (IgG) or IgM antibodies against heparin-platelet factor 4 complex, is more commonly induced with bovine versus porcine UFH and least with LMWHs. Given the frequency of HIT in the nondialysis population, it is surprising that it is not encountered more often in a dialysis setting. Diagnosis of type 2 HIT is a clinical diagnosis supported by a positive enzyme-linked immunosorbent assay (ELISA) using bound platelet factor 4 complexed with heparin in combination with an abnormal platelet aggregation test.

   LMWH should not be used to treat HIT, because there often is cross-reactivity of the heparin-platelet factor 4 antibodies with these drugs. The alternative anticoagulants of choice include the direct thrombin inhibitor argatroban (Nilius, 2021) and the heparinoids danaparoid and fondaparinux (Esposito, 2014). Warfarin should only be introduced once the platelet count has recovered to greater than 150,000 × 106/L, as it may lead to skin necrosis and venous limb gangrene if given in the acute phase of the disease (Srinivasan, 2004).
3. **Pruritus.** Heparin can cause local itching when injected subcutaneously, and it has been speculated that heparin may be the cause of itching and other allergic reactions during dialysis. On the other hand, LMWH has been used to treat the itching associated with lichen planus, on the basis of inhibition of T-lymphocyte heparinase activity (Hodak, 1998). There is no evidence that removal of heparin from the extracorporeal circuit reliably improves uremic pruritus.
4. **Anaphylactoid reactions.** See Chapter 12.
5. **Hyperkalemia.** Heparin-associated hyperkalemia, attributable to heparin-induced suppression of aldosterone synthesis, has been well described. In patients with oliguria undergoing dialysis, it has been speculated that aldosterone might still aid potassium excretion via a gastrointestinal mechanism (Hottelart, 1998).
6. **Osteoporosis.** Long-term administration of heparin can cause osteoporosis.

D. Heparin-free dialysis

1. **General comments.** Heparin-free dialysis is the method of choice in patients who are actively bleeding, who are at moderate to high risk of bleeding, or in whom the use of heparin is contraindicated (eg, persons with heparin allergy). The indications for heparin-free dialysis are listed in Table 13.5. Because of its simplicity and safety, many centers now use heparin-free dialysis routinely for most dialysis treatments

being given in an intensive care unit setting. Careful priming to minimize blood-air interfaces is important in preventing clotting in the extracorporeal circuit. The dialysis circuitry should be chosen to minimize the length of tubing, avoiding areas of stagnation and turbulence due to changes in internal lumen diameter, and three-way connectors. Platelet activation is reduced by cooling the dialysate.

TABLE 13.5 Anticoagulation Strategy: Indications for Heparin-Free Dialysis

Pericarditis
Recent surgery, with bleeding complications or risk, especially:
Vascular and cardiac surgery
Eye surgery (retinal and cataract)
Renal transplant
Brain surgery
Parathyroid surgery
Coagulopathy
Thrombocytopenia
Intracerebral hemorrhage
Active bleeding
Routine use for dialysis of acutely ill patients by many centers

2. **The heparin-free prescription.** There are a variety of techniques, but all are similar to the one given below.

   Rx: Heparin-free dialysis

   a. **Heparin rinse.** (This step is optional. Avoid if heparin-associated thrombocytopenia is present.) Rinse the extracorporeal circuit with saline containing 3,000 IU/L UFH so that heparin can coat extracorporeal surfaces and the dialyzer membrane to mitigate the thrombogenic response. To prevent systemic UFH administration to the patient, allow the heparin-containing priming fluid to drain by filling the extracorporeal circuit with either the patient's blood or unheparinized saline at the outset of dialysis.

   b. **Relatively high blood flow rate.** Set the blood flow rate to 300 to 400 mL/min if tolerated. If a high blood flow rate is contraindicated owing to the risk of disequilibrium (eg, small patient, very high predialysis plasma urea level), consider giving ultrashort (eg, 1 hour) periods of dialysis interspersed with periods of isolated ultrafiltration. In addition, one can consider using a small-surface-area dialyzer and/or markedly slowing the dialysate flow rate. Generally, double-lumen hemodialysis catheters deliver sufficiently high blood flows for heparin-free dialysis to be effective.

   c. **Periodic saline rinse.** The utility of this step is controversial; one recent study suggested that the use of a saline rinse may actually promote clotting (perhaps via the introduction of microbubbles into the circuit) (Sagedal, 2006). The purpose of the periodic rinsing is to allow inspection of a hollow-fiber dialyzer for evidence of clotting and to allow for timely discontinuation of

treatment or changing of the dialyzer. Also, periodic saline rinsing is believed by some to reduce the propensity for dialyzer clotting or interfere with clot formation.

Procedure: Rinse the dialyzer rapidly with 250 mL of saline while occluding the blood inlet line every 15 minutes. The frequency of the flushes can be increased or decreased as needed. The use of volumetric control is desirable for the accurate removal of volumes of ultrafiltrate equal to those of the administered saline rinses.

d. **Dialyzer membrane materials.** Heparin is a very negatively charged molecule that can adsorb to the dialyzer surface, and this has been used to develop heparin-coated dialyzer membranes, which have been reported to allow heparin-free or heparin-reduced dialysis (Evenepoel, 2007). However, the multicenter HepZero study did not show superiority for a heparin-bonded dialyzer over intermittent predilution boluses or continuous predialyzer saline infusion techniques (Laville, 2014). One small randomized trial found that a combination of heparin-bonded dialyzer use with intermittent flushes reduced clotting risk to a greater extent than when these maneuvers were applied singly (Gois, 2024). Heparin-bonded dialyzers should not be used for patients with HIT.

e. **Dialyzer surface area.** Large-surface-area dialyzers theoretically are associated with a higher clotting risk, especially if there is slower flow in the outer fibers; smaller-surface-area dialyzers are designed to provide faster flow in the outer capillary fibers and are preferred.

f. **Ultrafiltration and hemodiafiltration.** A very high ultrafiltration rate leads to hemoconcentration and increases the risk of platelet-dialyzer membrane interactions and clot deposition on the dialyzer surface.

g. **Blood product transfusion or lipid administration.** Administration via the inlet blood line has been reported to increase clotting risk during dialysis.

E. Bicarbonate dialysis solution with low-concentration citrate (Citrasate). A small amount of citric acid is used instead of acetic acid as the acidifying agent. When the acid and base concentrates are mixed, the resulting dialysis solution commonly contains 0.8 mmol/L (2.4 mEq/L) citrate. This small amount of citrate, by complexing with calcium, has been suggested to inhibit blood coagulation and platelet activation locally at the dialyzer membrane surface, resulting in improved dialyzer clearance and increased dialyzer reusability (Ahmad, 2005). This type of dialysis solution can be used with a reduced dose of heparin, or as part of a heparin-free dialysis technique, with a reduced incidence of dialyzer clotting. The amount of citrate used is low enough such that monitoring of ionized calcium is not required (Nseir, 2017).

V. OTHER ANTICOAGULATION TECHNIQUES

A. LMWH. LMWH fractions (molecular weight [MW] = 4,000-6,000 Da) are obtained by chemical degradation, enzymatic digestion, or sieving of crude heparin (MW = 2,000-25,000 Da). LMWHs inhibit factor Xa, factor XIIa, and kallikrein, but cause so little inhibition of thrombin and factors IX and XI that APPT and thrombin times are raised by only 35% during the first hour, and are minimally prolonged thereafter, decreasing bleeding risk.

Hemodialysis using LMWHs as the sole anticoagulant has been shown in long-term studies to be safe and effective. LMWH's longer half-life permits anticoagulation with a single bolus dose at the start of dialysis, though split dosing may be better for extended dialysis sessions. Compared with UFH, LMWHs have higher bioavailability, with less nonspecific binding to the endothelium, plasma proteins, and platelets. As such, LMWHs have a more rapid onset of action and cause less platelet and leukocyte activation (Aggarwal, 2004) and fibrin deposition on dialyzer surfaces than UFH. As LMWHs are smaller molecules, some of the bolus dose may be lost when injected upstream into the dialyzer, particularly during hemodiafiltration treatments (Belmouaz, 2022).

LMWHs are now commercially available in the United States, but are not widely used there for hemodialysis because of greater expense and regulatory issues. The dose of LMWH is generally expressed in anti–factor Xa Institute Choay units (aXa ICU). A series of LMWHs are available: they differ in MW, half-life, and relative anti-Xa to IIa activity. The characteristics of commonly available LMWHs and usual starting doses are given in Table 13.6. Lower dosages should be used in patients who have a mildly increased risk of hemorrhage. Coagulation tests are not routinely monitored with LMWH treatments because anti-Xa activity assays are not readily available. A bedside anti-Xa assay has shown promising results in assessing tinzaparin anticoagulation levels in one preliminary study (Pauwels, 2014). Potential benefits of LMWH, as discussed earlier, include ease of administration and more predictable effects, and LMWH may reduce the risk of heparin-induced osteoporosis associated with long-term UFH administration (Lai, 2001). The European Best Practice Guidelines recommend the use of LMWH over UFH.

TABLE 13.6 Commonly Used LMWH Compounds

Name	Molecular Weight (Da)	Anti-Xa/IIa Activity Ratio	Average Dialysis Bolus Dose
Dalteparin	6,000	2.7	5,000 IU
Nadroparin	4,200	3.6	70 IU/kg
Reviparin	4,000	3.5	85 IU/kg
Tinzaparin	4,500	1.9	1,500-3,500 IU
Enoxaparin	4,200	3.8	0.5-0.8 mg/kg

LMWH, low-molecular-weight heparin.

1. **Anaphylactic reactions to bolus LMWH.** The so-called first-use syndrome (Chapter 12) has been reported not only with UFH but also with LMWH (Warkentin and Greinacher, 2009). When reactions occur, patients seem to react to all types of heparins. Because heparins are very negatively charged, bradykinin and anaphylatoxins (C3a and C5a) can be generated as heparinized blood passes through the dialyzer, leading to hypotension (Kishimoto, 2008), which may explain the case report of an apparently heparin-allergic patient who could be dialyzed when the heparin was infused using a constant-infusion method but not when a bolus dose was given (De Vos, 2000).
2. **Bleeding complications.** In patients with chronic kidney disease being treated

with LMWH who are also receiving clopidogrel and aspirin, bleeding complications have been reported (Farooq, 2004).

B. **Heparinoids (danaparoid and fondaparinux).** Danaparoid is a mixture of 84% heparin, 12% dermatan, and 4% chondroitin sulfates. Danaparoid predominantly affects factor Xa and therefore has to be monitored with anti-Xa assays. The half-life is prolonged in renal failure such that monitoring is sometimes used to check anti-Xa activity prior to the succeeding dialysis session. In patients weighing more than 55 kg, a 750-IU loading dose is recommended, while the loading dose can be 500 IU in patients weighing 55 kg or less. Subsequent doses are titrated to achieve an anti-Xa activity of 0.4 to 0.6 post bolus. Danaparoid may cross-react with HIT antibodies in up to 10% of cases. More recently, a series of synthetic pentasaccharides, such as fondaparinux, have been developed, which do not cross-react with HIT antibodies. A typical predialysis dose is 2.5 to 5.0 mg. Fondaparinux also has an extended half-life. Anti-Xa monitoring is designed to prevent the accumulation of heparinoids, aiming for a predialysis anti-Xa of less than or equal to 0.2 IU/mL (Harenberg, 2015). Hemodiafiltration will increase losses of both danaparoid and fondaparinux, and higher dosages may be required.

C. **Regional (high-concentration) citrate anticoagulation.** An alternative to heparin-free dialysis is to anticoagulate the blood in the extracorporeal circuit by lowering its ionized calcium concentration (calcium is required for the coagulation process). The extracorporeal blood-ionized calcium level is lowered by infusing trisodium citrate (which complexes with calcium) into the arterial blood line and by using a dialysis solution containing no calcium. To prevent the return of blood with a very low ionized calcium concentration to the patient, the process is reversed by infusion of calcium chloride into the dialyzer blood outlet line. About one-third of the infused citrate is dialyzed away, and the remaining two-thirds are quickly metabolized by the patient. The advantages of regional citrate anticoagulation over heparin-free dialysis are (a) the blood flow rate does not have to be high and (b) clotting rarely occurs (Goet, 2021). The principal disadvantages are the requirement for two infusions (one of citrate and one of calcium) and the requirement for monitoring the plasma-ionized calcium level. As sodium citrate metabolism generates bicarbonate, the use of this method results in a greater-than-usual increment in the plasma bicarbonate value. Hence, regional citrate anticoagulation should be used with caution in patients who are at risk for alkalemia, and high bicarbonate dialysates should be avoided. This technique is not widely used for intermittent hemodialysis but is more popular for the continuous forms of dialysis therapy. One theoretical advantage of citrate anticoagulation is the prevention of platelet activation/degranulation (Gritters, 2006).

D. **Thrombin inhibitors.** Argatroban, a synthetic peptide derived from arginine, acts as a direct thrombin inhibitor. It is primarily metabolized in the liver. Argatroban is licensed for treating patients with HIT. For hemodialysis, one can give an initial bolus of 250 mcg/kg followed by an infusion starting at 2 mcg/kg/min, or 6 to 15 mg/h (Esposito, 2014; Murray, 2004), titrated to achieve an APPTr of 2.0 to 2.5. As with heparin, the infusion should be stopped 20 to 30 minutes prior to the end of the dialysis session to prevent excessive bleeding from fistula needle sites. Argatroban is not significantly cleared during high-flux hemodialysis or hemodiafiltration owing to protein binding, but much lower doses are required for those with liver disease (Greinacher, 2008). A related drug, melagatran, has been used for anticoagulation when added to the dialysate, but this

treatment remains experimental (Flanigan, 2005).

Lepirudin is a recombinant irreversible thrombin inhibitor, which is renally cleared and has a prolonged biologic half-life in dialysis patients. The loading dose for intermittent hemodialysis ranges from 0.2 to 0.5 mg/kg (5-30 mg). Lepirudin is cleared during hemodiafiltration and with most high-flux dialyzers (Benz, 2007). Hirudin antibodies have been reported to develop in approximately one-third of patients, potentiating the anticoagulant effect. Dose adjustments are made to the bolus dose by measuring the APPTr prior to the subsequent dialysis, aiming for an APPTr less than 1.5 to prevent accumulation, but as the APTTr does not correlate with plasma lepirudin concentration, lepirudin assays have now been developed, targeting a therapeutic range of 0.5 to 0.8 mcg/mL. Bleeding is a major risk, and there is no simple antidote, so fresh frozen plasma or factor VIIa concentrates may be required. Lepirudin may occasionally cause anaphylactoid reactions. Bivalirudin is a reversible direct thrombin inhibitor that has a much shorter half-life than lepirudin. A typical infusion rate is 1.0 to 2.5 mg/h (0.009-0.023 mg/kg/h) adjusted to achieve a target APPTr of around 1.5 to 2.0.

E. Prostanoids. Prostacyclin (PGI2) and its analog epoprostenol are potent antiplatelet agents that block cyclic adenosine monophosphate (cAMP). They can be used as regional anticoagulants in patients at risk of bleeding. Although PGI2 is a potent vasodilator, the risk of hypotension can be reduced by starting a systemic infusion at 0.5 ng/kg/min, steadily increasing to 5 ng/kg/min, and then switching the infusion into the dialysis circuit once dialysis starts, as around 40% of the dose is lost into the dialysate. The half-life is very short, and hypotensive episodes can usually be rapidly reversed by stopping the infusion.

F. Nafamostat mesylate. Nafamostat mesylate is a protease inhibitor with a short half-life that can be used as a regional anticoagulant. Most experience comes from Japan, using an initial bolus dose of 20 mg, followed by an infusion starting at 40 mg/h, adjusted to maintain a target APPTr of 1.5 to 2.0, or ACT of 140 to 180 seconds.

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14 Continuous Kidney Replacement Therapies

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The most widely used continuous kidney replacement therapies (CKRTs) for the treatment of critically ill patients with kidney failure are continuous hemodialysis and continuous hemodiafiltration. Two prolonged intermittent kidney replacement therapies (PIKRTs), sustained low-efficiency hemodialysis and sustained low-efficiency hemodiafiltration, are also quite popular. Continuous hemofiltration and slow continuous ultrafiltration are used, but less commonly.

I. NOMENCLATURE.

In the *Handbook*, we abbreviate continuous hemodialysis as C-HD, whether it is applied using an arteriovenous (AV) or venovenous access. Similarly, continuous hemofiltration is abbreviated as C-HF, and their combination, slow continuous hemodiafiltration, is C-HDF. Historically, one would insert "AV" or "VV" after the letter "C" to specify that the blood flow for the procedure was obtained from either an artery or a vein, respectively, giving CAVHD or CVVHD (hemodialysis), CAVH or CVVH (hemofiltration), and CAVHDF or CVVHDF (hemodiafiltration); but today, most treatments are given using a venous catheter–based access, and so use of the "VV" has become superfluous. Slow continuous ultrafiltration is abbreviated as SCUF, and sustained low-efficiency hemodialysis and hemodiafiltration are abbreviated as SLED and SLED-F, respectively. SLED and SLED-F are collectively grouped as forms of prolonged intermittent kidney replacement therapy, or PIKRT. Conventional intermittent treatment is called IHD (intermittent hemodialysis) or, more generally, IKRT (intermittent kidney replacement therapy), given that the intermittent treatment being given is not always hemodialysis.

A. What are the differences among C-HD, C-HF, and C-HDF?

Each of these procedures involves slow, continuous passage of blood through a filter. Table 14.1 shows a comparison of these techniques.

TABLE 14.1 Comparison of Techniques

	IHD	SLED	SCUF	C-HF	C-HD	C-HDF
Membrane permeability	Variable	Variable	High	High	High	High
Anticoagulation	Short	Long	Continuous	Continuous	Continuous	Continuous
Blood flow rate (mL/min)	250-400	100-200	100-200	200-300	100-300	200-300
Dialysate flow rate (mL/min)	500-800	100	0	0	16-35	16-35
Filtrate (L/d)	0-4	0-4	0-5	24-96	0-4	24-48
Replacement fluid (L/d)	0	0	0	22-90	0	23-44
Effluent saturation (%)	15-40	60-70	100	100	85-100	85-100
Solute clearance mechanism	Diffusion	Diffusion	Convection (minimal)	Convection	Diffusion	Diffusion + convection
Urea clearance (mL/min)	180-240	75-90	1.7	17-67	22	30-60
Duration (h)	3-5	8-12	Variable	>24	>24	>24

C-HD, slow continuous hemodialysis; C-HF, slow continuous hemofiltration; C-HDF, slow continuous hemodiafiltration; IHD, intermittent hemodialysis; SCUF, slow continuous ultrafiltration; SLED, sustained low-efficiency dialysis.

Modified from Metha RL. Continuous renal replacement therapy in the critically ill patient. *Kidney Int*. 2005;67:781-795.

1. **C-HD.** In C-HD (Figure 14.1), dialysis solution is passed through the dialysate compartment of the filter continuously and at a slow rate. In C-HD, diffusion is the primary method of solute removal. The amount of fluid that is ultrafiltered across the membrane is low (usually about 3-6 L/d) and is limited to excess fluid removal.

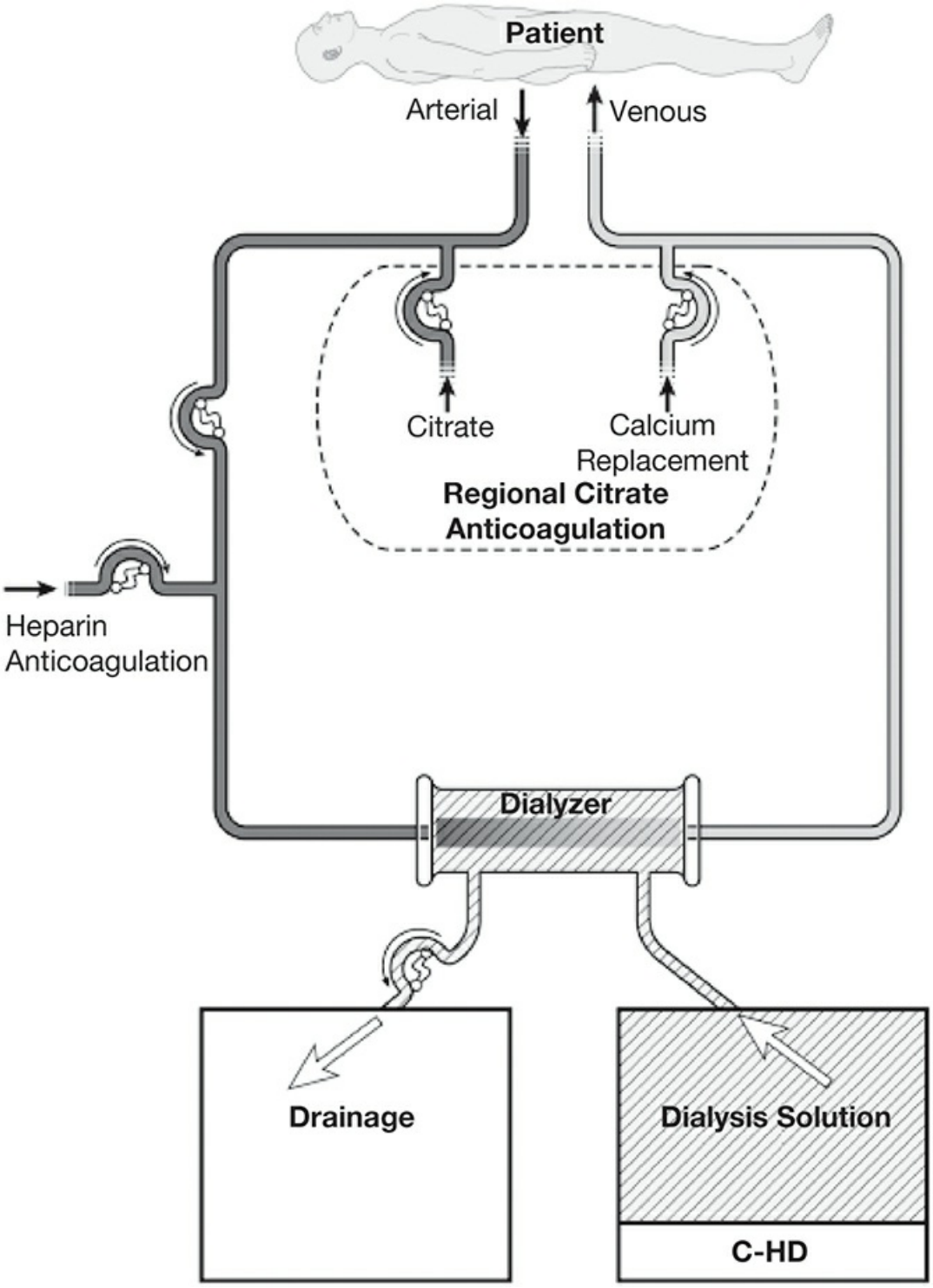


FIGURE 14.1: Typical circuit for slow continuous hemodialysis. Anticoagulation with either heparin or regional citrate is shown. For slow continuous ultrafiltration, the circuit is the same, except that dialysis solution inflow is not used. C-HD, continuous hemodialysis.

2. **C-HF.** In C-HF (Figure 14.2), dialysis solution is not used. Instead, a large volume (about 25-50 L/d) of replacement fluid is infused into either the inflow or the

outflow blood line (predilution or postdilution mode, respectively). With C-HF, the volume of fluid that is ultrafiltered across the membrane is the sum of replacement fluid and excess fluid removed, and so is much higher than with C-HD.

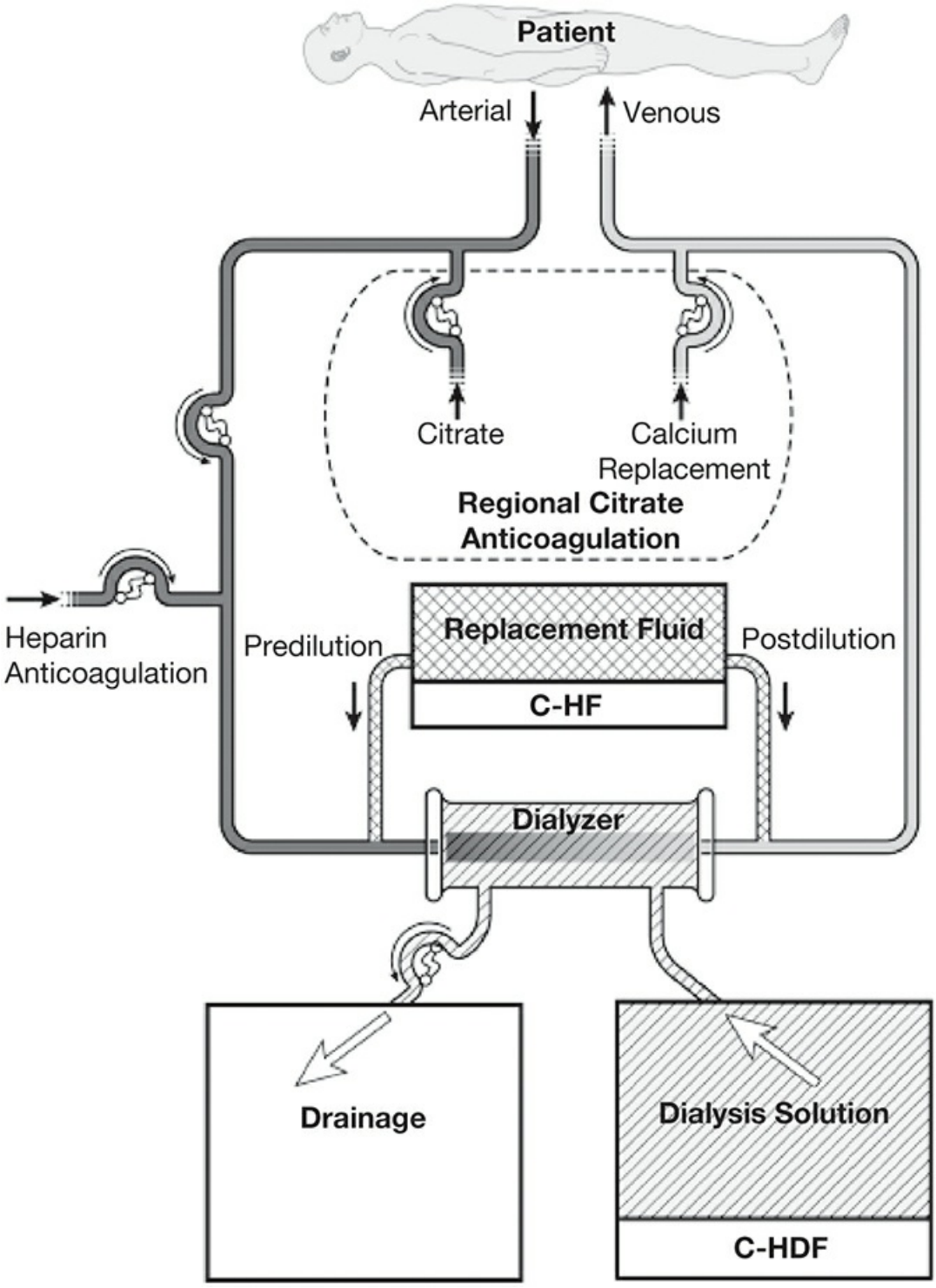


FIGURE 14.2: Typical circuit for continuous hemofiltration and slow continuous hemodiafiltration. In slow continuous hemofiltration (C-HF), replacement fluid can be infused in the predilution mode, or postdilution mode, or both simultaneously. In slow continuous hemodiafiltration, hemodialysis is performed concurrently with C-HF.

Anticoagulation with either heparin or regional citrate is shown. C-HDF, continuous hemodiafiltration.

3. **C-HDF.** This (Figure 14.2) is simply a combination of C-HD and C-HF. Dialysis solution is used, and replacement fluid is also infused into either the inflow or the outflow blood line. The daily volume of fluid that is ultrafiltered across the membrane is equal to the replacement fluid infused plus the net volume removed. Usually, the replacement fluid volume with C-HDF is about half that used with C-HF, but the total effluent volume (replacement fluid + dialysis solution + excess fluid volume removed) with C-HDF is similar to that with C-HF, where effluent volume is the sum of replacement fluid and excess fluid volume only.
4. **SCUF.** The setup is similar to that for C-HD and C-HF, but neither dialysis solution nor replacement fluid is used. Daily ultrafiltered fluid volume across the membrane is low (usually about 3-6 L/d), similar to C-HD.

B. Sustained low-efficiency dialysis and hemodiafiltration (SLED and SLED-F). SLED is a form of IHD using an extended (6- to 10-hour) session length and reduced blood and dialysate flow rates. Typically, blood flow rates are about 200 mL/min, and dialysate flow rate is 100 to 300 mL/min. Regular hemodialysis equipment can be used as long as low blood and dialysate flow rates are supported; a software update may be required with certain dialysis machines to provide the lower flow rates. The same machine used for IHD during the day often can be used for SLED during the night, and hemodialysis nurses can easily be trained to perform SLED, offering some economy of staff instruction. SLED allows units where CKRT equipment or personnel are unavailable or limited to offer a treatment modality that should achieve similar benefits as CKRT. SLED-F requires additional infusion of replacement fluid unless replacement fluid can be made from dialysis solution online by the dialysis machine (Marshall, 2004).

II. CLINICAL INDICATIONS FOR CKRT VERSUS IKRT.

The potential advantages of the various CKRT procedures as well as SLED are listed in Table 14.2. When compared with standard IHD, they include a lower rate of fluid removal as well as enhanced control of azotemia. Despite the seemingly obvious advantages of slow continuous therapies, there has been no evidence from several randomized trials that, in the acute kidney failure setting, use of CKRT offers a survival advantage over IHD (Rabindranath, 2007). However, most trials excluded the sickest patients from treatment with conventional IHD. The 2012 Kidney Disease Improving Global Outcomes (KDIGO) Guidelines for acute kidney injury (AKI) suggest (level 2B evidence) that clinicians use CKRT rather than standard IKRT for hemodynamically unstable patients, and also suggest using CKRT to treat patients with AKI with acute brain injury or other causes of increased intracranial pressure or generalized brain edema (KDIGO, 2012). However, the guidelines recognize that the use of prolonged IKRT therapies such as SLED or SLED-F may be as useful to treat hemodynamically unstable patients as CKRT, but point to the paucity of outcome trials comparing CKRT with prolonged IKRT. Some early comparisons (Marshall, 2011; Van Berendoncks, 2010) suggest that outcome results with prolonged IKRT are similar to those of CKRT and that considerable cost savings are achieved with prolonged IKRT (Nash, 2017).

TABLE

14.2 Potential Advantages of Slow Continuous Therapies

1. Hemodynamically well tolerated; smaller change in plasma osmolality
2. Better control of azotemia and electrolyte and acid-base balance; correct abnormalities as they evolve; steady-state chemistries
3. Highly effective in removing fluid (postsurgery, pulmonary edema, ARDS)
4. Facilitates administration of parenteral nutrition and obligatory intravenous medications (ie, pressor, inotropic drugs) by creating unlimited "space" by virtue of continuous ultrafiltration
5. Less effect on intracranial pressure
6. User-friendly machines available

ARDS, acute respiratory distress syndrome.

III. TRAINING AND EQUIPMENT COSTS. The use of continuous procedures requires an effort on the part of nursing staff in the intensive care unit (ICU) to become familiar with the procedures. In units with high staff turnover rates and in units where continuous therapies are done infrequently, use of prolonged intermittent therapies such as SLED may be a more practical option. However, in high-volume units where continuous therapies are a common part of the dialysis armamentarium, use of such therapies can aid in the fluid, solute, and nutritional management of the most challenging patients.

IV. DIFFERENCES AMONG C-HD, C-HF, AND C-HDF IN CLEARANCE OF SMALL- AND LARGE-MOLECULAR-WEIGHT (MW) SOLUTES

A. Solute clearance with C-HD. In C-HD, where the blood flow rate is 150 to 200 mL/min or more, and the dialysate flow rate is typically 25 to 30 mL/min, clearance of urea and other small molecules is determined primarily by the dialysis solution flow rate. **As a rule of thumb, the blood flow rate in C-HD should be at least 3 times the dialysate flow rate.** At this slow blood flow rate and high blood-to-dialysate flow ratio, the outflow dialysate is almost 100% saturated with urea and other small-MW solutes. Urea clearance can thus be simply estimated by the effluent volume, which includes the volume of dialysis solution used plus any excess fluid removed.

The standard dialysis solution inflow rate is now about 20 to 25 mL/kg/h. In a 70-kg individual, this translates into a flow rate of 23 to 29 mL/min. If we assume a flow rate of 26 mL/min and 100% saturation, this will deliver a urea clearance of 26 mL/min or about 37 L/d, and if we add 3 L/d of excess fluid removal, this gives a daily effluent volume and urea clearance of 37 + 3 = 40 L. In terms of urea kinetics, this 40 L can be thought of as the familiar ($K \times t$) measure of clearance. For a patient with a urea distribution volume of 40 L, such a prescription would translate to a daily Kt/V of 40/40 = 1.0 or about 7.0 per week.

B. Solute clearance with C-HF. C-HF is a purely convection-based blood cleansing technique. As blood flows through the hemofilter, a transmembrane pressure gradient between the blood compartment and the ultrafiltrate compartment causes plasma water to be filtered across the highly permeable membrane. As the water crosses the membrane, it sweeps along with it (nonprotein-bound) small and large molecules (pore size permitting) and thus leads to their removal from the blood. The removed ultrafiltrate is replaced by a balanced electrolyte solution infused into either the inflow (predilution) or the outflow (postdilution) line of the hemofilter. Typically, about 20 to

25 mL/kg/h of replacement fluid is infused. The filter outflow or “drainage fluid” is nearly 100% saturated with urea when the postdilution mode is used.

1. **Filtration fraction.** This is the fraction of plasma flowing through the hemofilter that is removed. Filtration fraction can be calculated as the ultrafiltration rate divided by the plasma flow rate. The latter is simply blood flow rate × (1 − hematocrit/100). For example, if the blood flow rate is 150 mL/min and the hematocrit is 33%, the plasma flow rate will be 0.67 × 150 = 100 mL/min. If the ultrafiltration rate is 25 mL/min, then the filtration fraction will be 25/97, or about 25%. The rule of thumb is to keep the filtration fraction at 25% or lower to avoid overconcentration of red cells and plasma proteins in the hemofilter. Overconcentration results in fouling of the membrane pores, which can impair ultrafiltration efficiency and lower the sieving coefficient, and overconcentration can also increase the likelihood of clotting. When a high replacement fluid infusion rate in postdilution mode is desired, to avoid overconcentration and keep filtration fraction below 25%, the blood flow rate needs to be increased above the usual 150 mL/min.
2. **Predilution mode.** Another way to keep the filtration fraction from increasing is to use predilution mode. With predilution, there is a slight lowering of the urea concentration of ultrafiltrate (usually to 80%-90% of the corresponding plasma value), but this small amount of dilution is outweighed by the ability to deliver an increased replacement solution infusion rate, enhancing overall middle-molecule clearances. We recommend using predilution whenever it is desirable to remove more than 25 L/d. Predilution is also performed if the baseline blood viscosity is relatively elevated (eg, if the hematocrit is >35%). A combination of pre- and postdilution has been advocated by some practitioners.
3. **Calculating the dilutional effects of predilution mode.** As an example, assume that the replacement fluid infusion rate is 25 mL/min (36 L/d) and blood flow rate is 150 mL/min (216 L/d). The amount of dilution of waste products in the blood entering the filter will be 25/(150 + 25) or (36/[216 + 36]) = 14%. Assuming that 36 L/d of replacement fluid is used and that 4 L/d of excess fluid is removed, daily effluent volume will typically be about 40 L/d. In postdilution mode, ($K \times t$) will be 40 L. In predilution mode, ($K \times t$) will be about 15% less, 34 L, and so, assuming V = 40 L, then daily Kt/V with C-HF will be about 40/40 = 1.0 in postdilution mode or 34/40 = 0.85 in predilution mode.

C. Urea clearance with C-HDF. With postdilution C-HDF, the sum of the dialysis solution flow rate, replacement fluid infusion rate, and removal of excess fluid usually is set at a level similar to the outlet flow rate in C-HD. The clearance calculations are similar to those discussed earlier. Thus, the clearance of small molecules with C-HDF is similar to that with postdilution C-HD or C-HF when the daily effluent volumes are comparable.

D. Small- versus middle-MW solute removal with C-HF versus C-HD. With C-HD, the outflow dialysate is not as highly saturated with larger-MW substances that diffuse slowly in solution and thus have a lower rate of diffusive transfer across the dialyzer membrane. In contrast, with C-HF, the plasma ultrafiltrate is almost completely saturated with both low- and middle-MW solutes because the convective removal rates of small- and larger-MW solutes are similar. Hence, C-HF is more efficient than C-HD in terms of larger-MW toxin removal, including peptides, certain antibiotics, and

vitamin B_{12}. The theoretical advantage of C-HF is technically demanding to realize, as it can be challenging to ultrafilter greater than 25 L from patients who cannot deliver the high blood flow rates required to prevent overconcentration. Also, fluid balancing becomes critical when the replacement fluid infusion rate is high. With high-volume C-HF, any slowing of the blood flow rate will result in transient hemoconcentration in the hemofilter, with attendant risk of clotting. On the other hand, it is easy to perform C-HD using dialysis solution flow rates of 50 L/d. For this reason, in daily practice, C-HD tends to be the more popular therapy, and if enhanced removal of middle molecules is desired, a convective, replacement fluid component is added (C-HDF).

1. **Filter surface area and clearance of larger-MW substances:** One in vitro study of clearance of larger-MW substances by C-HF versus C-HD with two different-sized filters (0.4 vs 2.0 m^2) came up with some counterintuitive results: with the larger membrane, the clearance of large-MW substances was identical with C-HD and C-HF, and with the smaller membrane (0.4-m^2 membrane), clearance of large-MW substances was actually worse with C-HF than with C-HD (Messer, 2009). The proposed explanation was increased protein fouling of the smaller membrane in C-HF mode. These results suggest that using a high replacement fluid flow rate with a small hemofilter may not be an efficient way to increase the removal of larger, middle molecules.

V. VASCULAR ACCESS

A. Venovenous blood access.

Vascular access is obtained using a dual-lumen cannula inserted into a large (internal jugular or femoral) vein. The subclavian vein can be used but is not the site of first choice. The 2012 KDIGO AKI guidelines recommend using uncuffed venous catheters for CKRT. The level of evidence for this is weak (2D). The rationale is that insertion of an uncuffed catheter is easier, that the need for a cuffed catheter might sometimes delay initiation of therapy, and that the average duration of CKRT is only 12 to 13 days (KDIGO, 2012). One study (Morgan, 2012) compared use of longer (20-24 cm) soft, silicone temporary catheters for CKRT targeting placement of the catheter tip near the right atrium versus shorter (15-20 cm) catheters targeting placement of the catheter tip in the superior vena cava; the longer catheters were associated with longer filter life and improved dose of therapy. In another study looking at the success rate of CKRT achieved by femoral venous access, filter longevity averaged 15 hours when the venous catheter was inserted on the right side versus 10 hours when the left femoral vein was used (Kim, 2011). The mechanism of the advantage of right-sided femoral catheters was not clear.

B. AV blood access.

One can cannulate a large artery, usually the femoral artery, and propel blood through the extracorporeal circuit by using the patient's own arterial pressure instead of a pump. Blood is returned via any large vein. Use of AV blood access for CKRT is no longer widely practiced. There is a risk of damage to the femoral artery with possible distal limb ischemia, plus AV access will often not deliver high enough blood flows to be able to support the more intensive CKRT therapies in common use today. However, CKRT using AV access may be lifesaving in situations where a mass catastrophe has occurred (eg, earthquake with kidney injury due to rhabdomyolysis) and electrical power sources are unreliable, because blood flow is then driven by a patient's own blood pressure and ultrafiltration is adjusted by using gravity

(or clamp) via the height of the effluent collection container. For a detailed description of CKRT using an AV access, please refer to the third edition of the *Handbook.*

C. Catheter changes: Scheduled changes versus changing only when clinically indicated. CKRT catheters should be changed only when clinically indicated; catheters should not be changed according to some predetermined schedule in the hopes of minimizing the rate of catheter sepsis. The practice of routine, scheduled catheter changes, once popular, is not recommended by the Centers for Disease Control and Prevention (CDC), and studies do not support this approach.

VI. CKRT FILTERS.

The terms "hemofilter" and "dialyzer" are used interchangeably in this chapter. Hemofilters have only one outlet in the housing, making use of dialysis solution impossible. Dialyzers have a second port. Dialyzers used for CKRT should have high water permeability, and so will be in the "high-flux" category. Some of the early filters designed primarily for C-HF had excellent water permeability and convective solute clearance, but had poor diffusive clearance when used for C-HD; there was poor optimization of contact between dialysis solution and all parts of the membrane in these filters. Currently used CKRT filters allow urea in the blood compartment of the filter to equilibrate promptly with dialysate, making them suitable for both C-HF and C-HD.

A. Filter surface area and size. The size of the filter should take the blood flow rate into account. When large filters are used at low blood flow rates, the risk of clotting may be increased, as such filters will have been designed for much higher blood flow rates. Flow velocity through each fiber will be slow. Furthermore, the permeation of the fiber bundle by dialysis solution may be suboptimal with large dialyzers designed to be used at high dialysate flow rates. On the other hand, larger dialyzers can be used at higher blood flow rates such as those in some higher-efficiency SLED protocols, in order to maximize middle-molecule solute clearances. The study by Messer (2009) described above also suggests that use of a larger-size filter might be considered when removal of larger-MW solutes is desired and a high replacement fluid rate is to be used.

VII. DIALYSATES AND REPLACEMENT SOLUTIONS.

CKRT fluids come premixed as commercially prepared sterile solutions. They are typically packaged in 2.5-L or 5-L bags; in some cases, fluids are supplied in bags with two compartments that need to be mixed immediately prior to use.

A. Composition. Table 14.3 lists the composition of some commonly available commercially prepared solutions for CKRT.

TABLE 14.3 Composition of Some Continuous Kidney Replacement Therapy Solutions

Component (mM)	Dialysis Machine Generated[a]	Peritoneal Dialysis Fluid[b]	Lactated Ringer Solution	B. Braun Duosol (5-L Bag)	Baxter Accusol[b] (2.5-L Bag)	Baxter Prismasol[c] (5-L Bag)	NxStage PureFlow-B[d] (5-L Bag)
Sodium	140	132	130	136 or 140	140	140	140
Potassium	Variable	–	4	0 or 2	0 or 2 or 4	0 or 2 or 4	0 or 2 or 4
Chloride	Variable	96	109	107-111	109.5-116.3	106-113	111-120
Bicarbonate	Variable	–	–	25 or 35	30 or 35	32	25 or 35
Calcium	Variable	1.75 (3.5 mEq/L)	1.35 (2.7 mEq/L)	0 or 1.5 (0 or 3.0 mEq/L)	1.4 or 1.75 (2.8 or 3.5 mEq/L)	0 or 1.25 or 1.75 (0 or 2.5 or 3.5 mEq/L)	0 or 1.25 or 1.5 (0 or 2.5 or 3.0 mEq/L)
Magnesium	0.75 (1.5 mEq/L)	0.25 (0.5 mEq/L)	–	0.5 or 0.75 (1.0 or 1.5 mEq/L)	0.5 or 0.75 (1.0 or 1.5 mEq/L)	0.5 or 0.75 (1.0 or 1.5 mEq/L)	0.5 or 0.75 (1.0 or 1.5 mEq/L)
Lactate	2	40	28	0	0	3	0
Glucose (mg/dL)	100	1,360	–	0 or 100	0 or 100	0 or 100	100
Glucose (mM)	5.5	75.5	–	0 or 5.5	0 or 5.5	0 or 5.5	5.5
Preparation method	6-L bag via membrane filtration	Premix	Premix	Two-compartment bag	Two-compartment bag	Two-compartment bag	Two-compartment bag
Sterility	No	Yes	Yes	Yes	Yes	Yes	Yes

1. **Buffers.** Solutions contain either lactate or bicarbonate.
   a. **Lactate-based solutions.** Pure lactate-based replacement fluid usually contains 40 to 46 mM of lactate. Lactate-based solutions effectively correct metabolic acidosis in most patients. Lactate is metabolized on a 1:1 molar basis to bicarbonate, but in practice, the dialysis solution lactate concentration needs to be higher than dialysis solution bicarbonate to effect similar degrees of correction of acidosis.
   b. **Bicarbonate-based solutions.** Bicarbonate-containing bags are sold as two-compartment systems, similar to those used to prepare bicarbonate-containing dialysis solution for peritoneal dialysis. Bicarbonate is the buffer of choice, and total base concentrations are typically 25 to 35 mM. Some solutions contain a small amount (3 mM) of lactate, left over from lactic acid used to acidify the final solution. There is no evidence that this small amount of lactate contributes to hyperlactatemia.

      When a high dialysis solution or replacement solution flow rate (eg, >30 mL/kg/h) is prescribed, use of lower bicarbonate solutions may help prevent metabolic alkalosis. Lower bicarbonate concentration solutions or bicarbonate-free solutions are also indicated when using regional citrate anticoagulation (RCA), because citrate is metabolized to bicarbonate by the liver.
   c. ***When high-lactate solutions should be used with caution:*** Use of solutions using lactate as the primary bicarbonate-generating base has been shown to worsen hyperlactatemia in patients who have severe circulatory instability with tissue hypoperfusion and in patients with severe liver compromise. The 2012 KDIGO AKI guidelines suggest using bicarbonate-based solutions for all patients with AKI at a low level of evidence (2C), but recommend using such solutions more strongly for patients with liver failure and/or lactic acidosis (level of evidence 2B) and for patients in circulatory shock (level of evidence 1B).
   d. **Citrate-based solutions.** These fluids evolved from attempts to merge the buffering and anticoagulation properties of citrate and the need to simplify complex RCA protocols. The bulk of citrate-based fluids has to be administered prefilter to allow adequate filter anticoagulation. In all, 40% to 60% of citrate infused in predilution mode is removed in the effluent, and the remainder is

mainly metabolized by the liver into bicarbonate (1 mmol citrate yielding 3 mmol of bicarbonate). Therefore, it is not appropriate to use these solutions in C-HD where dialysate flow is countercurrent to blood or C-HF/HDF with predominantly postfilter replacement. Preparations containing citrate at concentrations of 11 to 12 mM may not provide adequate buffering capacity (Naka, 2005). Fluids with a higher citrate concentration (14 mM) provide better acidosis correction with improved filter life (Egi, 2005, 2008). Citrate-based solutions at 18 mM are available, but the acid-base consequences have not been adequately studied. It is best to infuse citrate-containing replacement fluid predilution, adjusting the flow to achieve an optimum prefilter citrate to blood flow ratio, and then additional solute removal can be achieved by using bicarbonate-based solutions, given either as dialysate or as postdilution replacement fluid. Additional methods of citrate anticoagulation as well as potential advantages of this approach are discussed later in this chapter.

2. **Sodium.** Commercially available CKRT fluids usually contain physiologic sodium concentrations at or close to 140 mM. When treating patients with severe, and especially long-standing, hyponatremia, where the goal is to slowly increase the serum sodium at a rate no greater than 6 to 8 mmol/L/d, the replacement fluid or dialysis solution needs to be diluted with water, to a concentrate just slightly greater than the predialysis sodium value. For details, please see Yessayan (2014). In some anticoagulation methods requiring infusion of trisodium citrate into the blood lines, custom-made, low-sodium (100 mM) dialysis/replacement solutions can be used to limit the occurrence of hypernatremia.
3. **Potassium.** CKRT fluids with no potassium are suitable for initial treatment of patients with AKI with severe hyperkalemia. Once serum potassium has decreased to a safe level, fluids containing 4 mM of potassium are used to minimize arrhythmia risk and depletion of body potassium. Commercially made fluids come premixed with potassium concentrations of 0, 2, or 4 mM. The lower potassium content solutions also may be used as needed in patients who are highly catabolic with persistent hyperkalemia.
4. **Phosphate.** Hypophosphatemia during extended CKRT is common and can result in respiratory muscle weakness and prolonged respiratory failure in critically ill patients (Demirjian, 2011). Phosphate replacement for severe hypophosphatemia is routine, but frequent monitoring of serum phosphate levels is necessary. Off-label addition of phosphate to CKRT fluid to maintain a level of 1.2 mM has been reported to maintain serum phosphate with good clinical efficacy (Troyanov, 2004). A replacement solution containing phosphate at 1.2 mM and bicarbonate at 30 mM is available, but its use has been associated with mild metabolic acidosis and hyperphosphatemia compared with conventional CKRT fluids (Chua, 2012; Thompson Bastin, 2022). The ideal fluid phosphate content should probably be lower, and further research is desirable.

   AKI has been reported after phosphate enemas and after intravenous (IV) phosphate infusion. In one audit, infusion of an IV solution of sodium/potassium phosphate containing 20 mM phosphate over an average of 5 hours was not associated with elevation of creatinine in patients with residual kidney function, but was associated with some reduction in ionized calcium concentration (Agarwal,

2014).

5. **Calcium and magnesium.** Most dialysis/replacement solutions contain 1.5 to 1.75 mM of calcium and 0.5 to 0.6 mM of magnesium, and their use usually allows maintenance of desired systemic levels. During RCA, citrate binds to and depletes serum calcium and magnesium. CKRT solutions used during RCA often contain no calcium to facilitate reduction of ionized calcium in the filter by citrate to allow adequate circuit anticoagulation. With RCA, separate systemic infusions of calcium and sometimes magnesium with strict monitoring protocols are thus necessary.
6. **Glucose.** Modern CKRT solutions are either glucose free or contain physiologic glucose concentrations, usually 5.5 mM (100 mg/dL). Use of glucose-free fluids in CKRT is associated with hypoglycemia, and glucose-containing CKRT fluids are preferred; regular monitoring and administration of insulin is necessary to prevent hyperglycemia and to achieve a target serum glucose of 6 to 8 mM, a level that has been associated with the best outcomes. Another argument against use of glucose-free CKRT solutions is that substantial amounts of glucose can be removed from the body with their use, and this may adversely affect nutritional balance (Stevenson, 2013).

B. Methods of preparing bicarbonate-based CKRT solutions when prepackaged solutions are not available. Customized solutions can be prepared in the pharmacy or by the dialysis machine in the form of ultrapure solutions; the latter is appropriate only in countries where regulatory approval for online hemodiafiltration has been granted. One can prepare sterile dialysis/replacement fluid manually to achieve solutions containing 30 to 35 mM bicarbonate. Bicarbonate is in equilibrium with carbonic acid, which breaks down to CO_2 and H_2O; therefore, bicarbonate solutions are unstable. Bicarbonate also forms insoluble salts when in solution with calcium and magnesium. Therefore, bicarbonate-based dialysis/replacement solutions should be prepared just before use.

1. **Single-bag method.** Dialysis or replacement solution containing bicarbonate and no lactate is made by adding (usually, this is done by the hospital pharmacy service) $NaHCO_3$ and some additional NaCl to 0.45% NaCl obtained commercially. A small amount of $CaCl_2 \cdot 2H_2O$ is added as well, and magnesium is given parenterally as needed.

   Formulation: 1.0 L of 0.45% NaCl + 35 mL of 8.4% $NaHCO_3$ (35 mmol) + 10 mL of 23% NaCl (40 mmol) + 2.1 mL of 10% $CaCl_2 \cdot 2H_2O$ (1.45 mmol or 2.9 mEq); total volume = 1.047 L.

   Final concentrations in mM: Na, 145; Cl, 114; HCO_3, 33; and Ca, 1.35 (2.7 mEq/L).
2. **Two-bag method.** Bags of 0.9% saline with added calcium are alternated with bags of 0.45% saline with added bicarbonate.

   Formulation: *Solution A:* 1.0 L of 0.9% saline + 4.1 mL of 10% $CaCl_2 \cdot 2H_2O$ (2.8 mmol or 5.6 mEq). *Solution B:* 1.0 L of 0.45% saline + 75 mL of 8.4% $NaHCO_3$ (75 mmol); total volume = 2.079 L.

   Final concentrations in mM (when considered together): Na, 147; Cl, 114; HCO_3, 36; and Ca, 1.35 (2.7 mEq/L).
3. **Dialysis machine method (C-HD only).** One can prepare bicarbonate-

containing dialysis solution for C-HD by ultrafiltering dialysis solution prepared by a standard dialysis machine across a dialyzer (to remove bacteria) and storing the solution in a 6.5-L sterile bag. The fluid preparation does not show growth of bacteria for at least 72 hours and for up to 1 month in tests. In more than 25 years of use, there have been no reported adverse events, and Limulus amebocyte lysate assays for endotoxin are reliably below the limit of detection (Moses, 2021; Tallercio, 2021; Teo, 2006).

C. Sterility. Sterile dialysis solution is used for C-HD and C-HDF because the slow dialysate transit time plus the extended time of use of the same circuit and dialyzer could otherwise encourage bacterial growth in the dialysate circuit. All replacement fluid infusions given directly into the blood lines must be sterile.

D. Temperature of dialysis solution/replacement fluid. CKRT can be set up so that dialysis solution and replacement fluid are infused at room temperature. This is a departure from conventional dialysis, where dialysis solution is warmed. Use of room temperature fluid results in heat subtraction from the patient; in fact, the hemodynamic benefits of CKRT appear to be due largely to such thermal cooling effects. When applied over long periods, CKRT-associated heat subtraction may mask the presence of fever, thus reducing the reliability of body temperature as a marker for infection or inflammation. Whether this heat subtraction has an effect on the body's ability to resist infection has not been studied. One study done in a septic shock model using sheep suggested that warming of blood in the extracorporeal circuit increased survival rate (Rogiers, 2006). Current CKRT delivery systems have heating systems. Heating sometimes is associated with an appearance of bubbles in the replacement or dialysis solutions, especially with bicarbonate formulations; the clinical importance of this effect remains to be determined.

VIII. PRESCRIBING AND DELIVERING CKRT

A. Dose versus outcome. The suggested dose of CKRT in AKI is a delivered effluent volume of 20 to 25 mL/kg/h (KDIGO, 2012). This was, however, presented as an ungraded recommendation by KDIGO, and there is no evidence that lower levels of therapy give worse results. A handful of randomized controlled trials suggested that use of a markedly higher effluent volume led to better outcomes, but these results were not confirmed. One mechanistic analysis has suggested that use of a higher effluent volume results in only a very small increase in middle-molecule clearance (Hofmann and Fissell, 2010) and that the best way to increase middle-molecule removal is to increase blood flow and membrane surface area. There is no evidence that convective therapies (C-H or C-HDF) lead to better outcomes than diffusion-based treatments (C-HD). The adequate dose of CKRT remains an area where more research is needed.

To deliver an effluent volume of 20 to 25 mL/kg/h, one normally would need to prescribe a lower inflow fluid rate, as the effluent volume will also include 2 to 5 L/d of excess fluid removed from the patient. However, technical problems often arise, yielding to interruption of therapy or reduction of efficiency due to partial clotting of the dialyzer, and so it is wise to prescribe a slightly higher inflow volume than the target. As noted previously, when predilution mode is used, the infusion rate of the replacement fluid should be increased by about 15% to 20%, depending on the ratio of predilution fluid infusion rate to blood flow. The dilution effect will be more pronounced for

compounds removed from the plasma only, as it will be proportional to the ratio of replacement fluid infusion rate to plasma flow rate rather than the ratio of replacement fluid infusion rate to the blood flow rate.

B. Empiric dosing. The intensity of treatment should be adjusted on the basis of clinical circumstances. CKRT intensity may need to be increased in highly catabolic patients, to facilitate nutritional support, in tumor lysis syndrome, or for drug intoxication where intermittent therapies are not tolerated. It may be helpful to consider adequate CKRT dosing by evaluating the daily serum urea nitrogen (SUN) level while on treatment. Based on information from the RENAL study recruitment population (the RENAL Study Investigators, 2008; VA/NIH Acute Renal Failure Trial Network, et al, 2008), the average SUN achieved should be less than 45 mg/dL (16 mmol/L). A method of dosing to target a given level of blood urea nitrogen is given in Table 14.4. A simplified nomogram to target a given blood urea nitrogen level is given in Figure 14.3.

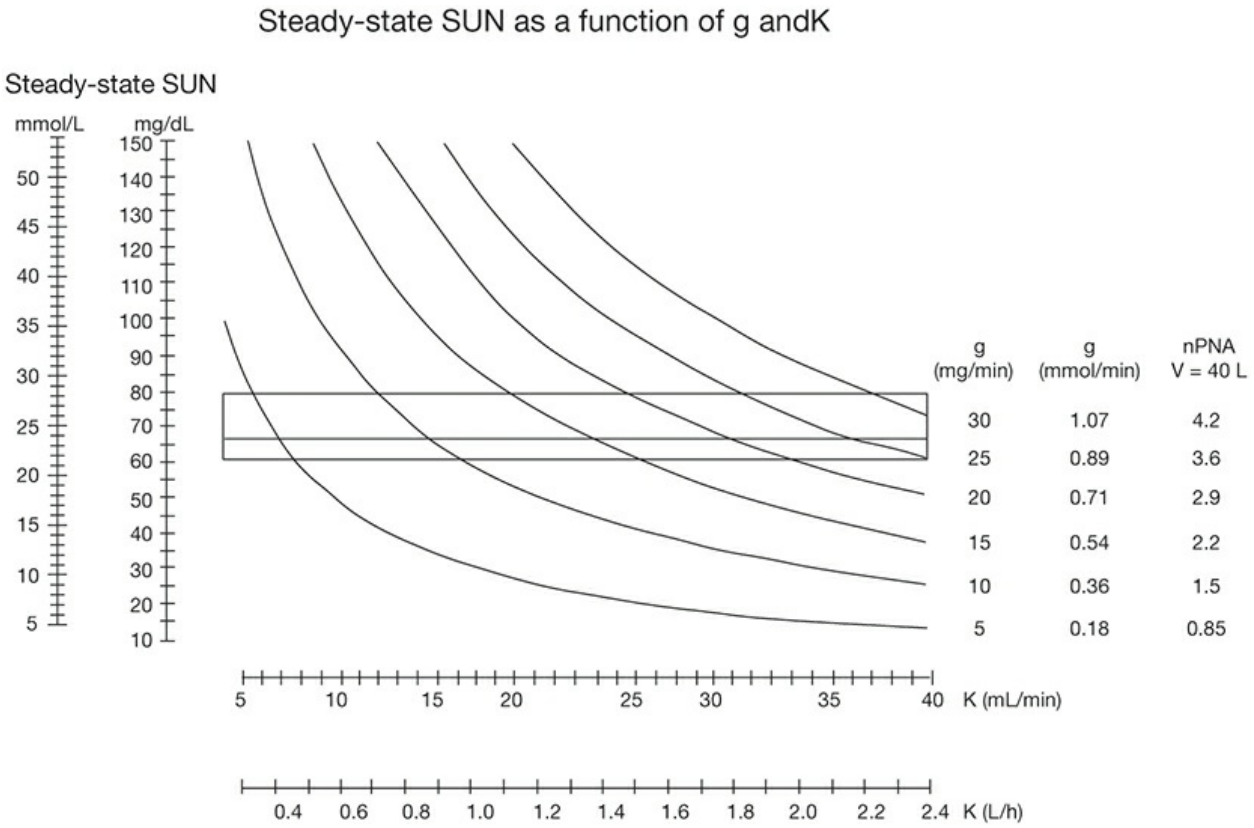


FIGURE 14.3: Estimated total extracorporeal urea clearance required to attain various steady-state serum levels of urea nitrogen. Clearance, on the bottom, is read from the intersection of the urea nitrogen generation level (g) and the steady-state goal serum urea nitrogen (SUN). (Used with permission from Garred L, et al. Urea kinetic modeling for CRRT. *Am J Kidney Dis*. 1997;30(5 Suppl 4):S2-S9. doi:10.1016/s0272-6386(97)90535-7.)

TABLE 14.4 Dosing of CKRT to Target a Specific Level of Blood Urea Nitrogen

Solute equilibration between effluent and serum will decline with time owing to membrane clogging (Claure-Del Granado, 2011). Furthermore, urea kinetic modeling does not consider middle- or large-molecular-weight solute clearance, and the impact of the latter remains unclear.

1. Six steps to estimating the prescription

a. Estimate or measure the patient's **urea generation rate**.
b. Decide on the **desired level of SUN**.
c. Calculate the **total urea clearance** necessary to keep the SUN at the desired level for the urea generation rate obtained from Step 1.
d. Measure **residual kidney urea clearance**. If desired, subtract this from the total urea clearance to obtain the **extracorporeal urea clearance** that will be required.
e. Calculate the **required drainage fluid volume**. Set this equal to the required extracorporeal urea clearance, assuming 100% saturation. Exception: With predilution C-HF or with C-HD when using a dialysis solution inflow rate >2 L/h, the urea saturation of the drainage fluid will be <100%. In such cases, the required "drainage volume" should be increased appropriately (usually by 15%-20%), on the basis of a measurement of percentage saturation.
f. Calculate the **required dialysis solution/replacement fluid inflow rate**. This is simply equal to the required drainage volume minus the **expected removal (L/d) of excess fluid**.

2. **Sample problem:** A **60-kg** male patient has a SUN of **40** mg/dL (14 mmol/L) on day 1 and **65** mg/dL (23 mmol/L) on day 2. A 24-h urine collection from day 1 to day 2 contains **5 g** (178 mmol) of urea nitrogen. On day 2, weight has increased to **64 kg**. Estimated edema fluid is **8 L** on day 1 and is **12 L** on day 2. Calculate the clearance necessary to maintain the SUN at 40 mg/dL (14 mmol/L).

Solution:

1. **Estimate initial and final total-body water.**
   Initial total-body water: Initial weight is 60 kg with 8 kg estimated edema fluid. Edema-free weight is then 52 kg. Estimate total-body water as 55% of the "edema-free" weight.
   Total-body water is therefore 8 L + (0.55 × 52) = 8 L + 28.6 L = **36.6 L**.
   Final total-body water: Final weight is 64 kg, or 4 kg higher, all of which is water, so final total-body water is 36.6 + 4 = **40.6 L**.
2. **Estimate initial and final total-body urea nitrogen.**
   i. Initial and final SUN levels are 40 and 65 mg/dL, respectively (about 14 and 23 mmol/L).
   ii. Total-body urea nitrogen at time 1 = 36.6 L × 0.40 g/L = 14.6 g.
   iii. In SI units: Total-body urea at time 1 = 36.6 L × 14.3 mmol/L = 523 mmol.
   iv. Total-body urea nitrogen at time 2 = 40.6 L × 0.65 g/L = 26.4 g.
   In SI units: Total-body nitrogen at time 2 = 40.6 × 23.2 mmol/L = 942 mmol.
3. **Calculate change in total-body urea nitrogen.**
   i. Change in total-body urea nitrogen content from time 1 to time 2 is 26.4 g − 14.6 g = 11.75 g urea nitrogen (or, in SI units, 942 mmol − 523 mmol = 419 mmol).
   ii. This 11.75-g change in urea nitrogen now needs to be corrected to a daily basis. If time 1 and time 2 are 24 h apart, then the change in body urea nitrogen content is ~11.75 g/d (419 mmol/d).
4. **Account for urinary losses.** Urinary urea nitrogen loss during the 24-h observation period was measured to be 5 g/d (179 mmol/d).
5. **Calculate urea nitrogen generation rate.** This is equal to 11.75 + 5 = 16.75 g/d (or, in SI units, 419 + 179 = 598 mmol/d).
6. **Decide on a target SUN level.** As discussed above, let us say it should be 40 mg/dL (14.3 mmol/L).
7. **Calculate desired total clearance.** Assume target SUN = 40 mg/dL = 0.40 g/L.
   Urea N removal = clearance (K_D) × serum level = K_D × 0.40 g/L.
   At steady state, urea generation = removal, 16.75 = K_D × 0.40.
   K_D = (16.75 g/d)/(0.40 g/L) = **42 L/d**.
   In SI units: Assume target serum urea = 14.3 mmol/L.
   Urea N removal = clearance (K_D) × serum level = K_D × 14.3 mmol/L.
   At steady state, urea generation = removal, 598 = K_D × 14.3.
   K_D = (598 mmol/d)/(14.3 mmol/L) = **42 L/d**.
8. **Adjust for residual kidney function.** This patient actually had a urea clearance of about 10 L/d (about 7 mL/min), so we can subtract this from the required total clearance. Therefore, the required extracorporeal clearance is 32 L/d.
9. **Determine dialysis solution inflow rate.** This should be 32 L/d (assuming 100% saturation) minus the volume of excess fluid removal. For example, if we need to remove 3 L of fluid per day to offset hyperalimentation and

fluid given with medications, subtract 3 L from 32 L in the example to obtain a required dialysate inflow rate of 29 L/d. We usually ignore residual kidney function, because this may be ephemeral, and so we would add back the 10 L/d and use a dialysis solution inflow rate of 39 L/d.

C-HD, continuous hemodialysis; C-HF, continuous hemofiltration; CKRT, continuous kidney replacement therapy; SUN, serum urea nitrogen.

C. Dosing for SLED and SLED-F. Given the relative absence of dose-finding studies, there are no specific guidelines for the amount of SLED or SLED-F to be given. The KDIGO AKI guidelines recommend that a weekly *Kt/V* of at least 3.9 be given when intermittent KRT (IKRT) is used, where the weekly *Kt/V* is defined simply as the sum of the treatments given each week. Usually, SLED is done for 6 to 12 hours, 4 to 7 times/wk, with a blood flow rate of 200 to 300 mL/min and dialysis solution flow rate of 300 to 400 mL/min (Kumar, 2000). Such a prescription far exceeds the 3.9 "weekly *Kt/V*" guideline recommended by KDIGO.

IX. EQUIPMENT.

Many advanced machines are available to deliver various forms of CKRT. Some of them can also perform plasmapheresis, which is beyond the scope of this chapter. One cannot review them all, and the selection of devices described below should not be considered an endorsement of these devices over their competitors.

A. Prismaflex System from Baxter (Vantive) (Deerfield, IL). The Prismaflex System consists of five integrated pumps (blood, dialysate, effluent, substitution fluid, and preblood pump) and four pullout weighing devices with removable handles (for effluent, preblood pump, dialysate, and substitution fluid), which allow for fluid control with different variants of CKRT. The addition of the preblood pump allows for infusion of fluid in predilution mode or for continuous infusion of anticoagulant into the circuit. Simultaneous pre- and postfilter dilution can be performed by two integral pinch valves that control delivery of replacement fluid to the circuit. Different sources for dialysis and substitution fluids can be used. Control of ultrafiltration and net patient fluid removal is achieved using an integrated control panel with touch screen, which regulates the dialysate, effluent, preblood pump, and substitution fluid pump speeds. Other features include preconnected cartridge sets that include the filter, a programmable anticoagulant syringe, and optional blood warmer.

B. Use of modified "2008K" or "2008T" dialysis machines from Fresenius USA (Walnut Creek, CA). C-HD can be done using standard dialysis equipment (Burgner and Golper, 2021), but some standard dialysis machines need to be altered to permit delivery of a dialysis solution flow rate of 100 mL/min. Blood lines and dialyzers are replaced every 24 hours.

C. Use of upgraded "2008 H/K" dialysis machines from Fresenius USA (Walnut Creek, CA). Further advancements have been introduced to allow C-HD to become an integrated treatment option without any machine alteration. The machine may be calibrated to run at dialysate flows as low as 100 to 200 mL/min, but this option must be selected in service mode, and additional calibration is required. Ultrafiltration or variable sodium profiles are not available, and there is no ultrafiltrate time or target goal to set. The extracorporeal circuit, including dialyzer, should be replaced every 48 hours per manufacturer's recommendations. These machines are also popular to deliver SLED, where more conventional blood and dialysate flow rates are used.

D. NxStage System One from Fresenius Medical Care (Lawrence, MA). The

NxStage System One is a modular system that consists of a touch screen display, cycler with user interface, stand with IV pole, and optional fluid warmer. It can be used both as a portable hemodialysis machine and for CKRT therapies. The drop-in, single-use cartridge design, with or without a preattached filter, allows for a range of therapies and minimizes cycler maintenance and disinfection requirements. The cartridge has volume chambers for volumetric balancing, thus eliminating the need for scales, and discharges effluent directly to drain. One special feature is the absence of a blood-air interface in the cartridge; this is designed to optimize blood flow and reduce clotting.

The System One can be used for C-HD or C-HF, but is not configured to perform C-HDF.

E. Braun Diapact from B. Braun Medical Inc. (Bethlehem, PA). The Diapact CKRT system is a simple and compact dialysis unit originally designed for use in emergency situations where a purified water supply is not available. It operates on a three-pump system (blood, dialysis/infusion solution, ultrafiltration) and an electronic single weighing cell. This machine also features a simplified user interface, an integrated fluid plate warmer, and choice of dialyzer capabilities. Flexible treatment options other than CKRT include IHD and hemofiltration.

F. Tablo from Outset Medical (San Jose, CA): The Tablo is a small HD machine that is used in SLED and extended therapies for intensive care unit patients.

G. Quanta SC+ from Quanta Dialysis Technologies (Alcester, UK). The Quanta SC+ is a compact HD machine that has been used for SLED therapy for hospitalized patients.

H. multiFiltrate from Fresenius USA (Walnut Creek, CA): This system offers C-HD, C-HF, and C-HDF, and in addition, it offers citrate anticoagulation in C-HD and post filter C-HDF modes. An innovative augmented reality training program is available from the manufacturer.

I. SAMI from i-Dialco Medical (Mississauga, Canada). This is a CKRT machine that aims to simplify training and setup and to reduce costs.

X. ANTICOAGULATION.

In most patients at low risk of bleeding, systemic heparin is routinely used as it is inexpensive and easy to implement. A patient already on systemic therapeutic anticoagulation for another indication (eg, intra-aortic balloon pump) would not require additional anticoagulation. Patients with severe thrombocytopenia or impaired coagulation should have a trial of anticoagulation-free CKRT. In immediate postoperative patients or patients at high risk of bleeding, heparin-free CKRT or RCA can be used. In patients with nonimmune heparin-induced thrombocytopenia (HIT type I), RCA may be employed. Systemic anticoagulation therapy is often required in patients with immune-mediated HIT type II, a disorder that is associated with venous or arterial thrombosis in addition to the thrombocytopenia. In such patients who also require CKRT, use of systemic anticoagulation with lepirudin or argatroban has been described.

A. Heparin. After attachment of the primed hemofilter or dialyzer, if baseline clotting times are not elevated, 2,000 to 5,000 units of heparin are injected into the patient, ideally via the venous (outflow) blood line. One should then wait for 2 to 3 minutes to allow the heparin to mix with the patient's blood. Next, a constant infusion of heparin (at a rate of 500-1,000 units/h) is begun via an IV infusion pump emptying into the arterial (inflow) blood line, and blood flow through the extracorporeal circuit is begun.

Heparin therapy is monitored as per Table 14.5.

TABLE 14.5 Heparin Protocol for Continuous Therapies (for patients at low risk of bleeding)

1. *Initial therapy:* Heparin in priming and rinsing solution as described in text. At start of procedure, give 2,000-5,000 IU heparin to the patient via the venous line or other access. Wait 2-3 min for the heparin to mix with the circulation. Then start 500-1,000 IU/h constant heparin infusion into the arterial (inlet) blood line.
2. *Monitoring:* PTT measured at the arterial and venous blood lines every 6 h.

   Maintain arterial PTT 40-45 s.

   Maintain venous PTT >65 s.

   If arterial PTT >45 s, decrease heparin by 100 IU/h.

   If venous PTT <65 s, increase heparin by 100 IU/h, but only if arterial PTT <45 s.

   If arterial PTT <40 s, increase heparin by 200 IU/h.

PTT, partial thromboplastin time; RCA, regional citrate anticoagulation.

B. Heparin-free method. In patients with liver disease, in postoperative patients, in patients with active or recent bleeding, or in patients with HIT, CKRT can be performed without heparin. The filter will clot periodically and will need to be changed at more frequent intervals. If acute bleeding occurs while CKRT with heparin is being performed, the procedure can be continued even after heparin administration has been stopped. When heparin is not given, several steps may be taken to reduce the likelihood of clotting.

1. With C-HD, the dialysis solution inflow rate is increased by 20% to 40%. The higher dialysate flow rate will compensate for the anticipated loss of clearance as the unheparinized dialyzer slowly clots. When using the heparin-free method for C-HD, we usually do not infuse saline into the arterial blood line on a periodic basis, in contrast to what is commonly practiced in the case of heparin-free IHD, for fear of introducing microbubbles into the filter, which may lead to clot formation.
2. In C-HF done without heparin, the predilution mode is preferred because prefilter fluid replacement reduces the hemoconcentration within the hemofilter when plasma water is removed. Keeping the blood flow at 200 mL/min or higher may also prevent early or excessive clotting.

   When heparin is not used in patients without coagulation disturbances, the dialyzers will usually clot within 8 hours. A sign of early clotting is a reduction to less than 0.8 in the ratio of dialysate to serum UN levels. When the ratio is less than 0.6, clotting is imminent.

C. Regional citrate anticoagulation (RCA). Citrate chelates calcium (and magnesium) and impedes the coagulation cascade. Calcium citrate complexes are removed in the effluent and those that return to the circulation are metabolized by the liver and skeletal muscles. RCA may reduce bleeding risk in comparison with heparin for CKRT (Wu, 2012), with similar or better efficacy on circuit patency depending on the citrate dose administered (Monchi, 2004). Citrate anticoagulation, by reducing local ionized calcium concentration, may also reduce neutrophil and complement activation in the extracorporeal circuit (Schilder, 2014). For patients who have no contraindications to use of citrate, the KDIGO 2012 AKI guidelines recommend use of RCA for CKRT.

On average, 3 mmol of citrate per liter of blood circulated is required to suppress

the postfilter plasma ionized calcium to 0.3 to 0.4 mmol/L, the level needed for effective circuit anticoagulation. Calcium and magnesium losses are replaced by systemic infusions according to strict protocols. Toxicity is determined by the total citrate load and is exacerbated in patients with liver dysfunction and multiorgan failure; in such patients, the amount of citrate infused can overwhelm the patient's ability to metabolize it, causing accumulation of calcium citrate complexes and inadequate regeneration of free calcium. This in turn can lead to high anion gap metabolic acidosis (citrate) and a high (>2.5) ratio of total calcium to ionized calcium (Meier-Kriesche, 2001), findings that require cessation of RCA and correction of hypocalcemia. A citrate protocol for patients with liver failure has been developed and proposed (Szamosfalvi, 2020).

ACD-A solution (anticoagulant citrate dextrose form A) containing 3% trisodium citrate (2.2 g per 100 mL), citric acid (0.73 g/mL per 100 mL), and dextrose (2.45 g per 100 mL) (Baxter-Fenwal Healthcare Corp., Deerfield, IL) is preferred over trisodium citrate for routine RCA, as ACD-A is commercially prepared and is less hypertonic, reducing the potential for mixing errors and dangers of overinfusion.

Many RCA protocols have been described for CKRT. The major complications of RCA are symptomatic reductions in serum ionized calcium levels and metabolic alkalosis from citrate metabolism. We prefer RCA methods that minimize the amount of citrate infused, and these typically use calcium-free dialysis or replacement fluids, because the citrate infusion needs only to counteract the calcium in the patient's blood. However, methods of RCA have been reported where calcium is maintained in the replacement fluid or the dialysis solution (Mitchell, 2003; Rhee, 2021). These have the advantage of avoiding the return of a low-ionized calcium infusate close to the heart in the event that the calcium replacement solution pump fails.

1. **Swartz protocol** (Figure 14.4). As an example, here is a procedure for RCA in C-HD according to Swartz (2004).

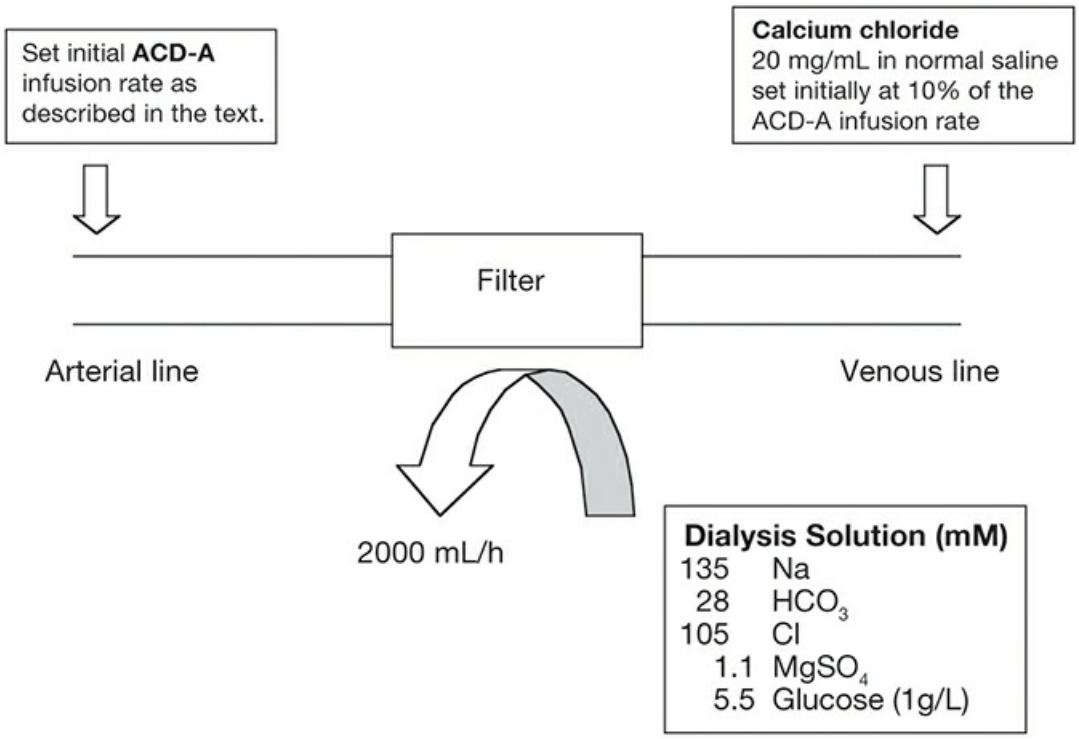


FIGURE 14.4: Circuit diagram for citrate slow continuous hemodialysis. The $MgSO_4$ level has been modified to 1.1 mM (vs 1.3 mM as originally depicted in the Swartz publication). ACD-A, anticoagulant citrate dextrose form A (Based on information in Swartz R, et al. Improving the delivery of continuous renal replacement therapy using regional citrate anticoagulation. *Clin Nephrol.* 2004;61:134-143.)

a. Attach the ACD-A 1,000-mL bag to an infusion pump infusing into the arterial line closest to the patient. A negative pressure valve is inserted into this line so that the infusion will occur in the direction of the blood pump and not directly into the patient should the blood pump stop. The rate of infusion in milliliters per hour is initially 1.5 times the blood flow rate in milliliters per minute. For example, when the blood flow rate is set at 200 mL/min, the citrate rate will then be 300 mL/h.

b. A calcium chloride infusion (20 mg/mL in normal saline) is infused via a three-way stopcock valve placed at the venous port of the dialysis catheter. Calcium gluconate infusion may also be given via a peripheral vein catheter, but this will result in higher fluid volumes. The initial calcium infusion rate should be set at 10% of the ACD-A infusion rate. For example, if the ACD-A rate is 300 mL/h, then the calcium infusion rate is 30 mL/h.

c. Ionized calcium is sampled every 2 hours × 4, then every 4 hours × 4 for the first 24 hours, then every 6 to 8 hours thereafter. The ionized calcium should be checked within 1 to 2 hours whenever the site of the infusion or tubing is changed. The ionized calcium samples should be drawn from two sites and labeled carefully, one being “postfilter” from the postfilter venous sample port and the other from the patient via a systemic arterial or a venous line. Basic chemistries and total calcium should be checked every 6 to 8 hours. The titration of ACD-A citrate and calcium chloride infusions is done according to Table 14.6.

TABLE 14.6 ACD-A Citrate and Calcium Titration Guidelines (for Swartz RCA Protocol)

Postfilter Ionized Calcium (mM)	**Adjustment of ACD-A Rate**
<0.20	Reduce rate by 5 mL/h.
0.20-0.40	No adjustment
0.40-0.50	Increase rate by 5 mL/h.
>0.50	Increase rate by 10 mL/h.
Calcium chloride infusion is titrated to **systemic** ionized calcium level.	
Systemic Ionized	
Calcium (mmol/L)	**Adjustment of Calcium Infusion**
>1.45	Reduce rate by 10 mL/h.
1.21-1.45	Reduce rate by 5 mL/h.
1.01-1.20	No adjustment
0.90-1.00	Increase rate by 5 mL/h.
<0.90	10 mg/kg calcium chloride bolus; increase rate by 10 mL/h.

ACD-A, anticoagulant citrate dextrose form A; RCA, regional citrate anticoagulation.

d. The dialysis solution with this method is calcium free and contains sodium 135 mM, magnesium (in the form of magnesium sulfate) 1.1 mM (2.2 mEq/L), bicarbonate 28 mM, chloride 105 mM, sulfate 1.1 mM, and glucose 5.5 mM (1 g/L). The lower concentrations of sodium and bicarbonate help to counteract the tonicity and bicarbonate delivery from the infusion of ACD-A. Dialysis solution flow rate is 2.0 L/h. Note: The dialysis solution magnesium concentration (1.1 mM) in the method shown is higher than that of most other available solutions (0.5-0.75 mM; Table 14.3).

D. Regional citrate protocols for SLED. A number of these have been described, including that by Fiaccadori (2013), as well as an automated system by Szamosfalvi (2010); the latter group is also working on sensors to measure citrate and ionized calcium levels (Yang, 2011).

E. Anticoagulation with lepirudin and argatroban. See Table 14.7 for dosing parameters. **Lepirudin** (recombinant hirudin) and argatroban are direct thrombin inhibitors. Lepirudin is eliminated mainly by the kidneys. The dose has to be adjusted according to residual kidney clearance and dialysis clearance. It can be administered as a continuous infusion or as repetitive boluses. Typical doses are 0.005 to 0.025 mg/kg body weight per hour. The anticoagulation effect is monitored by measuring the activated partial thromboplastin time (aPTT), aiming to keep it about 1.5 to 2.0 times normal, thereby ensuring anticoagulation without an excess of bleeding complications. After more than 5 days of lepirudin use, anti-lepirudin antibodies may develop. These antibodies enhance the anticoagulation effects of lepirudin, and a reduction of the infusion dose may be needed to minimize bleeding risk. It is recommended that with prolonged use of lepirudin, daily aPTT measurements be taken. **Argatroban** is eliminated predominantly by liver metabolism and biliary secretion, and for this reason may be a preferred agent in kidney failure patients. Argatroban infusion is initiated at 0.5 to 1.0 mcg/kg/min, using lower doses in patients with hepatic dysfunction. The

anticoagulation effect is also monitored by measuring aPTT. The administration of fresh frozen plasma is required to reverse bleeding due to overdosage of lepirudin or argatroban. Hemofiltration with high-flux dialyzers can reduce the plasma concentration of hirudin.

TABLE 14.7 Dosing Parameters for Continuous Kidney Replacement Therapy With Lepirudin or Argatroban

	Lepirudin	Argatroban
Infusion rate	Initiate at 0.005-0.01 mg/kg/h.	Initiate at 0.5-1.0 mcg/kg/min; start at lower doses in patients with hepatic dysfunction.
Monitoring test	aPTT	aPTT
Target	1.5-2.0 times normal	1.5-2.0 times normal

aPTT, activated partial thromboplastin time.

F. Other anticoagulants

1. **Low-MW heparins:** Sagedal and Hartmann (2004) reviewed the use of low-MW heparins in CKRT. Monitoring anticoagulation requires measuring anti–factor Xa activity, but use of this measurement to guide low-MW heparin use in CKRT remains to be defined. Low MW is not readily reversible with protamine. In C-HDF, **dalteparin** can be given as a bolus of about 20 U/kg followed by an infusion of 10 U/kg/h for adequate anticoagulation without an excess of bleeding. In a study of C-HD, a dalteparin dose of 35 U/kg bolus followed by 13 U/kg/h resulted in good filter patency rates, but there were bleeding episodes. At a lower dalteparin dose of 8 U/kg bolus and infusion of 5 U/kg/h, circuit life was poor, so perhaps the optimal dose is somewhere in between. **Enoxaparin** and **nadroparin** may be used, but the experience is limited. Nadroparin was compared with RCA for C-H; in patients who weighed more than 100 kg, nadroparin was given as a 3,800 IU (international units) bolus followed by continuous infusion at a rate of 456 IU/h. In patients weighing less than or equal to 100 kg, the nadroparin dose was a 2,850 IU bolus followed by a 380 IU/h infusion. This was done without anti-Xa monitoring. Patients in the nadroparin arm suffered more bleeding complications than those treated with RCA (Oudemans-van Straaten, 2009).
2. **Nafamostat mesylate** is a synthetic serine protease inhibitor and prostacyclin analog with minimal hypotensive activity. Its use in CKRT has been associated with improved circuit life and relatively low bleeding risk. The starting dose was a continuous infusion of nafamostat solution (200 mg of nafamostat mixed with 20 mL of 5% dextrose solution) at a rate of 10 mg/h. A bedside activated clotting time (ACT) test was used to monitor circuit coagulation, and the infusion rate was adjusted as necessary (Baek, 2012).

G. Microbubbles.

Microbubbles can be introduced into the extracorporeal circuit during priming and any time a connection is made or reset upstream to the filter. The microbubbles can get into the hollow fibers, and this can lead to clotting of the filter. Care should be taken to minimize this problem during priming and infusions.

H. Signs of filter clotting.

Signs of markedly reduced blood flow include darkening of the blood in the extracorporeal circuit, coolness of blood in the venous blood line, and

separation of erythrocytes and plasma in the extracorporeal circuit. Saline infusion can help diagnose a near-clotted system: This can make clots in transparent parts of the hemofilter visible.

When using C-HD, one can check the filtrate urea nitrogen (FUN):SUN ratio. If it is less than 0.6, clotting is imminent. An ultrasound method has been used to measure filter fiber bundle volume during use, but online fiber bundle volume measurements have not been found to predict filter longevity. One problem is that the majority of clotting seems to occur in the venous air trap chamber rather than in the dialyzer itself (Liangos, 2002).

XI. VITAMINS AND MINERALS. Total amino acids are removed in the amount of 12 g per 24 hours at effluent flow rates of 1 L/h and when standard parenteral nutrition solutions are infused at a rate of 60 to 100 mL/h. Water-soluble vitamins and trace elements are substantially removed by CKRT. If prolonged therapy is expected, supplementation is recommended; administration of active vitamin D, vitamin E, vitamin C, zinc, selenium, copper, manganese, chromium, and thiamine should be considered.

XII. PRINCIPLES OF DRUG REMOVAL BY CKRT. Drug clearance by CKRT is dependent on (a) drug properties such as MW, extent of protein binding, volume of distribution, and proportion of kidney drug elimination; (b) patient characteristics such as residual kidney function, volume status, serum albumin concentration, and function of other organs involved in drug metabolism/excretion (eg, liver); and (c) CKRT parameters (eg, dialysate/ultrafiltration/blood/effluent rate, hemofilter size). Both C-HD and C-HF remove small solutes effectively, but C-HF is superior at removing middle- and high-MW drugs because of convection. In general, C-HF is considered to have higher drug clearance than C-HD at the same effluent flow rate (Hoff, 2020).

The different intensities of CKRT treatments and patient residual kidney function can result in marked variability in drug removal. Literature available on drug dosing in patients being treated by CKRT should be used only as a guide, realizing that they may not be applicable to the particular CKRT prescription being used in a given patient. One way of determining drug dosing in patients receiving CKRT is to estimate the total creatinine and urea clearances based on a patient's residual kidney function and the expected CKRT clearance (Matzke, 2011; Mueller, 2022). The CKRT procedure can be thought of as an extra kidney, the glomerular filtrate rate (GFR) of which will depend on the total effluent volume. Each 10 L/d of effluent volume is equivalent to about 7 mL/min of GFR (7.0 mL/min × 1,440 min/d = 10.08 L/d). Thus, when prescribing drugs to otherwise anuric patients receiving CKRT, one should write the drug dose as for a patient with a GFR of 7 mL/min for every 10 L of effluent volume.

Table 14.8 lists the approximate dosages for antibiotics in patients with kidney failure being treated with CKRT. Dosing guidelines using contemporary CKRT technology, commonly used CKRT flow rates, and updated pharmacokinetic and pharmacodynamic principles have been adopted. Whenever possible, therapeutic drug monitoring should be performed for antibiotics such as vancomycin, aminoglycosides, and other drugs that have a narrow therapeutic index. Any change to the CKRT prescription or clinical status (eg, worsening or improvement in kidney function) may require additional monitoring and dosage adjustment.

TABLE 14.8 Dosing of Antimicrobials in CKRT

Drug[a]	LD	C-H	C-HD or C-HDF
Acyclovir[a-c] (IV)	None	5-10 mg/kg/dose q12-24 h (use higher end of dosing range for viral meningoencephalitis and varicella-zoster infections)	Same
Amikacin[a-c]	15-25 mg/kg	15-25 mg/kg q48 h then per level (depending on infection site, severity, and susceptibility of organism)	Same
Ampicillin[a] (IV)	2 g	2 g q8-12 h (based on usual dose of 1-2 g q6 h) 2 g q6-8 h (based on usual dose of 2 g q4 h)	Same
Ampicillin-sulbactam[a]	3 g	3 g q8-12 h (based on usual dose of 1.5-3 g q6 h)	Same
Azithromycin (IV/PO)	None	No dosage adjustment necessary 250-500 mg q24 h	Same
Aztreonam[a]	2 g	1 g q8 h or 2 g q12 h	Same
Cefazolin[a]	2 g	1 g q8 h or 2 g q12 h (based on usual dose of 1-2 g q8 h)	Same
Cefepime[a]	2 g	2 g q8-12 h If effluent rate <20 mL/kg/h: 2 g q12 h If effluent rate ≥35 mL/kg/h: 2 g q8 h	Same
Cefotaxime[a]	None	1-2 g q12 h (based on usual dose of 1-2 g q8 h) 1-2 g q8 h (based on usual dose of 1-2 g q6 h) 2 g q6-8 h (based on usual dose of 2 g q4 h)	Same
Ceftazidime[a]	2 g	2 g q8-12 h (frequency depends on MIC of organism or severity of infection)or LD of 2 g then 3 g continuous infusion over 24 h daily to maintain concentration ≥4 times MIC for susceptible pathogens.	Same
Ceftriaxone	2 g	No dosage adjustment necessary 1-2 g q24 h Meningitis, *Enterococcus faecalis* endocarditis: 2 g q12 h	Same
Ciprofloxacin[a] (IV)	None	200-400 mg q8-12 h; use 400 mg q8 h only in severe infections or when difficult-to-treat organisms are suspected or confirmed.	Same
Ciprofloxacin[a] (PO)	None	250-750 mg q12 h	Same
Clindamycin (IV)	None	No dosage adjustment necessary 600-2,700 mg/d in 2-4 divided doses	Same
Clindamycin (PO)	None	No dosage adjustment necessary 600-1,800 mg/d in 2-4 divided doses (up to 2,400 mg/d in four divided doses may be given for severe infections)	Same
Colistin[a,e] (IV)	300 mg CBA[e]	220 mg CBA[e] q12 h as maintenance starting 12 h after LD	Same
Daptomycin[a,c]	None	6 mg/kg q24 h	Same
Fluconazole[a] (IV/PO)	400-1,200 mg	Increased clearance in patients receiving CKRT 400 mg once daily (based on usual dose of 200 mg once daily) LD of 800 mg, then MD of 800 mg/day in 1-2 divided doses (based on usual dose of 400 mg once daily) LD of 1.2 g, then MD of 1.2 g/d in 1-2 divided doses (based on usual dose of 800 mg once daily)	Same
Ganciclovir IV[a]	2.5 mg/kg	Induction: 2.5 mg/kg q24 h (based on usual dose of 5 mg/kg q12 h) Maintenance: 1.25 mg/kg q24 h (based on usual dose of 5 mg/kg q24 h)	Same

Gentamicin[a,c]	2-3 mg/kg		
• Synergy		• 1-1.5 mg/kg q24-36 h then per level	• Same
• UTI		• 1-1.5 mg/kg q24-36 h then per level	• Same
• Systemic gram-negative infection		• Initial: 2.5-3 mg/kg/dose; up to 5 mg/kg/dose may be considered q24-48 h per level	• Same
Imipenem-cilastatin[a]	1 g	250 mg q6 h or 500 mg q6-8 h	Same
Levofloxacin[a] (IV/PO)	500-750 mg	LD 500 mg then 250 mg q24 h or 500 mg q48 h (based on usual dose of 500 mg q24 h) LD 750 mg then 500 mg q24 h or 750 mg q48 h (based on usual dose of 750 mg q24 h)	Same
Linezolid[a] (IV/PO)	None	No dosage adjustment necessary 600 mg q12 h High variability observed in critically ill patients; consider alternative agent or use higher dose guided by TDM in patients at risk of toxicity or treatment failure.	Same
Meropenem[a]	1 g	LD then 500 mg to 1 g q8 h (over 30 min) or 1 g q12 h (over 12 h)	Same
Metronidazole[a] (IV/PO)	None	No dosage adjustment necessary 500 mg q6-12 h	Same
Moxifloxacin (IV/PO)	None	No dosage adjustment necessary 400 mg q24 h	Same
Nafcillin	None	No dosage adjustment necessary 1-2 g q4-6 h	Same
Penicillin G[f] (IV)	4 MU	LD then 2 MU q4-6 h	C-HD: LD then 2-3 MU q4-6 h C-HDF: LD then 2-4 MU q4-6 h
Piperacillin-tazobactam[a]	4.5 g	IV: 4.5g q8 h or LD then 2.25 g q6 h Continuous infusion: LD then 9 g over 24 h daily Initiating therapy with high dose may be considered in view of drug's favorable safety profile.	Same
Rifampin (IV/PO)	None	No dosage adjustment necessary 300-600 mg q12-24 h	Same
Ticarcillin-clavulanate[f]	3.1 g	LD then 2 g q6-8 h	C-HD: LD then 3.1 g q6-8 h C-HDF: LD then 3.1 g q6 h
Tigecycline[a]	100 mg	No dosage adjustment necessary 50 mg q12 h Reserve for use in situations where alternatives are not suitable or available	Same
Tobramycin[b,c,f]	2-3 mg/kg		
• Mild UTI		• 1 mg/kg/dose q24-36 h then per level	• Same
• Mod-severe UTI		• 1-1.5 mg/kg/dose q24-36 h then per level	• Same

• GNR infection		• 1.5-2.5 mg/kg/dose q24-48 h then per level	• Same
TMP-SMX[a,c] (IV/PO)	None	No dosage adjustment necessary IV: 8-20 mg/kg/d (TMP) divided q6-12 h PO: 1-2 double-strength tablets q12-24 h	Same
Vancomycin[a,d,f] (IV)	20-25 mg/kg	7.5-10 mg/kg q12 h with more frequent TDM	Same
Voriconazole[a,c] (IV/PO)	PO: 400 mg twice daily × 2	No dosage adjustment necessary *Aspergillosis*: IV: 6 mg/kg twice daily × 2 doses, then 4 mg/kg twice daily PO: 200-300 mg twice daily or weight-based dosing of 3-4 mg/kg twice daily *Candidiasis*: IV: 400 mg twice daily × 2 doses, then 200-300 mg twice daily, or weight-based dosing of 6 mg/kg twice daily × 2 doses, then 3-4 mg/kg twice daily PO: 200-300 mg twice daily or weight-based dosing of 3-4 mg/kg twice daily	Same

CBA, colistin base activity; C-H, continuous hemofiltration; C-HD/C-HDF, continuous hemodialysis/continuous hemodiafiltration; CKRT, continuous kidney replacement therapy; CMS, colistimethate sodium; ICU, intensive care unit; IV, intravenous; LD, loading dose; MD, maintenance dose; MIC, minimum inhibitory concentration; MU, million units; PO, oral; TMP, trimethoprim; SMX, sulfamethoxazole; TDM, therapeutic drug monitoring; UTI, urinary tract infection.

[a]Drug clearance is dependent on effluent flow rate, filter type, and method of CKRT. Recommendations are based on high-flux dialyzers and dialysate flow/ultrafiltration rates of 20-25 mL/kg/h (or 1.5-3 L/h).

[b]Use ideal body weight (IBW) (kg); IBW (male) = 50 kg + (2.3 × height in inches >60 inches), IBW (female) = 45 kg + (2.3 × height in inches >60 inches).

[c]Use adjusted body weight (BW) (kg) in people who are obese; adjusted body weight (ABW) (kg) = IBW + 0.4 (total-body weight [TBW] − IBW).

[d]Use actual body weight (kg).

[e]Dose expressed in terms of mg of CBA, where CBA 1 mg is equivalent to colistimethate sodium (CMS) 30,000 units, which is equivalent to ~2.4 mg CMS.

[f]Based on dialysate/ultrafiltration rates of 1-2 L/h and minimal residual kidney function.

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The amount of pressor drugs removed during CKRT is usually not a clinical issue, as pressor infusion rates are usually titrated to maintain a desired hemodynamic response. Table 14.9 gives doses of additional drugs commonly used in ICU patients with information on dose adjustment during CKRT.

TABLE 14.9 Recommended Adult Dosages of Some Common Drugs Used in the ICU

Drug	Indication	Normal Dose	Dose Based on Type of CKRT	
			C-H	C-HD or C-HDF
Amiodarone	Atrial fibrillation	150 mg over 10 min, then 1 mg/min for 6 h, then 0.5 mg/min for 18 h. Continue for total load of up to 10 g (may finish load with oral dosing).	Same	Same
Digoxin	Atrial fibrillation (avoid use if possible, use LD with caution and only when rapid rate control is necessary)	Loading dose (LD): 0.25-0.5 mg over several min, with repeat doses of 0.25 mg every 6 h to a max of 1.5 mg over 24 h Maintenance dose (MD): 0.125-0.25 mg PO once daily	LD: reduce dose by 50%. MD: 0.0625-0.125 mg every 48 h may be considered.	LD: reduce dose by 50% MD: 0.0625-0.125 mg every 48 h may be considered.
Haloperidol	Delirium in ICU	Initial: 0.5-20 mg depending on the degree of agitation (mild: 0.5-2.5 mg, moderate 2-5 mg, severe 10-20 mg); if inadequate, may repeat or increase bolus dose q15-30 min until calm achieved; then administer MD of ~25% of total loading dose q6 h if needed.	Same (monitor ECG and QTc interval)	Same (monitor ECG and QTc interval)
Lorazepam	Status epilepticus Agitation	4 mg per dose (given as slow IV, max rate: 2 mg/min); may repeat in 3-5 min if seizures continue 0.5-2 mg q4-6 h as needed up to 10 mg/d; adjust dose based on response and tolerability; doses up to 4 mg repeated after 10-30 min have been recommended in severe agitation	Same (risk of propylene glycol toxicity; monitor osmolar gap closely as surrogate for propylene glycol accumulation if using for prolonged periods or at high doses)	Same (risk of propylene glycol toxicity; monitor osmolar gap closely as surrogate for propylene glycol accumulation if using for prolonged periods or atC-High doses)
Phenytoin	Status epilepticus	LD: 20 mg/kg at rate of 25-50 mg/min. May give additional dose of 5-10 mg/kg 10 min after LD if necessary, max total loading dose: 30 mg/kg MD: 4-7 mg/kg/d (usual 300-400 mg/d) in 2-4 divided doses (adjust dose based on response and serum concentrations). Begin MD 8-12 h after LD.	Same. Titrate dose according to response, and perform TDM to maintain free phenytoin conc 1-2 mg/L.	Same. Titrate dose according to response, and perform TDM to maintain free phenytoin conc 1-2 mg/L.
Phenobarbital	Seizures/status epilepticus	LD (status epilepticus): 15-20 mg/kg as a single dose (recommended as second-line option) MD (seizures): 2 mg/kg/d in divided doses	Same (monitor levels)	Same (monitor levels)

CKRT, continuous kidney replacement therapy; C-H, continuous hemofiltration; C-HD, continuous hemodialysis; C-HDF, continuous hemodiafiltration; ECG, electrocardiogram; ICU, intensive care unit; TDM, therapeutic drug monitoring.

All dosages above are for intravenous administration and assume use of high-flux dialyzers and effluent flow rates of 20-25 mL/kg/h (or ~1,500-3,000 mL/h). Dosing ranges are provided to accommodate for differences in ultrafiltration and dialysis flow rates, and residual renal function of patient. Where applicable, close monitoring of response, serum drug concentrations, and adverse reactions is essential.

From: Lexi-Comp, Inc. *Lexi-Drugs*™. Lexi-Comp, Inc; 2022.

XIII. ISOLATED ULTRAFILTRATION AND SCUF.

Isolated ultrafiltration is achieved using standard dialysis equipment by simply putting the dialysate in bypass and can be performed prior to dialysis, after dialysis, or independently of dialysis. In patients with kidney failure, isolated ultrafiltration is most often performed just prior to hemodialysis. SCUF is achieved using the same circuitry as for C-HD (Figure 14.1) but omitting dialysis solution.

A. Isolated ultrafiltration.

Isolated ultrafiltration is usually carried out when IHD is being given. Isolated ultrafiltration is useful to remove additional fluid while avoiding disequilibrium syndrome for the initial one or two dialysis treatments in acutely uremic patients. It is also used in some outpatient dialysis units in patients with difficulty in fluid removal. The principal advantage of isolated ultrafiltration is that fluid removal is better tolerated than with conventional hemodialysis. Today, isolated ultrafiltration may no longer be a superior method of fluid removal. Historically, poor tolerance to fluid removal during IHD was due partly to use of acetate-containing dialysis solution, to use

of excessively warmed dialysis solution, and to use of solutions containing an inappropriately low-sodium concentration (eg, 5-10 mM below that of plasma). If these factors are avoided (ie, if a bicarbonate-containing, high-sodium, slightly cooled dialysis solution is used), then the superiority of isolated ultrafiltration in terms of hemodynamic stability is no longer demonstrable. Waste product removal is minimal during isolated ultrafiltration. For this reason, the subsequent hemodialysis session length should not be shortened, and thus the total treatment time for the separated isolated ultrafiltration-hemodialysis combination must be prolonged.

Despite the relatively good tolerance to fluid removal with isolated ultrafiltration, hypotension can still occur if the ultrafiltration rate is excessive. If overt edema is present, then hypotension is rare at ultrafiltration rates of up to 1.5 L/h, but one should not go higher unless one is monitoring blood volume status using a hematocrit sensor. A rebound hyperkalemia has been reported after intensive isolated ultrafiltration, perhaps due to exit of intracellular potassium into the extracellular fluid. Although the existence of this complication is controversial, any possible hyperkalemia with isolated ultrafiltration can best be avoided by routinely following isolated ultrafiltration with a period of hemodialysis.

B. SCUF. SCUF is used primarily in an ICU setting to remove excess fluid from patients in whom residual kidney function is substantial and in whom electrolyte and acid-base imbalances are not an issue. SCUF is also used in inpatient treatment of patients with refractory heart failure and mildly impaired kidney function, as described below. A disadvantage of SCUF is that acid-base disturbances and electrolyte imbalances need to be corrected by nondialytic means.

1. **SCUF for congestive heart failure.** Patients with congestive heart failure may develop concomitant kidney failure, resulting in fluid overload. They may have anuria, oliguria, or insufficient urine output (<1 L/d) despite optimal medical treatment with maximal doses of IV diuretics, inotropes, and natriuretic peptides. Ultrafiltration is a treatment option in such situations. Although inpatient and outpatient intermittent isolated ultrafiltration for treating congestive heart failure have been described, there are several advantages of SCUF that should be considered. Slow removal of fluid results in less hemodynamic issues, such as symptomatic hypotension. Also, many of these patients are volume-overloaded substantially, sometimes 10 to 15 kg over their “feel good” weight; continuous therapy allows for larger volumes of fluid to be removed while minimizing the hemodynamic problems. Ultrafiltration techniques can be further enhanced by using a Swan-Ganz catheter for central volume monitoring, thereby guiding the end point of treatment, and by using an online blood volume monitoring instrument to protect against an excessive ultrafiltration rate. Small, portable machines designed specifically for SCUF have become available. However, a large randomized trial of stepped pharmacologic treatment versus ultrafiltration for patients hospitalized for acute decompensated heart failure and worsened kidney function found that the pharmacologic approach resulted in better preservation of kidney function at 96 hours after start of treatment (Bart, 2012).

XIV. INTERMITTENT HEMODIAFILTRATION.

This is described in Chapter 16.

XV. CKRT POINTERS FOR CERTAIN GROUPS OF PATIENTS

A. Brain edema. In critically ill patients with acute kidney failure, CKRT has been shown to cause fewer changes in terms of brain edema when compared with IHD. KDIGO 2012 AKI guidelines specifically recommend use of CKRT in place of conventional IHD in patients with evidence of brain edema or increased intracranial pressure. CKRT minimizes rapid perturbations of the cardiovascular system, particularly in terms of blood volume and blood pressure, thereby reducing large variations in cerebral perfusion pressure and intracranial pressure. Patients with liver failure are one group at risk for developing cerebral edema, owing to difficulty in maintaining cerebral autoregulation of blood flow. Davenport (1999) has used C-HF and C-HD to cope with the increased intracranial pressure and cerebral edema. There are few data comparing CKRT versus SLED in this regard. In one study, SLED and CKRT had the same effects on intracranial pressure in patients being dialyzed after brain hemorrhage (Wu, 2013).

In patients at risk for cerebral edema, C-HF and C-HD systems with tight volumetric control and biocompatible membranes should be used. If possible, anticoagulation should be avoided, as it may increase the risk of intracerebral hemorrhage either at the site of injury or around an intracranial pressure monitor.

Dialysis or replacement fluid should have a relatively higher sodium (>140 mM) and a lower bicarbonate (30 mM) concentration. A higher sodium concentration will reduce the blood-brain osmotic gradient and minimize water movement into the brain. A rapid rise in plasma bicarbonate increases CO_2 movement into brain cells. Because bicarbonate ions are charged, they enter cells less readily than CO_2, thus causing a paradoxical decrease in brain pH. A sudden decrease in brain pH results in the generation of idiogenic osmoles, which increase the osmotic gradient favoring water entry into the brain.

In severe cases of uncontrolled intracranial pressure, cooling of the dialysis or replacement solutions may be helpful, in addition to other measures used to cool the patient to 32 °C to 33 °C. At these temperatures, cranial oxygen demands are reduced (Davenport, 2001).

B. Sepsis and multiorgan failure. Multiple organ dysfunction syndrome occurs as a result of an outpouring of proinflammatory (tumor necrosis factor β, thromboxane B_2, platelet activating factor) and anti-inflammatory mediators (interleukin-10). This response is provoked by gram-negative bacteria endotoxins, gram-positive bacteria, viruses, splanchnic ischemia, and trauma. With C-HF, many of these septic mediators are found in the filtrate of septic patients or are adsorbed to the filter membrane, suggesting that C-HF has the ability to remove septic mediators from the circulation. Use of high-volume C-HF has been advocated for such patients. However, septic mediator concentrations appear to be reduced similarly by both C-HD and C-HF (Chen, 2018). Nevertheless, many centers will treat septic patients with C-HDF instead of C-HD to increase removal of potential sepsis-mediating molecules while retaining the efficiency associated with use of dialysis. Using a clearance dose of 35 mL/kg/h and dividing equally between dialysis and hemofiltration is a common strategy. See Joannidis (2009) for a review of this topic.

C. Acute lung injury and acute respiratory distress syndrome (ARDS). Early institution of CKRT for volume removal may be helpful in improving oxygenation and

ventilator parameters (PaO_2/FIO_2 ratio and oxygenation index) in patients with ARDS with concomitant acute kidney failure. Respiratory improvement appears to be due more to the volume removal effect rather than to the removal of inflammatory mediators (Hoste, 2002).

D. Prevention of radiocontrast-induced nephropathy. Although some studies found a benefit of periprocedural CKRT in patients with chronic kidney disease (CKD) undergoing IV contrast administration (Marenzi, 2003), the KDIGO 2012 AKI review group concluded that the evidence for CKRT use in this situation was not strong and does not recommend such intervention until more conclusive research has been done.

E. Intoxication with dialyzable or filter-permeable drugs or toxins. Use of various modes of CKRT can be advantageous in treating various poisonings, especially when there is a risk of rebound in serum concentrations of the drug or toxin after IHD (see Chapter 18).

F. Extracorporeal membrane oxygenation (ECMO). SCUF or C-HD may be performed on patients receiving ECMO without the need for a separate CKRT system. The ECMO blood lines can be adapted to connect in parallel to a dialyzer. This allows C-HD or SCUF to be performed concurrently. Because these patients have ARDS or volume overload that requires ECMO in the first place, further volume removal may be helpful, especially in patients with chronic kidney insufficiency. When C-HD is desired for the treatment of concomitant acute renal failure (ARF) in these patients, use of sterile dialysis solutions is preferred, as there may be high backfiltration due to high pressures in the ECMO circuit. Anticoagulation using regional citrate has been used (Shum, 2014).

XVI. INFANTS AND CHILDREN.

Use of CKRT in children is beyond the scope of this *Handbook.* See the review by Fuhrman (2023).

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15 Home and Intensive Hemodialysis

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Interest in home hemodialysis (home HD)—particularly in the wake of the COVID-19 pandemic—continues to grow. Provider and patient preferences, decreasing costs of equipment, new funding models, and more user-friendly technology may be facilitating factors. The home setting lends itself to longer and more frequent (collectively, "intensive") HD sessions than are typically available in-center. It is useful to distinguish among (a) conventional HD (3-5 hours, 3 per week), (b) frequent HD (5-7 per week), which can be frequent short (1.5-3 hours), frequent standard (3-5 hours), or frequent long (>5 hours), and (c) long-session-length regimens (>5 hours) given 3 d/wk or every other day. Short and standard frequent HD schedules are typically referred to as daily HD, while long, frequent HD is typically done at night and is called frequent nocturnal HD.

I. MODALITY SELECTION. In the absence of evidence-based practice guidelines addressing modality selection, we propose some general guiding principles: (a) patients approaching renal replacement therapy should receive education regarding all available modality options, including conservative care without dialysis, preemptive transplantation, home HD, peritoneal dialysis (PD), and in-center HD; (b) where medically appropriate and feasible, home modalities (including PD) should be promoted as first-line therapies when transplantation is not imminent; (c) the choice between PD and home HD should be based on patient preference, availability, feasibility, and medical factors (eg, patients seeking pregnancy should preferentially receive frequent nocturnal HD; patients at risk for suboptimal clearance with PD should consider home HD); (d) home HD should be considered following the failure of PD or a renal allograft—this approach requires carefully timed education and planning, but can lead to more patients maintaining their independence from in-center HD; and (e) more intensified (home or center) HD regimens may be considered to improve extracellular fluid volume management (especially in those with high fluid gains), blood pressure, left ventricular mass, phosphate, and quality of life.

A. Frequent versus conventional HD. Prescription patterns vary geographically, and also according to program and provider preferences. There are no evidence-based guidelines that directly address the choice between conventional and frequent (long or short) HD. In the majority of cases, the treatment schedule will depend on patient preferences (such as convenience and noninterference with work, sleep, and social schedules), along with clearance and ultrafiltration needs. Starting with one particular regimen does not preclude switching to another. Many patients use long and short treatments to accommodate their schedules. Where possible, we recommend avoiding a 3-day interdialytic interval, setting a lower boundary of every other day for home HD, as this approach is less likely to be available in-center.

B. Incremental HD.

Residual kidney function associates with improved mortality. Incremental HD constitutes any dialysis prescription that is less than "standard" and may preserve residual kidney function. Incremental dialysis is commonly used when starting peritoneal dialysis, and is now being tested with HD. Goals of an incremental prescription include easing the transition for patients starting dialysis, reducing ischemic injury (to preserve residual kidney function and prevent adverse effects), and potentially reducing costs of consumables. Patients must be followed closely and patients counseled that dialysis frequency will be increased as residual kidney function decreases in order to reduce risk of underdialysis. The Kidney Disease Outcomes Quality Initiative (KDOQI) in 2006 recommended a twice-weekly dialysis schedule among patients with Kidney urea clearance >3 mL/min. These sentiments were reinforced in the 2015 update; however, this recommendation was and continues to be opinion-based.

Dai (2020) found similar inflammatory, nutritional outcomes and adverse events between twice versus thrice weekly HD, while perceived quality of life was improved in the incremental group. Vilar et al randomized 54 patients to two versus three sessions per week and found no discernible difference in residual kidney function preservation, adverse events, blood pressure, volume status, or biochemical profile. In contrast, Murea (2022) demonstrated preservation of renal function with twice weekly dialysis in a randomized trial of around 50 patients. A larger, definitive trial of twice versus thrice weekly in-center HD is underway: the RandomizEd ClinicAL triaL on the Efficacy and saFety of Incremental Hemodialysis (REAL-LIFE). Another trial (the VA IncHVets Trial) comparing safety and efficacy of twice versus thrice-weekly HD in VA-based dialysis units is also underway (Rhee, 2025), as is a third randomized trial, the TwoPlus study (Murea, 2024).

Frequent six nightly HD has been shown to unequivocally accelerate loss of residual kidney function compared with 3 times weekly home HD in a randomized trial (FHN Nocturnal Trial, Daugirdas, 2013), lending support for the long suspected notion that HD therapy itself contributes to loss of residual kidney function An incremental approach to home HD for patients may thus be warranted for incident patients, increasing to intensive more frequent therapy as residual kidney function dwindles.

A better understanding of the net balance of benefits and harms of incremental versus intensive HD, triggers for intensifying incremental therapy, and optimal timing of clinical follow-up are important research questions that will inform the optimal future use of incremental HD.

C. Home HD

1. **Patient selection.** Reported prevalent rates for home HD are generally <5% in most regions, but as high as 21% in others. Work by Zhu (2024) highlights a concerning racial disparity in the United States, where the majority of home HD recipients are White. The primary prerequisite for home HD is a willing patient or partner able to learn and safely perform the dialysis procedure. Uncontrolled seizures, hypoglycemia, noncompliance with medical care, and significant intradialytic hemodynamic instability requiring frequent nursing interventions are relative contraindications. Inability to use heparin precludes long HD with lower blood flow rates (eg, 150 mL/min), but not prescriptions with higher (eg, >300 mL/min) blood flow. The presence of multiple or severe comorbidities are not contraindications to home HD, but frailty and inability to perform self-care HD may

represent significant barriers if no assistance is available. Home HD programs should develop standardized intake procedures, and criteria for home HD eligibility should consider the patient's or helper's motor skills, strength, vision, hearing, reading ability, motivation, and adherence. When significant functional barriers are identified, the help of paid caregivers can be considered, if available.

2. **Home environment suitability.** The home needs to be assessed by a renal technologist, focusing on (a) water quantity and quality, (b) electrical supply, (c) storage space, and (d) cleanliness. These rarely pose insurmountable barriers to home dialysis, though the patient must understand the nature and extent of the changes needed to accommodate the necessary equipment. Local building codes should be adhered to, and, occasionally, permission from landlords must be sought prior to beginning any alterations to plumbing and electrical infrastructure.

D. In-center HD. Reasons for choosing in-center over home-based HD include (a) patient safety concerns, (b) vascular access or cannulation problems, (c) patient or partner inability or unwillingness to perform the HD procedure at home, (d) unsuitable home environment (space, electrical, hygiene, or plumbing limitations), and (e) patient preference.

While conventional regimens predominate in-center, intensified center HD is increasingly available, with practices varying by region. In Canada, Australia, and Europe, daily HD is offered for a wide range of indications, including (a) refractory volume overload, (b) refractory hyperphosphatemia and/or calciphylaxis, (c) failure to thrive, and (d) pregnancy, though evidence to support these indications is limited. In France, long, thrice-weekly, in-center, daytime HD is common, and long, thrice-weekly nocturnal HD is becoming increasingly available in the United States. Long, frequent nocturnal HD is not usually available in-center. Transportation, proximity to the treatment center, patient lifestyle, and demands on the patient's family are important factors that may determine whether in-center intensive HD is considered. In-center intensified regimens impose increased demands on space, equipment, and nursing and technical support staff. Programs generally require a "critical mass" of patients receiving intensified regimens to maintain a pool of adequately trained staff and to realize economies of scale. Lack of availability of overnight staff and ability to rapidly "turn over" larger numbers of daily HD treatments may require alternative staffing models.

II. TECHNICAL CONSIDERATIONS FOR HOME HD

A. Training. The length of the training period depends on the patient's previous experience with HD. Without prior experience, patients typically require one-on-one training with an experienced nurse for at least 6 weeks to become safe and proficient. There currently is no standard approach to training and ensuring safety (Platnich and Pauly, 2024). Patients previously undergoing self-care HD require less training time. Some programs with long wait times for home HD training offer training in self-care HD units. Educational manuals written in the patient's language at the appropriate reading and comprehension level are also useful. Recent research has brought attention to appreciating different learning styles of the patient and the need to tailor educational material to these strengths (Auguste, 2018). Many programs require patients to "recertify" annually, by demonstrating in the training unit that they are able to correctly

perform the dialysis procedure and troubleshoot effectively. More recently, some programs are implementing Objective Structured Clinical Exams (OSCE) to ensure a standardized approach to assuring safety (McIsaac, 2022).

B. Vascular access. The Canadian Society of Nephrology (CSN) guidelines for the management of patients with end-stage kidney disease (ESKD) treated with intensive HD (Nesrallah, 2013) recommend arteriovenous (AV) fistulas and grafts over catheters, because of lower infection risk (conditional/weak recommendation, very low quality evidence), but acknowledge that the technical demands of cannulation may represent a barrier to home HD for some patients. Importantly, low blood flows of 200 to 250 mL/min and single needle are sufficient for nocturnal HD, where high dialysis efficiency is not required

In patients with AV fistulas, the "buttonhole" technique, which involves recannulation of precisely the same two (or two pairs of) sites with blunt needles, had been popular due to ease of learning, but has mostly been abandoned in favor of the "rope-ladder" (rotating site), method (see Chapter 6) due to the risk of *Staphylococcus aureus* bacteremia with the former (Muir, 2014). If a buttonhole technique is used, guidelines recommend using topical antimicrobial prophylaxis with mupirocin (conditional/weak recommendation, very low quality evidence) (Nesrallah, 2010, 2013). With synthetic grafts, needle sites are rotated in the usual fashion.

C. Dialysis membranes. There is no evidence favoring the use of one kind of dialyzer membrane over another in home HD. Most centers use high-flux dialyzers. Dialyzers with a smaller surface area have been used for long HD (Pierratos, 1999).

D. Patient safety and precautions. Appropriate patient selection, training, and ongoing supervision can help optimize patient safety at home. The dialysis machine display should be easily visible at all times, from whichever position the patient dialyzes, and the controls should be easily accessible. Some additional precautions include:

1. **Alarms and communication.** The patient (or caregiver) must be able to hear the dialysis machine and its alarms and be trained on how to respond to them. Patients must have a telephone that is audible and within reach while dialyzing to contact emergency services or receive calls from their monitoring center. Some programs prefer a wired landline over a cellular phone, to ensure function in case of power failure or inadequate connectivity.
2. **Prevention of blood tubing disconnection**
   a. **Proper cannulation technique.** Patient or caregiver competence with cannulation and with securing the cannula are prerequisites for home treatment.
   b. **Securing lines.** Meticulous taping of the blood tubing connection to the dialysis catheter is important to reduce the risk of exsanguination from accidental disconnection. Plastic clamshell locking boxes have been used to prevent catheter–tubing separation (Pierratos, 1999). A small blood line connector clip (HemaClip, Fresenius NA, Lexington, MA) is widely available.
3. **Prevention of morbidity when lines disconnect**
   a. **Closed connector devices.** The use of a closed connector device is recommended if the patient performs dialysis while asleep (conditional/weak recommendation, very low quality evidence) (Nesrallah, 2013) to prevent air embolization and bleeding resulting from accidental disconnection from the

dialysis catheter. These are catheter caps with a slit diaphragm, allowing blood flow while in place. They are replaced periodically from every week to every month, depending on local practices and manufacturer recommendations. The InterLink System (Becton Dickinson, Franklin Lakes, NJ) can be used only for long HD, as it results in increased arterial and venous pressures at the higher pump speeds used in other regimens. The TEGO (ICU Medical, CA) connector provides less resistance to flow and can be used with higher blood flow rates. The Swan-Lock connector (Codan, Lensahn, Germany) has also been used.

b. Moisture detectors. An enuresis alarm, such as the Drisleeper (Alpha Consultants Ltd., Nelson, New Zealand), can be attached to the cannula entry points to detect bleeding. Disposable leak detectors are also available (RedSense Medical AB, Halmstad, Sweden). A wireless wetness detector, which stops the machine blood pump, was recently released (Fresenius Medical Care, Lexington, MA). Finally, moisture sensors can be placed on the floor around the machine and near the water supply to detect blood, dialysate, and water leaks (Pierratos, 2000).

c. Two-pump, single-needle system. With accidental disconnection of the venous line, substantial blood loss and even exsanguination can occur. One cannot rely on a drop in the venous line pressure after line disconnection to stop the blood pump (see Chapter 4), and the technology described above must be relied upon. Single-needle dialysis reduces the risk of bleeding due to line disconnection, as bleeding will then be restricted to flow from the fistula or catheter, rather than via the blood pump. Accordingly, single-needle dialysis is likely to be safer for frequent nocturnal HD. The length and frequency of long HD sessions compensate for the reduced clearance associated with single-needle HD.

4. Remote Patient Monitoring. Remote patient monitoring was initially used to provide added reassurance and safety while patients slept during nocturnal HD. Hardwired or wireless internet connectivity can enable real-time monitoring of technical problems and alarms as they arise (eg, air and blood leaks), prompting call-center personnel to contact the patient or activate an emergency response if needed. While there is no published evidence that remote monitoring prevents catastrophic events, some jurisdictions require it by law, and prescribers should be aware of local requirements. Remote monitoring systems can also automate logging of technical and clinical data, reducing or eliminating the need for paper-based records, enabling better data capture, quality measurement, and analytics. Some platforms have reported better patient satisfaction and engagement with providers, as well as better adherence with remote patient monitoring. While some programs monitor all patients remotely, others have reported monitoring only during the first 3 months (Heidenheim, 2003), or not at all (Humber River Hospital, Toronto).

III. INFRASTRUCTURE REQUIREMENTS FOR HOME HD

A. Support staff. Specially trained nurses, biomedical technicians, and physicians are required. Nurses are required for assessment and training, telephone follow-up and troubleshooting, ordering supplies, and home visits. Technicians provide machine maintenance and monitor water quality. Biomedical engineering personnel should be

involved in the development of local policies governing practices, standards, and protocols for the installation and maintenance of equipment. The dialysis program's payment carrier should be informed of any changes to services provided.

B. Space. Adequate clinic space with appropriate plumbing is needed to allow patient training, patient assessments, and follow-up clinic visits with the physician and allied health personnel.

C. Water supply. Water quality should be assessed regardless of the source. Endotoxins, mineral content, and chloramines should be quantified. Rural water supplies must also be tested for coliform bacteria. International standards exist for water purity (see Chapter 5) and should be followed. Water purification system and HD equipment manufacturers typically specify water pressure requirements.

1. **Water purification.** Both reverse osmosis and deionization systems have been used successfully in home dialysis. Purification systems have become increasingly compact and quiet enough to install in a patient's bedroom, though more remote installation is also possible where desired. Patients should be instructed in maintenance procedures for their water systems, including filter changes and disinfection of lines and units. Ultrapure dialysate (generated by using an ultrafilter) has also been used by most programs and may be preferable for nocturnal HD, where the quantity of dialysate exposure (~108-144 L per session) can compound the effects of inferior water quality. Disinfection and water sampling frequency (usually monthly) will depend on the system utilized and must follow national water standards.

D. Dialysis machines. While any machine used for in-center therapy can be used for home dialysis, the large physical size and technical complexity of standard dialysis equipment has driven innovation and the proliferation of newer devices tailored to home HD. Desirable features include quiet operation, reliability, shorter setup time, and various factors promoting ease of use, including automation (for priming and rinse-back), visual and audio prompts, visibility of the display, accessibility of controls (touch display), integration of lines and dialyzers into cartridges, and simple maintenance and disinfection procedures. Systems that rely on external water purification equipment can generate large volumes of dialysate, and are well suited to longer treatment times and higher dialysate flow rates. Devices that rely on premixed bags provide slower flow dialysis, and are better suited to shorter sessions. Devices with integrated on-demand dialysate generation can produce up to 60 L of fluid and enable longer treatments with slow flow. A recent, U.S. Food and Drug Administration (FDA)-approved addition to the home HD space is the new Tablo Hemodialysis system. The Tablo is an all-in-one, patient-centered, easy-to-learn system, with on-demand dialysate production, and two-way wireless connectivity. Studies have supported its perceived ease of use, safety, and efficacy. However, the Tablo Hemodialysis system has not been directly trialed against other systems currently used for home hemodialysis. Early studies suggest training can take on average four sessions and set up a maximum of 20 minutes.

The NxStage System One (NxStage Medical Inc., Lawrence, MA) is described separately, as it differs from other devices in the use of lower dialysate flow rate with prefilled dialysate bags, as well as a cartridge-based dialyzer and tubing setup (Clark and Turk, 2004). Their lactate-based dialysate can be delivered in ready-made 5-L bags or can be produced by the PureFlow system from powdered dialysate mix, and made up

in volumes of between 15 and 60 L for longer treatments. The amount of water needed is similar to the dialysate volume, as is the case when deionizers are used. The NxStage device is transportable and can be used when traveling. It requires fewer or no renovations at the home of the patient. One limitation of the NxStage device at the present time is a maximal dialysate flow rate of 200 mL/min. Although there is no incorporated heparin pump, low-molecular-weight heparin or an external heparin pump can be utilized. The clinical significance of low dialysate flow is discussed below.

1. **Equipment maintenance programs.** These are central to patient safety. Most manufacturers provide suggested maintenance schedules, and these should serve as a bare minimum requirement to prevent complications and equipment failure. In addition to a rigorous water purification maintenance schedule, microbiological and endotoxin screening of product water and dialysis solution are critically important, particularly with high-flux membranes. Some recommend doing such screening monthly.

E. Remote overnight monitoring. Commercially available devices and software tools are listed above. Programs may choose to have their own central monitoring station with trained overnight personnel; alternatively, one centralized station for multiple programs may be considered to reduce costs.

IV. PRESCRIPTION OF INTENSIVE HD

A. Physiological rationale

1. **Solute removal advantage of increased weekly dialysis time.** In the absence of the large volume ultrafiltration afforded by convective therapies, large solutes (eg, middle-molecules), and solutes with slow multi-compartmental kinetics (eg, phosphate) are cleared in a time-dependent manner. Distributing the same weekly time over more frequent sessions is of limited benefit and greater total weekly hours are needed to enhance the elimination of these solutes.
2. **Solute removal advantage of increased frequency.** For solutes such as urea, and for the theoretically "sequestered" solutes modeled using standard *Kt*/*V* (for a description of standard *Kt*/*V* [std *Kt*/*V*] see Chapter 3), the intradialytic plasma concentration continues to fall as a dialysis session progresses, and for this reason, prolongation of a dialysis session beyond 4 hours is of limited benefit, and it is advantageous to distribute the same weekly time over more frequent sessions. The most efficient solute removal occurs during the early part of the dialysis session, when the plasma solute concentration is the highest. The standard *Kt*/*V* measure best reflects the effect of more frequent dialysis schedules on highly sequestered, but easily dialyzable solutes.

   There also is an advantage for phosphate removal in terms of increasing dialysis frequency, as removal of phosphate is substantially higher during the initial hour of dialysis than during the "plateau phase." When the weekly dialysis time is long (>20 hours), the total weekly time is the main determinant of phosphate removal. When weekly dialysis time is <12 hours, breaking this up into six, as opposed to three, sessions per week often will decrease predialysis serum phosphate level, albeit slightly.
3. **Ultrafiltration advantage of increasing weekly dialysis time.** The amount of fluid that needs to be removed per week will be a function of weekly fluid

ingestion minus weekly residual urine volume. If one doubles the weekly dialysis time, if fluid ingestion remains constant, the ultrafiltration rate will be halved, greatly reducing hemodynamic stress associated with fluid removal.

4. **Ultrafiltration advantage of increasing dialysis frequency.** Even if weekly dialysis time is not increased, there may be some advantage to increasing frequency, because at the beginning of a dialysis session, more of the excess fluid is associated with the central blood volume compartment. In the Frequent Hemodialysis Network (FHN) "Daily" Trial (Chertow, 2010), where weekly dialysis time was increased marginally, and in which weekly fluid ingestion also increased slightly, there was a benefit in terms of reduction of intradialytic hypotensive episodes per treatment, but as a greater number of treatments per week were given, the number of hypotensive episodes per week was increased (Kotanko, 2015).
5. **Benefit of avoiding a long interdialytic interval.** Several observational studies show that in patients being dialyzed with 3 times-per-week schedules, mortality is highest on Mondays in patients following a Mon-Wed-Fri schedule, and on Tuesdays in patients following a Tues-Thurs-Sat schedule. This mortality difference by day of the week is not observed with peritoneal dialysis. It is not clear whether the increased mortality is due to the requirement for increased fluid removal or to the buildup of various uremic toxins, including potassium, over the 3-day interdialytic interval. This observation argues against use of a 3 times-per-week schedule at home in situations where an every-other-day schedule is feasible.
6. **Potential adverse effect of frequent, long nocturnal hemodialysis schedules on residual kidney function.** In the FHN Nocturnal Trial, loss of residual kidney function was accelerated in patients dialyzing more often than 4.5 times per week using long session lengths (weekly dialysis time longer than 28 h/wk) (Daugirdas, 2013). This was not found in patients with shorter weekly dialysis times. In patients with substantial residual kidney function, a very intensive (frequent and long) dialysis schedule may not be optimal unless needed to control refractory volume overload or hyperphosphatemia.

B. Adequacy and urea clearance

1. **Standard Kt/V.** The standard *Kt*/*V* (std *Kt*/*V*) concept that has been described in Chapters 3 and 11 is generally used to quantify urea clearance in daily and nocturnal HD. Std *Kt*/*V* is a frequency-independent measure of dialysis dose. It is a weekly expression (normalized to *V*) of a modified equivalent urea clearance, and is defined as the urea generation rate divided by the mean peak predialysis serum urea nitrogen (SUN) level. The effect of dialysis frequency on the std *Kt*/*V* can more easily be seen graphically (Figure 15.1). It can be seen that when 3 times-per-week dialysis sessions are given, each lasting about 3.5 hours and delivering a single-pool *Kt*/*V* of 1.2, the resulting std-*Kt*/*V* will be 2.15 (when calculated using modeling or the so-called "FHN equation"). Increasing the sp *Kt*/*V* using a 3 times-per-week schedule has only a modest effect on increasing std *Kt*/*V*. One can see that, to achieve the same std *Kt*/*V* of 2.15 using 6 times-per-week short daily HD, a single-pool *Kt*/*V* of about 0.5 needs to be delivered during each session. In the context of home HD, recent observational data suggest that *Kt*/*V* targets had very little correlation to biochemical and clinical outcomes, with the exception of hypertension (Rivara, 2017). For simplified methods of calculating std *Kt*/*V* see Appendix C.

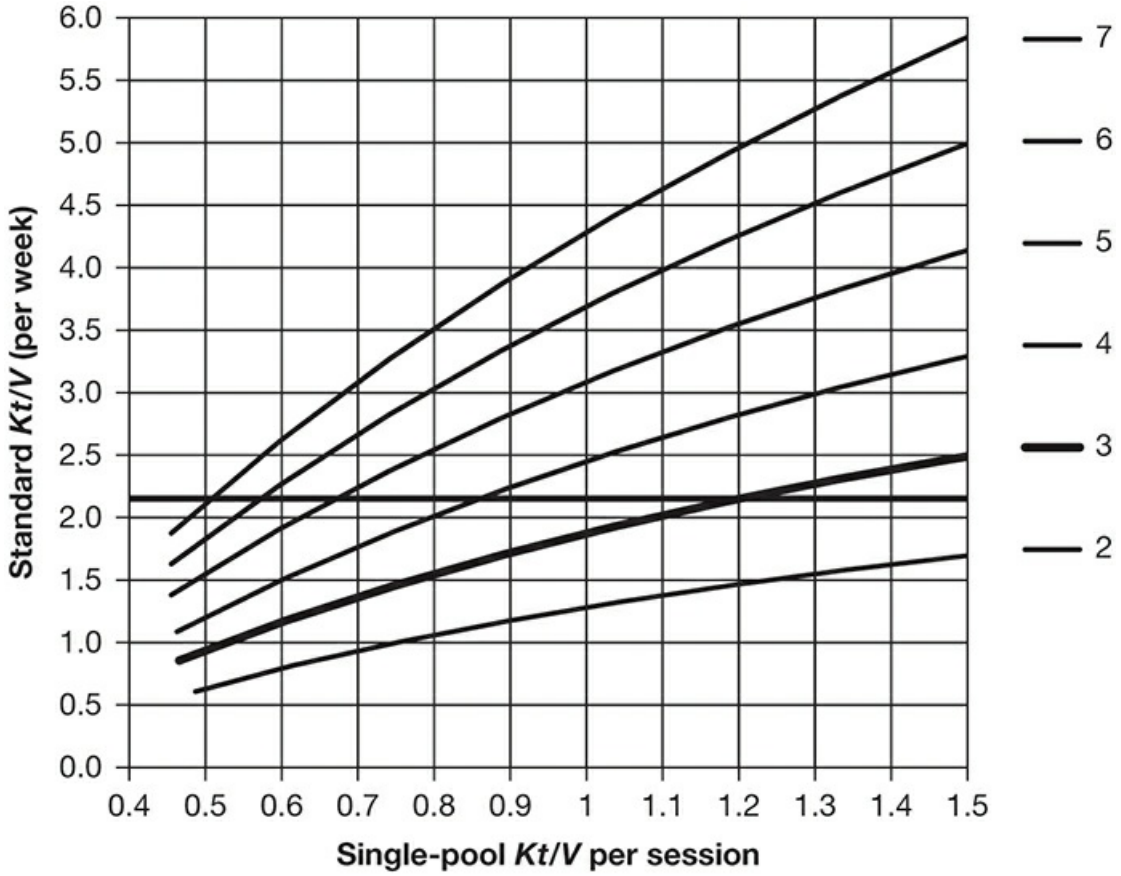


FIGURE 15.1: The relationship between weekly std *Kt*/*V* and per-dialysis single-pool *Kt*/*V*. The data assume a patient *V* of 40 L, dialyzer clearance of 200 mL/min, and dialysis time ranging from 30 to 270 min. The horizontal line at 2.15 represents the std *Kt*/*V* (calculated using the FHN method or urea kinetic modeling) associated with the KDOQI minimum session single-pool *Kt*/*V* of 1.2 with a 3 per week dialysis session. The numbers on the right show number of treatments per week.

2. **Compliance to home HD therapy.** It should be remembered that a single *Kt*/*V* measurement is but a snapshot of the patient's dialysis clearance. Uremic symptoms, combined with increasing creatinine and urea over time and worsening metabolic parameters may be clues to nonadherence to therapy even when the single *Kt*/*V* is adequate. When direct monitoring is not used, it is important to carefully examine the home HD runsheets to verify adherence to HD frequency and time.
3. **Holistic approach to adequacy.** The usual weekly *Kt*/*V* targets (eg, *stdKt*/*V* > 2.1) are easily achievable with intensive HD prescriptions, with short-daily and nocturnal HD providing 40% and 100% increased small solute clearance over conventional HD, respectively. Thus while not currently reflected in current guidelines, there has been a paradigm shift to focus less on *Kt*/*V* in favor of a more multi-dimensional approach to adequacy. This shift stems from the growing recognition that urea, a readily dialyzable small solute, is not a reliable surrogate for other uremic toxins that are cleared in a time-dependent manner, and does not fully capitalize on the longer or more frequent sessions available to patients dialyzing at home. Accordingly, including clinical elements in the assessment of adequacy, including the entire biochemical profile, burden of uremic and dialysis-related symptoms, volume and blood pressure control, and overall burden of therapy to both

patients and caregivers, provides a more robust perspective of the patient's overall well-being on home HD. With the flexibility afforded by the home treatment environment, prescription parameters can be adjusted to provide a highly-individualized and person-centered care plan.

4. **Typical values for urea clearance**

   a. ***Daily HD.*** Patients following a 6 times-per-week daily HD schedule have been treated with session lengths ranging from 1.5 to 3 hours (Table 15.1) 6 times weekly, corresponding to weekly dialysis times of 9 to 18 hours. Blood and dialysate flow rates are usually similar to those used for in conventional dialysis, as well as the dialyzers. In the FHN Daily Trial, patients receiving daily HD received an average standard *Kt*/*V* of 3.6 per week, corresponding to an average equilibrated *Kt*/*V* of 1.06 per session given on average 5 times per week. It is reasonable to start with 2-hour treatments, 12 h/wk. This schedule may then be adjusted depending on the measured delivered dose and patient satisfaction, remembering that every dialysis session need not be of the same length. In selected patients, further increases in dialysis session length (beyond 2 hours) should be considered, as this may be of help in removing more phosphate and also salt and water, as described below. Daily HD sessions in the 1.5-hour range may be sufficient for those with substantial residual renal function.

TABLE 15.1 Typical Short Daily HD and Frequent Nocturnal HD Prescriptions

	Short Daily HD	Frequent Nocturnal HD
Frequency (sessions per week)	6-7	5-7
Duration (h)	1.5-3.0	6-10
Dialyzer (high-flux preferred)	Any	Any (smaller)
QB (mL/min)	400-500	200-300
QD (mL/min)	500-800	100-300
Access	Any	Any
Remote monitoring	None	Optional
Dialyzer reuse	Optional	Optional

   b. **Nocturnal HD.** With HD for 6 to 10 hours, 3 or more times per week, std *Kt*/*V* values will typically be well above 2.0, assuming that a single-pool *Kt*/*V* of at least 1.2 is delivered per session. The std *Kt*/*V* is affected to a modest degree by session length, and going from a 3.5- to a 6- to 10-hour session results in a modest increase in std *Kt*/*V* for 3 times-per-week dialysis, even when single-pool *Kt*/*V* is unchanged. Because of the marked increase in clearance with nocturnal HD, relatively low blood flows with single-needle dialysis can be used to optimize safety, and lower dialysate flows may be used to save water costs. We recommend a QB of 200 to 250 mL/min with single needle, with QD of 300 mL/min. In the FHN Nocturnal Trial, the typical prescription was at least 6 hours, given on average 5 nights per week, achieving a std *Kt*/*V* of 5.0.

C. Dialysate composition. There is little evidence on optimal dialysate composition for frequent and long-duration HD. Similar dialysate composition may be used when switching from conventional dialysis to frequent or long-duration HD, with the exception that bicarbonate may need to be reduced and phosphate may need to be

added. Dialysate composition should be individualized to achieve pre- and postdialysis levels in the local laboratory "normal" range (see below). A typical dialysate contains Na^+ 135 to 140 mM, K^+ 2.0 to 3.5 mM, HCO_3^- 28 to 33 mM, Ca^{++} 1.25 to 1.75 mM (2.5-3.5 mEq/L), and Mg^{++} 0.5 mM (1 mEq/L).

1. **Bicarbonate:** HCO_3^- concentration should be adjusted to achieve a predialysis bicarbonate of 22 to 24 mmol/L. We usually start with a bicarbonate of 28 to 33 mmol/L for patients receiving frequent HD (either daily HD or noctunal HD). One must remember that the bicarbonate concentration readout on most dialysis machines does not take into account the alkalinizing effect of sodium acetate or sodium citrate present in bicarbonate dialysate solutions. Especially with frequent, long nocturnal HD, the dialysis solution bicarbonate should be set toward the lower end *of* the above range to limit the occurrence of postdialysis alkalemia.
2. **Phosphate.** To control serum phosphate without use of phosphate binders in patients ingesting a usual amount of protein, about 24 to 28 h/wk of dialysis is required. Increasing dialysis frequency in short daily HD without increasing weekly dialysis time will have only a modest effect on serum phosphate, especially because many patients will tend to increase their protein and phosphate intake. Patients treated with three nocturnal sessions per week, or every other night nocturnal dialysis will have a more marked reduction in serum phosphate and some may no longer need phosphate binders, although a substantial number will continue to require them. Those patients treated with long dialysis sessions 5 to 6 times per week typically will go into negative phosphate balance unless some phosphate is added to the dialysate. Whereas hypophosphatemia at the end of dialysis is common, predialysis hypophosphatemia is undesirable and is associated with an elevated risk of mortality. Hypophosphatemia can be exacerbated during periods of reduced food intake, for example, during intercurrent illness. For this reason, most patients dialyzed more than 30 h/wk will need some phosphate added to the dialysate.

   Sodium phosphate preparations have been used to enrich dialysate with phosphate to prevent or treat hypophosphatemia in patients treated with chronic high-intensity dialysis. The dialysate phosphate concentration is usually 0.32 to 0.65 mM (1-2 mg/dL) although higher concentrations may be necessary in some patients. The phosphate can be added to either the acid or the bicarbonate liquid concentrate. Enema preparations containing sodium phosphate (C. B. Fleet Company, Lynchburg, VA) consisting of a mixture of $NaH_2PO_4 \cdot H_2O$ and $Na_2HPO_4 \cdot 7H_2O$ have been widely used for this purpose. However, nonrectal use of phosphate enemas has not been approved by the FDA, and the purity of such phosphate preparations is not known. The enema solutions do contain a small amount of benzalkonium chloride (a biocide and preservative) and disodium EDTA, which are then markedly diluted further in the final dialysis solution. An alternative method of phosphate supplementation is to add an appropriate amount of phosphate using United States Pharmacopeia (USP)-grade sodium phosphate salts (Sam, 2013). Phosphate preparations for intravenous use (Hussain, 2005; Troyanov, 2004) have been added to hemodiafiltration solutions to increase their phosphate concentration, but their routine use in long nocturnal dialysis would be quite expensive owing to the large volume of dialysis solution needed.
3. **Calcium.** Patients receiving frequent, long nocturnal HD can deplete their total

body calcium unless a slightly higher-than-usual dialysis solution calcium concentration is used (Al-Hejaili, 2003). Use of a dialysate calcium concentration of 2.5 mEq/L (1.25 mM) in such patients has been shown to result in hyperparathyroidism that is refractory to vitamin D analog therapy, especially if the patient is no longer taking calcium-based phosphate binders. The ideal dialysate calcium concentration for an individual patient will vary with dietary calcium intake, ingestion of supplemental calcium (including calcium-based phosphate binders), vitamin D analog use, ultrafiltration volume, and the level of parathyroid gland activity. Measurement of pre- and postdialysis calcium levels can help identify an ideal bath calcium concentration for a given patient. The Canadian Society of Nephrology clinical practice guideline for intensive HD (Nesrallah, 2013) currently recommends using a dialysate calcium of 1.5 mM (3.0 mEq/L) or higher for long, frequent HD. If concentrates with the desired calcium concentration are not available, one can add the required amount of powdered calcium chloride (the Humber program uses $CaCl_2 \cdot 2H_2O$ USP) to the acid concentrate. The need for a higher dialysate calcium is a problem only for long, frequent nocturnal HD; short daily HD is not associated with marked changes in calcium levels, and for these treatments, standard dialysate calcium concentrations of 1.25 mM (2.5 mEq/L) are typically used.

D. Anticoagulation. Standard heparin protocols may be used for all frequent HD schedules. Some programs have used low-molecular-weight heparin as a bolus with or without a mid-dialysis top-up dose for longer session length treatments, but published evidence of safety and efficacy is lacking.

E. Ultrafiltration, adjustment of target weight, and antihypertensive medications. Improvement in blood pressure control may be noted as early as 1 week after changing to intensified HD, is most marked within the first few months, and may continue for many months thereafter. Not uncommonly, the blood pressure may be so markedly improved by long or frequent HD that a patient will no longer need antihypertensive drugs. Cardioprotective agents such as angiotensin-converting enzyme inhibitors or β-blockers may still be prescribed, if desired, but at lower doses as tolerated.

Target weight with intensive HD is set as per usual practice, aiming for clinical euvolemia and normal pre- and postdialysis blood pressure while avoiding intradialytic hypotension and symptoms. Larger interdialytic weight gains can be expected as patients liberalize dietary sodium and fluid intake with longer and more frequent sessions. Patients can be trained to self-adjust ultrafiltration goals on the basis of weight and blood pressure parameters, making small incremental changes (eg, 0.3-0.5 kg per session) to their target weights until desired values are achieved.

F. Follow-up

1. **Clinic visits.** Most patients should be seen within 2 to 4 weeks of starting home therapy, then monthly for 3 months, then every 2 to 3 months thereafter. This assumes that 24-hour on-call nursing support is available. The use of dialysis “run sheets” allows for documentation of weights, blood pressures and intradialytic complications. Patients should bring these to each clinic visit.
2. **Blood tests.** Patients dialyzing at home can be provided with blood centrifuges and can be instructed in the proper handling and preparation of blood samples.

V. COMPARATIVE EFFECTIVENESS AND SAFETY OF HOME AND INTENSIVE HD VERSUS OTHER MODALITIES

A. Conventional home HD.

To date, there have been no randomized trials comparing home with in-center HD when giving similar amounts of dialysis. Observational studies have suggested better survival with home HD as well as increased likelihood of transplant, but unmeasured patient characteristics, including health literacy, motivation, psychological well-being, social support structures, functional ability, and socioeconomic factors, may account for the greater survival rates observed in home HD populations. A critical literature review by Miller (2018) of 13 studies (one randomized control trial) comparing home HD with incenter HD demonstrated positive effects on survival. Nocturnal home HD in particular was associated with reduced risk of death. Six studies showed reduction in blood pressure. Seven studies of low quality did demonstrate higher quality of life. Although not directly measured, the freedom associated with self-scheduling, self-management, and more liberal diet likely improve patient quality of life with home HD. Patient unwillingness to be randomly allocated to the home or in-center setting is a major barrier to conducting randomized trials.

B. Frequent HD

1. **Short and standard frequent HD.** No clinical trials have compared home daily HD with any other modality. An observational study from Australia suggested no mortality difference between patients receiving intensive home HD compared with those receiving conventional home HD (Marshall, 2011). Similarly, a study from Tennankkore and colleagues (2018) demonstrated no differences in terms of mortality or treatment failure between short daily HD or nocturnal HD when comparted to conventional (3/wk incenter) HD. In the FHN Daily Trial, patients who received short daily HD in-center had statistically and clinically significantly better SF-36 (physical composite summary) scores and regression of ventricular hypertrophy compared with patients who received conventional center HD (Chertow, 2010). It should be noted that the delivered treatments in these patients averaged 2.5 hours in duration, and were given on average 5.2 times per week. There is preliminary evidence that survival was better in the patients randomized to the frequent-treatment arm (Chertow, 2013). A recent multinational survival study showed a higher risk of death with short daily HD; however, this study was prone to residual confounding, as patients treated with short daily HD likely had higher (unmeasured) baseline risk than could be adjusted for in statistical models (Suri, 2013b). Although there are several observational studies evaluating physiological outcomes with daily HD, the FHN Daily Trial provides the least biased estimates of these effects. In this study, patients receiving short daily HD had better phosphate and blood pressure control, but no differences in nutritional variables, anemia management, mental health, or cognitive function were detected.

   An important safety signal in the FHN trials was an increased need for interventions to maintain AV access patency. Whether this was due to differential surveillance (more frequent visits) or an effect of frequent cannulation was not clear. There was a trend to reduced complications with buttonhole cannulation with daily HD (Suri, 2013a).

2. **Long, frequent HD.** To date, two randomized trials have compared frequent nocturnal HD with conventional HD. A Canadian study demonstrated regression of

left ventricular hypertrophy among patients randomized to nocturnal HD (Culleton, 2007), while the larger FHN nocturnal study did not (Rocco, 2011). The effect of nocturnal HD on left ventricular mass may have been attenuated by preserved residual renal function in the FHN study population. Both studies found improved blood pressure and phosphate control with nocturnal HD. Studies evaluating the effects of nocturnal HD on patient survival have been observational. As with studies of conventional home HD, nocturnal HD is associated with greater survival compared with conventional HD, but residual confounding should be considered when interpreting these results.

In the FHN Nocturnal Trial, the number of procedures needed to maintain the vascular access was significantly increased with home long, frequent HD compared with conventional home HD, and there was a trend to increased perceived burden on caregivers as well. Finally, patients who received frequent nocturnal HD had increased risk of complete loss of residual renal function at 12 months compared to patients assigned to a 3-days-per-week schedule. These potential adverse effects should be discussed with patients before starting frequent nocturnal HD. The mortality effects are unclear; patients randomized to the 6-nights-per-week group had an increased risk of long-term mortality compared with those randomized to conventional HD (Rocco, 2013), but the significant cross-over rates and minute sample size preclude definitive interpretation of these results.

C. Long-session dialysis given 3 times per week or every other day. The Tassin experience showed marked improvements in survival, blood pressure and phosphate control among recipients of thrice-weekly in-center HD lasting 8 hours per session (Charra, 2004). More recently, large dialysis organizations in the United States have provided three-per-week in-center nocturnal HD and have reported better survival and physiological variables compared with conventional center HD; the published experience with every-other-day home HD in Australia and New Zealand has shown similar results. In 2023, Ok et al demonstrated improved survival rates with 3 times weekly but extended HD sessions compared to conventional HD counterparts. However, all of this evidence is observational, with the potential problem of bias due to patient selection and confounding.

D. Other home modalities. Little evidence exists comparing home hemodialysis against peritoneal dialysis. However, one study demonstrated improved cardiovascular outcomes with home hemodialysis compared to patients on peritoneal dialysis (Shah, 2024), but the frequency and intensity of home hemodialysis was not delineated.

VI. CONCLUSIONS AND FUTURE DIRECTIONS.

Home dialysis in general, as well as intensified HD regimens are increasing in popularity, particularly in high-income countries. Efforts to understand the benefits and risks of such alternative dialysis prescriptions continue to rely on observational studies, as randomized trials are difficult to carry out. Until higher-quality evidence is available to inform decision making, providers would serve their patients well by focusing modality discussions on patients' values and preferences, and the specific physiological considerations described in this chapter.

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16 Hemodiafiltration

Bernard Canaud and Andrew Davenport

Conventional diffusion-based dialysis modalities, including low- and high-flux hemodialysis, are limited in their capacity to effectively remove middle- and large-molecular-weight uremic toxins. By combining diffusive and enforced convective clearances, hemodiafiltration (HDF) enhances solute clearance and expands the molecular weight range to middle and large uremic toxins in a dose-related manner. In addition, the online substitution mode allows adjustment of the delivered convective dose to individual patient needs and goal-oriented targets.

Online HDF is an established treatment supporting the lives of almost 400,000 patients with end-stage kidney disease worldwide, predominantly in Europe and Asia. Online HDF is associated with a number of biologic and clinical benefits including, most importantly, improved patient outcomes.

I. DIFFUSION VERSUS CONVECTION-BASED CLEARANCES.

Low-flux hemodialysis relies mainly on diffusive transport. The rate of diffusion of uncharged molecules is inversely proportional to the square root of their molecular weight. Larger molecules have a relatively lower speed of diffusion and therefore a relatively slower clearance by hemodialysis. Convective transport depends on the solvent drag effect, where molecules, regardless of their molecular weight, are transported across the membrane by bulk fluid flow. The extent to which the solute passes through the membrane depends on the so-called sieving coefficient, which varies from 0 (completely impermeable) to 1.0 (completely permeable). The sieving coefficient differs according to the molecular weight and charge of solutes and also depends on membrane characteristics. Convective transport markedly increases the removal of middle- and large-sized molecules that are poorly cleared by diffusion-based therapies.

High-flux hemodialysis relies on diffusive and limited convective transport. Convective transport, in that case, depends on the internal filtration phenomenon (ultrafiltration/backfiltration) induced by the transmembrane pressure equilibrium changes, as exerted by the ultrafiltration controller of the hemodialysis machine. Depending on fiber diameter, membrane permeability, and dialyzer geometry, internal filtration and convective transport may be increased. In a conventional high-flux dialyzer, internal filtration may reach up to 4 to 6 L per session, contributing to increased convective clearances (Ronco, 2000).

II. INTERNAL HDF VERSUS EXTERNAL HDF

A. Internal HDF refers to a recently developed dialysis modality, so-called expanded hemodialysis (HDX). In this case, a super high-flux membrane is used, and the internal filtration phenomenon is maximized by increasing blood flow resistance (reduced inner capillary lumen). Internal filtration may then reach up to 4 L/h, significantly increasing clearances of middle- and large-sized molecules (Lorenzin, 2018; Ronco, 2018).

B. External HDF refers to online HDF modalities where substitution fluid is infused

externally into the blood circuit (post-, prefilter, or mixed post and pre simultaneously) by means of an adjustable infusion pump and a dedicated port connection (Tattersall, 2013). In this chapter, we refer exclusively to external online HDF as a reference to convective-based therapies.

III. (EXTERNAL) ONLINE HDF. Online HDF is a "hybrid" therapy that combines within the same dialyzer module the two main solute transport mechanisms (diffusion and convection), with the external infusion of substitution fluid produced from fresh dialysis fluid. Target substitution fluid delivery rates are implemented via an adjustable pump, flow meter, and control screen. Fluid balancing (substitution/ultrafiltration) is managed by the use of flow meters and an ultrafiltration controller. The fluid pathways are depicted in Figure 16.1.

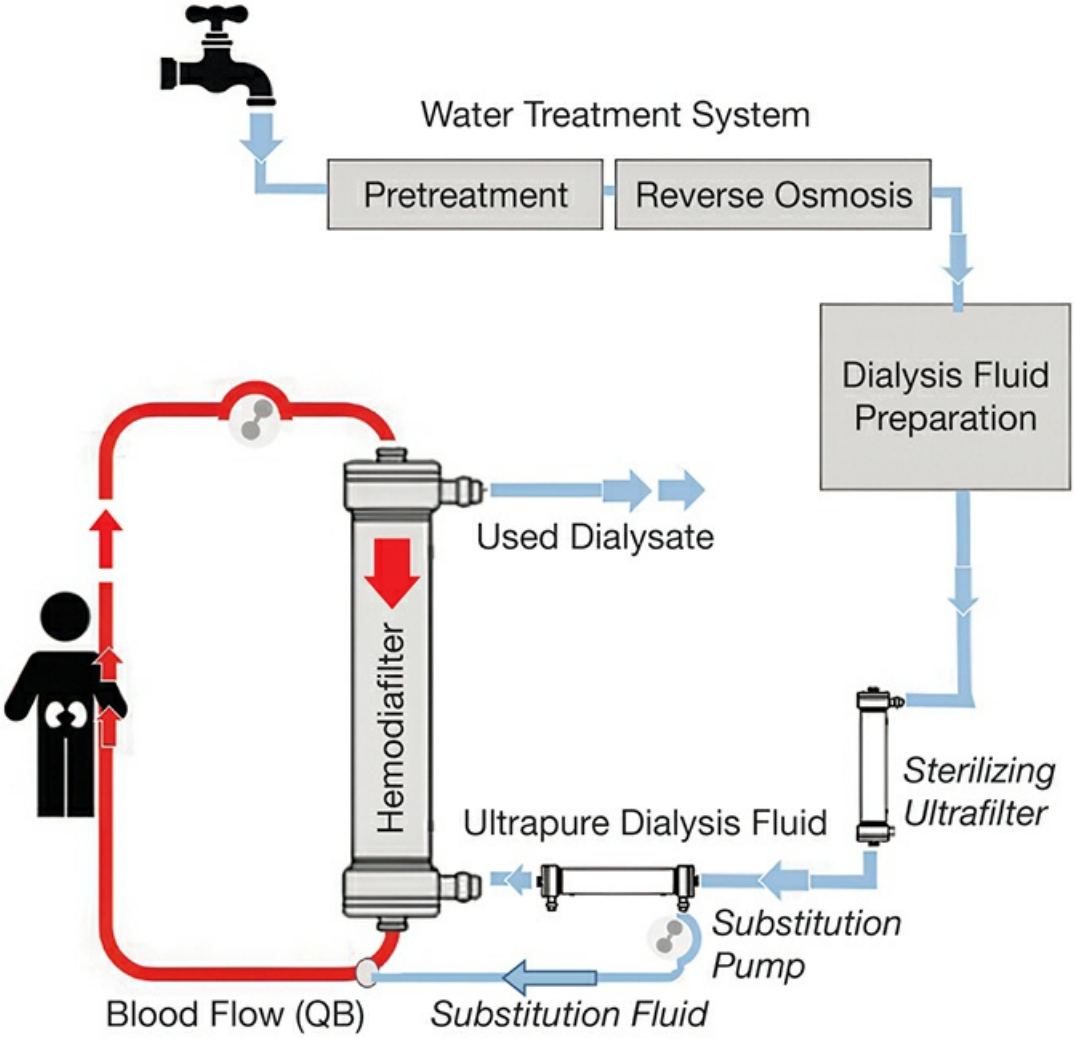


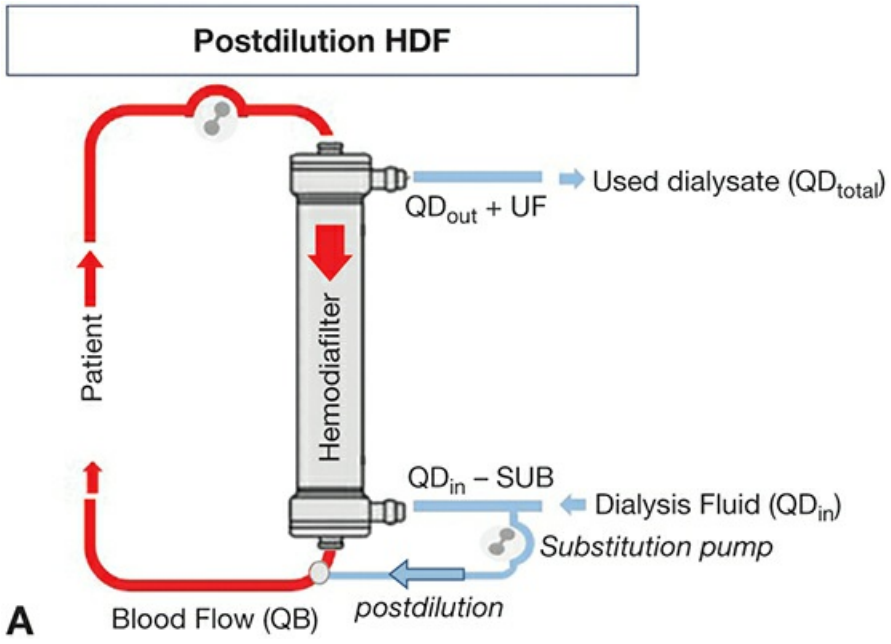
FIGURE 16.1: Principle of production of substitution fluid in external online hemodiafiltration.

A. Clearance. In online HDF, the delivered clearance is due to a combination of diffusion and convection. Detailed equations are shown in Appendix E. In vivo measurement of solute clearances may be obtained using conventional arterial and venous blood sampling methods, provided the venous (blood outflow) sample is taken from a point in

the blood line where there is complete mixing of blood with substitution fluid. Convective clearance for a given solute depends on the total ultrafiltered volume, the effective solute sieving coefficient for the membrane (permeability, surface) being used, and the operating conditions (blood flow, transmembrane pressure control). The total ultrafiltered volume (convection dose) is the sum of the volume of "replacement or substitution fluid" infused during the treatment for the purpose of enhancing convection and the fluid removed during the treatment for the purpose of correcting extracellular fluid overload (ultrafiltration).

B. Substitution mode: Postdilution, predilution, or mixed dilution

1. **In postdilution mode,** substitution fluid is added to the fluid stream as it exits the hemodiafilter (Figure 16.2A). This is the most efficient option for solute clearances because there is no dilution of blood solutes in the dialyzer where convection is occurring. One major problem with postdilution mode is that the substitution fluid infusion rate needs to be matched by the removal of an equivalent volume of plasma water from the blood while it is transiting the dialyzer. If one targets an infusion rate of 100 mL/min, for example, and the blood flow rate through the dialyzer is 350 mL/min, then the plasma flow rate through the dialyzer is approximately 200 mL/min, and removal of 100 mL/min of fluid in the dialyzer will result in marked hemoconcentration and protein concentration in the blood compartment of the dialyzer, with an increased risk of clotting and filter clogging.



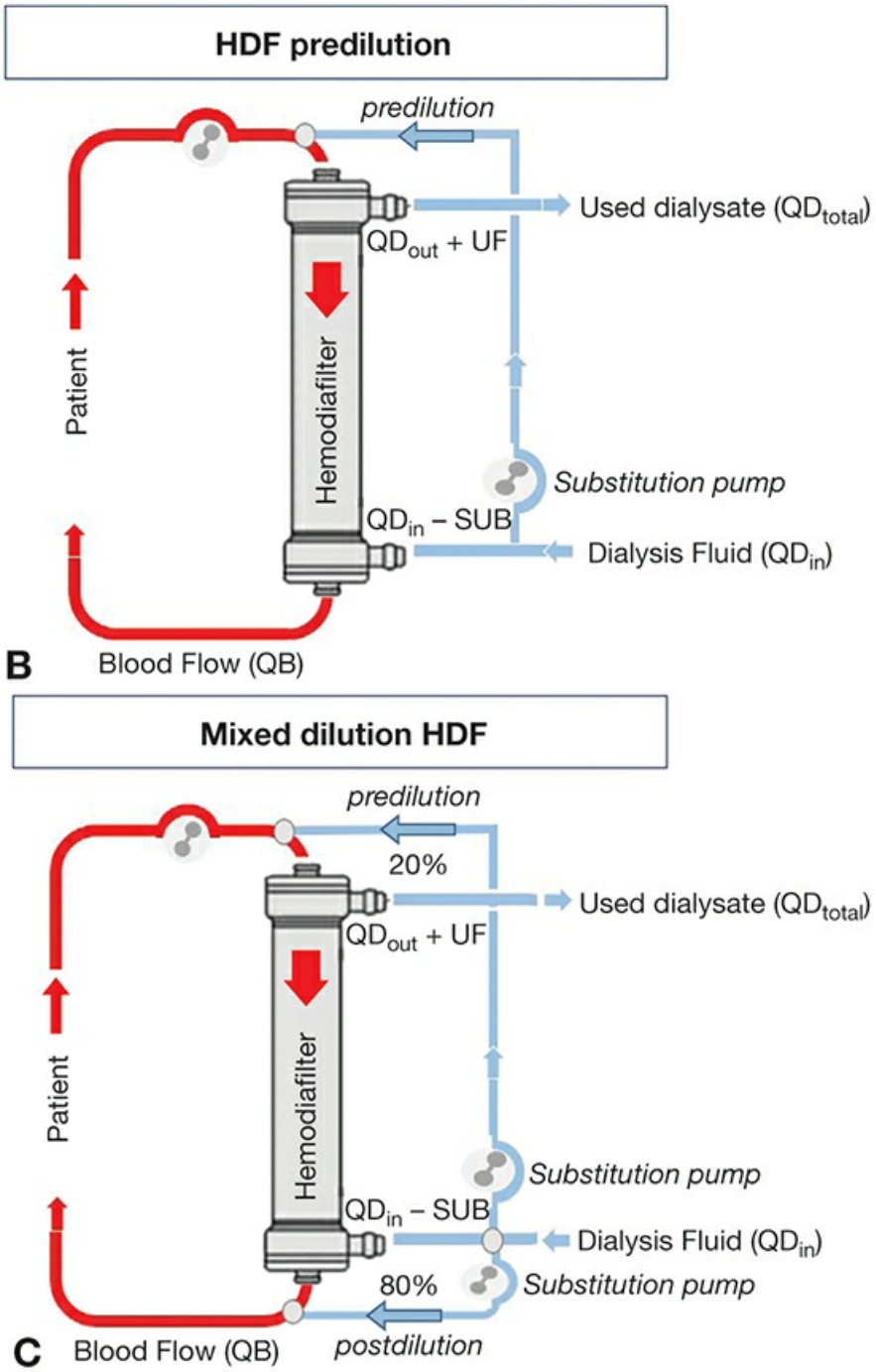


FIGURE 16.2: A. Schematic representation of online postdilution hemodiafiltration. B. Schematic representation of online predilution hemodiafiltration. C. Schematic representation of online mixed (pre + post) dilution hemodiafiltration. HDF, hemodiafiltration; UF, ultrafiltration.

2. **In predilution mode,** one infuses all of the replacement fluid into the bloodline upstream to the dialyzer (Figure 16.2B). This obviates the problem of hemoconcentration of blood in the dialyzer and in fact, the hematocrit and protein concentration of blood in the dialyzer will be reduced due to the dilution effect of the substitution fluid. Because the rate of blood and plasma flow through the

dialyzer are increased with predilution HDF, the clearance of the dialyzer, which is flow dependent, will be increased as well. However, predilution replacement fluid is toxin free, so its infusion upstream to the dialyzer will reduce the concentration of uremic toxins that the dialyzer will remove. The increased clearance and dilution effects partially offset each other on the net removal of solute. With predilution HDF, the net clearance adjusted for dilution will be similar to the clearance when not doing any HDF for smaller molecules such as urea, creatinine, and phosphate. For β-2-microglobulin, the net clearance with predilution HDF will be increased, but not as much as with postdilution HDF.

3. **Mixed-dilution HDF** (Figure 16.2C) combines an infusion of substitution fluid upstream to the dialyzer and also downstream. There is some amount of hemoconcentration in the dialyzer, as the ultrafiltration rate needs to be set to compensate for the infusion of HDF fluid both upstream and downstream to the dialyzer. However, the hemoconcentration problem is mitigated, and the net increase in clearance, while less than with postdilution HDF alone, is still substantial.

   In mixed-dilution HDF mode, the total substitution fluid volume should be increased by a factor of about 2, and the ratio of the predilution to postdilution flow rate should be around 1.33 to 1.0.

   The advantages and disadvantages of each replacement fluid infusion mode are shown in Table 16.1.

TABLE 16.1 Advantages and Drawbacks of Various HDF Modalities According to Substitution Mode

Postdilution	Predilution	Mixed Dilution
PROs		

• High solute clearance and removal of small-, middle-, and high-molecular-weight solutes
• Reduced consumption of substitution fluid
	• Hemodilution
	  • Decrease in serum protein concentration and hematocrit
	  • Reduced viscosity and oncotic pressure
	  • Reduced fiber and membrane fouling
	• Permits HDF with suboptimal blood flow or unfavorable hemorheologic conditions
	• Preserves hydraulic and solute membrane permeability (reduces membrane stress)
		• Avoids drawbacks of both post- and predilution methods
		• Permits HDF under suboptimal blood flow conditions and unfavorable hemorheologic conditions

CONs		

• Hemoconcentration
  • Increase in serum protein concentration and hematocrit
  • Increase in viscosity and oncotic pressure
  • Potential membrane fouling
• Reduced hydraulic and solute membrane permeability
• Increase in transmembrane pressure
  • Reduced sieving coefficient
  • Fiber clotting
	• Reduce solute clearance and removal
	  • Small- > middle- and high-molecular-weight solutes
	• Increased volume of substitution fluid needed (2-fold)
		• Require specific hardware equipment
		  • Two infusion pumps
		  • Specific blood tubing set
		  • Requires specific software and algorithm
		  • Accounting for hematocrit and serum protein concentration changes
		• Adjusting post-/preinfusion ratio keeping transmembrane pressure in target range

• Potential alarms • Increased membrane stress • Potential albumin leakage	• Increased volume of replacement fluid, but not only 1.5-fold

HDF, hemodiafiltration

C. Technical prerequisites

1. **Water treatment system.** Water used for convection-based therapies needs to comply with very stringent criteria of purity (Ward, 2022). Such high refinement in water purification has led to the concept of "ultrapure water"—that is, virtually sterile and nonpyrogenic water. Technical options required to produce ultrapure water include a pretreatment system (microfiltration, softeners, activated carbon, downstream microfiltration), which is followed by one or two reverse-osmosis modules in series. Ultrapurified water is delivered to dialysis machines via a distribution loop that ensures continuous recirculation of water.

   The microbiologic quality of dialysis fluid derived from this chemically pure water is further improved by the use of a sterilizing ultrafilter incorporated within the dialysis machine. The ultrapure dialysis produced in this manner is then diverted by the infusion pump and passed through a second ultrafilter. The doubly filtered substitution fluid is then infused into the patient's blood through the extracorporeal circuit downstream to the dialyzer (postdilution mode), upstream to the dialyzer (predilution mode) or both upstream and downstream to the dialyzer (mixed mode).

   Studies have shown that online production of replacement fluid is a safe, reliable, and economically viable solution for routine clinical applications. This approach has gained the approval of all European regulatory bodies operating under the European Community label and also Japanese regulatory bodies.

2. **Quality assurance.** A quality assurance process is required to maintain the ultrapurity of water produced and delivered to all HDF machines on a regular basis. This includes monitoring of chemical composition and for contaminants as well as microbiologic surveillance (Canaud, 2000a, 2000b). The sterilizing ultrafilters are incorporated in the dialysis fluid paths and are disinfected in situ within the machine. They need to be periodically replaced according to defined criteria (either number of sessions or duration of use) to prevent loss of their endotoxin adsorption and microbiologic retention capacity.

IV. PRESCRIPTION AND MONITORING OF HDF.

In patients with chronic kidney disease (CKD), conventional HDF treatment schedules are based on three dialysis sessions per week each of 4 hours duration (12 h/wk). A discussion of incremental (1-2× weekly) or intensified treatment schedules (nocturnal or 4 to 6× weekly) is not within the scope of this chapter, but HDF can be equally prescribed with alternative dialysis schedules.

A. Vascular access and extracorporeal blood flow.

Patients treated with HDF in postdilution mode require a vascular access capable of delivering an extracorporeal blood flow of at least 350 to 400 mL/min on a reliable basis. An arteriovenous fistula or arteriovenous graft is preferable for high volume HDF; however, a large-bore tunneled central venous catheter may be used. A double-needle or dual-catheter setting is highly suitable. Needle size should be preferably 15G or 14G.

B. High-flux hemodiafilter.

Dialyzers used for HDF should be made of membranes with a high hydraulic permeability (Ultrafiltration coefficient [KUf] > 50 mL/h per mm Hg),

a high solute permeability (sieving coefficient for β_2-microglobulin > 0.6), and optimal surface area of exchange (1.6-2.5 m^2).

C. Target total ultrafiltered volume. Based on the results of randomized comparisons of HDF versus hemodialysis (see below), the total ultrafiltered volume (a surrogate of convective dose) in a 4-hour session in postdilution mode should be targeted to be 24 L/session (100 mL/min) or higher. To achieve an equivalent convective dose in predilution mode, the targeted ultrafiltration volume should be multiplied by 2 (ie, 200 mL/min), or in mixed-dilution mode, the total ultrafiltration volume should be multiplied by 1.5 (ie, 150 mL/min with 80% of the substitution fluid being infused in postdilution mode). Predilution and postdilution substitution fluid infusion rates can be set manually. Some machines distribute a total volume of substitution fluid between prefilter and postfilter infusion sites, with the goal of avoiding excessive hemoconcentration via monitoring of transmembrane pressure within the dialyzer and maximizing the percentage of fluid delivered in postdilution mode.

D. Anticoagulation. HDF may result in higher blood procoagulant activity when compared to standard hemodialysis due to rapid ultrafiltration, hemoconcentration, and potential loss of anticoagulant. Administration of low-molecular-weight heparin and to a lesser extent unfractionated heparin via the arterial line results in significant clearance of low-molecular-weight heparin molecules, since HDF may remove this size range of molecules. Heparin should not be given as a bolus into the hemodiafilter inlet blood line because up to 50% of unfractionated heparin or 80% of low-molecular-weight heparin can be removed on first passage through a high-efficiency HDF setup (Hebibi, 2020). Instead, the initial heparin bolus dose should be infused via the venous needle or blood line. If bolus heparin is injected into the arterial port, then the onset of treatment should be delayed for at least 3 to 5 minutes after initiating extracorporeal blood flow (Dhondt, 2015). The dose of heparin needed can vary widely from patient to patient and requires a stepwise, titration-based increase. Failure to achieve adequate ultrafiltration or clotting within the circuit usually responds to an increase in the heparin dose. Dose adjustment protocols need to be based on an assessment of the bleeding risk, patency of the extracorporeal circuit, and type of heparin used.

E. Treatment time. HDF use is not intended to reduce treatment time but rather to enhance efficiency and tolerance within the same time frame. Conventional HDF treatment schedules are based on three sessions weekly, each lasting about 240 minutes (720 min/wk). Longer treatment times and/or more frequent sessions (ie, 4× weekly) are likely beneficial, since they further lower serum levels of uremic toxins and improve hemodynamic stability (Cornelis, 2014, 2015).

F. Electrolyte composition. Considerations regarding choosing concentrations of sodium, potassium, calcium, and magnesium in the dialysate and substitution fluid are no different from those for hemodialysis without HDF and are described elsewhere in this handbook.

G. Patient monitoring. Monitoring of patients treated with HDF is not different from those treated by hemodialysis without HDF.

V. SOLUTE REMOVAL WITH HDF

A. Small molecules. Clearance of small molecules (urea or its surrogate ionic clearance) as well as urea mass removal are increased by 10% to 15% with HDF. Removal of

phosphate is increased when predialysis serum values are comparable, and this should result in a lowering of predialysis serum phosphate level (Daugirdas, 2022).

B. Middle molecules. The increased clearance of molecules such as β-2-microglobulin (molecular weight 11,800) with HDF (Roumelioti, 2018) results in a 10% to 20% decline in predialysis serum concentrations relative to high-flux hemodialysis and a larger decline in time-averaged serum values (Pedrini, 2011; Ward and Daugirdas, 2024). Observational studies demonstrate that high predialysis serum β-2-microglobulin concentrations are associated with mortality, including cardiovascular mortality and deaths related to infection (Cheung, 2006; Kanda, 2020).

C. Very large molecules. Higher removal rates with HDF compared to dialysis of a number of other putative uremic toxins have been documented. Many of these have molecular weights greater than β-2-microglobulin, in the range of 15 to 45 kDa. Examples include complement factor D (a proinflammatory mediator), leptin (16 kDa; effective removal of leptin may favor the improvement of patient nutritional status), FGF23 (30 kDa; a mediator implicated in metabolic bone disorders and vascular calcification), various cytokines, erythropoiesis inhibitors such as 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF), immunoglobulin light chains (κ,λ), and circulating advanced glycosylation end products (AGEs) and AGE precursors.

D. Protein-bound uremic toxins. There has been interest in serum levels of protein-bound uremic toxins such as indoxyl sulfate, *p*-cresyl sulfate, and similar molecules, which may contribute to uremic toxicity. HDF does not appear to lower serum levels of such compounds markedly. In some studies, serum levels of *p*-cresyl sulfate were reduced by 5% to 10% (Takkavatakarn, 2021).

VI. CLINICAL EFFECTS

A. Intradialytic symptoms. Randomized controlled trials have shown a substantial reduction in intradialytic hypotensive (IDH) episodes and morbid events compared to conventional hemodialysis with HDF (Locatelli, 2010; Morena, 2017). This beneficial effect has been ascribed to a negative thermal balance (due to infusion of relatively cool replacement fluid), removal of vasodilating mediators, and/or improvement of endothelial vascular dysfunction and sympathetic activity. In studies in which HDF was compared to hemodialysis with similar thermal balance or volume control, no benefit in terms of hemodynamic stability could be demonstrated (Buchanan, 2017).

B. Patient-reported quality of life. Randomized trials have provided conflicting results, with some studies reporting significant improvement in physical and social domains of the health-related quality of life (HR-QOL) questionnaire (Aichi, 2022) while others finding no change (Mazairac, 2013). One meta-analysis showed an improvement in social functioning and a reduction in fatigue (Suwabe, 2018). In the CONVINCE trial, patients assigned to the HDF arm had a significantly slower HR-QOL decline in physical function, cognitive function, pain interference, and social participation compared to patients assigned to high-flux hemodialysis (Rose, 2024).

C. Residual renal function. Several studies have suggested that HDF might contribute to a longer and better preservation of residual renal function than conventional HD. However, this issue has not been well studied.

D. Anemia correction and ESA usage. Several prospective studies and a large cohort of incident patients have shown a significant reduction in the erythropoietin resistance

index with HDF (Panichi, 2011, 2015). This positive effect on anemia correction has been ascribed to greater removal of erythropoietic inhibitor substances such as furanpropanoic acid (CMPF) (Niwa, 2013), a reduction of inflammation, and better use of iron (Lin, 2002; Sun, 2023).

E. Nutritional status and body composition. Several studies have reported an improvement in appetite along with an increase in dietary protein intake. Recent controlled studies in infants and adult patients undergoing dialysis demonstrated a better preservation of lean tissue mass and fat mass with HDF, indicating a superior preservation of anthropometric and nutritional parameters (Molina, 2018; Paglialonga, 2023). Visceral protein markers of nutrition (albumin, prealbumin) generally remained stable over time with HDF in randomized trials.

Studies have shown that losses of essential nutrients (amino acids, water-soluble vitamins, and trace elements) were marginally increased with HDF, such that oral supplementation may be required for some patients (Bévier, 2022; Murtas, 2019).

F. β-2-Microglobulin amyloidosis. Several large cohort studies, mostly from 30 or more years ago, reported that high-flux membranes and convective therapies reduced the incidence of carpal tunnel syndrome and other manifestations of β-2-microglobulin amyloidosis. This beneficial effect probably resulted from the regular use of ultrapure water and biocompatible materials, reducing inflammation along with enhanced β-2-microglobulin removal with HDF (Schiffl, 2002). No recent comparisons of β-2-microglobulin amyloidosis in patients undergoing HDF versus those being treated with dialysis have been reported.

G. Bone mineral disease. As indicated earlier, HDF tends to facilitate phosphate control, reducing parathyroid hormone (PTH) concentrations as well as FGF23 by a combination of higher clearances and potential positive calcium mass balance (Bouma-de Krijger, 2020; Movilli, 2011), all of which tend to improve bone turnover and reduce vascular calcification.

VII. CLINICAL OUTCOMES

A. Morbidity and mortality benefits in adults. Five major randomized comparisons of HDF versus hemodialysis in terms of mortality have now been performed. Of these initial four randomized trials, three—CONTRAST (Grooteman, 2012), the Turkish Study (Ok, 2013), ESHOL (Maduell, 2013), and FRENCHIE (Morena, 2017)—did not show a significant benefit for survival or hospitalizations, while the ESHOL Study reported a 30% improvement in mortality with HDF. It was argued that the lack of benefit in the three studies with negative results may have been due to the relatively low amount of substitution fluid infused over the 4-hour treatments. When individual patient data were combined from these four studies (Peters, 2016), an overall reduction in mortality was found, and the survival benefit appeared to be stronger in patients who had received at least 24 L of substitution fluid over their 4-hour treatments. Subsequently, a fifth multicenter randomized comparison of HDF versus hemodialysis was performed, the CONVINCE trial, in which enrollment was limited to patients in whom it was anticipated that a high volume of substitution fluid could be delivered (Blankestijn, 2023). In this more recent study, a clear survival benefit of hemodialysis versus high-flux hemodialysis was found, which was similar in magnitude to the combinatorial analysis of the previous four randomized trials (about a 20% reduction in

relative mortality risk). A combinatorial analysis of five randomized trials, including CONVINCE, came up with similar findings (Vernooij, 2024).

B. Clinical outcomes in infants. In children, HDF given in a more frequent schedule (short daily or alternate day) has been reported to be associated with reduction in serum markers of inflammation, slowing of progression of carotid intima-media thickness, and resumption of catchup in growth (Shroff, 2019).

C. Protein and albumin loss. Albumin loss with HDF is not of current concern, as improvements in membrane manufacturing technology have reduced the sieving coefficient for albumin in commonly used HDF membranes to a very low number (<0.001). However, intradialytic albumin loss might become excessive if HDF is attempted using high-molecular-weight cutoff membranes, which already leak some albumin when used for regular hemodialysis. Some limited albumin loss during hemodialysis may increase the removal of albumin-bound uremic toxins, and clinical benefits of such protein-leaking membranes have been suggested by studies from Japan (Abe, 2021). However, further investigation in this area is needed. Use of protein-leaking membranes in hemodiafiltration (HDF) remains contraindicated and is considered off-label.

D. Risk of deficiency syndromes. Enhanced loss of nutrients is a theoretical risk associated with all modalities that use high-flux membranes. Soluble vitamins, trace elements, amino acids, small peptides, and proteins are lost during HDF. The amount lost per session remains low and, in most cases, can be compensated for by a balanced diet and/or supplementation.

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17 Therapeutic Apheresis

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Therapeutic apheresis refers to a group of extracorporeal procedures in which blood separation technology is used to remove abnormal blood cells and/or plasma constituents in order to treat an underlying disease, with the return of the remaining components back to the patient along with any replacement fluid as needed. Common therapeutic apheresis procedures include therapeutic plasma exchange (TPE), red blood cell (RBC) exchange or erythrocytapheresis, thrombocytapheresis, leukocytapheresis, and hematopoietic progenitor cell collections. Specialized apheresis instruments are used to perform lipoprotein apheresis and extracorporeal photopheresis.

I. RATIONALE FOR THERAPEUTIC APHERESIS (TPE). There are several mechanisms by which TPE exerts its beneficial effects (Table 17.1). Its major mode of action is the rapid depletion of pathologic substances in the plasma, such as autoantibodies, in order to treat an underlying disease. Another effect is its ability to remove other high-molecular-weight proteins that may participate in the inflammatory process (intact complement C3, C4, activated complement products, fibrinogen, and cytokines). Several other theoretical effects of TPE on immune function have been proposed, including immunomodulatory actions such as alterations in idiotypic/anti-idiotypic antibody balance, a shift in the antibody-to-antigen ratio to more soluble forms of immune complexes (facilitating their clearance), and stimulation of lymphocyte clones to enhance cytotoxic therapy. TPE also allows the isovolemic infusion of large amounts of normal plasma, which may replace a deficient plasma component, perhaps the principal mechanism of action of TPE in thrombotic thrombocytopenic purpura (TTP).

TABLE 17.1 Possible Mechanisms of Action of Therapeutic Plasma Exchange

Removal of Abnormal Circulating Factor
Antibody (anti-GBM disease, myasthenia gravis, Guillain-Barré syndrome)
Monoclonal protein (Waldenström macroglobulinemia, myeloma protein)
Circulating immune complexes (cryoglobulinemia, SLE)
Alloantibody (Rh alloimmunization in pregnancy)
Toxic factor
Replenishment of Specific Plasma Factor
TTP
Other Effects on the Immune System
Improvement in function of reticuloendothelial system
Removal of inflammatory mediators (cytokines, complement)
Shift in antibody-to-antigen ratio, resulting in more soluble forms of immune complexes
Effects on the cellular immune system

GBM, glomerular basement membrane; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura.

A. Principles of treatment

1. **Use of concomitant immunosuppression.** Because of the immunologic nature of most kidney diseases treated by TPE, therapy should almost always include concomitant immunosuppression. Adjunct medication protocols usually include high doses of corticosteroids, cytotoxic drugs, and biologic agents. These medications are expected to reduce the rate of resynthesis of pathologic antibodies and to further modulate cell-mediated immunity, which may contribute to many of these disorders.
2. **Early treatment.** Diseases that respond to TPE are best treated early to halt the inflammatory response that often contributes to disease progression. For example, TPE of anti-glomerular basement membrane (GBM) disease is most effective if therapy is initiated when serum creatinine is less than 5 mg/dL (440 mcmol/L).

II. PHARMACOKINETICS OF IMMUNOGLOBULIN REMOVAL

A. Plasma half-life. Immunoglobulins, such as IgG, have relatively long half-lives, approaching 21 days for IgG but only 5 days for IgM. Because of the relatively long plasma half-life of IgG, the use of immunosuppressive agents to decrease the production rate cannot be expected to lower the plasma levels of a pathogenic autoantibody for at least several weeks, even if production is completely blocked. This is the basic rationale for immunoglobulin removal by extracorporeal means.

B. Extravascular distribution and equilibration rate. IgG has a substantial extravascular distribution, whereas IgM is largely intravascular (Table 17.2). The extent of intravascular versus extravascular distribution will determine how effectively an immunoglobulin can be removed in the course of a single TPE session. IgG exhibits an intravascular-to-extravascular equilibration that is approximately 1% to 2% per hour, whereas extravascular-to-intravascular equilibration may be somewhat faster because it is governed by the rate of lymphatic flow. Still, since the extravascular-to-intravascular equilibration is relatively slow, the kinetics of immunoglobulin removal by plasma exchange can be calculated by using first-order kinetics governing removal rates from a single compartment (the intravascular space).

TABLE 17.2 Distribution Volumes of Immunoglobulins

Substance	Molecular Weight	% Intravascular	Half-life (days)	Normal Serum Concentration (mg/dL)
Albumin	69,000	40	19	3,500-4,500
IgG	180,000	45	21	640-1,430
IgA	150,000	50	6	30-300
IgM	900,000	80	5	60-350
LDL cholesterol (β-lipoprotein)	1,300,000	100	3-5	140-200

Ig, immunoglobulin; LDL, low-density lipoprotein.

C. The macromolecule reduction ratio (MRR) and V_e /V_p. In Chapter 3, the

relationship between the urea reduction ratio (URR) and Kt/V was described. A similar relationship holds for the removal of immunoglobulins by TPE.

The kinetics of immunoglobulin removal by TPE follows an exponential relationship:

$$C_t = C_0 \, e^{-V_e/V_p}$$

where C_0 = the initial plasma concentration of the macromolecule in question, C_t = its concentration at time t, V_e = the volume of plasma exchanged at time t, and V_p = the estimated plasma volume, which, while smaller than the volume of distribution of many of these macromolecules, functions as the volume from which they are removed, given the slow rate of equilibration between the extravascular and intravascular compartments.

MRR, expressed as a percentage, is $100 \times (1 - C_t/C_0)$, so MRR = $100 \times (1 - e^{-V_e/V_p})$. If we plug in numbers for V_e from 1,400 to 8,400 mL (Table 17.3), and if we assume that a patient's V_p is 2,800 mL, we will get values of V_e/V_p from 0.5 to 3.0. TPE using these V_e/V_p ratios will result in values for the MRR (Table 17.3) ranging from 39% (when V_e/V_p = 0.5) to 95% (when V_e/V_p = 3.0). Note that for V_e/V_p = 1.0, the MRR is 63%. The largest decrease (MRR) occurs with the removal of the first plasma volume; removal of subsequent plasma volumes during the same session becomes progressively less effective in decreasing the concentration of the macromolecule in question. The effectiveness of the procedure after one plasma volume is further reduced because of the dilution of the substance to be removed by the exchange fluid. For this reason, usually 1.0 to 1.5 plasma volume equivalents (V_e/V_p) are exchanged during a TPE session.

TABLE 17.3 Relationship between Plasma Volume Removed and Concentration of Substance

Portion of Plasma Volume[a] Exchanged (V_e/V_p)	Volume Exchanged (V_e, mL)	Immunoglobulin or Other Substance Removed (*MRR*, %)
0.5	1,400	39
1.0	2,800	63
1.5	4,200	78
2.0	5,600	86
2.5	7,000	92
3.0	8,400	95

V_e, volume of plasma exchanged; V_p, estimated plasma volume; MRR, macromolecule reduction ratio.

[a]Plasma volume = 2,800 mL in a 70-kg patient, assuming hematocrit = 45%.

D. Reaccumulation. Subsequent to the removal of the macromolecule in question, there is a reaccumulation of its concentration in the vascular space from two sources: redistribution and further synthesis. Redistribution from the extravascular space occurs via lymphatic drainage into the vascular space, as well as from diffusion of the macromolecule across capillaries from the interstitial to the intravascular space. Endogenous synthesis has been documented in anti-GBM disease, in which the anti-GBM antibodies will be predictably lowered by a given TPE treatment, but

intertreatment increases in serum levels are too rapid to be compatible with simple reequilibration from extravascular stores. Additionally, in certain circumstances, the production rate of a substance exceeds the ability of TPE to have a sustained impact on plasma levels; a classic example of this is in select cases of multiple myeloma, where even with daily TPE, the light-chain production rate may overwhelm the ability of TPE to offer the 50% or greater reduction in free light chains that has been associated with improved renal outcomes.

E. Pharmacokinetic basis for TPE prescriptions. Based on these concepts, a rational approach to prescribing TPE is generally to recommend one (1×) to one-and-one-half (1.5×) times the total plasma volume (TPV) to be exchanged daily or every other day, depending on the disease process, to allow time for adequate redistribution of macromolecules via lymphatic drainage into the vascular space. The rate of accumulation and the frequency of TPE should be targeted to the specific macromolecule that is pathogenic, if this is known. For example, since IgM is largely intravascular with a half-life of approximately 5 days, it can be removed effectively with a few daily treatments. On the other hand, patients with presumed IgG autoantibodies, which are only approximately 45% intravascular and have a longer half-life, should generally be treated every other day to allow for IgG redistribution from the extravascular space into the intravascular compartment. If the substance to be removed is measurable by reliable quantitative means (such as with specific autoantibody), then the treatment schedule should be designed to achieve a significant reduction of that substance based on kinetic considerations. If treatments are performed without the identification of the offending agent, then the physician remains dependent on empirical treatment regimens.

F. Estimation of plasma volume. An estimate of the plasma volume is required to arrive at an appropriate TPE prescription. For this purpose, there is not one standard accepted calculation; however, there are several common nomograms and equations using height, weight, and hematocrit. Commonly used equations to estimate the total blood volume (TBV) in adults include the Gilcher Rule of Fives and the Nadler Formula (Table 17.4). In pediatrics, the Linderkamp Nomogram can be used to estimate TBV. Once the TBV has been estimated, the total plasma volume (TPV) can be calculated as: TBV = TPV × (1 − hematocrit). It is also important to know the patient's TBV in comparison to the extracorporeal volume of the circuit, as a blood prime may be required if more than 10% to 15% of the patient's TBV is extracorporeal during the procedure. Another useful rule of thumb is to consider plasma volume to be approximately 35 to 40 mL/kg of lean body weight, with the lower number (35 mL/kg) applicable to patients with normal hematocrit values and 40 mL/kg applicable to patients with hematocrit values that are less than normal. For example, in a 70-kg patient with a normal hematocrit (45%), plasma volume (V_p) would be 70 × 40 = 2,800 mL. It is important to remember that these calculations are based on lean body weight. Therefore, for patients who are obese, one must use lean body mass to avoid unnecessary and dangerously large-volume exchanges.

TABLE 17.4 Estimating the Total Blood Volume (TBV)

Gilcher Rule of Fives	Blood Volume (mL/kg of body weight)			
Patient	Obese	Thin	Normal	Muscular
Male	60	65	70	75
Female	55	60	65	70

Nadler Formula (*Should not be used when body weight <25 kg*)

Male

$$TBV\ (in\ mL) = (0.3669 \times Height\ [m]) + (0.03219 \times Weight\ [kg]) + 0.6041$$

Female

$$TBV\ (in\ mL) = (0.3561 \times Height\ [m]) + (0.03308 \times Weight\ [kg]) + 0.1833$$

Studies have shown that performing a 1 × TPV exchange will reduce IgG by approximately 63%, and a 1.4 × TPV exchange will reduce IgG by 75%. Exchange of more than 1.5 × TPV during a single session provides only minimal additional removal of large molecules but increases time, cost, and further depletion of coagulation factors.

III. TECHNICAL CONSIDERATIONS. TPE can be performed by either centrifugation or membrane-based plasma separation. Centrifugation devices are commonly used for blood banking since they are capable of selective cell removal (cytapheresis) in addition to TPE. Membrane TPE utilizes highly permeable hollow-fiber filters, similar to dialyzers but with large pore sizes and appropriately modified dialysis equipment. The advantages and disadvantages of each technique are summarized in Table 17.5.

TABLE 17.5 Comparison of Membrane Plasma Separation and Centrifugal Apheresis

	Centrifugal TPE	**Membrane TPE**
Usage	Common in the United States	Common in Japan/Germany
Functionality	TPE and cytapheresis	TPE and dialysis
Vascular access	Peripheral or central	Central
Plasma extraction	80%	30%-35%
TBV processed to achieve 1.2 × TPV	1.5 × TBV	3-4 × TBV
Blood flow	30-80 mL/min (1 mL/kg/min)	100-200 mL/min
Anticoagulant	Citrate	Heparin
Treatment time[a]	Shorter (54-128 min)	Longer (82-150 min)
Setup time[b]	Shorter (11 min)	Longer (23-40 min)
IgG/IgM reduction[a]	Equivalent	Equivalent

TBV, total blood volume; TPE, therapeutic plasma exchange; TPV, total plasma volume.

[a]Hafer C, et al. Membrane versus centrifuge-based therapeutic plasma exchange: a randomized prospective crossover study. *Int Urol Nephrol*. 2016;48:133-138.

[b]Kes P, et al. A randomized crossover study comparing membrane and centrifugal therapeutic plasma exchange procedures. *Transfusion*. 2016;56(12):3065-3072.

A. Centrifugal TPE. During centrifugation, blood cells are separated by gravity, based on

the different densities (specific gravity) of the blood components. The components from highest to lowest specific gravity are RBCs, granulocytes (polymorphonuclear cells, eosinophils, then basophils), mononuclear cells (monocytes, B lymphocytes, and then T lymphocytes), platelets, and finally plasma. There are two centrifugation methods used in blood cell separators: intermittent-flow (or discontinuous-flow) devices and continuous-flow devices. RBCs move to the outside of the spinning container, while plasma, the lightest component, remains on the inside. Platelets and white blood cells (WBCs) localize between the red cell and plasma layers. Any of these components can be collected, discarded, or reinfused (Figure 17.1).

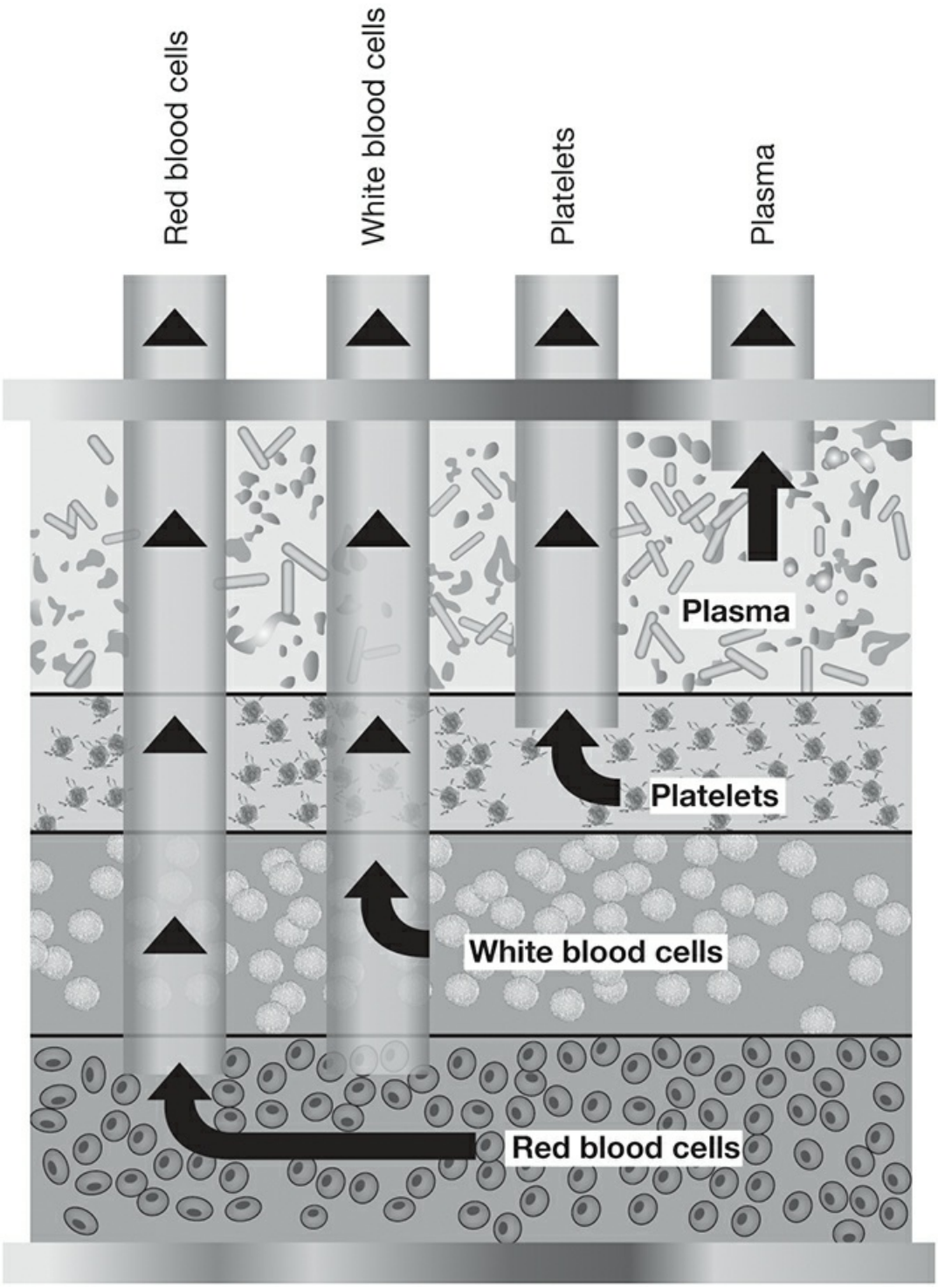


FIGURE 17.1: During centrifugal apheresis, plasma and cells are separated in layers depending on specific gravity. Each layer can be removed, depending on the procedure and fluid and/or cell replacement infused simultaneously. (Courtesy of Dobri Kiprov, MD. Reprinted from Linz W, et al. *Principles of Apheresis Technology*. 5th ed. American Society for Apheresis; 2014. www.apheresis.org)

In the intermittent-flow separation devices, multiple aliquots of blood are sequentially withdrawn and routed to a bowl, where each aliquot is processed and then

reinfused. In the continuous-flow method, blood is withdrawn, centrifuged, and separated, and the desired component is removed or returned to the patient in a continuous mode using a hoop-shaped annulus that has strategically placed sampling ports (Figure 17.1) for the collection of plasma, RBCs, WBCs, and platelets. The intermittent-flow method requires a single-needle vascular access, while the continuous-flow system typically requires two venous accesses (one for withdrawal and a second one for return), though newer software on certain apheresis equipment also allows for a single-needle mode. Intermittent-flow blood cell separators (Haemonetics Corporation, Braintree, MA) are rarely used today for therapeutic apheresis and are more commonly used in blood banking. The continuous-flow devices are preferred for therapeutic procedures because of their smaller extracorporeal blood volume, significantly shorter procedure time, and lesser anticoagulant requirement. The most widely used centrifugal blood cell separators for therapeutic apheresis are made by Terumo Blood and Cell Technologies (Lakewood, CO) and Fresenius-Kabi (Bad Homburg, Germany).

B. Membrane plasma separation. Membrane plasma separators are derived from the technology used in dialysis. Hollow-fiber filters for membrane TPE look very similar to dialysis filters. It is easy to assume that one can simply exchange the dialysis filter with a membrane plasma separation filter and perform a hemofiltration procedure without dialysate. However, removing plasma is physiologically different from removing ultrafiltrate. When water is removed from the intravascular compartment, extravascular fluid can diffuse in to buffer the volume removal. When plasma is removed from the intravascular compartment, the refilling rate of the vascular compartment is reduced. Therefore, there is a higher risk of cardiovascular complications during TPE. Equipment specifically designed for membrane plasma separation must be used to assure patient safety. Membranes with a molecular weight cutoff of about 3 million daltons are used, which is sufficient to allow passage of immune complexes (molecular weight ≈1 million). These filters can be manufactured in either a hollow-fiber or a parallel-plate configuration with a pore size of 0.3 to 0.5 micrometers. Examples of hollow-fiber plasma separators are the Plasmaflo OP-05W (Asahi Kasei Medical Co. Ltd., Tokyo, Japan) and the PrisMax TPE-2000 plasma filter (Baxter). The membrane allows plasma only to pass, as the pores are small enough to hold back the formed elements of the blood. These membranes have sieving coefficients (ratio of concentration in the filtrate to blood) between 0.92 and 1 for albumin, IgG, IgA, IgM, C3, C4, fibrinogen, cholesterol, and triglycerides (Figure 17.2).

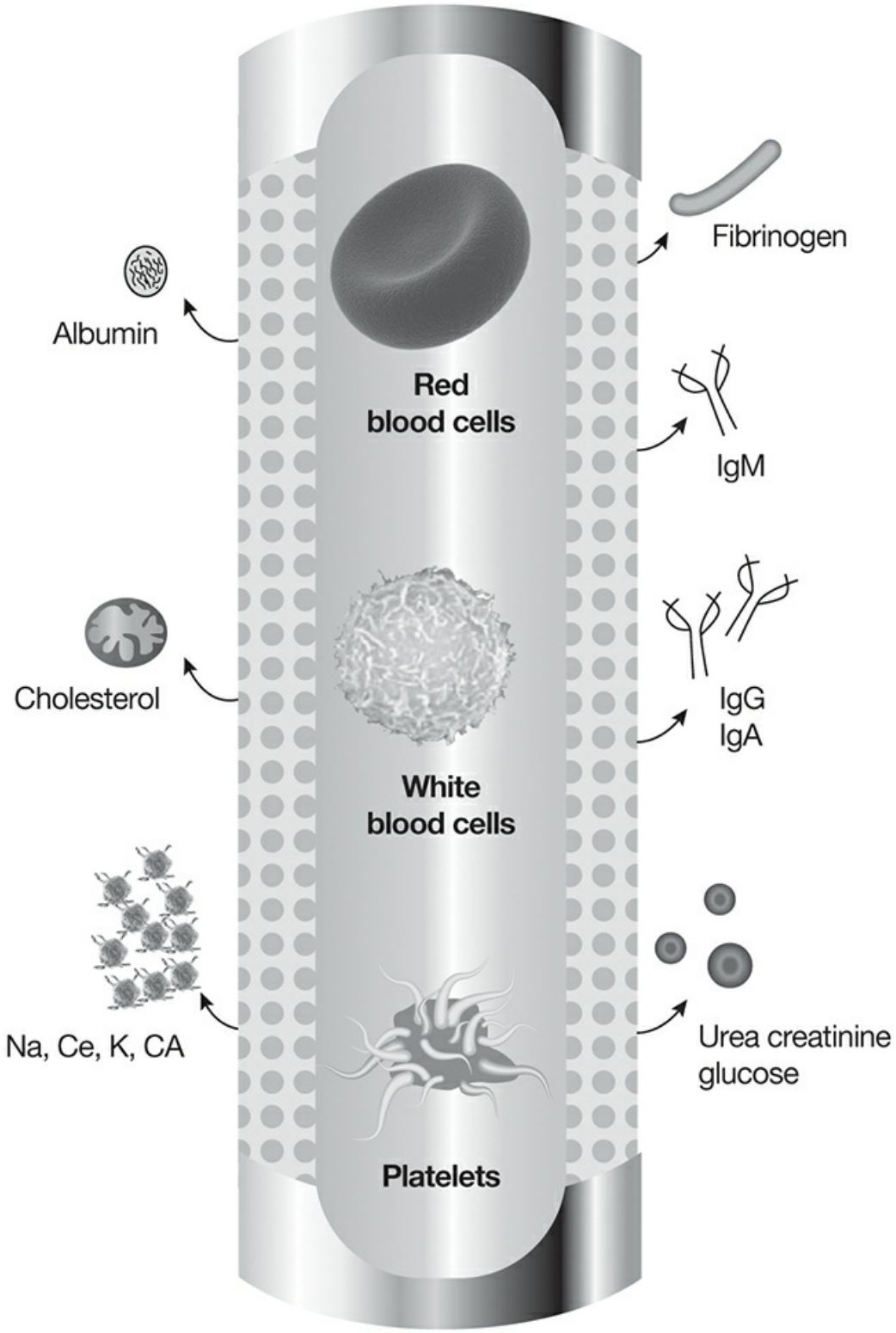


FIGURE 17.2: During membrane plasma separation, blood cells are not allowed to pass through the pores of the filter, while plasma constituents pass through. Ig, immunoglobulin. (Courtesy of Dobri Kiprov, MD. Reprinted from Linz W, et al. *Principles of Apheresis Technology*. 5th ed. American Society for Apheresis; 2014. www.apheresis.org)

Membrane-based plasma separation must be performed at low transmembrane

pressure (<200 mm Hg) to avoid hemolysis (Kaplan, 2007). With hollow-fiber devices, the blood flow rate should exceed 50 mL/min to avoid clotting. The ideal blood flow rate is usually 100 to 200 mL/min.

C. Comparison of membrane and centrifugation devices (Table 17.5). Centrifugal blood cell separators are the preferred therapeutic apheresis devices in the United States, while membrane-based systems predominate in Japan and Germany. Both are equally efficacious at reducing immunoglobulin levels (Hafer, 2016; Kielstein, 2020). Centrifugal machines pack red cells to a hematocrit of 80% or higher and thereby can remove 80% or more of the plasma coming through the machine. Thus, to remove 1.2× the patient's TPV, one must process 1.5× the blood volume. In contrast, membrane TPE systems extract approximately 30% to 35% of the passing plasma, so they must process 3 to 4 times the patient's blood volume to achieve a similar plasma removal. However, the higher blood flow rate with membrane TPE assists in making treatment times fairly similar. Centrifugal-based systems are capable of performing cellular apheresis procedures (leukapheresis, erythrocytapheresis, thrombocytapheresis, and harvesting stem cells) in addition to TPE. Centrifugal devices also operate at lower blood flow rates and therefore peripheral access can be sufficient, whereas membrane TPE typically requires central access to achieve the higher blood flow rates that are necessary. Citrate-based anticoagulation is standard with centrifugal TPE, whereas its use in membrane TPE is rare, and heparin is the standard anticoagulant.

IV. VASCULAR ACCESS.

As noted earlier, for the centrifugal device systems, the typical blood flow rate is in the range of 40 to 80 mL/min; therefore, a large peripheral vein (antecubital vein for draw) can be sufficient and is the preferred access type as it avoids the risks of central access. If peripheral access is not an option, then dialysis-type catheters, certain ports, or arteriovenous (AV) fistulas can be used. With membrane TPE, to achieve the required blood flow rate of 100 to 200 mL/min, a dual-lumen dialysis-type catheter is necessary; if a patient has a preexisting AV fistula or graft, this can also be used. The majority of other intravascular devices available for nondialysis use, such as triple-lumen and peripherally inserted central catheters (PICCs), almost never provide adequate blood flow for either method of TPE.

V. ANTICOAGULATION.

Anticoagulation is typically necessary for most therapeutic apheresis procedures (although with some systems, the use of prefilter heparin is not associated with reduced clotting risk; Elali, 2021). In general, membrane TPE devices use heparin, whereas with centrifugal TPE citrate is the preferred anticoagulant.

A. Heparin. Heparin sensitivity and half-life vary greatly in patients, and individual adjustment of dosage is necessary. Heparin doses may need to be increased in patients with low hematocrit (increased volume of distribution) and when the plasma filtration rate is high (a high plasma filtration rate results in increased net removal of heparin, which has a sieving coefficient of 1.0). While some of the passing heparin will be extracted with the plasma, a portion will be returned to the patient, thereby delivering systemic anticoagulation.

B. Citrate. Anticoagulant citrate dextrose (ACD) is used as the anticoagulation solution for most centrifugal TPE procedures. Citrate is given at a ratio of incoming whole blood to anticoagulant solution of 12:1; that is, 12 parts whole blood to 1 part citrate solution.

Citrate chelates calcium, which is a necessary cofactor in the coagulation cascade, and this inhibits thrombus formation and platelet aggregation. ACD comes in two standard formulations. Formula A (ACD-A) contains 2.2 g/dL of sodium citrate and 0.73 g/dL of citric acid. Formula B (ACD-B) contains 1.32 g/dL of sodium citrate and 0.44 g/dL of citric acid. ACD-A is typically used for all continuous-flow centrifugal devices. Citrate provides regional anticoagulation, and the patient is not systemically anticoagulated. Low plasma ionized calcium can occur; therefore, patients must be carefully observed for signs and symptoms of hypocalcemia (perioral and/or acral paresthesias; some patients may experience shivering, light-headedness, twitching, tremors, and, rarely, continuous muscular contractions that result in involuntary carpopedal spasm). If plasma ionized calcium levels fall more severely, symptoms can progress to frank tetany with spasm in other muscle groups, including life-threatening laryngospasm. Grand mal seizures have been reported. These symptoms may be accentuated by alkalosis due to hyperventilation. Reductions of ionized calcium values also lengthen the plateau phase of myocardial depolarization, manifested electrocardiographically by prolongation of the QT interval. Very high citrate levels, with correspondingly low ionized calcium, lead to depressed myocardial contractility, which, though very rare, can provoke fatal arrhythmias in patients undergoing apheresis.

1. **Prevention of low ionized calcium levels during citrate anticoagulation.** The following measures can be considered.
    a. **Limiting the rate of citrate delivery to the patient.** The rate of citrate infusion must not exceed the capacity of the body to metabolize citrate rapidly. The ability to metabolize citrate varies from patient to patient. Because the amount of citrate infused is proportional to the blood flow rate, high blood flow rates should not be used. Patients with liver and renal insufficiency may have an impaired ability to metabolize citrate, and in these patients, citrate infusion should be performed with caution. Fresh frozen plasma (FFP) contains up to 14% citrate by volume. In cases where FFP, instead of albumin, is being used as the replacement fluid, the total citrate reinfusion rate to the patient should include the citrate in the FFP. If the patient is experiencing symptoms of hypocalcemia, one can lower the blood flow rate, which will decrease the amount of citrate delivered, or alternatively, if no circuit clotting is occurring then the ratio can be adjusted for less citrate delivery (ie, if the whole blood to anticoagulant ratio is 12:1, it is adjusted to 14:1). The procedure should be halted if more moderate to severe symptoms of hypocalcemia are observed and not resumed until resolution of symptoms occurs.
    b. **Providing additional calcium to the patient during the TPE procedure.** Calcium can be given either orally or intravenously. One can, for example, give orally 500 mg (5 mmol) tablets of calcium carbonate every 30 minutes or give intermittent boluses of intravenous 10% calcium gluconate, though symptoms of hypocalcemia have been reported to occur in approximately a third of treatments with this approach (Weinstein, 1996). Another method is a continuous infusion of calcium gluconate 10% intravenously, which decreases the rate of citrate toxicity to 1% of procedures (Mokrzycki, 1994). In addition to these measures, intravenous boluses of calcium can be given whenever symptoms of hypocalcemia become manifest. Most therapeutic apheresis

programs utilize some form of intravenous calcium delivery to avoid the symptoms of hypocalcemia, whereas in blood donation procedures, oral calcium is typically employed.

2. **Alkalosis during citrate infusion.** There is the possibility of developing metabolic alkalosis (although this is a very rare occurrence) because citrate in the form of sodium citrate is metabolized to bicarbonate. In patients with liver disease, who may have impaired ability for citrate metabolism, or when plasma is used as the replacement, acid-base status during TPE using citrate anticoagulation should be monitored with special care. If a patient is receiving both TPE and intermittent hemodialysis, it is best to perform TPE first, followed by dialysis in order to correct any alkalosis, electrolyte abnormalities, or excess volume gains as a result of the apheresis therapy.

VI. REPLACEMENT SOLUTION.

The selection of the type and amount of replacement fluids is an important consideration in the prescription of TPE. Replacement fluid should be both isotonic and iso-osmotic to plasma to maintain hemodynamic stability, such as 5% albumin or donor plasma. The use of plasma should have clear clinical justification as it carries increased risks. The advantages and disadvantages of each are listed in Table 17.6.

TABLE 17.6 Choice of Replacement Solution

Solution	Advantages	Disadvantages
Albumin	No reported transmission of infection	Expensive
	Stored at room temperature	No coagulation factors
	Allergic reactions are rare.	No immunoglobulins
	No concern about ABO blood group	
	Depletes inflammation mediators	
Fresh frozen plasma	Coagulation factors	Risk of transmission of infection
	Immunoglobulins	Allergic reactions
	“Beneficial” factors	Must be thawed
	Complement	Must be ABO compatible
		Additional citrate load to patient

A. Donor plasma.

FFP has the advantage of being similar in composition to the filtrate being removed from the patient but is associated with side effects such as allergic reactions. Urticaria and hives, which may be severe, are frequently present with the use of FFP. Rarely, anaphylactic reactions caused by passive transfusion of leukoagglutinins result in a form of noncardiogenic pulmonary edema (known as transfusion-related acute lung injury [TRALI]). The risk of TRALI with solvent detergent pooled plasma is exceedingly rare, though this product is more expensive than single donor plasma. Another cause of anaphylaxis is an infusion of IgA-containing FFP to a patient with selective IgA deficiency. Because FFP may contain appreciable amounts of anti-A and anti-B isoagglutinins, ABO compatibility between donor and recipient is necessary. As noted earlier, FFP contains citrate, and the use of FFP increases the risk of citrate-

mediated low ionized calcium reactions. Also, there is a small but measurable risk for transmission via blood products of hepatitis B (1 in 300,000 chances per unit), hepatitis C (1 in 1.5 million chances per unit), HIV (1 in 2 million per unit), and West Nile Virus (1 in 350,000 chances per unit).

The use of FFP as the replacement fluid makes measurement of the efficacy of TPE more difficult in certain patients (eg, one cannot simply follow serum levels of IgG and other immunoglobulins). Also, FFP may replenish some factors removed during TPE that could participate in the inflammatory process.

At present, the specific indications for replacing some or all of the removed plasma with FFP during plasma exchange are (a) TTP/hemolytic uremic syndrome (HUS), (b) preexisting defect in hemostasis and/or low pretreatment serum fibrinogen level, and (c) patients at risk for bleeding; for example, pre- or postsurgery patients or those with diffuse alveolar hemorrhage or advanced liver disease (eg, high baseline international normalized ratio [INR]). With regard to TTP/HUS, there is a rationale for using FFP as the sole replacement fluid because the infusion of FFP by itself may be therapeutic and because in the presence of thrombocytopenia the risk of bleeding as a consequence of minor perturbations in coagulation factors may be higher.

In general, because TPE depletes coagulation factors, replacement by albumin and crystalloid alone may result in depletion of these factors and place the patient at increased risk of bleeding. This is not likely to occur after one or two plasma exchanges, particularly if they are performed more than a day apart because the half-life for most clotting factors is approximately 24 to 36 hours.

B. Albumin. Because of the above concerns with the use of donor plasma, we recommend albumin as the initial replacement solution. Albumin solution at a concentration of 5 g/dL (50 g/L) in saline with 130 to 160 mmol of sodium chloride per liter can be replaced in a volume equal to that of the removed plasma. With modern equipment, this can be done simultaneously and at the same rate as plasma removal. However, because a substantial proportion of the albumin that is infused early during the procedure is exchanged during the course of a TPE procedure, a more economical approach (when the exchange volume is equal to one plasma volume and in the absence of hypoalbuminemia) is to replace the initial 20% to 30% of the removed plasma volume with crystalloid, such as 0.9% saline and then substitute the balance with the above-mentioned 5% albumin solution. This method would result in a final concentration of albumin in the vascular space of approximately 3.5 g/dL (35 g/L), sufficient to maintain oncotic pressure and avoid hypotension. The approach should not be used in patients with hyperviscosity, patients with neurologic diseases, and patients susceptible to hypotension.

Purified human serum albumin (HSA) solutions do not transmit viral diseases because of prolonged heat treatment during processing and have become a favored replacement fluid in TPE. They have an excellent overall safety record. The incidence of adverse reactions of any kind has been estimated to be 1 in 6,600 infusions. Severe, potentially life-threatening reactions occur in approximately 1 of every 30,000 infusions. When preparing 5% albumin solution from more concentrated solutions, 0.9% saline must be used as the diluent; the use of water as a diluent has resulted in severe hyponatremia and hemolysis (Steinmuller, 1998).

The amount of fluid replacement given depends on the patient’s volume status

though generally for hemodynamic support the total balance when accounting for replacement solutions, anticoagulant, and calcium infusions ranges from 100% to 115% and is set by the ordering physician. Although the replacement volume can be set to less than 100%, it is generally not advised since this may contract the intravascular volume and result in hemodynamic instability.

VII. COMPLICATIONS. The side effects observed with TPE are generally not severe and can be managed easily if they are anticipated. The rate of all adverse events during TPE is approximately 4% to 5%. The World Apheresis Association Registry has shown that the incidence of mild and severe adverse events has decreased over time, likely as a result of preventive measures and increased awareness of best practices (Vrielink, 2023). Mild adverse events were classified as being tolerated without medication, moderate adverse events signified the need for medication, and severe was defined as an adverse event leading to interruption of the procedure. The most common mild and moderate adverse events in this registry were tingling/pricking sensations, followed by hypotension and nausea/vomiting. Serious adverse events were rare (<1%), and the most common causes were hypotension (typically with all albumin replacement) and urticaria (with plasma replacement). This registry identified the following factors as having the highest risk for an adverse event: first apheresis procedure, plasma as replacement fluid, filtration procedures that led to more complement activation, older age, female sex, and an underlying diagnosis of kidney or rheumatologic disease (Stegmayr, 2007). In a Swedish registry of therapeutic apheresis procedures, adverse events were more likely to occur when treating TTP/HUS or Guillain-Barré syndrome, followed by anti-GBM disease (Norda, 2003). No fatalities were attributed to apheresis during 20,485 procedures reported from the Swedish registry, and only one fatality potentially linked to apheresis was reported out of more than 140,000 procedures in the World Apheresis Association Registry update in 2023. The most important complications are summarized in Table 17.7. Strategies for avoidance and management of these complications are summarized in Table 17.8.

TABLE 17.7 Complications of Therapeutic Plasma Exchange

Related to Vascular Access
Hematoma
Pneumothorax
Retroperitoneal bleed
Local or systemic infection

Related to the Procedure
Hypotension from externalization of blood in the extracorporeal circuit
Hypotension due to decreased intravascular oncotic pressure
Bleeding from reduction in plasma levels of coagulation factors
Edema formation due to decreased intravascular oncotic pressure
Loss of cellular elements (platelets)
Hypersensitivity reactions (ethylene oxide)

Related to Anticoagulation
Bleeding, especially with heparin
Hypocalcemic symptoms (with citrate)
Arrhythmias

Hypotension
Numbness and tingling of extremities
Metabolic alkalosis from citrate
Related to Replacement Fluids
Hypotension (use of hypo-oncotic saline)
Anaphylaxis (fresh frozen plasma [FFP])

TABLE 17.8 Strategies to Avoid Complications During Plasmapheresis

Complication	Management
Low ionized calcium	Prophylactic infusion of 10% calcium gluconate during treatment
Hemorrhage	2-4 units of fresh frozen plasma (FFP) at the end of the procedure
Volume-related hypotension	Adjust volume balance.
Infection post-apheresis	Infusion of intravenous immunoglobulin (100-400 mg/kg)
Hypokalemia	Monitor and supplement as needed.
Membrane biocompatibility	Change membrane or consider centrifugal method of plasma separation.
Hypothermia	Warm replacement fluids.
ACE inhibitors	Discontinue ACE inhibitor therapy 24-48 h before certain treatments (eg, columns).
Sensitivity to FFP or albumin	Consider measuring anti-IgA titers.
	Premedication regimen for sensitized individuals: (a) hydrocortisone IV or prednisone, (b) diphenhydramine IV or orally, and (c) H_2 antagonists (cimetidine) IV

ACE, angiotensin converting enzyme; IV, intravenous.

A. Hypocalcemia from citrate. The most common complication of therapeutic apheresis when using centrifugal machines is related to citrate toxicity, as described in the "Anticoagulation" section.

B. Hemodynamic complications. Hypotension (2% overall incidence) is due mainly to intravascular volume depletion, which may be exaggerated by the volume of blood externalized in the extracorporeal circuit (160-375 mL). Other causes include vasovagal episodes, use of hypo-oncotic fluid replacement, delayed or inadequate volume replacement, bradykinin reactions, anaphylaxis, TRALI, disease-related hypotension (eg, autonomic instability in Guillain-Barré syndrome), hemorrhage, cardiac arrhythmia, and cardiovascular collapse.

C. Hematologic complications. Hemorrhagic episodes are rare. Bleeding after insertion of a central venous catheter, bleeding from a previous catheter site, hematemesis, and epistaxis have been described.

After a single plasma exchange using albumin as the replacement fluid, the serum fibrinogen level typically falls by 65% to 70%, and prothrombin and many other clotting factor levels also fall by about 50% to 70%. The partial thromboplastin time usually increases by 100%. Recovery of plasma levels of coagulation factors is biphasic, characterized by a rapid initial increase up to 4 hours post-apheresis, followed by a slower increase 4 to 24 hours postexchange. Twenty-four hours after treatment, fibrinogen levels are approximately 50%, and antithrombin III levels are 85%, of initial levels; both require 48 to 72 hours for complete recovery. One day following treatment,

the prothrombin level is 75% and factor X is 30% of the original level; by this time, all other coagulation factors will have completely recovered to normal values. When multiple treatments are performed over a short period, the depletion in clotting factors is more pronounced and may require several days for spontaneous recovery. For patients undergoing a series of daily treatments, the use of a couple of units of FFP as the last replacement solution may be warranted. In the past, device-specific thrombocytopenia was reported as a result of TPE; however, with newer apheresis systems, both centrifugal and membrane based, platelet loss is minimal and should not be a factor when choosing a TPE modality to treat disorders such as TTP.

D. **Angiotensin converting enzyme (ACE) inhibitors.** Anaphylactic or atypical anaphylactoid reactions have been reported in patients taking ACE inhibitors during hemodialysis, LA, other apheresis-specific columns, and with the use of albumin as replacement. These reactions have been related to negatively charged membranes or columns. Experimental evidence has shown that this reaction is not related to extracorporeal circulation alone. It is speculated that the fragments of prekallikrein-activating factor present in human albumin led to endogenous bradykinin release. The severity of the reactions depends on different variables, including drug type and lot of albumin (which may contain different concentrations of the prekallikrein-activating factor). However, whether to hold an ACE inhibitor prior to TPE has been controversial, except in the case of lipoprotein apheresis with the dextran sulfate column, where the use of an ACE inhibitor is an absolute contraindication due to resultant bradykinin-mediated hypotension.

E. **Infection.** The true incidence of infection in TPE is controversial. Studies have not clearly shown a significantly higher occurrence of opportunistic infections among patients treated with immunosuppression and TPE compared to those treated with immunosuppressive therapy alone. However, if a severe infection develops in the immediate post–plasma exchange period, a reasonable approach would be a single infusion of immunoglobulins (100-400 mg/kg intravenously) though this practice is not evidence based.

F. **Electrolyte, vitamin, and drug removal**

1. **Hypokalemia.** Commercially available solutions of 5% albumin have a potassium level of less than 2 mmol/L. When the replacement solution is albumin in saline, there could be a 25% reduction in serum potassium levels in the immediate post-apheresis period; however, given its low molecular weight and highly diffusible nature, potassium quickly returns to the intravascular compartment following TPE.
2. **Metabolic alkalosis.** This may result from the infusion of large amounts of sodium citrate from the anticoagulant with centrifugal TPE and/or from donor plasma. In healthy individuals, exogenous citrate is rapidly metabolized in mitochondria via the citric acid cycle, with every molecule of citrate releasing bound calcium, consumption of three hydrogen ions, and release of three molecules of bicarbonate, which contributes to blood alkalinity.
3. **Drugs.** In general, drugs that are significantly cleared by plasma exchange are the ones that have small volumes of distribution and extensive protein binding. Evidence shows that supplemental dosing of prednisone, digoxin, cyclosporine, ceftriaxone, ceftazidime, valproic acid, and phenobarbital is not necessary after plasma exchange. In contrast, the dosages of salicylates, azathioprine, and

tobramycin should be supplemented. The many reports of phenytoin clearance are conflicting; thus, it is necessary to carefully monitor unbound drug levels. Rituximab and other monoclonal antibodies will have significant removal with TPE. When rituximab is used for TTP, it is best to give it immediately following the procedure and wait 24 hours to perform the next TPE. We generally recommend that all scheduled medications be given immediately after the procedure if possible.

VIII. INDICATIONS FOR TPE. The most comprehensive guidelines for the use of therapeutic apheresis are published by the American Society of Apheresis (ASFA) approximately every 3 years. Their evidence-based approach assigns categories to diseases after a systematic review of the literature. Furthermore, the quality of the supporting evidence is graded. Category I includes disorders for which apheresis is accepted as the first line of therapy. Category II includes diseases for which apheresis is accepted as a second-line therapy (usually after failure of the first line of therapy). Category III includes entities for which the optimal role of apheresis is not established. In these cases, decision-making should be individualized. Category IV includes disorders in which published evidence demonstrates apheresis to be ineffective or harmful. Below is a summary of the use of TPE in renal disorders.

A. Anti-GBM disease. There is convincing evidence of the pathogenicity of anti-GBM antibodies in this disease, which historically was rapidly fatal in untreated patients. Early use of TPE is strongly indicated since the response rate is highest when the serum creatinine is relatively low (<500 mcmol/L or 5.7 mg/dL). In a large long-term study using TPE together with immunosuppressive drugs, almost all patients with creatinine less than 500 mcmol/L (5.7 mg/dL) recovered kidney function, compared with only 8% of those who were already on dialysis. In oliguric patients who are dialysis dependent, particularly with a high percentage of crescents on renal biopsy, TPE should probably be reserved for those with pulmonary hemorrhage, because renal function is unlikely to recover.

The frequency of TPE should be high enough to rapidly decrease circulating anti-GBM antibody levels. In the large series described earlier, patients received exchanges of 50 mL/kg (~1.5 plasma volumes) for 14 consecutive days or until anti-GBM antibody levels became undetectable. Other authors would advise the exchange of two plasma volumes daily for 7 days, followed by alternate-day TPE for another week. In another large series, with shorter follow-up, a median of 13 plasma exchanges was used and patient survival was better in those receiving greater than eight exchanges (Huart, 2016). Although renal biopsy is preferred to confirm the diagnosis, if the clinical suspicion is high and a reliable assay for anti-GBM antibodies is positive, then treatment should be started immediately. If still indicated clinically, a renal biopsy could be performed after the first two or three exchanges, deferring TPE for 24 hours after the biopsy. Citrate anticoagulation may be preferred, where available, in the presence of lung hemorrhage or after renal biopsy. TPE may need to be continued beyond the second week, depending on clinical features and anti-GBM antibody levels.

In general, plasma is replaced with 5% albumin, but using FFP for the last liter of the exchange in patients with lung hemorrhage or recent biopsy. If the patient is severely fluid overloaded, the amount of albumin solution can be reduced to 85% (but not less) of the removed plasma volume.

B. TTP and HUS. Both TTP and HUS lead to thrombotic microangiopathy, which, in HUS, particularly affects the kidney and, in TTP, often affects the central nervous system. HUS is divided into cases preceded by diarrhea (D+) and those that occur sporadically (D−). (D−) HUS may be associated with genetic defects of complement regulators or autoantibodies to these proteins (atypical HUS [aHUS] or complement-mediated thrombotic microangiopathy). In TTP, there may be a genetic deficiency of the von Willebrand factor–cleaving protease (ADAMTS13) or autoantibodies against it. TPE will replace normal plasma components, regardless of etiology, and will remove autoantibodies when present.

For suspected TTP, TPE (1-1.5 × TPV) should be started as soon as possible and continued daily until platelet count is normalized and hemolysis has largely ceased (lactate dehydrogenase below 400 IU/L) for 2 to 3 consecutive days. The benefit of tapering TPE over a longer duration after the platelet count has normalized has been debated. Since relapse may recur promptly upon stopping treatment, vascular access should be maintained until the platelet count is stable. In patients who experience a relapse of TTP, daily TPE should be resumed.

Diarrhea-positive (D+) HUS in children is frequently a self-limiting disease, which improves with supportive treatment. During the 2011 outbreak of D+HUS in Europe, TPE appeared to benefit some adults with neurologic symptoms. In diarrhea-negative (D −) HUS (aHUS or complement-mediated thrombotic microangiopathy), there are no controlled trials, but there are several anecdotal reports of the benefit of TPE with FFP in severely affected patients.

In general, removed plasma is replaced by the same volume of FFP, since the FFP will provide the deficient plasma components. In repeated large-volume exchange for TTP, care needs to be taken to avoid hypocalcemia.

Eculizumab (a monoclonal antibody against C5 that inhibits the formation of the membrane attack complex of complement) is now the recommended treatment for (D−) HUS, once the diagnosis is confirmed, but TPE could be used while awaiting diagnosis or when eculizumab is not available.

C. Cryoglobulinemia. TPE has been used for the treatment of cryoglobulinemia for several decades due to the effective removal of the large immune complexes responsible for clinical features. Although there are no controlled trials, there are multiple reports demonstrating the efficacy of TPE in patients with acute vasculitis and renal involvement; however, the advances in antiviral therapies for hepatitis C have made the need for TPE less frequently necessary in hepatitis C–associated cryoglobulinemia. TPE can also be considered for hyperviscosity syndrome or where a patient is about to undergo surgery requiring hypothermia. There is increasing evidence for the effectiveness of rituximab in mixed cryoglobulinemia, and this is often used after an initial course of TPE in severe disease.

In general, exchange of one plasma volume for 7 days is suggested, while others use TPE on alternate days for 2 to 3 weeks. Replacement fluid should be 5% albumin, which must be warmed to avoid precipitation of circulating cryoglobulins. In occasional patients, long-term treatment once a week is required to control symptoms. The use of a centrifugation device is often preferred because of the possibility of the cryoglobulins blocking the plasma filter as they cool and precipitate. Alternative techniques such as double cascade filtration and cryofiltration are expensive and technically difficult and

are not widely used.

D. Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis. These patients have small- and medium-sized vessel vasculitis often affecting the kidney, with pauci-immune rapidly progressive glomerulonephritis. This group of diseases includes granulomatosis with polyangiitis (previously Wegener granulomatosis), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (previously Churg-Strauss syndrome). The pathogenic role of ANCA antibodies underlies the scientific rationale for the use of TPE in ANCA-associated vasculitis. The treatment is divided into two phases: induction of remission and maintenance therapy given the risk for relapse. The current standard of care for the induction phase is a combination of high-dose glucocorticoids with either cyclophosphamide or rituximab. For decades, TPE has been considered an appropriate adjunctive therapy during the induction phase. Although early trials did not produce clear-cut results, Pusey (1991) demonstrated the benefit of TPE, together with immunosuppressive drugs in patients already requiring dialysis, which was later confirmed for patients with creatinine more than 500 mcmol/L (5.7 mg/dL) or on dialysis by the Methylprednisolone versus Plasma Exchange (MEPEX) trial (Jayne, 2007). Long-term follow-up from MEPEX (median 4 years) failed to show a net benefit of TPE in the composite outcome of death and end-stage kidney disease (ESKD) (Walsh, 2013). The addition of TPE remained a mainstay of induction until the results of the Plasma Exchange and Glucocorticoids in Severe Antineutrophil Cytoplasmic Antibody-Associated Vasculitis (PEXIVAS) trial, the largest RCT in ANCA-associated vasculitis, failed to demonstrate a benefit of TPE on the composite primary outcome of ESKD and mortality at 12 months. PEXIVAS randomized patients with GFR less than 50 to receive TPE or not in addition to immunosuppressive therapy and to receive standard or reduced dose glucocorticoids. The long-term combined outcome of kidney failure or death was not different whether or not TPE was used and whether standard or reduced dose glucocorticoids were used. However, the short-term effect of plasma exchange on recovery of kidney function has not yet been reported, and subgroup analysis revealed a nonsignificant benefit in patients with creatinine greater than 5.6 mg. A subsequent meta-analysis of trials of TPE in ANCA-associated vasculitis, including the results from PEXIVAS, revealed that plasma exchange reduced the risk of kidney failure at 12 months but increased the risk of infections. The benefit was greatest in those with creatinine greater than 500 mcmol/L (5.7 mg/dL) but was also of clinical importance in those with creatinine 300 to 500 mcmol/L (3.4-5.7 mg/dL). Patients in PEXIVAS were not required to have a kidney biopsy, and a subsequent large series of patients showed that kidney histopathology could help predict the probability of kidney recovery following plasma exchange.

While TPE may not benefit all cases of ANCA-associated vasculitis, it may still be of benefit in select patients with severe renal failure, particularly those with high activity scores on biopsy with minimal fibrosis. The typical regimen is daily exchanges of 1.5 × TPV when diffuse alveolar hemorrhage is present and daily or every other day exchange in the absence of diffuse alveolar hemorrhage for a total of seven exchanges. FFP should be used for the last liter of exchange for those with pulmonary hemorrhage or a recent kidney biopsy. Some patients may require longer periods of treatment, depending on their clinical response. A separate indication for TPE in ANCA-associated vasculitis is the additional presence of anti-GBM antibodies, which occurs in around 10% of

patients (McAdoo, 2017).

E. **Multiple myeloma.** Multiple myeloma can lead to renal impairment through a wide variety of mechanisms, the commonest of which is light-chain cast nephropathy. The treatment of elevated serum free light chains includes volume expansion with crystalloid solutions, chemotherapy, proteasome inhibitors, immunomodulatory drugs, or corticosteroids, and in select cases, the addition of extracorporeal removal with TPE or high-cut off (HCO) hemodialyzers. Although TPE effectively removes the paraprotein responsible, early trials produced conflicting results. A more recent, larger study failed to show significant benefit of TPE in addition to standard chemotherapy, but few of those patients had cast nephropathy confirmed by kidney biopsy. A retrospective study from the Mayo Clinic showed that when TPE achieved greater than or equal to 50% reduction in free light chains, then it was effective in reversing kidney failure and extending survival (Leung, 2008). However, HCO hemodialysis has been shown to remove more free light chains than TPE, and a phase 2 trial of hemodialysis using HCO membranes failed to show a benefit in patients with biopsy-proven cast nephropathy that required dialysis (Hutchison, 2019).

   In general, if TPE is being used, we would suggest monitoring serum free light chains to determine the efficacy of TPE, and treatment frequency (daily vs every other day) should be dictated by the ability to achieve a 50% or greater reduction in free light chains.

F. **Systemic lupus erythematosus (SLE).** In the past, TPE has been widely used in lupus nephritis to remove circulating autoantibodies and immune complexes. Despite positive anecdotal reports, one randomized controlled trial showed no benefit from the addition of TPE to immunosuppressive drugs in patients with lupus nephritis followed up for 3 years. However, patients with crescentic nephritis and those requiring dialysis were excluded, and it could be argued that short-term interventions such as TPE would have a better effect in such patients. An international trial using high-dose cyclophosphamide synchronized with TPE was suspended because of a high incidence of adverse effects, so this approach cannot be recommended. In our experience and based on many anecdotal reports, TPE should be considered in patients with life-threatening manifestations of SLE, for example, those with crescentic nephritis, pulmonary hemorrhage, cerebral lupus, or catastrophic antiphospholipid syndrome. The use of plasma exchange may also be indicated in select patients with active lupus nephritis who also have positive ANCA. There are reports of the use of immunoadsorption using protein A columns in patients with severe disease unresponsive to other treatments.

   We would suggest an initial course of seven exchanges of 1 to 1.5 plasma volumes for 5% albumin in patients with life-threatening disease. FFP should be used for the last liter of the exchange in the presence of lung hemorrhage or recent kidney biopsy.

G. **Recurrent focal segmental glomerulosclerosis (FSGS).** Recurrent FSGS in renal transplants appears to be mediated in some cases by a circulating factor that increases glomerular permeability. The use of TPE in FSGS of the native kidney has produced variable results, perhaps because some of these patients have a genetic defect in proteins contributing to the glomerular filtration barrier. FSGS can recur promptly following renal transplantation (15%-55% of cases) and, in these patients, TPE is frequently reported to be of benefit.

In the absence of adequate information, we would suggest the use of exchange of one plasma volume for 5% albumin for at least 5 consecutive days, and perhaps for longer, depending on clinical response, in patients with rapid recurrence of proteinuria following renal transplantation. In one study, monthly cycles of five exchanges for 6 months were used together with rituximab, with good clinical response (Koutroutsos, 2019). In the United States, lipoprotein apheresis using a dextran sulfate column–based system is US Food and Drug Administration (FDA) approved for FSGS with nephrotic syndrome in native or transplanted kidneys when standard treatment options are unsuccessful or not tolerated.

H. Henoch-Schönlein purpura and IgA nephropathy. Patients with Henoch-Schönlein purpura (IgA vasculitis) and primary IgA nephropathy may develop rapidly progressive glomerulonephritis due to crescentic glomerulonephritis. The histologic features may be similar to those with ANCA-associated vasculitis. The successful use of TPE, usually with immunosuppressive drugs, has been reported in several small series of patients. We have observed improvement in renal function in some patients treated with this approach.

It would be reasonable to perform seven exchanges of 1 to 1.5 plasma volumes for 5% albumin in patients with active crescentic nephritis and deteriorating renal function, based on the experience in ANCA-associated vasculitis.

I. Hyperviscosity syndrome. This occurs most commonly with Waldenström macroglobulinemia (50% of cases) and occasionally with myeloma and cryoglobulinemia. Hyperviscosity leads to RBC aggregation and reduced blood flow, leading to ischemic dysfunction of several organ systems, including the central nervous system, retina, and kidney. Although there are no controlled trials, there are several reports of the benefit of TPE in controlling clinical features pending the effects of treatment for the underlying disorder.

In the absence of adequate evidence, we would suggest using daily exchange of one plasma volume for 5% albumin for 3 to 5 days or until blood viscosity normalizes and the patient is clinically stable.

J. Renal transplantation. For decades, TPE has been used for treating antibody-mediated rejection and, more recently, as part of the desensitization protocol for ABO-incompatible or highly sensitized patients. Indications for TPE in renal transplant rejection are not yet clear-cut, but several trials have suggested a benefit in patients with acute antibody-mediated rejection, often with concomitant intravenous immunoglobulin therapy. However, there was no apparent benefit in chronic rejection. Both TPE and protein A immunoadsorption have been used to remove preformed anti-human leukocyte antigen (HLA) antibodies in highly sensitized patients, with around 70% graft survival at 1 year. There are also reports that TPE is effective in allowing renal transplantation in ABO-incompatible patients, often with the use of additional immunosuppression such as rituximab.

We would suggest five exchanges of one plasma volume for 5% albumin, together with intravenous immunoglobulin (IVIG), for acute antibody-mediated rejection. The use of TPE in desensitization protocols for high-risk patients should only be carried out in specialized centers.

K. Poisoning and drug overdose. There are no American Society of Apheresis class I indications for TPE in this area. However, there are case reports of TPE being used in

Amanita phalloides mushroom poisoning, to help clear digoxin-Fab complexes in patients with renal failure, to treat snakebite or cisplatin overdose, and to remove infused monoclonal antibodies when this is required.

IX. THE SELECTIVE APHERESIS PROCEDURES

A. Rationale. Although conventional TPE can remove target plasma elements such as immunoglobulins, cryoproteins, and lipids, it does so without specificity and requires replacement solutions such as albumin and donor plasma, which can be expensive and lead to adverse reactions. Selective apheresis procedures have been developed to target and remove a specific element from the plasma and return all other plasma proteins, thus eliminating the need for replacement solutions and the loss of beneficial plasma constituents. However, it should be remembered that the nonselective nature of TPE could be of benefit when used in antibody-mediated diseases through the removal of inflammatory mediators such as complement and coagulation components.

B. Lipoprotein apheresis. In lipoprotein apheresis, either whole blood or separated plasma is treated to remove low-density lipoprotein (LDL) cholesterol. In the United States, lipoprotein apheresis is currently approved for patients with homozygous familial hypercholesterolemia or in patients with LDL greater than or equal to 300 mg/dL or LDL greater than or equal to 100 mg/dL plus documented coronary or peripheral arterial disease, as well as for those with LDL greater than or equal to 100 and lipoprotein(a) greater than or equal to 60 mg/dL with coronary or peripheral arterial disease despite maximal medical therapy. Other health care systems have less stringent criteria. In general, these procedures are performed once every 1 to 2 weeks, depending on LDL level, though intervals may be lengthened if the patient is tolerating lipid-lowering therapy. Lipoprotein apheresis should be considered a chronic lifelong therapy, and therefore, peripheral IVs or AV fistulas are recommended for access over tunneled dialysis catheters.

There are a variety of techniques available worldwide for the selective removal of LDL cholesterol; in the United States, only the Liposorber system (Kaneka Corporation, Osaka, Japan) is currently available. With the Liposorber system, blood is passed through a membrane plasma separator before entering one of two dextran sulfate–based immunoadsorption columns (LA-15 column) on the MA-03 machine. Dextran sulfate is a negatively charged molecule with low toxicity that selectively binds the positively charged Apo-B–containing lipoproteins (LDL, very low-density lipoprotein [VLDL], and Lp[a]) with high affinity, thus removing them from the circulating plasma. Heparin is used for anticoagulation. A 1.5 plasma volume is targeted for processing to achieve an LDL reduction of 73% to 83% after a single treatment. The negatively charged surface of the adsorbers promotes bradykinin release; thus, ACE inhibitors are contraindicated in patients on this modality, but angiotensin receptor blockers may be used instead. The Liposorber system (Kaneka Corporation, Osaka, Japan) is also FDA approved as a Humanitarian Use Device for the treatment of FSGS.

Several other techniques are available worldwide to selectively remove LDL cholesterol. In Europe, an immunoadsorption column containing anti-apoprotein B100-antibodies (Therasorb-LDL, Miltenyi Biotec, Germany) is available for the treatment of hyperlipidemia. Owing to high costs, these columns are typically regenerated and stored, which can be a cumbersome process. Two whole blood systems are also in use

that do not require plasma separation: DALI (Direct Adsorption of Lipoprotein, Fresenius, Germany) and a whole blood version of the Liposorber system (Liposorber D, Kaneka Pharma Europe N.V.). There is also an immunoadsorptive device (Lipopak, Pocard, Moscow, Russia) that is marketed to target lipoprotein(a), which is an independent risk factor for coronary heart disease. Additionally, the Heparin-induced Extracorporeal Lipoprotein/fibrinogen Precipitation (HELP) system (B. Braun) is a plasma separation device that selectively precipitates lipoproteins and fibrinogen via heparin buffered at a pH of 5.12. The precipitate is then removed from the plasma by a polycarbonate membrane, and the heparin by a heparin adsorber, and finally, the plasma is restored to a physiologic pH via bicarbonate dialysis.

C. **Immunoadsorption columns.** There are a variety of columns available worldwide that have been designed to selectively bind a target molecule and remove it from the circulating plasma (Figure 17.3). The columns currently available either contain staphylococcal protein A (SPA), a specific peptide or synthetic antigen, or an immobilized antibody covalently bound to an inert and insoluble matrix (such as cellulose) in a column of gel beads. SPA has a high affinity for the Fc portions of IgG1, IgG2, and IgG4 and depletes the plasma of IgG autoantibodies or circulating immune complexes that contain IgG. There is an SPA column (Immunosorba, Fresenius Medical Care) available in other countries used for the treatment of antibody-mediated rejection in kidney transplant, dilated cardiomyopathy, SLE, pemphigus vulgaris, and anti-FVIII antibody. Examples of immunoadsorption columns that utilize immobilized antibodies include anti-apoprotein B (Therasorb-LDL) used for hyperlipidemia as mentioned earlier and anti-IgG antibody columns (Therasorb-Ig) used in Europe for the treatment of autoimmune diseases such as SLE, myasthenia gravis, dilated cardiomyopathy, and ABO-incompatible kidney transplantation. Finally, many immunoadsorption columns have been developed that contain either an immobilized antigen or peptide designed to bind a specific circulating antibody or molecule. An example is the Glycosorb ABO column, which contains terminal trisaccharide A or B blood group antigen immobilized on Sepharose, which binds circulating anti-A or anti-B antibodies, and which can be used to facilitate ABO-incompatible organ transplantation.

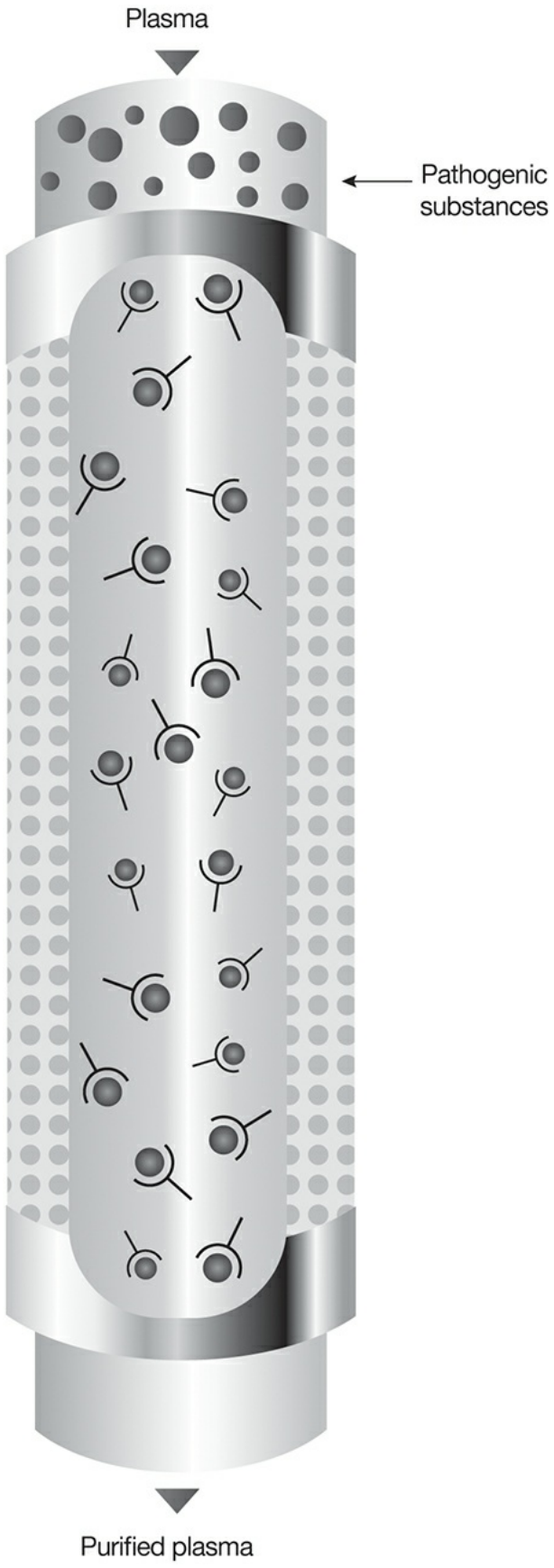

Plasma
Pathogenic substances
Purified plasma

FIGURE 17.3: Immunoadsorbent columns retain pathogens by binding them to elements in the column. (Courtesy of Dobri Kiprov, MD. Reprinted from Linz W, et al. *Principles of Apheresis Technology*. 5th ed. American Society for Apheresis; 2014. www.apheresis.org)

D. Double filtration plasmapheresis. Double filtration plasmapheresis or "cascade filtration" refers to the process of using a primary membrane plasma separator to isolate the plasma, followed by a secondary plasma fractionator to remove target solutes based on molecular size and weight. It has been used for the treatment of hypercholesterolemia, cryoglobulinemia, Waldenström macroglobulinemia, and diseases with impaired microcirculation. There are a variety of secondary plasma fractionators available with varying pore sizes to allow for targeted filtration of the desired molecule. Although it is more selective than conventional plasmapheresis, valuable proteins such as IgM can be lost in the filter, and the capacity of the system is limited by filter clotting with retentate.

X. CELLULAR-BASED APHERESIS PROCEDURES

A. RBC exchange or erythrocytapheresis. This therapy requires the use of a centrifugal-based apheresis instrument in order to remove defective or excessive RBCs and replace them with either donor cells (eg, for treating sickle cell disease) or isotonic fluids (erythrocytapheresis, used in hereditary hemochromatosis). RBC exchange is commonly performed for both acute and chronic complications of sickle cell disease but has also been employed in severe cases of parasite-infected red cells (malaria or babesiosis). The number of units of blood exchanged can be determined by various factors including the starting and desired end procedure hematocrit, the desired reduction in hemoglobin S percentage (HbS%), and the hematocrit of the transfused blood. RBC exchange can rapidly lower the HbS% without causing transfusional volume overload or increased viscosity associated with an hematocrit greater than 31 in sickle cell disease, as well as maintaining a more iron-neutral state. For patients on chronic RBC exchange therapy, a technique called isovolemic hemodilution, otherwise known as a "deplete-exchange," is an option to reduce the number of units of blood needed over time. RBC exchange programs should perform extended antigen matching of transfused blood (at minimum testing for the red blood cell antigens C/c, E/e, and K [Kell]) which greatly mitigates the risk for new antibody formation.

B. Leukapheresis. Leukapheresis or white cell depletion can be performed for removal of blasts in patients with acute leukemia with symptomatic leukostasis (typically when WBC > 100k) or in acute lymphoblastic leukemia (typically when >400k). For leukapheresis, typically processing 1.5 to 2 TBVs will reduce the WBC count by 30% to 50% per treatment. Often a replacement solution such as normal saline or 5% albumin is given to prevent hypovolemia.

C. Thrombocytapheresis. Thrombocytapheresis is performed for symptomatic hyperproliferative malignancies, typically when the platelet count is greater than 1000×10^9 /L. A 1.5 to 2.0 TBV exchange similarly will reduce platelet count by 30% to 50%. With platelet depletion, patients may be fluid balance positive due to anticoagulant volume (ACD-A) and may not require additional replacement fluids.

D. Collection of hematopoietic progenitor or immune effector cells. Hematopoietic progenitor cell collections and immune effector cell collections (such as

chimeric antigen receptor (CAR) T cell therapy) use centrifugal-based apheresis equipment to collect the cells needed for the treatment of hematologic and other oncologic conditions. Typically, the procedure is performed by processing 2 to 4 times the TBV on 1 to 4 consecutive days in order to achieve a prespecified number of target cells.

E. Extracorporeal photopheresis. This is an online processing modality initially developed for the treatment of cutaneous T-cell lymphoma (Sezary syndrome). It is also used as a treatment for selected patients with cell-mediated alloimmune disorders such as graft-versus-host disease and cellular-type rejection in heart and lung transplantation. During this procedure, centrifugation is used to collect WBCs. The WBC product is then injected with 8-methoxypsoralen (8-MOP) and exposed to a controlled dose of ultraviolet-A (UV-A) light prior to being returned to the patient. UV-A light activates 8-MOP, leading to cross-linking of DNA, thereby inducing apoptosis in T cells and modifying dendritic cells. This is thought to induce clonal-specific changes in ongoing immune responses, including the production of T-regulatory cells, which shift the balance toward tolerance. There is one current closed system circuit available (CELLEX, Mallinckrodt Pharmaceuticals). Heparin is typically used for anticoagulation (though citrate protocols exist); access is either peripheral or via an apheresis port, and blood flow rates are low at approximately 25 to 30 mL/min. Treatments are done in pairs on consecutive days and repeated every 2 or more weeks; clinical benefit accrues gradually. This is a unique apheresis therapy, as it leads to an actual cell modification; there is no replacement fluid necessary, and due to the design of the apheresis centrifuge, the extracorporeal volume is not set and is dependent on the patient's hematocrit. It is not recommended to perform the procedure if the hematocrit is less than 27 and the extracorporeal volume in the circuit approaches greater than or equal to 500 mL, which can be problematic even in an adult population.

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18 Use of Dialysis and Hemoperfusion in the Treatment of Poisoning

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The opioid epidemic has grown to a catastrophic level in both the United States and Canada, leading to nearly 100,000 overdose deaths per year in the United States alone. Unintentional poisoning is now the leading cause of death for Americans below the age of 44. The scale of the opioid overdose epidemic has also transformed treatment paradigms, leading to wide distribution of the antidote naloxone for intranasal administration by family, first responders, and community-based programs. Reports of drug abuse and overdose are more likely to accrue in crime statistics and mortality data than in poison control networks. The majority of reported toxic exposures involve just a few classes of prescription medications (opioids/analgesics, sedatives/hypnotics, antipsychotics, and antidepressants) or readily available cleaning or personal care products.

Of the reported millions of exposures to poisons, the majority are unintentional, occur in children, and do not require hospitalization. On the other hand, exposures in teenagers and adults are more likely to be intentional and require hospitalization and focused treatment. Multiple-dose activated charcoal (MDAC) and alkalinization treatments far outnumber hemodialysis or continuous kidney replacement therapy (CKRT), and these in turn far outnumber the rarely used modality, hemoperfusion (Gummin, 2021).

Management of poisoning remains a multidisciplinary effort. The approach to the intentional or accidentally poisoned patient involves mostly supportive care, but also consideration of antidotes, enteric decontamination, and/or enhanced corporeal elimination. Hemodialysis and hemoperfusion remain useful adjuncts in the management of drug overdose and poisoning on a selective basis. Evidence-based recommendations for the use of dialysis and related modalities are available for many common poisonings.

I. DIALYSIS AND HEMOPERFUSION

A. Indications.

Extracorporeal techniques should be considered in the setting of criteria listed in Table 18.1. Any procedure used in poisoning treatment (particularly extracorporeal treatments) should have a greater effect on drug elimination than that which occurs spontaneously, such as with endogenous kidney or hepatic clearance. Early use of dialysis or hemoperfusion can be considered if the serum concentrations of a drug or poison are found to be increased to values known to be associated with adverse outcomes, organ injury, or death. Critical serum concentrations for initiation and cessation of extracorporeal toxin removal (ECTR) and specific recommendations for several drugs are listed in Table 18.2. The information given in Tables 18.1 and 18.2 only represents a set of recommendations; the decision to institute dialytic modalities or hemoperfusion must be made on an individual clinical basis. In addition to providing

extracorporeal drug elimination, dialysis can provide metabolic control and essential supportive care to poisoned patients with multiorgan or kidney injury.

TABLE 18.1 Criteria for Consideration of Dialysis or Hemoperfusion in Poisoning

1. Progressive deterioration despite intensive supportive therapy
2. Severe intoxication with depression of midbrain function, leading to hypoventilation, hypothermia, and hypotension
3. Development of complications of coma, such as pneumonia or septicemia, and underlying conditions predisposing to such complications (eg, obstructive airway disease)
4. Impairment of normal drug excretory function in the presence of hepatic, cardiac, or renal insufficiency
5. Intoxication with agents with metabolic and/or delayed effects (eg, methanol, ethylene glycol, and paraquat)
6. Intoxication with an extractable drug or poison, which can be removed at a rate exceeding endogenous elimination by the liver or kidney

TABLE 18.2 Summary of Evidence-Based Recommendations for Extracorporeal Treatment of Common Poisons

	Indications				
Poison	**Poison Concentration**	**Clinical and Laboratory**	**Choice of ECTR**	**Cessation of ECTR**	**Other Considerations**
Acetaminophen	>900 mg/L (5,954 mcmol/L)	Metabolic acidosis, altered consciousness, or coma	HD > CKRT	Clinical improvement	Dose of IV NAC should be at least 12.5 mg/kg/h.
Baclofen	Not specified	Coma requiring mechanical ventilation *and* impaired kidney function	HD	Clinical improvement	Not recommended if normal kidney function
Barbiturates (long acting)	Increasing or persisting (not specified)	Coma, mechanical ventilation, shock	HD > HP /CKRT	Clinical improvement	Coadminister MDAC
β-Adrenergic antagonists	Not specified	Refractory bradycardia/ hypotension *and* kidney impairment (atenolol and sotalol only)	HD	Clinical improvement	
Calcium channel blockers	None				
Carbamazepine	Increasing or persisting (not specified)	Refractory seizures, life-threatening dysrhythmias, prolonged coma, respiratory depression requiring mechanical ventilation, toxicity despite MDAC	HD > CKRT/ HP	Clinical improvement *or* carbamazepine <10 mg/L (42 mcmol/L)	MDAC therapy should be continued.
Chloroquine/ hydroxychloroquine	None				

Ethylene glycol	>310 mg/dL (50 mmol/L; if antidote used) >62 mg/dL (10 mmol/L; if no antidote used)	Shock, coma, seizures, anion gap >24 mmol/L[a], impaired kidney function	HD > CKRT	Anion gap <18 mmol/L, normalization of acid-base parameters, ethylene glycol <25 mg/dL (4 mmol/L)	ECTR may not be required if normal kidney function and fomepizole are used. The dose of ethanol and fomepizole must be adjusted during ECTR.
Gabapentin/ pregabalin	Not specified	Coma requiring mechanical ventilation *and* impaired kidney function	HD	Clinical improvement	Not recommended if normal kidney function
Isoniazid	Not specified	If standard dose pyridoxine cannot be administered and if there are refractory seizures	HD		
Lithium	>5.0 mEq/L	Decreased LOC, seizures, dysrhythmias, impaired kidney function	HD > CKRT	Clinical improvement *or* Li <1.0 mEq/L	Consider CKRT after HD.
Metformin	Not specified	Shock, failure of standard supportive measures, decreased LOC, lactate >20 mmol/L, pH < 7.0	HD > CKRT	Lactate <3 mmol/L *and* pH > 7.35	Repeat sessions using HD or CKRT. Closely monitor lactate and pH for additional ECTR courses.
Methanol	>70 mg/dL (21.8 mmol/L; if fomepizole used) >60 mg/dL (18.7 mmol/L; if ethanol used) >50 mg/dL (15.6 mmol/L; if no antidote used)	Coma, seizures, new vision deficits, pH ≤ 7.15, anion gap >24 mmol/L[a]	HD > CKRT	Clinical improvement *and* methanol <20 mg/dL (6.2 mmol/L)	ECTR may not be required if normal kidney function and fomepizole used. Folic acid should be continued during ECTR.
Methotrexate	None				
Salicylates	>100 mg/dL (7.2 mmol/L)	Altered mental status, ARDS, kidney impairment, pH ≤7.20	HD > HP > CKRT	Clinical improvement *and* salicylate <20 mg/dL (1.4 mmol/L)	ET may be used in children/coadminister MDAC.
Theophylline	>100 mg/L (555 mcmol/L; acute exposure) >60 mg/L (333 mcmol/L; chronic poisoning)	Seizures, life-threatening dysrhythmias, shock, clinical deterioration despite optimal care, GI decontamination cannot be administered	HD> HP> CKRT	Clinical improvement *or* theophylline <15 mg/L (83 mcmol/L)	Coadminister MDAC.
Valproic acid	>1,300 mg/L (9,000 mcmol/L)	Cerebral edema, coma, shock, acute hyperammonemia, pH ≤ 7.10, respiratory depression	HD > CKRT/ HP	Clinical improvement *or* valproic acid <100 mg/L (700 mcmol/L)	

ARDS, acute respiratory distress syndrome; CKRT, continuous renal replacement therapy; ECTR, extracorporeal toxin removal; ET, exchange transfusion; GI, gastrointestinal; HD, intermittent hemodialysis; HP, hemoperfusion; IV, intravenous; LOC, level of consciousness; mcmol, micromole; MDAC, multiple doses of activated charcoal; NAC, *N*-acetylcysteine.

[a]The anion gap is calculated by (Na + K) – (Cl + HCO_3).

B. Choice of therapy

1. **Peritoneal dialysis** is not very effective in removing drugs from the blood, with maximal poison clearance rarely above 15 mL/min (about one-tenth of what usually can be reached with hemodialysis). Nevertheless, when hemodialysis is delayed or technically difficult, such as in small children, a prolonged session of peritoneal dialysis can be a valuable adjunctive treatment for poisoning. In the hypothermic-poisoned patient, peritoneal dialysis may be useful to help in core rewarming.
2. **Hemodialysis** is the therapy of choice for water-soluble drugs, especially those of low molecular weight (MW) and low level of protein binding, as such compounds will diffuse rapidly across the dialyzer membrane. Examples of well-dialyzed toxins include methanol, ethanol, ethylene glycol, lithium, and salicylates. Water-soluble drugs with high MWs (eg, amphotericin B [MW 9,241] and vancomycin [MW 1,500]) diffuse across dialyzer membranes more slowly and are less well removed.

Removal of larger solutes is accelerated by the use of the now standard high-flux membranes and the addition of convection (hemodiafiltration). Hemodialysis is not efficient for lipid-soluble drugs with large volumes of distribution (eg, amitriptyline) or drugs with extensive protein binding (eg, nonsteroidal anti-inflammatory drugs). The limits of hemodialysis for the removal of highly protein-bound drugs may be overcome if drug displacers become available (see below).

3. **CKRT,** which combines diffusion and/or convection but with lower blood and effluent flows, is commonly employed in poisoned patients with marked hemodynamic instability that precludes conventional hemodialysis. Prolonged continuous treatment is potentially useful in drugs with slow intercompartmental transfer times because posttherapy rebound of plasma drug levels and the need for repeat dialysis are avoided. Clear advantages of continuous treatment over repeated conventional treatments for drug rebound remain to be demonstrated. However, CKRT offers substantially lower poison clearance than intermittent hemodialysis, which is problematic in patients urgently needing poison removal. The use of conventional dialysis for initial toxin removal followed by CKRT for continued removal and to limit rebound can also be considered.
4. **Hemoperfusion** is a process whereby blood is passed through a cartridge device containing particles that compete with plasma proteins and adsorb and remove the drug. Most commonly, the adsorbent particles are activated charcoal or resin. Although hemoperfusion historically removed many large protein-bound drugs from the blood more efficiently than hemodialysis, this modality has been supplanted by modern high-flux dialysis. In the United States, hemoperfusion cartridges are expensive, have been discontinued, and may not be available (Shalkham, 2006). If a drug is equally well removed from the blood by hemoperfusion and hemodialysis, then hemodialysis is preferred, avoiding potential problems of cartridge saturation and complications such as thrombocytopenia and leukopenia. Additionally, experience with hemodialysis is widespread, and this modality can correct any associated acid-base, electrolyte, or volume disturbances. One indication for the use of hemoperfusion in poisoning is in the first few hours following paraquat/diquat ingestion. Although unavailable in the United States (except for emergency use), the CytoSorb hemoperfusion device containing modified polystyrene beads has been shown in European studies to remove the anticoagulants bivalirudin and apixaban and the antiplatelet agent ticagrelor (Javanbakht, 2020; Mendes, 2021; Scandroglio, 2021).

C. Pharmacokinetics. Poisons have various molecular characteristics that make them more or less amenable to extracorporeal removal. Dialyzability of a poison is possible only if it can be extracted from the plasma compartment, if a significant proportion of its total body stores can be eliminated, and if extracorporeal clearance contributes a significant amount to total clearance. Removal from the plasma compartment is best reflected by the dialyzer extraction ratio, which can be calculated as $(A - V)/A$, where A represents the inflow (prefilter or precolumn) concentration of the solute to be removed and V represents the dialyzer outflow concentration. The amount of toxin that can be removed by extracorporeal treatment is greatly affected by the volume of its distribution in the body. The ratio of extracorporeal removal to endogenous removal depends on the endogenous clearance of a particular poison and the current condition of the body

organs (liver and/or kidney) that normally participate in endogenous removal. The following factors will influence poison dialyzability (Lavergne, 2012).

1. **MW.** Small MW toxins diffuse quickly through dialyzer membranes and can often be efficiently removed by dialysis. Removal of larger MW toxins is limited both by a reduced diffusion rate due to their size and by progressive difficulty in passing through the pores of conventional high-flux dialyzer membranes. Such membranes easily pass compounds of MW up to about 20 to 25 kDa, whereas larger molecules (25-50 kDa) are not as efficiently removed. Adding a convective component to the treatment, for example, hemodiafiltration, can increase the removal of such larger molecules to a degree. Adsorption to certain membranes during hemodialysis, hemoperfusion, or plasmapheresis can be used to remove very large MW compounds.
2. **Protein binding.** Complexes formed by proteins with toxins or drugs cannot freely pass through dialyzers or hemofilters; only the largely unbound (or free) fraction can be removed by these techniques. However, at higher concentrations (such as in overdose), the protein binding of a drug can become saturated; under such conditions, a higher proportion of the drug is unbound or "free," which is then available for removal by extracorporeal treatment. The employment of drug displacers is a possible future method to increase the dialyzability of highly protein-bound toxins (Madero, 2019).
3. **Volume of distribution.** V_D is the theoretical volume into which a drug is distributed. Heparin, for example, a drug confined to the blood compartment, has a V_D of approximately 0.06 L/kg. Drugs distributed primarily in the extracellular water (eg, salicylates) will have a V_D of approximately 0.2 L/kg. Some drugs will have V_D values exceeding the volume of total body water because they are extensively bound to, or stored in, tissue sites. With drugs that have a high V_D (eg, digoxin, tricyclics), the amount of drug present in the blood represents only a small fraction of the total body load. In such instances, even if a hemodialysis or hemoperfusion treatment extracts most of the drug present in the blood flowing through the extracorporeal circuit, the amount of drug removed during a single treatment session will represent only a small percentage of the total body drug burden. Subsequently, additional drug will enter the blood from tissue stores, sometimes causing a recurrence of the toxic manifestations. On the other hand, even transiently lowering the blood concentration of some agents may mitigate their toxic effects. Hence, hemodialysis or hemoperfusion can sometimes effectively reduce drug toxicity even when the V_D is large.
4. **Endogenous clearance.** Extracorporeal removal is usually not indicated when endogenous clearance by metabolism and elimination is expected to exceed the rate of ECTR. However, in the presence of kidney impairment for renally eliminated poisons (eg, lithium), extracorporeal removal can be useful.

D. Technical points

1. **Vascular access for hemodialysis or hemoperfusion in poisoning.** In patients without permanent vascular access in place, percutaneous cannulation of a large central vein and placement of a temporary (nontunneled) dialysis catheter are required.

2. **Choice of hemofilter.** High-flux, high-efficiency dialyzers with high urea clearances should generally be used. The development of high-cutoff hemodialysis membranes (with an increased pore size of 8-10 nm) may allow clearance of larger toxins and molecules as large as 50 to 60 kDa (eg, albumin). Hemofilters using the AN69 membrane are known to have adsorptive capacity for many compounds, and so may be useful to treat overdose with certain drugs.
3. **Choice of a hemoperfusion cartridge.** Some of the available cartridges are listed in Table 18.3. Typical sorbents are activated carbons (charcoals), ion exchange resins, or nonionic exchange macroporous resins. Charcoal has a greater affinity for water-soluble drugs while resin has a greater affinity for lipophilic drugs. Sorbent particles have been rendered biocompatible by coating the surface with a polymer membrane. The cartridges contain various amounts of sorbent, the smaller ones being designed for pediatric use. A detailed comparative evaluation of in vivo performance of the various brands of cartridges has been published (Ghannoum, 2014b).

TABLE 18.3 Some Available Hemoperfusion Devices

Manufacturer	Device	Sorbent Type	Amount of Sorbent	Polymer Coating
Asahi	Hemosorba	Spherical charcoal	170 g	Polyhema
Gambro	Adsorba	Norit charcoal	100 or 300 g	Cellulose Acetate
Cytosorbents	CytoSorb[a]	Polystyrene divinylbenzene copolymer	300 g	None
Jafron Biomedical	HA 130/230/330/380[a]	Polystyrene divinylbenzene copolymer	Various	None
ExThera	Seraph-100 Microbind Affinity Blood Filter[a]	Polyethylene	Embedded in the filter	None
Baxter	Oxiris[a]	AN69 membrane polyethyleneimine membrane	N/A	Heparin

NA, not applicable.

[a]Available in Europe or Japan, and for compassionate or emergency use in the United States.

4. **The hemoperfusion circuit.** The hemoperfusion circuit is similar to the blood side of a hemodialysis circuit and includes an air detector and a venous air trap. Standard hemodialysis blood pumps and machines (without the use of dialysis

solution) are used to drive the blood through the tubing and cartridge.

5. **Priming the hemoperfusion circuit.** Setup and priming with saline or dextrose differ depending on the brand of cartridge used, and the manufacturer's literature should be consulted in all instances. The hemoperfusion cartridge must be primed in a vertical position with the arterial (blood inlet) side facing downward.
6. **Heparinization during hemoperfusion.** Once the cartridge has been primed, a bolus dose of heparin (usually 2,000-3,000 units) is administered into the arterial line, the cartridge is kept inlet side down, and blood flow through the cartridge is begun. As a rule, because of some adsorption on the sorbent, more heparin may be required for a hemoperfusion treatment (eg, ~6,000 units or 10,000 units for charcoal and resin, respectively, per session) than for hemodialysis. Heparin should be given in amounts sufficient to maintain the patient's activated clotting time or partial thromboplastin time at about twice the normal value.
7. **Duration of hemoperfusion.** A single 3-hour treatment will substantially lower the blood levels of most poisons for which hemoperfusion is effective. More prolonged use of a hemoperfusion cartridge is inefficient because the binding sites on the charcoal become saturated. Replacement of saturated devices with fresh ones is not usually required, and any rebound in blood drug concentrations consequent to tissue release can be treated with a second hemoperfusion session. On the other hand, continuous hemoperfusion treatment may be required for several days until clinical improvement or a nontoxic blood level is achieved. Hemoperfusion devices may need to be changed every 4 hours in the course of continuous treatment.

E. Complications. All extracorporeal techniques require vascular access through a central line, and this procedure itself is subject to complications.

1. **Central line.** The placement of a temporary, nontunneled dual-chamber large-caliber central venous catheter is necessary for ECTR in patients without a preexisting arteriovenous fistula or graft. The placement of this venous catheter involves a risk of blood stream infection, thrombosis, and occlusion (Smith and Nolan, 2013). Ideally, catheters should be placed in the internal jugular vein, using ultrasound guidance. The use of anticoagulants can increase the risk of bleeding from the access site.
2. **Due to the ECTR**
   a. **Bleeding.** As ECTR involves an extracorporeal blood circuit, the procedures involve the risk of exsanguination, and blood lines and access should be visualized during treatment. Modern machines have arterial pressure alarms and may have disconnect alarms to alert clinicians to look for signs of exsanguination. Hemoperfusion involves additional bleeding risk (see below).
   b. **Hypophosphatemia.** In contrast to end-stage kidney disease, patients being dialyzed for poisoning often do not have an elevated plasma phosphate value. Because phosphate is not present in standard dialysis solutions, intensive dialysis or continuous hemodiafiltration can severely lower the plasma phosphate level, resulting in respiratory insufficiency and other complications. Hypophosphatemia during dialysis can be avoided by supplementing the dialysis solution with phosphate.
   c. **Alkalemia.** Standard hemodialysis solutions contain unphysiologically high concentrations of bicarbonate, and they also contain a bicarbonate-generating

base in the form of acetate or citrate, as they have been designed to correct metabolic acidosis. Performing dialysis for poisoning in a patient with metabolic or respiratory alkalosis can provoke or worsen alkalemia unless the dialysis solution bicarbonate concentration is appropriately reduced.

d. Disequilibrium syndrome in patients with acute uremia. In patients with both severe uremia and poisoning, it may be dangerous to carry out a prolonged initial high-clearance conventional dialysis session. During a dialysis treatment for a metformin-associated lactic acidosis in a patient with marked uremia, enrichment of dialysate with an appropriate amount of urea in an attempt to attenuate the manifestations of the disequilibrium syndrome has been successfully performed (Doorenbos, 2001). Disequilibrium syndrome can be attenuated by shortening the treatment, lowering blood flow rate as in a CKRT or SLED (sustained low-efficiency dialysis) treatment, or using concurrent dialysate flow, although all of these measures necessarily reduce clearance of the poison.

e. Removal of antidotes. Hemodialysis and CKRT remove the *N*-acetylcysteine (NAC) administered for acetaminophen poisoning (Table 18.2), and dose adjustment is required. These modalities also remove ethanol and fomepizole used in the treatment of toxic alcohols, requiring dose adjustment (Table 18.4).

TABLE 18.4 Antidote Dosing for Toxic Alcohols

Antidote		Loading Dose	Maintenance Dose			
			Nondrinker	Chronic Drinker	HD, Nondrinker	HD, Drinker
Ethanol	43% oral solution	1.8 mL/kg	0.2 mL/kg/h	0.5 mL/kg/h	0.5 mL/kg/h	0.8 mL/kg/h
	10% IV solution	7.5 mL/kg	0.8 mL/kg/h	2.0 mL/kg/h	2.1 mL/kg/h	3.3 mL/kg/h
	Dialysate	300 mL 95% ethanol added to 4.5 L of acid concentrate, ultrafiltrate flow = 500 mL/min				
Fomepizole		15 mg/kg	10 mg/kg q 12 h × 4 doses, then 10-15 mg/kg q 12h		10 mg/kg q 4h (q8h in CKRT) or 1 mg/kg/h	

CKRT, continuous kidney replacement therapy; HD, hemodialysis; IV, intravenous.

f. Withdrawal. Clinically significant withdrawal syndromes may result from toxin removal. In acute baclofen poisoning in patients with long-term use, acute removal can precipitate delirium, spasms, and seizures and may require management with baclofen reintroduction and $GABA_A$ (γ-aminobutyric acid-A) receptor agonists (Ghannoum, 2021).

g. Hemoperfusion. Mild transient thrombocytopenia and leukopenia can occur, but cell counts usually return to normal within 24 to 48 hours following a single

hemoperfusion treatment. Bleeding risk may also increase due to impaired platelet aggregation and increased fibrinolysis (Park, 2019). Adsorption or activation of coagulation factors has also been observed rarely and may be clinically significant in patients with liver failure.

II. MANAGEMENT OF POISONING WITH SELECTED AGENTS. The EXTRIP (EXtracorporeal TReatment In Poisoning) work group has drafted guidelines for the use of blood purification in the context of overdose (Lavergne, 2012). A summary of evidence-based recommendations by EXTRIP for common poisoning is included in Table 18.2.

A. Acetaminophen (MW 151 Da). MDAC should be given to patients presenting within 4 hours of ingestion. Serum levels should be measured and plotted using the Rumack-Matthew nomogram to establish the risk of hepatotoxicity and the need for NAC therapy. Concomitant ingestion of moderate amounts of ethanol markedly increases the risk of liver damage. If serum acetaminophen levels are above 150 mg/L (1.0 mmol/L) at 4 hours, the likelihood of toxicity is high and NAC (orally [PO] or intravenously [IV]) should be given. NAC, by increasing reduced glutathione stores, prevents the accumulation of toxic acetaminophen by-products. Efficacy in preventing liver failure declines if started more than 10 hours after ingestion, but NAC is still recommended even after 24 hours. Although acetaminophen is moderately water soluble and is minimally protein bound and thus removed by dialysis, NAC remains the treatment of choice. Conventional hemodialysis is recommended when acetaminophen level is greater than 900 mg/L (5.9 mmol/L) with acidosis or altered consciousness; and in this setting, the rate of IV NAC administration should be greater than 12.5 mg/kg/h during dialysis (Dart, 2023).

B. Salicylates (acetylsalicylic acid, MW 180 Da, and methylsalicylate MW 152 Da). In adults, severe aspirin poisoning is usually accompanied by metabolic acidosis with respiratory alkalosis, whereas in children, isolated metabolic acidosis is often encountered. The appearance of central nervous system symptoms is a sign of severe poisoning. The Done nomogram (Done and Temple, 1971), relating serum levels and time of ingestion to outcome, gives some idea of the seriousness of salicylate poisoning in children but is less used in adult poisoning. MDAC should be initiated and enhanced elimination with urine alkalinization attempted if substantial urine output is achievable, particularly when symptoms are present and serum salicylate levels are greater than 50 mg/dL (2.8 mmol/L). Aspirin has a V_D of only 0.15 L/kg. Although the drug is about 50% protein bound, aspirin is well removed by hemodialysis. Hemodialysis should be considered when the serum level exceeds 100 mg/dL (5.6 mmol/L) or there is evidence of neurologic involvement (neurologic symptoms, hyperthermia, seizures), acute respiratory distress syndrome (noncardiogenic pulmonary edema), kidney impairment, or marked academia ($pH \leq 7.2$).

C. Barbiturates. Toxic serum levels of phenobarbital (MW 232 Da) are over 3 mg/dL (130 mcmol/L), and coma begins to appear at levels of 6 mg/dL (260 mcmol/L). MDAC should be administered as first-line therapy, and alkalinization of the urine may help remove long-acting barbiturates such as phenobarbital. Phenobarbital is 50% protein bound, but its V_D is only 0.5 L/kg; the drug is well removed by either hemodialysis or hemoperfusion. Hemodialysis should be contemplated in the setting of coma, shock, or the need for mechanical ventilation. Removal with hemodialysis using a synthetic

membrane dialyzer equals that of hemoperfusion (Palmer, 2000).

D. Digoxin (MW 781 Da). The probabilities of digoxin-induced arrhythmias are 50% and 90% at serum levels of 2.5 and 3.3 ng/mL (3.2 and 4.2 nmol/L), respectively. Treatment includes correction of hypokalemia, hypomagnesemia, and alkalosis and oral administration of MDAC. The V_D of digoxin is large (8 L/kg in normal patients, 4.2 L/kg in patients undergoing dialysis), and the drug is 25% protein bound. For these reasons, only 5% of the body load will be removed by a 4-hour hemodialysis treatment. Although hemoperfusion is more effective and has been shown to improve symptoms, it is not routinely recommended in the treatment of digoxin toxicity as the V_D of the drug is so large that total body clearance is limited. Most authors recommend treatment with digoxin-specific antibodies (Fab) in severe toxicity. In patients undergoing dialysis, Fab therapy remains preferred over hemoperfusion or plasmapheresis. Although Fab has been used successfully in patients with coexisting renal failure, digoxin may be released from the Fab-digoxin complex, leading to a rebound in toxicity, perhaps requiring a second treatment (Ujhelyi, 1993). Plasmapheresis performed soon after Fab fragment administration promotes the removal of the Fab-digoxin complexes (Zdunek, 2000), and high-cutoff membranes such as Theralite can also be used for this purpose (Fleig, 2011).

E. Toxic alcohols. Ethylene glycol and methanol are the most common causes of fatal toxic alcohol poisoning. Ethylene glycol is found in antifreeze solutions, deicing solutions, hydraulic brake fluid, foam stabilizers, and chemical solvents. Methanol is found in windshield washing fluids, paints, solvents, copier fluids, and illegally manufactured (wood) alcohol. Methanol and ethylene glycol are relatively nontoxic, but both are metabolized via the enzyme alcohol dehydrogenase to produce toxic metabolites formic acid and glycolic acid, respectively. In ethylene glycol poisoning, glycolate is further metabolized to oxalate, which can cause acute kidney injury.

Coingestion of ethanol may delay the formation of toxic metabolites and clinical toxidromes. Poisonings with toxic alcohols should be suspected in patients with inebriation and an increase in osmolal gaps and later, following metabolism, an increased anion gap metabolic acidosis. A normal osmolal or anion gap does not eliminate the possibility of significant toxic alcohol ingestion. Alcohols are rapidly absorbed and have the same V_D as water. MDAC or gastrointestinal decontamination has no role in the management of alcohol poisoning. Both ethanol and fomepizole (4-methylpyrazole) are competitive inhibitors of the alcohol dehydrogenase enzyme and prevent the formation of toxic metabolites. Fomepizole is preferred due to its predictable pharmacokinetics, ease of administration, and fewer adverse effects, and should be given as soon as possible after ingestion. In some patients with preserved kidney function, the use of fomepizole can prevent the need for hemodialysis, although the long elimination half-life can significantly prolong the need for intensive monitoring and hospitalization. As hemodialysis is highly effective in rapidly removing both toxic alcohols and their metabolites and in correcting metabolic abnormalities, the risks and costs of prolonged hospitalization and the cost of fomepizole must be weighed against those of hemodialysis. If dialysis is initiated, doses of ethanol or fomepizole should be increased (however, in the case of ethanol therapy, if ethanol is also used to enrich the dialysate, the systemic doses need not be increased) (Table 18.5).

TABLE

18.5 Indications for Treatment of Ethylene Glycol or Methanol Poisoning With Ethanol or Fomepizole

1. Documented plasma ethylene glycol or methanol concentrations >20 mg/dL

   or

2. Documented recent (hours) history of ingestion of toxic amounts of ethylene glycol or methanol and osmolal gap >10 mmol/kg

   or

3. History or strong clinical suspicion of ethylene glycol or methanol poisoning and at least two of the following criteria:
   - Arterial pH <7.3
   - Serum bicarbonate <20 mmol/L
   - Osmolal gap >10 mmol/kg[a]
   - Urinary oxalate crystals (in the case of ethylene glycol) or visual signs or symptoms (in the case of methanol) present

[a]Laboratory analysis by freezing point depression only.

Modified from Barceloux DG, et al. American Academy of Clinical Toxicology practice guidelines on the treatment of ethylene glycol poisoning. *J Toxicol Clin Toxicol*. 1999;37:537; Barceloux DG, et al. American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. *J Toxicol Clin Toxicol*. 2002;40:415.

1. **Ethylene glycol (MW 62 Da).** The first phase of toxicity due to ethylene glycol begins less than 1 hour after ingestion and is characterized by central nervous system depression similar to ethanol intoxication. In severe poisoning, this phase can result in coma and seizures and can last 12 hours. The second phase is due to the toxic effects of the metabolite, glycolic acid, on the cardiopulmonary system with the development of cardiac and respiratory failure 12 hours after ingestion. Severe metabolic acidosis commonly occurs. After 24 to 48 hours, kidney injury develops following oxalate precipitation in the kidney, delaying the excretion of the poison. This is characterized by flank pain, hypocalcemia, acute tubular necrosis, and oxalate crystals in the urine.

   Early aggressive management of acidosis with sodium bicarbonate is essential. Indications for the administration of an antidote (ethanol or fomepizole) are shown in Table 18.4. Indications for hemodialysis are shown in Table 18.2 and include the presence of shock, coma, seizures, anion gap greater than 24 mmol/L, or impaired kidney function (Ghannoum, 2023). An ethylene glycol level above 310 mg/dL (50 mmol/L) if an antidote is used is an indication for dialysis. In the absence of both kidney dysfunction and metabolic acidosis, the use of fomepizole may obviate the need for dialysis, even in patients with high serum ethylene glycol concentrations (Beaulieu, 2022). However, this requires close monitoring of the acid-base status, and hemodialysis should be initiated promptly if acidosis develops. The observed half-life of ethylene glycol during the use of fomepizole is approximately 34 hours (Levine, 2012). The dosing schedule for ethanol or fomepizole and the dose adjustments for hemodialysis are shown in Table 18.4. Hemodialysis should be performed until the anion gap is less than 18 mmol/L, acidosis has resolved, and the ethylene glycol concentration is below 25 mg/dL (4 mmol/L). Redistribution of ethylene glycol in blood (rebound) may occur after cessation of dialysis, and serum osmolality, electrolytes, and acid-base status should be monitored closely during the 24 hours after dialysis. Pyridoxine (50 mg intramuscularly 4 times daily) and thiamine (100 mg intramuscularly 4 times daily) should be considered to increase

the metabolism of glyoxylate. In addition, judicious intravenous fluids should be given to prevent calcium oxalate crystal deposition in the kidneys and acute tubular necrosis. Hypocalcemia may be worsened by bicarbonate treatment (increasing blood pH will lower the ionized calcium) and should be corrected if symptomatic or severe.

2. **Methanol (MW 32 Da).** Methanol poisoning causes early temporary central nervous system depression followed by a latent period lasting 6 to 24 hours before the development of metabolic acidosis and visual symptoms. The latter, due to formic acid accumulation, includes blurred vision, decreased visual acuity, photophobia, visual field defects, or even complete blindness. Early signs include optic disc hyperemia and decreased pupillary reflexes to light.

   Initial management is similar to that for ethylene glycol toxicity, including the correction of acidosis with intravenous sodium bicarbonate to pH 7.35 to 7.4. Ethanol or fomepizole should be administered to prevent the formation of formic acid according to indications (Table 18.4). Hemodialysis should be considered (Table 18.2) when there is coma, seizures, new vision defects, significant metabolic acidosis (pH < 7.15), or an anion gap greater than 24 mmol/L. Serum methanol concentration greater than 50 mg/dL (15.6 mmol/L) if no antidote was used, greater than 60 mg/dL (18.7 mmol/L) if ethanol was used, or greater than 70 mg/dL (21.9 mmol/L) if fomepizole was used are indications for hemodialysis.

   High serum methanol concentrations may require several days of treatment with ethanol or fomepizole. The half-life of methanol with fomepizole alone may be as high as 87 hours (Maskell, 2016). If a patient with high serum concentrations of methanol is not treated with hemodialysis, acid-base status should be monitored closely and hemodialysis should be initiated if acidosis develops. Hemodialysis should be continued until acidosis is corrected and serum methanol levels are less than 20 mg/dL (6.2 mmol/L). Ophthalmologic abnormalities may be transient or permanent and should not be considered an indication to continue dialysis. Formic acid is converted by 10-formyl tetrahydrofolate synthetase to carbon dioxide and water. Folinic acid IV (1 mg/kg [up to 50 mg] in 5% dextrose over 30-60 minutes every 4 hours) should be given to enhance formic acid metabolism until methanol and formate have been cleared. If folinic acid is unavailable, folic acid can be used.

3. **Isopropanol (MW 60 Da).** Isopropanol (isopropyl alcohol) is found in rubbing alcohol, antifreeze, and frost remover. Isopropanol is a common cause of poisoning but is only occasionally fatal. Isopropanol is oxidized by alcohol dehydrogenase to acetone. Unlike ethylene glycol and methanol, most of the clinical effects of isopropanol intoxication are due to the parent compound. Gastrointestinal and central nervous system symptoms, including confusion, ataxia, and coma, can occur in the first hour. Hypotension due to cardiac depression and vasodilatation can occur in severe intoxication. Hypoglycemia can be present. Acidosis is rare in the absence of severe hypotension and is usually due to lactic acidosis. A high serum osmolal gap without acidosis in association with an increased urinary or serum acetone level is highly suggestive of isopropanol poisoning. Supportive treatment is usually all that is necessary. Inhibition of alcohol dehydrogenase is not warranted because acetone is less toxic than the parent compound. Hemodialysis might be considered if the isopropanol levels are greater than 400 mg/dL (67 mmol/L) and significant

central nervous system suppression, renal failure, or hypotension exists.

4. **Other alcohols.** Poisonings with other alcohols used in a variety of industrial and household products have been reported with much less frequency. Metabolism of the parent compound may lead to the generation of toxic metabolites. Propylene glycol (MW 76 Da) is an excipient often used in pharmaceuticals such as lorazepam and nitroglycerine to enhance solubility. Toxicity is associated with lactic acidosis and an elevated osmolal gap. 2-Butoxyethanol (MW 118 Da) is found in a number of resins, varnishes, and glass- and leather-cleaning solutions. Diethylene glycol (MW 106 Da) produces metabolic acidosis, acute kidney injury, hypertension, and cardiac arrhythmias; fomepizole is recommended to prevent metabolism by alcohol dehydrogenase. Toxicity has been associated with metabolic acidosis, hepatic injury, and respiratory distress. Hemodialysis is effective in removing these alcohols and may be indicated in severe intoxications.

F. Lithium (MW 7 Da). Most intoxications result from chronic accumulation, renal failure, diuretic use and dehydration, and interactions with angiotensin converting enzyme (ACE) inhibitors and nonsteroidal anti-inflammatory drugs. Mild (serum Li = 1.5-2.5 mmol/L) and moderate (serum Li = 2.5-3.5 mmol/L) lithium toxicities are characterized by neuromuscular irritability, nausea, and diarrhea. Severe toxicity (serum Li > 3.5 mmol/L) can result in seizures, stupor, and permanent neurologic deficit. Initially, diuretics should be stopped and prompt rehydration initiated. Sodium polystyrene sulfonate may also facilitate Li elimination (Ghannoum, 2010). As lithium is 0% protein bound with a V_D of 0.8 L/kg, it is removed very well by dialysis. Hemodialysis should be initiated for decreased level of consciousness, presence of seizures, dysrhythmias, or impaired kidney function, or when serum Li is greater than 5 mmol/L. The serum lithium concentration may rebound following dialysis owing to a shift from the intracellular compartment; for this reason, additional dialysis sessions or CKRT are not uncommonly required following initial lowering of serum levels with conventional dialysis. Dialysis should be continued until serum Li levels remain below 1.0 mmol/L for 6 to 8 hours after dialysis. Prolonged continuous hemodiafiltration may reduce the extent of lithium rebound posttreatment (Leblanc, 1996).

G. Mushroom poisoning. Ingestion of certain poisonous mushrooms is associated initially with severe gastrointestinal symptoms followed by hepatic insufficiency and cardiovascular collapse. The toxins of these mushrooms (α-amanitin and phalloidin, MW for both ~900 Da) are removed by hemodialysis and hemoperfusion in vitro, but the efficacy of hemodialysis or hemoperfusion in patients poisoned by mushrooms has not been demonstrated. Activated charcoal adsorption of amanitin and administration of silibinin (a flavonolignan from extracts of milk thistle), which prevents amanitin uptake by liver cells, may be of use (Roberts, 2013). Early referral to a poison center and liver transplantation unit is recommended.

H. Paraquat (MW 257 Da). Delayed toxicity with pulmonary fibrosis and renal and multiorgan failure can occur following ingestion of more than 10 mL of paraquat concentrate. Survival is dependent on the amount ingested, the plasma levels with respect to the time of ingestion, and time to presentation for hospital care (Proudfoot, 1979). Plasma levels above 3 mg/L (12 mcmol/L) regardless of when they are measured are usually fatal. Initial management includes gastric lavage with the administration of activated charcoal or Fuller earth with cathartic, as well as immunosuppressants and

antioxidants. Hemodialysis or hemoperfusion may be beneficial within the first 4 hours after poisoning and should be considered when the plasma-paraquat level is 0.1 mg/L (0.4 mcmol/L) or higher. Repeated or continuous ECTR may be needed for several days to maintain plasma levels below 0.1 mg/L as paraquat has a slow intercompartmental transfer rate. Although the evidence that ECTR improves survival is controversial, these procedures should be considered since mortality surpasses 50% even after ingestion of as little as 10 mL. When the presentation is delayed, in patients already in respiratory failure, the prognosis is dismal and palliation should be offered.

I. **Phenothiazines and tricyclic antidepressants.** These agents are highly protein bound and have extremely large volumes of distribution (in the range of 14-21 L/kg). Hence, the total amount of these drugs removed by either hemodialysis or hemoperfusion is small. Treatment of intoxication with these agents is largely supportive, including bicarbonate therapy for widened QRS complex.

J. **Anticonvulsants**

1. **Phenytoin (MW 252 Da).** Nystagmus and ataxia occur at serum values greater than 20 and 30 mg/mL (79 and 119 mmol/L), respectively. Phenytoin is 90% protein bound (70% in patients with uremia) and has a V_D of 0.64 L/kg. Surprisingly, despite phenytoin's high protein binding, which is not saturable even in overdose, it is removed moderately well by hemodialysis or hemoperfusion. Hemodialysis can be considered for prolonged coma or ataxia.
2. **Valproic acid (MW 144 Da).** Valproic acid has a small V_D, is metabolized by the liver, and has significant protein binding. In overdose, protein binding becomes saturated, and free valproate can be subjected to extracorporeal removal. Hemodialysis should be considered when there is cerebral edema, coma, shock, liver dysfunction/acute hyperammonemia, pH less than or equal to 7.10, respiratory depression, or when levels exceed 1,300 mg/L (9,000 mcmol/L).
3. **Carbamazepine (MW 236 Da).** Hemoperfusion can be used for severe intoxications. High-flux hemodialysis also has been reported to give good results (Koh and Tan, 2006).

K. **Theophylline (MW 180 Da).** Toxic reactions occur when theophylline levels exceed 25 mg/L (139 mcmol/L) [therapeutic levels being 10 to 20 mg/L (56-112 mcmol/L)]. Chronic intoxication may have more pronounced symptoms at a given serum level. Seizures typically occur with levels greater than 40 mg/L (222 mcmol/L), but may occur at levels as low as 25 mg/L (139 mcmol/L). Cardiovascular collapse is rare until levels are greater than 50 mg/L (278 mcmol/L). Theophylline has V_D of 0.5 L/kg, poor intrinsic metabolism, and 56% protein binding, and is well adsorbed by charcoal, enabling efficacious removal by MDAC and hemoperfusion. MDAC should be used in significant poisonings even with intravenous theophylline overdose, although protracted vomiting is often a limiting factor. Propranolol (1-3 mg IV) may be used to treat tachyarrhythmia, and hypokalemia should be corrected. ECTR, with hemodialysis preferred to hemoperfusion, is indicated if vomiting prevents the use of MDAC, or in patients with seizures, shock, or arrhythmia. Hemodialysis should also be considered in patients with acute intoxication with levels above 100 mg/L (555 mcmol/L), in chronic toxicity with levels above 60 mg/L (333 mcmol/L), and in both the older adults and infants under 6 months of age above 40 mg/L (222 mcmol/L). Treatment should be continued until the plasma level is less than 15 mg/L (83 mcmol/L).

L. Dabigatran etexilate (Pradaxa) is an oral direct thrombin inhibitor for prophylaxis of thromboembolism in patients with nonvalvular atrial fibrillation. Since its US approval in 2010, dabigatran-associated hemorrhages have been reported, and reversal of its activity has been challenging, given that vitamin K, fresh frozen plasma, or cryoprecipitate used to reverse warfarin-associated coagulopathies are ineffective. Hemodialysis removes the anticoagulant (Chang, 2013; Chen, 2013). In a series of patients undergoing dialysis administered dabigatran at two dose levels, total dabigatran removal with 4 hours of hemodialysis was between 49% and 59% (Khadzhynov, 2013). The kinetics seem to follow first-order elimination during dialysis (Liesenfeld, 2013). Continuous venovenous hemodiafiltration may also be useful in severe cases (Chiew, 2014). The recent introduction of idarucizumab, a specific neutralizing monoclonal antibody to dabigatran, may obviate the need for hemodialysis where the agent is available (Peetermans, 2016; Yip and Deng, 2017).

M. Metformin (MW 129 Da). Metformin is a biguanide used as an oral antihyperglycemic agent in the treatment of type 2 diabetes. It acts by increasing cellular insulin sensitivity. Lactic acidosis may develop in the case of metformin overdose or from metformin accumulation in patients with impaired kidney function. Mortality in the range of 30% has been reported (Peters, 2008). Metformin is absorbed from the gut relatively rapidly and is not metabolized. Ninety percent of the drug is eliminated by glomerular filtration and tubular secretion with a serum half-life between 1.5 and 5 hours. Surreptitious use of metformin may be uncovered in the investigation of lactic acidosis in a normoglycemic or hypoglycemic comatose patient. The mainstay of therapy is supportive, including bicarbonate administration, hemodialysis for correction of acidosis, and removal of lactate and metformin. Although the dialyzer extraction ratio is high (60%) (Nguyen and Concepcion, 2011), metformin removal is limited by relatively large V_D (3 L/kg). Nevertheless, because hemodialysis rapidly corrects the associated metabolic acidosis, it is recommended in severe metformin poisoning when there is failure of standard supportive measures, shock, decreased level of consciousness, lactate level greater than 20 mmol/L, or severe acidosis/pH less than 7.0.

N. Thallium. Thallium is a highly toxic metal originally used for medicinal purposes. Poisoning is now related to industrial exposure, contamination of herbal products and drugs of abuse, or attempted homicide. The potentially fatal oral dose is as low as 6 mg/kg. Thallium poisoning presents with alopecia, painful ascending peripheral neuropathy, abdominal pain, vomiting, diarrhea, constipation, autonomic instability, and cranial nerve involvement, with the most severe poisoning exhibiting altered mental status, coma, loss of airway protection, respiratory paralysis, and cardiac arrest (Hoffman, 2003). Urine is used (although blood testing is available) as a screening test with a normal thallium concentration of less than 5 mcg/L. Treatment consists of removal from exposure, supportive care, and enhanced elimination; MDAC and Prussian blue enhance elimination via the gastrointestinal tract. Hourly thallium removal by hemodialysis and charcoal hemoperfusion appears superior to removal by normal kidney function and comparable to stool elimination via Prussian blue. Although thallium has a large V_D, hemodialysis can be beneficial if instituted early after ingestion, before full distribution in tissues (Ghannoum, 2012).

O. Other drugs. Management of poisoning due to other agents is beyond the scope of this handbook. The reader is referred to Table 18.6 for clinical information on many other

drugs and toxins.

TABLE 18.6 Extracorporeal Removal of Common Poisons

Specific Drug/Poison	Molecular Weight (Da)	Volume of Distribution (L/kg)	Protein Binding	Preferred Method of Removal and Comment
Acetaminophen	151	0.9	25%	Effective antidote. HD can be considered if mitochondrial toxicity.
Acyclovir	225	0.6	15%	HD (if KI)
Amanita mushroom	990	0.3	2%	HD (if soon after ingestion)
Amiodarone	645	66	99%	None (V_D too large)
Amphotericin B	924	4	95%	None (V_D too large)
Baclofen	214	0.9	30%	HD (if KI)
Boric acid	62	0.4	20%	HD
Bromide	79	0.6	0%	HD
Bupropion	240	30	80%	None (V_D too large)
Caffeine	194	0.7	35%	HD
Carbamazepine	236	1.1	75%	HD
Cefepime	481	0.7	10%	HD (if KI)
Ceftazidime	547	0.3	10%	HD (if KI)
Chloral hydrate	165	0.8	75%	HD
Chloroquine	320	130	60%	None (V_D too large)
Cibenzoline	262	40	50%	None (V_D too large)
Cisplatin	301	0.5	90%	HP, TPE
Cocaine	303	2	80%	None (CL too high)
Colchicine	399	3	50%	None (V_D too large)
Cyclophosphamide	261	0.5	20%	HD
Cyclosporine	1,203	4	95%	None (V_D too large)
Dapsone	248	1.0	80%	HD
Diethylene glycol	106	0.6	0%	HD
Digitoxin	765	7	95%	None (V_D too large)
Digoxin	781	6	25%	None (V_D too large, effective antidote)
Ethanol	46	0.6	0%	None (CL too high, supportive care sufficient in the vast majority)
Ethylene glycol	62	0.6	0%	HD
Fluoride	19	0.6	0%	HD
Formate	46	0.7	0%	HD
Gabapentin	171	0.7	2%	HD
Glycolate	76	0.6	0%	HD
Hydroxychloroquine	336	60	55%	None (V_D too large)
Isoniazid	137	0.7	7%	None (effective antidote)
Isopropanol	60	0.6	0%	HD
Lamotrigine	256	1.3	55%	

Lidocaine	234	1.2	70%	None (CL too high)
Lithium	7	0.8	0%	HD
Meprobamate	218	0.8	20%	HD
Metformin	165	4	$<5\%$	HD (if KI, V_D lower)
Methanol	32	0.7	0%	HD

Methaqualone	250	4	85%	None (V_D too large)
Methotrexate	454	0.8	50%	HD only if soon after IV exposure. Effective antidote
Paraquat	186	1.5	5%	HD, HP (Only if early after exposure)
Phenobarbital	232	0.7	40%	HD
Phenytoin	252	0.7	90%	HD, HP
Pregabalin	159	0.5	0%	HD
Procainamide	272	1.5	10%	HD
Propylene glycol	76	0.6	0%	HD
Quetiapine	384	10	83%	None (V_D too large)
Quinine	324	2	85%	None
Quinidine	324	2.5	80%	None
Salicylate	138	0.2	90%	HD (protein binding lower in overdose)
Thallium	204	5	0%	HD (only soon after exposure)
Thiocyanate	58	0.3	?	HD
Theophylline	180	0.5	50%	HD, HP
Thyroxine	777	0.2	99.9%	TPE
Valproic acid	144	0.3	90%	HD (protein binding lower in overdose)
Vancomycin	1449	0.7	55%	HD (if KI)
Venlafaxine	277	7	25%	None (V_D too large)
Vincristine	825	1.3	45%	HD

Drug/Poison Class	
Aminoglycosides	HD
Benzodiazepines	None (effective antidote)
β-Adrenergic antagonists	HD (V_D too large except for atenolol, bisoprolol, nadolol, sotalol)
Calcium channel blockers	None (V_D too large)
Endogenous metals (Mg, K, Ca, PO_4)	HD
Monoclonal antibodies	TPE (molecular weight >100,000 Da, but rarely indicated)
NSAIDs	TPE (but rarely indicated)
Opioids	None (effective antidote)
Organophosphates	None (V_D too large, slow intercompartmental transfer)
Other metals (aluminum, mercury)	HD with chelation
Tricyclic antidepressants	None (V_D too large)

CL, endogenous clearance; HD, hemodialysis; HP, hemoperfusion; KI, kidney impairment; TPE, therapeutic plasma exchange; V_D, volume of distribution.

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PART III

Peritoneal Dialysis

19 Physiology of Peritoneal Dialysis

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Peritoneal dialysis is the method of renal replacement therapy used by about 380,000 patients worldwide. Since the introduction of continuous ambulatory peritoneal dialysis (CAPD) almost five decades ago and of compact "easy-to-use" hydraulic cyclers for automated peritoneal dialysis (APD) three decades ago, the utilization of peritoneal dialysis has increased. This is because peritoneal dialysis is relatively simple, convenient, and relatively low cost, and because it can be done in the home.

I. WHAT IS PERITONEAL DIALYSIS?

In essence, peritoneal dialysis involves the movement of solutes and water across a "membrane" that separates two fluid-containing compartments: (a) the blood in the peritoneal capillaries, which in renal failure contains an excess of urea, creatinine, potassium, and other waste products; and (b) the dialysis solution in the peritoneal cavity, which typically contains sodium, chloride, and lactate or bicarbonate and which is rendered hyperosmolar by the inclusion of a high concentration of glucose. During the course of a peritoneal dialysis dwell, three transport processes occur simultaneously: diffusion, ultrafiltration, and absorption. The amount of clearance and fluid removal achieved depends mainly on the volume of dialysis solution infused (called the dwell volume), how often this dialysis solution is exchanged, the concentration of crystalloid osmotic or colloid oncotic agent present, and the properties of the patient's peritoneal membrane.

II. FUNCTIONAL ANATOMY

A. Anatomy of the peritoneal cavity.

The peritoneum is the serosal membrane that lines the peritoneal cavity (Figure 19.1). Its anatomic surface area is similar to body surface area and typically ranges from 1 to 2 m^2 in an adult, of which about half is estimated to be in contact with dialysis fluid. The peritoneum is divided into two portions:

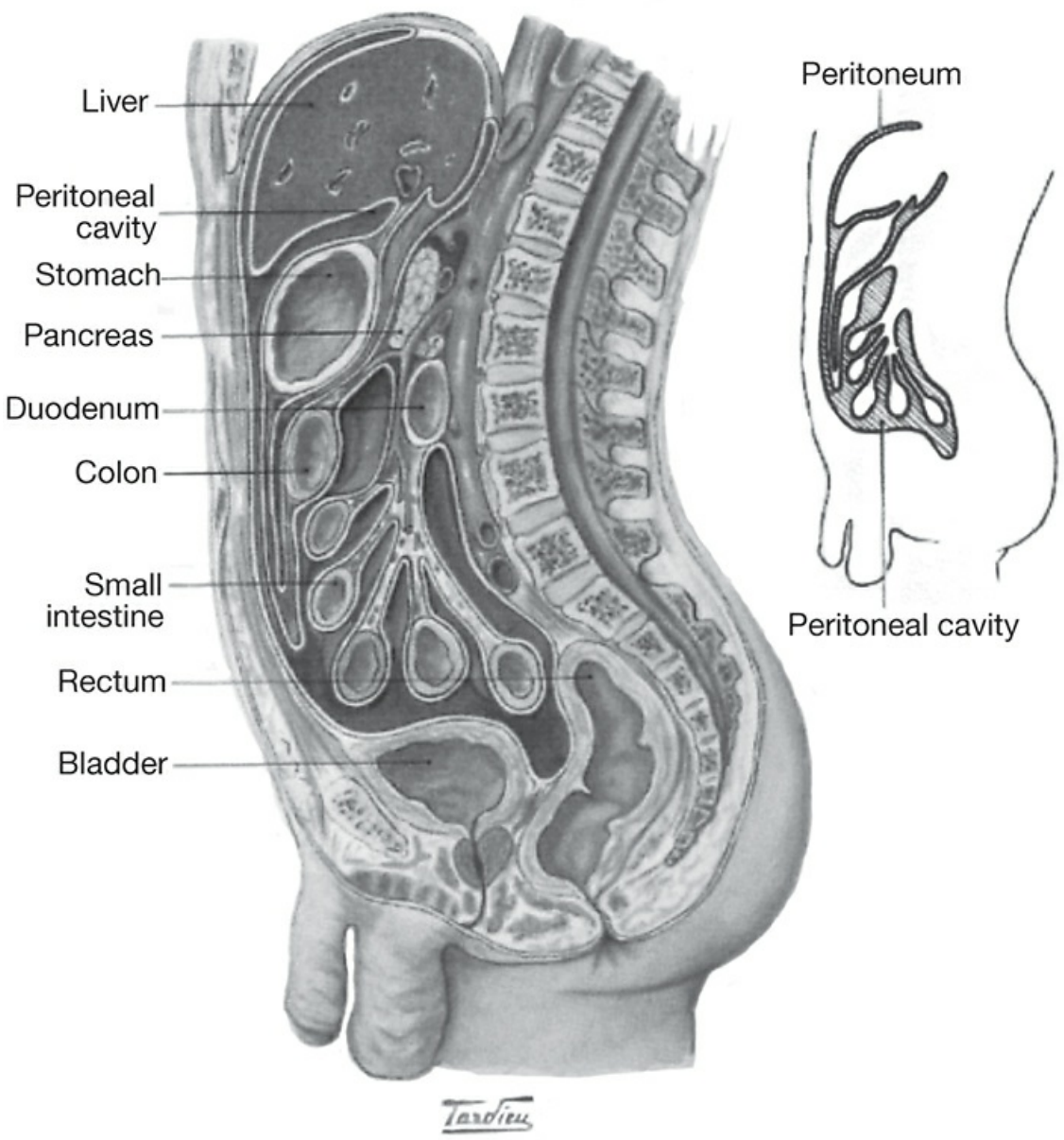


FIGURE 19.1: Simplified anatomy of the peritoneal cavity showing the visceral and parietal peritoneal membrane. (Adapted from Khanna R, et al, eds. *The Essentials of Peritoneal Dialysis*. Kluwer; 1993.)

1. The visceral peritoneum, which lines the gut and other viscera
2. The parietal peritoneum, which lines the walls of the abdominal cavity

The visceral peritoneum accounts for about 80% of the total peritoneal surface area. It receives its blood supply from the superior mesenteric artery, while venous drainage is via the portal system. The parietal peritoneum, which may be more important functionally in peritoneal dialysis, receives blood from the lumbar, intercostal, and epigastric arteries and drains into the inferior vena cava. Total peritoneal blood flow cannot be directly measured, but has been estimated to range from 50 to 100 mL/min. The main lymphatic drainage of the peritoneum and of the peritoneal cavity is via stomata in the diaphragmatic peritoneum, which ultimately

drain via large collecting ducts into the right lymphatic duct. Additional drainage occurs via lymphatics present in both the visceral and the parietal peritoneum.

B. Peritoneal membrane histology. The peritoneal membrane is lined by a monolayer of mesothelial cells equipped with microvilli that produce a thin film of lubricating fluid. Underlying the mesothelium is the interstitium, which comprises a gel-like matrix containing collagenous and other fibers, the peritoneal capillaries, and some lymphatics.

C. Models of peritoneal transport. There are six regions of resistance to moving solute and water across the peritoneum from capillary blood to peritoneal fluid: (a) the stagnant capillary fluid film overlying the endothelium of the peritoneal capillaries, (b) the capillary endothelium itself, (c) the endothelial basement membrane, (d) the interstitium, (e) the mesothelium, and (f) the stagnant fluid film that overlies the mesothelium.

Of these, the two stagnant fluid films and the mesothelial cell are thought to offer only trivial resistance to transport. Two concepts of peritoneal transport are popular; they are complementary and not mutually exclusive, and they emphasize the importance of the peritoneal capillaries and the interstitium, respectively. They are the three-pore model and the distributed model.

1. **The three-pore model.** This model, which has been well validated by clinical observations, holds that the peritoneal capillary endothelium is the critical barrier to peritoneal solute transfer and that solute and water movement across the peritoneal capillary is dependent on the relative abundance of pores of three different sizes (Figure 19.2; Rippe, 2004).

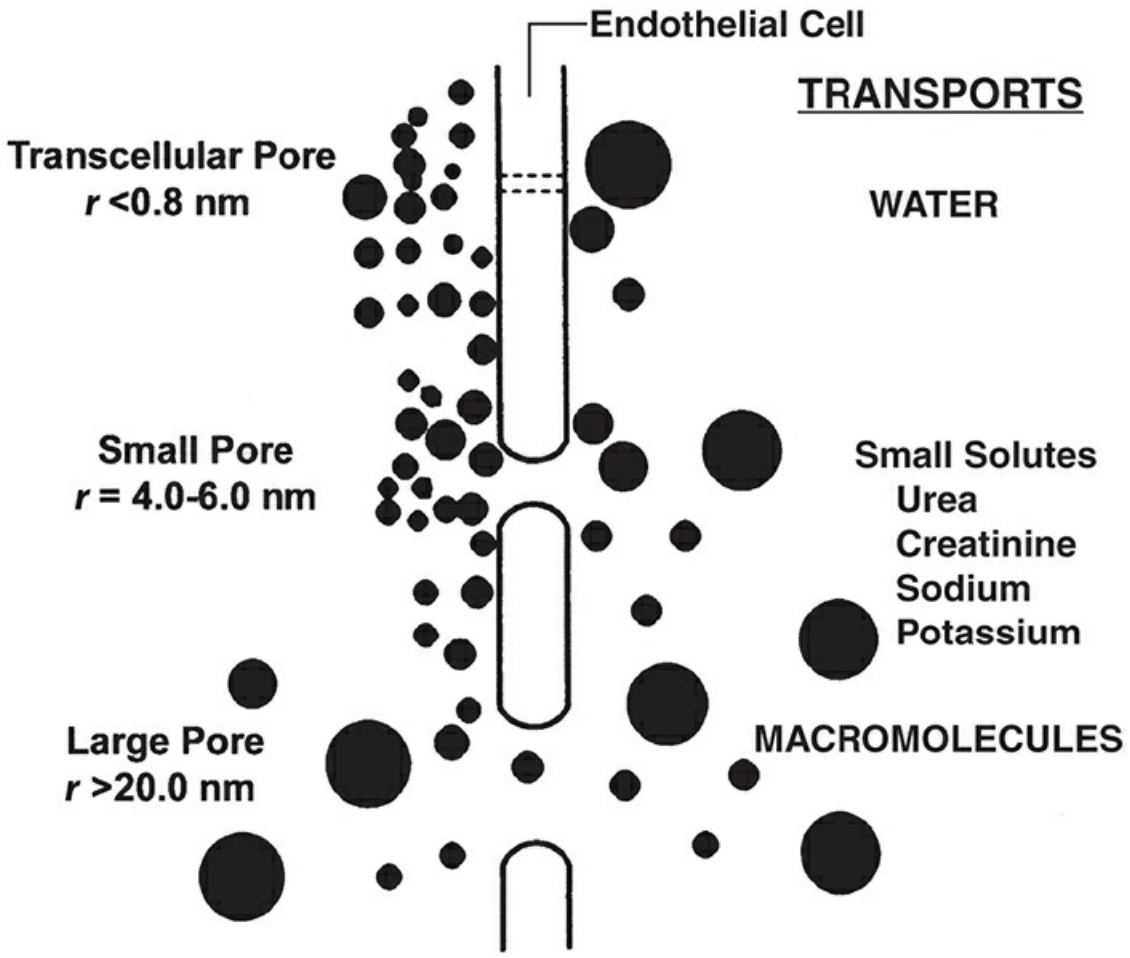


FIGURE 19.2: Diagrammatic representation of the three-pore model of peritoneal transport. (Adapted from Flessner MF. Peritoneal transport physiology: insights from basic research. *J Am Soc Nephrol*. 1991;2:122.)

a. **Large pores** with a radius of 20 to 40 nm are thought to be large clefts in the endothelium. Macromolecules, such as proteins, are transferred by convection through these pores.
b. **Small pores** with a radius of 4 to 6 nm likely represent smaller clefts in the tight junctions between endothelial cells. The total area of these small pores determines the overall rate of transfer by diffusion of small solutes, such as urea, creatinine, sodium, and potassium, in association with water.
c. ***Ultrasmall pores*** with a radius of less than 0.8 nm are now known to be aquaporin-1 transcellular water channels in the endothelial cell membrane. These ultrasmall pores are responsible for the transport of glucose-free water only and account for "sieving" by the peritoneal membrane (see what follows; Devuyst and Rippe, 2014; Devuyst, 2024).

2. **Distributed model and effective peritoneal surface area.** The distributed model emphasizes the importance of the distribution of capillaries in the peritoneal membrane and of the distance water and solutes have to travel from the capillaries across the interstitium to the peritoneal mesothelium (Figure 19.3; Flessner, 2001). Small-solute transfer is dependent on the surface area of the peritoneal capillaries, as with the three-pore model, rather than on the anatomic peritoneal surface area.

Furthermore, the distance of each capillary from the mesothelium determines its relative contribution. The cumulative contribution of all the peritoneal capillaries determines the effective surface area and the resistance properties of the membrane. From the distributed model, the concept of "effective peritoneal surface area" has arisen. This is the area of the peritoneal surface that is sufficiently close to the peritoneal capillaries to play a role in solute and water transfer. Therefore, two patients with the same anatomic peritoneal surface area may have markedly different peritoneal vascularity and very different effective peritoneal surface areas. In a given patient, effective peritoneal surface area may vary in different circumstances, increasing, for example, in peritonitis when inflammation increases vascularity. The degree of vascularity of the peritoneum is more important than its surface area in determining the solute and water transport characteristics of an individual patient.

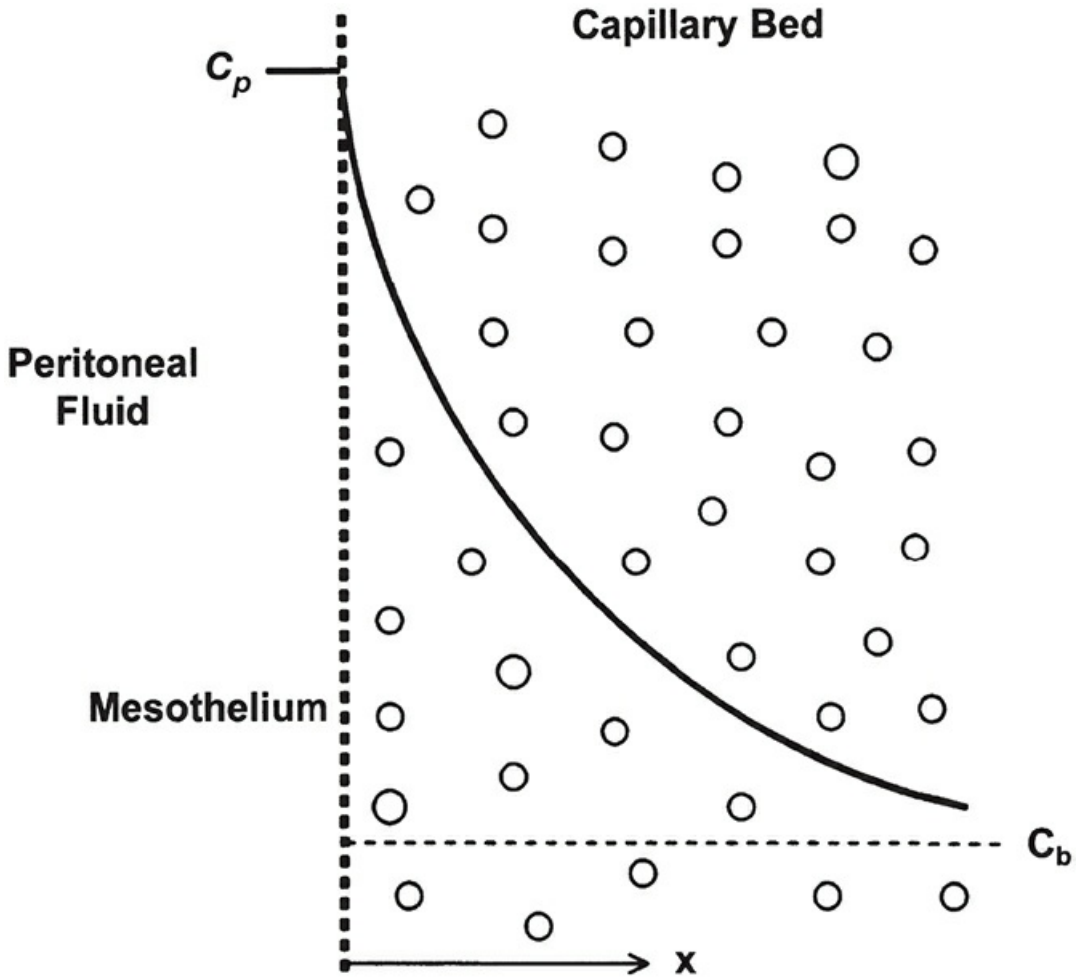


FIGURE 19.3: Distributed model concept showing the distribution of peritoneal capillaries in the interstitium and their distances from the mesothelium, represented by the dotted, vertical line. The solid, curved line, represents the efficiency of transport from a given capillary to the peritoneal space, increasing for capillaries located closest to the mesothelial boundary. Cp, soluteconcentration in the peritoneal cavity; C_b, solute concentration in the blood. (Adapted from Flessner MF. Peritoneal transport physiology: insights from basic research. *J Am Soc Nephrol*. 1991;2:122.)

D. Changes in the peritoneal membrane with time on peritoneal dialysis. Over

time, a variety of changes occur to differing degrees in patients on long-term peritoneal dialysis. The mesothelial layer is lost, and the peritoneal capillaries become hyalinized. More significantly, progressive submesothelial fibrosis typically occurs, and there is often increased vascularity of the membrane, which may have consequences for solute and water transfer (Davies, 2016; Krediet and Parikova, 2022).

III. PHYSIOLOGY OF PERITONEAL TRANSPORT. Solutes and water are transferred across the peritoneum by three processes that take place simultaneously: (a) diffusion, (b) ultrafiltration, and (c) fluid absorption.

A. Diffusion. Uremic solutes and potassium diffuse from peritoneal capillary blood into the peritoneal fluid, whereas glucose and lactate or bicarbonate present in the dialysate diffuse in the opposite direction. Peritoneal diffusion depends on the following factors:

1. **The concentration gradient.** For substances such as urea and creatinine, this is maximal at the start of a peritoneal dialysis dwell, when the concentration in the dialysis solution is zero. With ongoing diffusion during the course of the dwell, this gradient gradually decreases. The diminishing gradient can be counteracted partially by the performance of more frequent exchanges, as is typically done in APD, or by increasing dwell volumes, which allows the gradient to remain greater for a longer time.
2. **Effective peritoneal surface area.** This can be increased by using larger fill volumes, which recruit a greater portion of the peritoneal membrane, but this effect is limited in most individuals once volumes reach 2.5 to 3 L.
3. **Molecular weight of the solute.** Substances with lower molecular weight, such as urea (molecular weight 60), will diffuse more rapidly than those with higher molecular weight, such as creatinine (113) or uric acid (168).
4. **Mass transfer area coefficient (MTAC).** The combined effects of factors 1 to 3 can be measured by an index called the MTAC, which is analogous to the K_0A of a hemodialysis membrane. For a given solute, the MTAC is equivalent to the diffusive clearance of that solute per unit time in a theoretical situation in which dialysate flow is infinitely high so that the solute gradient is always maximal. Typical MTAC values for urea and creatinine are 17 and 10 mL/min, respectively. The MTAC is mainly a research tool and is not used much in clinical practice.
5. **Peritoneal blood flow.** Diffusion generally does not depend on peritoneal blood flow, which, at 50 to 100 mL/min, is already more than adequate relative to MTAC values for even the smallest solutes. Instead, in contrast to the situation in hemodialysis, diffusion in peritoneal dialysis is dependent primarily on the dialysate flow rate. Vasoactive agents do influence peritoneal solute transfer, but this is not related to their ability to increase peritoneal blood flow; rather, it is due to recruitment of larger numbers of peritoneal capillaries, increasing the effective peritoneal surface area. The same effect is seen in peritonitis, where inflammation increases peritoneal vascularity with a consequent increase in diffusion.

B. Ultrafiltration. This occurs primarily as a consequence of pressure gradients across the membrane, of which the most important is the osmotic or oncotic gradient between the dialysis solution and the peritoneal capillary blood.

1. **Determinants of the osmotic glucose gradient:**
   a. **The gradient can be maximized by using higher glucose**

concentration dialysis solutions.

b. **Dwell time.** The gradient is maximal at the start of a peritoneal dialysis dwell and decreases with time, partly due to dilution of dialysate glucose by ultrafiltrate from the plasma but mainly by diffusion of glucose from the dialysis solution into the blood (Figure 19.4). If the solute transfer rate is fast, as when the effective peritoneal surface area is large, then the gradient will dissipate more quickly. The gradient can be enhanced by more frequent exchanges to shorten dwell time, as is done with APD.

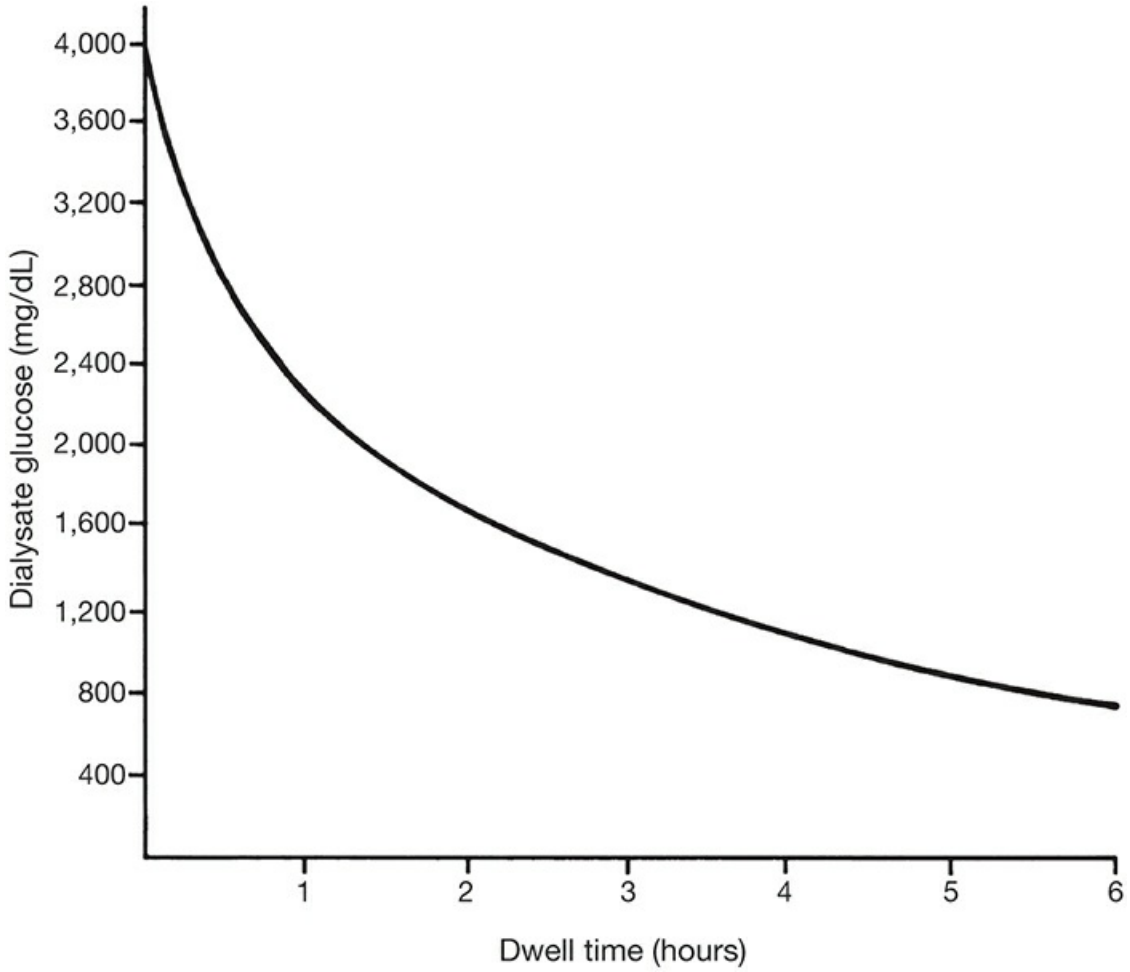


FIGURE 19.4: Dialysate glucose level after instillation of a 4.25% dextrose (3.86% glucose) exchange into the peritoneal cavity. The initial level is close to 3,860 mg/dL (214 mM).

c. **Blood glucose levels.** The gradient will be smaller in the presence of marked hyperglycemia.

d. ***The solute transfer characteristics of the peritoneal membrane.*** Glucose can easily diffuse from the peritoneal cavity across the small pores into the peritoneal capillaries, thus dissipating the glucose gradient. The speed at which this occurs depends on the solute transfer characteristics of the particular patient's membrane, which can be measured in clinical practice using the peritoneal equilibration test (PET).

2. **Determinants of ultrafiltration efficiency for a given osmotic gradient.** How effective an osmotic agent is at achieving ultrafiltration at whatever the gradient is varies considerably between individuals. This is called the osmotic conductance to glucose and typically varies between 50 and 100 mcL/min/mm Hg. It is partly determined by the number and function of the ultrasmall pores in the peritoneal capillaries. It has been shown that genetically determined reduced expression of aquaporin-1 leads to less ultrafiltration for a given gradient (Morelle, 2021a). Ultrafiltration efficiency is also affected by the membrane fibrosis seen in many people on long-term peritoneal dialysis. This fibrosis is thought to restrict fluid flow through the membrane (Morelle, 2021b).
3. **Sieving and the "sodium dip."** Solute moves along with water by convection, but if the membrane is in part semipermeable, some of the solute is held back or "sieved." Sieving therefore renders ultrafiltration a less effective form of solute removal, although water removal occurs unhindered. In peritoneal dialysis, this sieving is due to the ultrasmall pores, which on average account for about half of ultrafiltration. The remaining half of ultrafiltration occurs through the small pores, and here sieving is absent, and the solute concentrate of this portion of the ultrafiltrate is similar to that in plasma (La Milia, 2005). Ultrafiltrate therefore contains on average about 65 mmol/L sodium, and so in the early part of a dwell, dialysate sodium falls because it is being diluted by this dilute ultrafiltrate. The sieving coefficient for glucose-driven osmotic ultrafiltration is therefore said to be about 0.5. This sieving varies between patients and is initially determined by the density and efficacy of the ultrasmall pores. This initial fall in dialysate sodium level measured after 60 minutes is called the "sodium dip" and averages about 9 mmol/L, with a normal range of 6 to 11 mmol/L. The size of the sodium dip is a measure of free water transport; if this dip is less than 5 mmol/L, it indicates that free water transport is significantly low (La Milia, 2018). Decreased free water transport is typically due to impaired aquaporin function or, in patients on long-term peritoneal dialysis, to peritoneal fibrosis.
4. **Hydrostatic pressure gradient.** Normally, the mean peritoneal capillary pressure (~20 mm Hg) is higher than the intraperitoneal pressure in a patient with a 2-L dwell (~10 mm Hg), and this might be expected to favor ultrafiltration, but this is counteracted by the peritoneal capillary oncotic pressure (due to plasma proteins). However, these forces are all overwhelmed by the osmotic pressure from the hypertonic glucose in the dialysate, causing net ultrafiltration from blood to dialysate. Further rises in intraperitoneal pressure will decrease ultrafiltration, and this may be seen when larger dwell volumes are used or when the patient is seated or standing. In the course of a long-duration dwell, the glucose osmotic gradient is dissipated and the net effect over the course of the long dwell may be fluid absorption, especially when there is a high effective peritoneal surface area.
5. **Oncotic pressure gradient.** Oncotic pressure acts to keep fluid in the blood, and so opposes ultrafiltration. In patients with hypoalbuminemia, oncotic pressure is low and ultrafiltration may be greater than usual. The oncotic pressure can also be altered by icodextrin, a large molecular weight glucose polymer that can be used in place of glucose in peritoneal dialysis solutions for long-duration dwells. Icodextrin-containing peritoneal dialysis solution is iso-osmolar to serum and removes fluid by

virtue of its colloid oncotic pressure compared with that of plasma. Icodextrin has a reflection coefficient approaching 1.0 across the small pores because the molecule is too large to diffuse across the peritoneal membrane and so ultrafiltration using icodextrin is sustained at a relatively constant level throughout even a long-duration dwell. Because icodextrin is iso-osmotic with plasma, it does not cause ultrafiltration across the ultrasmall aquaporin pores. Icodextrin is however partially absorbed from the peritoneal cavity via lymphatics and metabolized.

C. Fluid absorption. Fluid absorption from the peritoneal space occurs via two mechanisms. First, some of the fluid goes through the subdiaphragmatic lymphatics and via the tissues of the abdominal wall into local lymphatics. This occurs at a relatively constant rate throughout the dwell time and can be measured by the rate of disappearance of large molecular weight molecules. Second, fluid is absorbed via the capillaries and postcapillary venules of the parietal peritoneum from where it enters the circulation. This component of fluid reabsorption is proportional to the effective peritoneal surface area. There is little or no solute sieving in either process and so fluid absorption reduces the efficiency of both solute and fluid removal by peritoneal dialysis. Typical rates of peritoneal fluid absorption are 1.0 to 2.0 mL/min. The factors that affect the rate of fluid absorption of a peritoneal dwell are as follows:

1. **Intraperitoneal hydrostatic pressure.** High pressures will increase the amount of fluid absorbed. High intraperitoneal hydrostatic pressure can result from increased intraperitoneal volume owing to effective ultrafiltration or to use of a large infusion volume. Intraperitoneal pressure is higher when sitting than when standing, and it is lowest when supine (Figure 19.5).

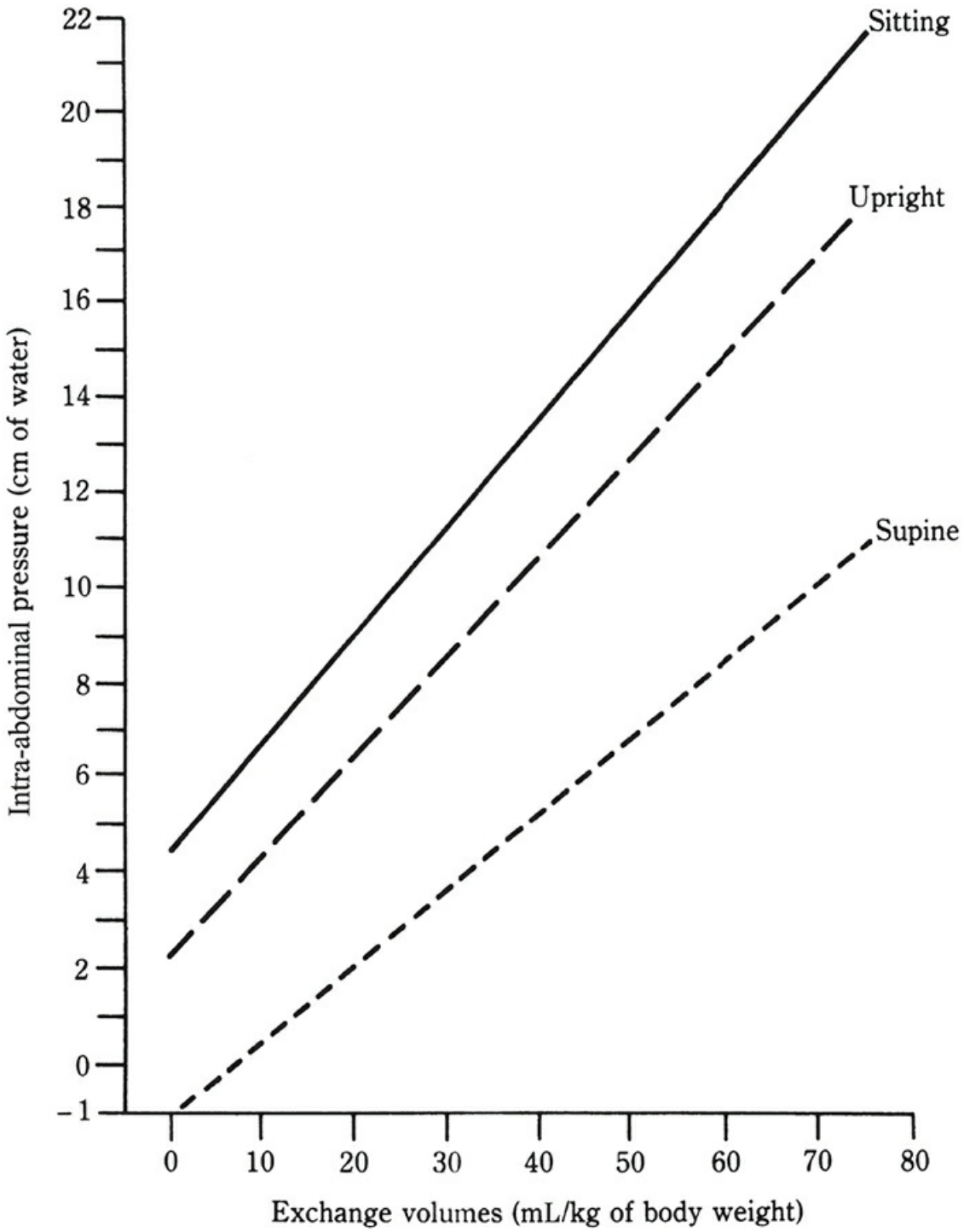


FIGURE 19.5: Intra-abdominal pressure after infusing various volumes of dialysis solution. (Modified from Diaz-Buxo JA. Continuous cycling peritoneal dialysis. In: Nolph KD, ed. *Peritoneal Dialysis*. Martinus Nijhoff; 1985.)

2. **Effective peritoneal surface area.** A high surface area, which as discussed earlier reflects the contact between vascular area and dialysate, is associated with more rapid fluid reabsorption.
3. **Effectiveness of lymphatics.** The effectiveness of lymphatics in absorbing fluid

from the peritoneal cavity can differ markedly from person to person for reasons that are not well understood.

IV. CLINICAL ASSESSMENT AND IMPLICATIONS OF PERITONEAL SOLUTE AND WATER TRANSFER

A. Peritoneal Equilibration Test (PET).

In clinical practice, indices such as the MTAC and osmotic conductance of the peritoneal membrane are too complex for routine measurement. The peritoneal solute transfer rate (PSTR) is assessed using equilibration ratios between dialysate and plasma for urea (*D*/*P* urea), creatinine (*D*/*P* creatinine), and sodium (*D*/*P* sodium) (Figure 19.6). Although these equilibration ratios measure the combined effect of diffusion and ultrafiltration, they correlate well with MTAC values and are a good surrogate measure of effective peritoneal surface area.

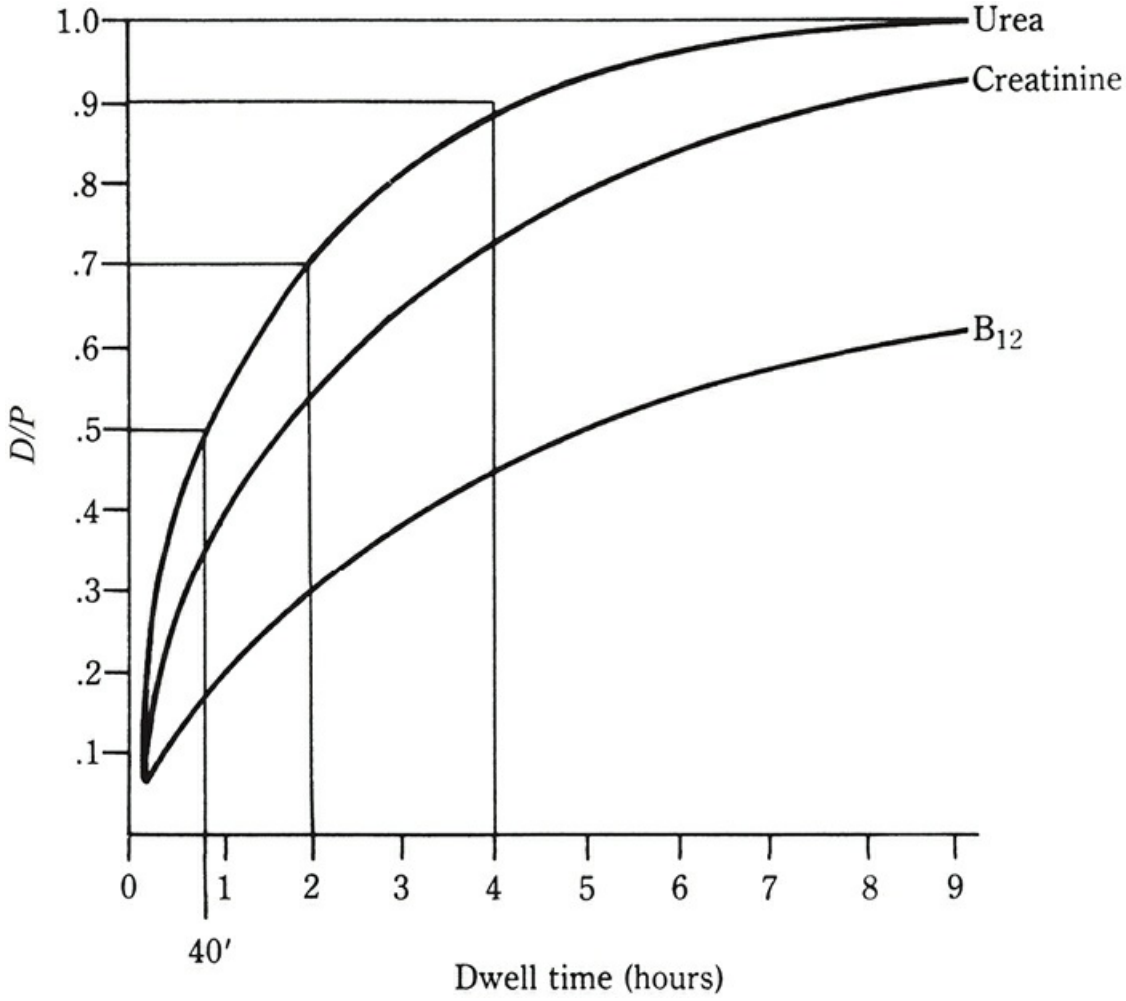


FIGURE 19.6: Rate of entry of urea, creatinine, and vitamin B_{12} into peritoneal dialysis solution that has been left in the abdomen. Results are expressed as the ratio of the level in dialysate (*D*) to the level in plasma (*P*). Typical *D*/*P* ratios for urea at time points of 40 minutes, 2 hours, and 4 hours are indicated.

Conventionally, PSTR is measured 6 to 12 weeks after initiation of peritoneal dialysis, as it takes some time for these rates to stabilize (Morelle, 2021b). They are

measured using a standardized PET that involves the instillation of a 2.5% 2-L dextrose dwell with dialysate samples taken at 0, 2, and 4 hours and a plasma sample at 2 hours.

The PET is also used to measure net fluid removal, also termed **ultrafiltration capacity** (volume drained at 4 hours minus volume instilled), and the ratio of dialysate glucose at 4 hours to dialysate glucose at time zero (D/D_0 glucose). Patients are classified on the basis of their 4-hour *D*/*P* creatinine into one of four PSTR categories: high or fast, high-average, low-average, and low or slow, although it should be recognized that this is in reality a continuous variable and differences in analytic methods between laboratories can lead to misclassification (Figure 19.7; Twardowski, 1987). The mean *D*/*P* creatinine in the largest studies is about 0.65. When the *D*/*P* creatinine is high (>0.8), there is a **fast PSTR** due to the larger effective peritoneal surface area, which leads to earlier dissipation of the glucose osmotic gradient and less efficient ultrafiltration. A high *D*/*P* creatinine will be associated with high *D*/*P* ratios for all solutes (*D*/*P* urea and *D*/*P* sodium) including albumin. A high *D*/*P* creatinine is also associated with higher dialysate protein losses and lower serum albumin values. In contrast, a **slow PSTR** (*D*/*P* creatinine < 0.5) will be associated with less complete equilibration for urea, creatinine, and glucose, reflecting low membrane permeability and/or small effective peritoneal surface area. Patients with slow PSTR will therefore have low *D*/*P* urea, *D*/*P* creatinine, and $_D/_P$ sodium and high $_D/_{D0}$ glucose with good net ultrafiltration. Dialysate protein losses are lower, and serum albumin values tend to be higher. The PSTR is normally distributed, so most patients will be between these extremes.

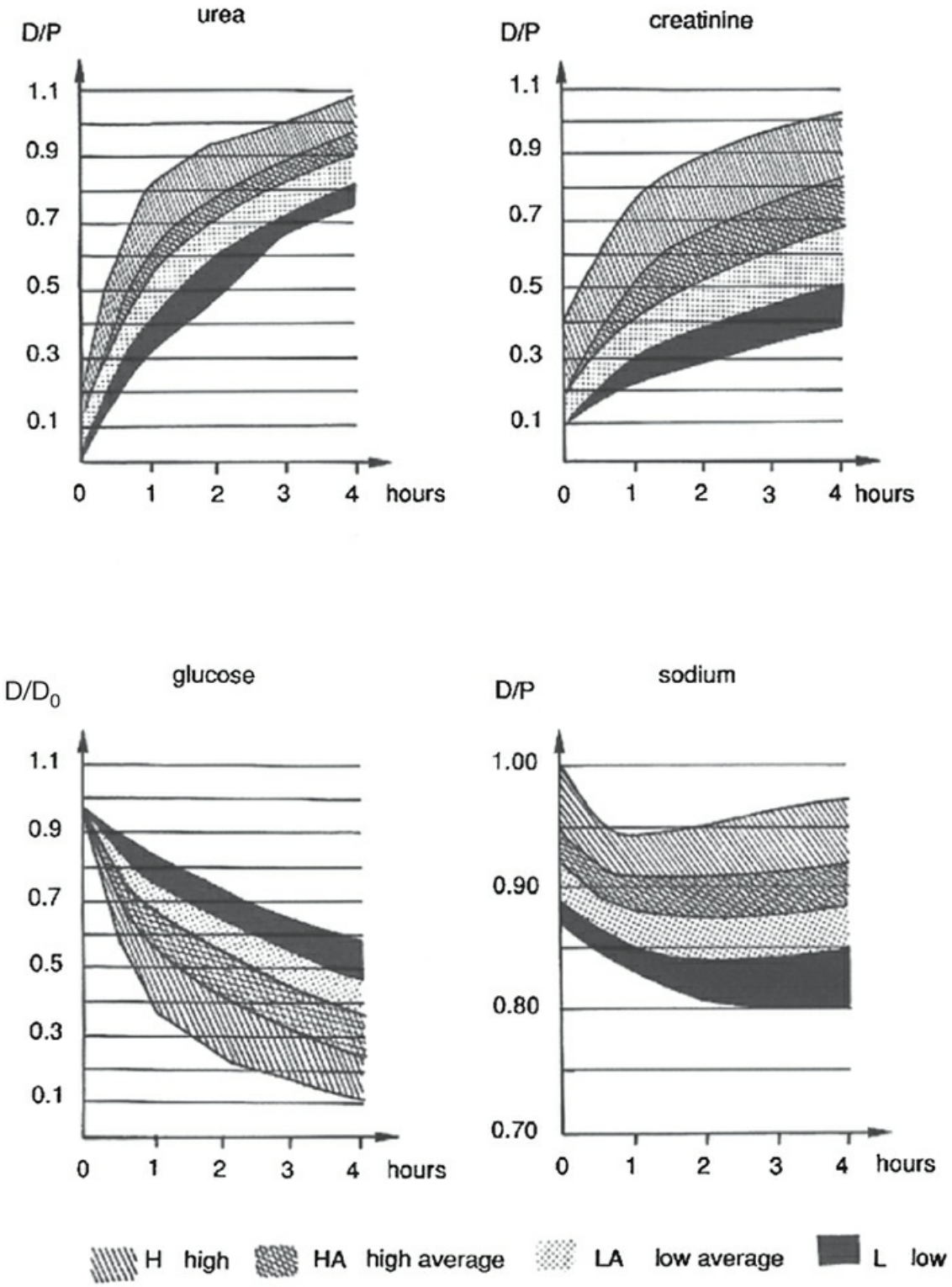


FIGURE 19.7: Standard peritoneal equilibration curves for urea, creatinine, and sodium, as well as glucose absorption showing ranges of values for high, high-average, low-average, and low transporters. (Modified from Twardowski ZJ, et al. Peritoneal equilibration test. *Perit Dial Bull*. 1987;7:138.)

B. Clinical implications of the PSTR. To optimize both solute clearance and

ultrafiltration, the length of the dialysis dwell should in theory be matched to the PSTR. If the PSTR is fast, then dwells should be shorter, as can be achieved using APD. The greatest potential problem is in the long day or overnight dwell where the risk of fluid reabsorption is the greatest, and this can be avoided by using icodextrin or higher concentrations of glucose in the dialysate. Conversely, if PSTR is slow, then the best regimens should be based on long-duration, high-volume dwells so that solute diffusion is maximized. In practice, in most units, patient lifestyle and other nonmedical issues influence the peritoneal prescription more than PSTR status; if residual renal function is preserved, those with slow PSTR can be well managed on APD, while those with fast PSTR can be treated with CAPD, provided the long nocturnal dwell is managed appropriately.

Baseline PSTR is determined by multiple factors, including age, comorbid conditions, and even genetic factors such as interleukin-6 genotype, which may influence the peritoneal inflammatory response to dialysis solutions (Mehrotra, 2021). In some patients, PSTR tends to increase gradually with time on peritoneal dialysis due to increased peritoneal inflammation and vascularity, and this, along with progressive submesothelial fibrosis, may lead to decreased ultrafiltration. The process is more likely to occur in people who have been exposed to more hypertonic glucose solutions (Davies, 2001). It has been shown in some studies that patients with a fast PSTR have higher rates of mortality, technique failure, ultrafiltration dysfunction, and even encapsulating peritoneal sclerosis (Brimble, 2006; Mehrotra, 2015). These effects may be partly related to greater baseline comorbidity in these patients, but some of these adverse risks appear to be reduced if rapid transporters are managed with APD and icodextrin.

C. Net fluid removal. Net fluid removal depends on the balance between peritoneal ultrafiltration and peritoneal fluid absorption. The solute and water transfer qualities of the membrane vary between patients and are subject to change. As is shown in Figure 19.8, the net fluid removal with a 1.5% 2-L dextrose dwell is maximal in the first hour, and intraperitoneal volume is typically greatest after about 90 minutes. After this time, the volume being ultrafiltered is less than that being resorbed, and by 6 to 10 hours, the intraperitoneal volume will have fallen below 2 L, and the patient is subject to a net fluid gain. If the more hypertonic 4.25% dextrose dialysis solution is used, initial fluid removal is greater and more sustained, and intraperitoneal volume is greatest after about 3 hours and will not fall below 2 L until many hours later. If the ultrafiltration capacity, which is the net fluid removal at 4 hours using a 2.5% dextrose concentration, is less than 100 mL, or using a 4.25% concentration is less than 400 mL, then this is strongly suggestive of a membrane that will struggle to provide sufficient daily ultrafiltration once the patient is anuric. If this low net fluid removal is due to a high *D*/*P* creatinine ratio, then using a combination of APD to get short exchanges and icodextrin in the long dwell should help ensure that sufficient ultrafiltration is achieved. However, if it is due to low membrane osmotic conductance, then higher glucose concentrations will need to be used. This problem can be confirmed by measuring the sodium dip at 1 hour using a 4.25% dextrose exchange—if the dip is less than 5 mmol/L, it is associated with worse outcomes and a switch to hemodialysis should be considered (La Milia 2018; Morelle 2021b).

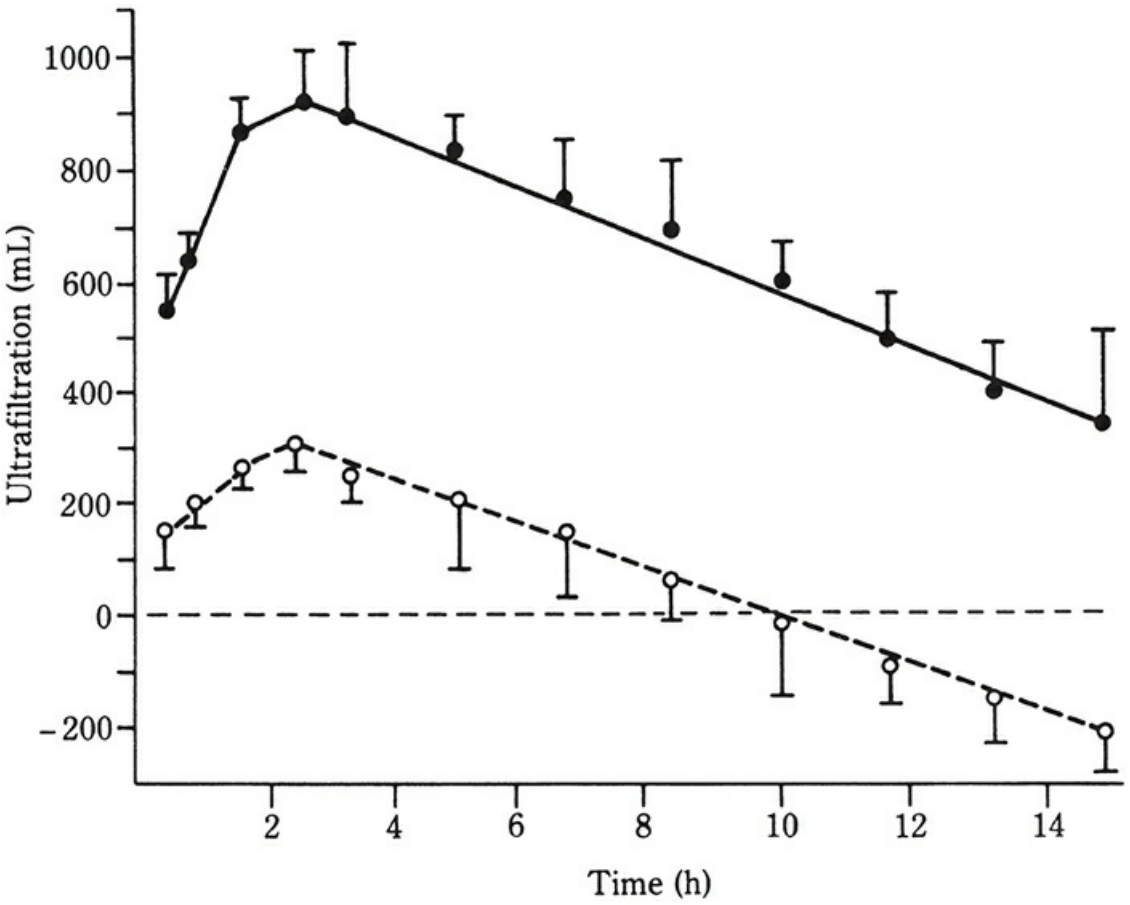


FIGURE 19.8: Ultrafiltration volume (volume drained minus volume instilled) as a function of time after infusion of dialysis solution containing 1.5% dextrose (1.35% glucose, *open circles*) or 4.25% dextrose (3.86% glucose, *closed circles*). (Modified from Diaz-Buxo JA. Continuous cyclic peritoneal dialysis. In: Nolph KD, ed. *Peritoneal Dialysis.* Springer; 1989.)

The effect of larger dwell volumes on net fluid removal is complex. On the one hand, fluid removal increases because the osmotic gradient persists longer due to the greater quantity of glucose in the peritoneal cavity and because the effective peritoneal surface area over which water is transported is likely increased. On the other hand, fluid removal may decrease because intraperitoneal pressure rises (Figure 19.5), decreasing the hydrostatic gradient that favors ultrafiltration and promoting peritoneal fluid absorption into the tissues and lymphatics. The net effect of these forces varies from patient to patient and is difficult to predict.

D. Peritoneal clearance. Clearance for a given solute, such as urea or creatinine, is defined as the volume of plasma cleared of that solute per unit time. Clearance in peritoneal dialysis is the net result of the effects of solute removal by diffusion plus ultrafiltration minus solute retention via fluid absorption. Clearance is usually calculated as the quantity of solute removed over a given period divided by the average plasma concentration of that solute during the removal period. Clearance is maximal at the start of the dwell, when both diffusion and ultrafiltration are greatest, but becomes less because both urea concentration and glucose osmotic gradients diminish as the dwell proceeds. However, because peritoneal clearance is measured per day or per week rather than per minute or per hour, the usual measures of adequacy reflect the average of

measures over that time.

Peritoneal clearance can be increased by (a) maximizing time on peritoneal dialysis (ie, no “dry time”), (b) increasing dwell volumes, (c) maximizing concentration gradient (ie, more frequent exchanges as in APD and larger dwell volumes), and (d) maximizing peritoneal fluid removal and preventing fluid reabsorption (as described earlier).

The mechanism by which increasing dwell volumes augment clearance is sometimes confusing. Larger dwell volumes enhance urea and creatinine diffusion from blood to dialysate because the greater volume makes the solute concentration gradient stay higher for longer. Also, the effective peritoneal surface area may increase because of the recruitment of more membranes by the greater fluid volume, and consequently, MTAC values may rise. This effect tends to be modest or absent once volumes exceed 2.5 L in adults, presumably because all the available membranes have been recruited. These two effects increase diffusive clearance even though *D*/*P* ratios tend to be a little lower when larger dwell volumes are used. Another aspect of larger dwell volumes that tends to decrease clearance is the hydrostatic effect, which diminishes ultrafiltration slightly, thereby lowering the amount of solute removed by convective transport. These last two factors combine to limit the increase in clearance with higher dwell volumes. For example, a switch from 2.0- to 2.5-L dwells represents a 25% increase in infused volume but might, for example, be associated with a decrease in *D*/*P* ratios by 3% and of ultrafiltration by 5%, limiting the increase in clearance to about 20%.

1. **Urea versus creatinine.** Changes in the peritoneal dialysis prescription alter urea and creatinine clearances to different degrees because the latter is more time dependent due to creatinine having a higher molecular weight than urea, with a slower rate of diffusion, resulting in a lower D/P ratio at any given time point in the course of a dwell. Thus, a switch from CAPD to APD without a day dwell may lead to a much more marked decrease in creatinine than in urea clearance, whereas the introduction of a long day dwell in APD will cause a disproportionately greater enhancement in creatinine clearance. These effects are especially marked in low transporters, in whom creatinine clearance is particularly time dependent, as reflected by the flat shape of the creatinine equilibration curve.
2. **Measurement of clearance.** Peritoneal clearance per day in peritoneal dialysis is easily measured and corresponds to the total daily dialysate drain volume multiplied by the solute concentration in that dialysate and divided by the simultaneously obtained plasma concentration of the same solute. Stated more simply, clearance equals the drain volume multiplied by the *D*/*P* ratio for either urea or creatinine.

   In CAPD, the plasma urea and creatinine levels do not change significantly during the day because dialysis is continuous. Thus, the plasma sample can be taken at any convenient time during the day on which dialysate is collected for analysis. In APD, there is significantly more intense dialysis at night than in the daytime; therefore, a constant plasma urea cannot be assumed, though variation is modest. Ideally, the plasma sample should be taken in the middle of the noncycling period (usually mid-afternoon) when the urea is about halfway between its lowest level (in the morning after cycling) and its highest level (at night before cycling).

   Clearance is measured per day but expressed per week to allow easier comparisons to hemodialysis. It is conventional to normalize urea clearance, which is expressed as *Kt*, to total body water (*V*), which is typically estimated using the

Watson or Morgenstern equations (see Chapter 23 and Appendix B), and this gives peritoneal *Kt/V*. Creatinine clearance is normalized to 1.73 m^2 surface area, which is estimated using the formula of DuBois or Gehan and George (see Chapter 23 and Appendix B).

Residual renal clearance needs to be measured from 24-hour urine collections and added to peritoneal clearance to give patient's total clearance on peritoneal dialysis. For examples of clearance calculations, see Chapter 23, Tables 23.2 and 23.3.

E. Sodium removal. In peritoneal dialysis, it is helpful to consider sodium removal separately from water removal. As already mentioned, ultrafiltration in peritoneal dialysis involves sodium sieving so that water losses are proportionately greater than sodium losses (La Milia, 2006). At the end of a 4-hour dwell using a conventional 132-mM sodium dialysis solution, the sodium level in the drained dialysate typically will have fallen to about 128 mM (Figure 19.7). In the early part of a dwell, dialysate sodium falls to an even greater extent, because it is being diluted by ultrafiltrate containing only about 65 mM of sodium. As the dwell proceeds, the dilutional effect of ultrafiltration on dialysate sodium is partly counteracted by the diffusion of sodium from body tissues to dialysate. Therefore, late in the dwell, when ultrafiltration has slowed, diffusion will have increased the dialysate sodium back up to about 128 mM (Rodriguez-Carmona, 2004). Overall, net sodium removal with a 4-hour, 1.5% dextrose, 2-L exchange is minimal, although with a 4-hour, 4.25% dextrose, 2-L dwell, sodium removal typically is in excess of 70 mmol. An alternative way of increasing sodium removal is to use dialysis solutions with a lower sodium concentration, for example, solutions containing 120 mM sodium instead of the usual 132 mM. With such low sodium solutions, diffusive sodium removal is increased, but greater concentrations of glucose are required to achieve the same osmotic effect. Such lower sodium dialysis solutions can be prepared but are not commercially available.

F. Protein losses. Obligatory dialysate protein losses are a feature of peritoneal dialysis and typically average 5 to 10 g daily. Half of the protein lost is albumin. These losses are the major cause of the slightly lower serum albumin levels typically seen in patients on peritoneal dialysis compared with those on hemodialysis. Albumin losses are greatest, and serum albumin is lowest, in patients with a fast PSTR. The losses or clearances of large molecular weight proteins such as albumin are relatively constant during the course of a dwell.

Protein losses are believed to occur via a relatively small number of large pores that correspond to inter-endothelial clefts but also through small pores. Peritoneal absorption of fluid is a form of "bulk flow" and so involves protein as well as other solutes. It thus acts to decrease net peritoneal protein losses. High dialysate protein losses are associated with decreased survival, likely due to associated comorbidity and systemic inflammation (Yu, 2019).

During peritonitis, protein losses increase markedly for a number of days, presumably because of an increase in effective peritoneal surface area due to increased peritoneal vascularity. This effect is, in part, mediated by prostaglandins. Protein losses on intermittent peritoneal dialysis regimens appear to be somewhat less per day than on continuous regimens, presumably because protein losses are decreased during the "dry" interdialytic periods.

V. RESIDUAL RENAL FUNCTION. There is evidence that residual renal function persists longer and at a higher level in patients on chronic peritoneal dialysis than in those on hemodialysis. Residual function contributes to salt and water removal and to clearance of both small- and medium-size solutes. Creatinine clearance is disproportionately higher in those with significant residual renal function, as tubular secretion of creatinine contributes to the overall clearance to a relatively large extent. The opposite is the case with urea clearance, where tubular resorption of urea acts to reduce urea excretion. There is evidence that the average of urea and creatinine clearance is a reasonable estimate of the true glomerular filtration rate in the failing kidney, and this estimate is used when calculating the renal contribution to total creatinine clearance in patients on peritoneal dialysis. Residual renal function has been shown to be predictive of patient outcome in peritoneal dialysis, perhaps because it is associated with better preserved renal endocrine and metabolic function and superior volume homeostasis, as well as greater small- and large-molecule clearance.

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20 Apparatus for Peritoneal Dialysis

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In this chapter, solutions and equipment for the maintenance of various forms of chronic peritoneal dialysis (PD) are described. PD catheters are reviewed in Chapter 21, and apparatus specifically for acute PD is reviewed in Chapter 22.

I. CONTINUOUS AMBULATORY PERITONEAL DIALYSIS (CAPD). In CAPD, dialysis solution is constantly present in the abdomen. The solution is typically changed 4 times daily, with a range of 2 to 5 times, depending on individual patient requirements. Drainage of "spent" dialysate and inflow of fresh dialysis solution are performed manually, using gravity to move fluid into and out of the peritoneal cavity. Technically, PD solution flows into the peritoneal cavity, and dialysate drains out (ie, the solution does not become dialysate until dialysis has occurred, although the term "dialysate" is commonly used for fresh as well as for used or "spent" solution). In this chapter, the term dialysate is used correctly to refer only to PD solution after it has been instilled into the peritoneal space.

A. Dialysis solutions. CAPD solutions are packaged in clear, flexible plastic bags, previously made from polyvinyl chloride, but Fresenius Medical Care (FMC) has switched to "Biofine," a multilayer thin polymer which contains no phthalates or polychlorinated hydrocarbons and which therefore may be more easily recycled and so is more environmentally friendly. Baxter uses "Clearflex" for some of their solutions. This plastic is also phthalate free and highly transparent but does contain polyvinyl chloride. Some PD solutions are in single-chamber bags while others are packaged with the different solution components in two-chamber bags, which are mixed before infusion into the peritoneal cavity.

1. **Dialysis solution volumes.** For adult patients, CAPD solutions are available in volumes of 1.5, 2.0, 2.25, 2.5, or 3.0 L, depending on the manufacturer. The commonly used bags are routinely overfilled by about 100 mL to allow for flushing, as will be described in a subsequent section. The standard volume prescribed has been 2.0 L, but 1.5 and 2.5 L are also widely used. Generally, larger volumes are prescribed in order to increase solute clearance, but they may not always be tolerated by patients because of symptoms due to the consequent increase in intraperitoneal hydrostatic pressure.
2. **Dialysis solution glucose, pH, and glucose degradation products (GDPs).** Dextrose (glucose) is the osmotic agent commonly used in standard CAPD solutions such as Baxter's "Dianeal" and FMC's "Delflex," and preparations containing 1.5%, 2.5%, and 4.25% dextrose (as glucose monohydrate, molecular weight [MW] 198) are routinely available and are labeled as such in North America. The true anhydrous dextrose or glucose concentrations (MW 180) in these solutions are 1.36%, 2.27%, and 3.86%, respectively, and this is how they are typically labeled in Europe. The approximate osmolarities of these solutions are 345, 395, and 484 mOsm/L, respectively. FMC's "balance," "bicaVera," and "bicaNova" solutions

contain 1.5%, 2.3%, and 4.25% anhydrous dextrose strengths, respectively, and are labeled as such in Europe. The heat sterilization of glucose leads to the generation of GDPs, which may have toxic effects both on the peritoneal membrane and systemically. Less GDPs are generated when glucose is heat sterilized at low pH, so in order to minimize GDP generation, the pH of standard lactate-based PD solutions is kept at about 5.5 during heat sterilization. Lowering pH further would decrease GDPs even more, but would also cause infusion pain in many more patients. A pH of 5.5 on infusion is normally well tolerated, and solution pH rises rapidly as bicarbonate diffuses into the peritoneal cavity from the plasma. However, some patients complain of pain during inflow. This pain can be relieved by neutralizing the dialysis solution pH with alkali prior to instillation, but this is not usually feasible in the long term.

The low pH of PD solution may have adverse effects on leukocytes, impairing their ability for phagocytosis and bacterial killing and may even be harmful to the peritoneal membrane. Therefore, another strategy to reduce GDP generation is used. This is the two-compartment solution bag (Figure 20.1). In one compartment, the glucose is heat sterilized at a very low pH (about 3.2), under which conditions the formation of GDPs is reduced even further. In the other compartment, the rest of the solution is maintained at an alkaline pH during sterilization. At the time of use, the two compartments are allowed to mix, bringing the pH of the resultant combined solution to normal. The end result, therefore, is a low GDP, normal pH PD solution. Examples are Baxter's "Physioneal" and FMC's "balance," which are marketed as having particularly low GDP levels.

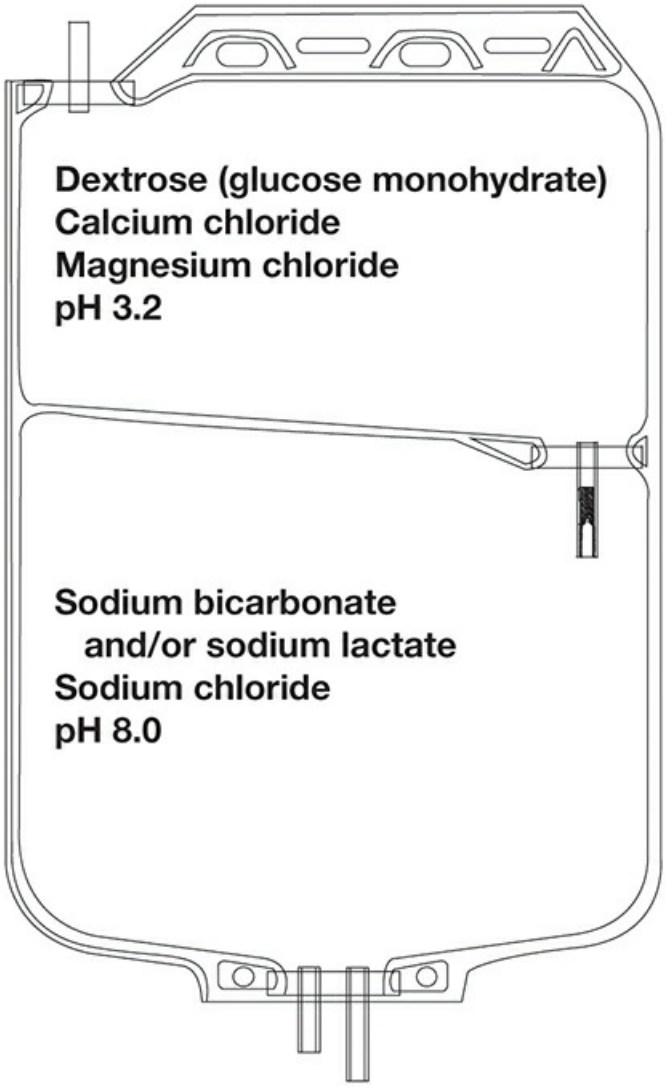


FIGURE 20.1: Two-compartment PD solution bag to allow delivery of a normal pH solution with low GDPs with or without bicarbonate buffer. GDPs, glucose degradation products; PD, peritoneal dialysis.

3. **Dialysis solution buffer and pH.** Most commonly marketed PD solutions contain lactate as the bicarbonate-generating base, usually in a 35- or 40-mM concentration. The lactate diffuses across the peritoneal membrane into the bloodstream and is soon metabolized into bicarbonate. A more direct way to supply bicarbonate is to add it directly to the dialysis solution. However, solutions containing bicarbonate and no CO_2 have a high pH, at which calcium and magnesium precipitate. For this reason, it is not possible to store bicarbonate-buffered solution in a single-bag system. The same two-compartment bag system described above to limit generation of GDPs can be used to enable inclusion of bicarbonate in PD solution. A solution containing calcium and magnesium, a small amount of acid, and other electrolytes is put into one of the compartments, and the bicarbonate-containing solution is kept in the other compartment. At the time of use, the solutions in the two compartments are mixed together, and the small amount of acid in the calcium/magnesium solution reacts with bicarbonate to generate carbonic

acid and CO_2, which keeps the pH of the final solution in the physiologic range, at which calcium and magnesium remain in solution. The process is very similar to providing bicarbonate dialysis solution for hemodialysis from a two-component set of concentrates.

There are a number of commercially available two-pouch systems for PD solutions. The "Balance" solution from FMC has low GDPs and normal pH as described previously and uses only lactate as the base. Physioneal, from Baxter, contains both bicarbonate and lactate (25 and 15 mEq/L, respectively), and here the two-bag system is used both to limit generation of GDP during sterilization and to allow bicarbonate to be used. "BicaVera" and "bicaNova," both from FMC, contain only bicarbonate at 35 and 39 mEq/L, respectively, and each has no lactate, and here again, the two-bag system allows use of bicarbonate and also greatly reduced generation of GDP (Table 20.1).

TABLE 20.1 Commonly Available Peritoneal Dialysis Solution Formulations

	Manufacturer	pH	Osmotic or Oncotic Agent	Na (mM)	Ca (mM)	Mg (mM)	Lactate (mM)	Bicarbonate (mM)	Pouches
Dianeal PD1	Baxter	5.5	Glucose	132	1.75	0.75	35	0	1
Dianeal PD4	Baxter	5.5	Glucose	132	1.25	0.25	40	0	1
Stay safe 2/4/3	FMC	5.5	Glucose	134	1.75	0.5	35	0	1
Stay safe 17/19/18	FMC	5.5	Glucose	134	1.25	0.5	35	0	1
Nutrineal	Baxter	6.5	Amino acids	132	1.25	0.25	40	0	1
Extraneal	Baxter	5.5	Icodextrin	132	1.75	0.25	40	0	1
Physioneal 35	Baxter	7.4	Glucose	132	1.75	0.25	10	25	2
Physioneal 40	Baxter	7.4	Glucose	132	1.25	0.25	15	25	2
Balance	FMC	7.4	Glucose	134	1.25 1.75	0.5	35	2.5	2
BicaVera	FMC	7.4	Glucose	134	1.25 1.75	0.5	0	34	2

These may differ slightly in name and in formulation from region to region.

All glucose-based solutions are available in three strengths (1.36, 2.27, and 3.86 mg/dL of glucose, equivalent to 1.5, 2.5, and 4.25 mg/dL of dextrose as glucose monohydrate).

To convert calcium from mmol/L (mM) to mg/dL multiply by 4.

To convert magnesium from mmol/L (mM) to mg/dL multiply by 2.43.

FMC, Fresenius Medical Care.

Because these two-bag system solutions are close to physiologic pH after mixing, and because they contain greatly reduced amounts of GDPs, they are theoretically more biocompatible than standard one-bag solutions where the pH is about 5.5. The hope was that these biocompatible solutions would lead to better long-term preservation of peritoneal transport function, including ultrafiltration. It was also hoped that they would enhance peritoneal host defenses and thereby decrease peritonitis rates, that their use would result in lower serum GDP levels and ultimately better preservation of residual renal function, and that all this would translate into improved technique and patient survival on PD.

There is evidence that these dual-bag solutions are effective in dealing with

infusion pain, which occurs in fewer than 5% of patients using standard low-pH PD solutions. With regard to other outcomes, results from randomized controlled trials have shown inconsistent results. The large randomized "balANZ" trial showed a significantly lower peritonitis rate with the Balance solution, but this has not been confirmed in other trials, and a meta-analysis has been negative (Cho, 2014; Johnson, 2012). Some trials, including "balANZ," have shown better preservation of residual renal function, but some have also shown less effective ultrafiltration, leading to concern that the improved preservation of renal function with this solution is simply or partly a consequence of hypervolemia (Davies, 2013). Randomized studies have not been large enough to allow conclusions about long-term patient or technique survival. These biocompatible solutions are widely used in Europe and in parts of Asia, and Balance has become FMC's standard solution in these regions, but they are used relatively little or not at all in North America and elsewhere, partly because of the lack of consistent high-level evidence supporting their use and partly because they are not approved for use in the United States.

4. **PD solution electrolyte concentrations.** The electrolyte concentrations of CAPD solutions vary little by manufacturer. The standard formulations from the two large international manufacturers are shown in Table 20.1. They contain no potassium, and sodium levels are mostly 132 or 134 mM. Higher sodium concentrations would lead to less diffusive removal of sodium during dwells. Lower sodium solutions have been proposed as a means of augmenting sodium removal, but would require more glucose to maintain a given osmolarity.

   With the widespread use of calcium carbonate or calcium acetate as phosphate binders, PD solutions containing 2.0 to 2.5 mEq/L (1.0-1.25 mM) rather than 3.5 mEq/L (1.75 mM) calcium are increasingly used with the goal of reducing the incidence of the hypercalcemia that is sometimes associated with oral calcium and vitamin D administration. This also protects against adynamic bone disease, which was previously common in patients with PD. However, lower calcium PD solutions have been associated with higher plasma parathyroid hormone (PTH) levels. Both standard and low-calcium PD solutions continue to be available in many countries. PD solutions typically contain magnesium levels of 1.0 or 0.5 mEq/L (0.5 or 0.25 mM), and this can occasionally result in magnesium depletion.

5. **Nonglucose solutions.** Glucose as an osmotic agent in PD has the advantage of being familiar, relatively safe, and inexpensive, and is also a source of calories. There is concern, however, that the instillation of large amounts of glucose into the peritoneal cavity predisposes patients to hyperglycemia, dyslipidemia, obesity, and long-term peritoneal membrane damage, both directly and likely via GDPs and the formation of advanced glycosylation end products (Davies, 2005). Glucose-based solutions often become less effective in patients who are fast transporters, especially after 2 to 3 years on PD, and inadequate ultrafiltration may result. Alternative osmotic agents are available.

   a. **Icodextrin.** This is a polyglucose solution and is widely used. It is iso-osmolar and induces ultrafiltration by its oncotic effect. Absorption of polyglucose is by the lymphatics and so is much slower compared with glucose. The oncotic effect and the consequent ultrafiltration are therefore more sustained than with glucose. For this reason, the main indication to use icodextrin is for the long nocturnal

dwell in CAPD and for the long day dwell in automated peritoneal dialysis (APD), especially in patients with poor ultrafiltration. It is generally used for just one dwell daily, as it is less effective at ultrafiltration than glucose for short dwell times. Icodextrin use is associated with unphysiologic blood levels of maltose and maltotriose, but no associated toxicity has been identified. The increased maltose levels will cause interference with the glucose dehydrogenase pyrroloquinoline quinone assay (which reacts with both glucose and maltose) for blood glucose measurements. Therefore, blood glucose should be measured with other methods in patients using icodextrin. In addition, use of icodextrin is associated with mild translocational hyponatremia (owing to movement of sodium-poor fluid from cells to the extracellular fluid). Measured amylase levels can be factitiously low, as a result of interaction between metabolites of icodextrin and commonly used amylase assays.

Icodextrin has been shown in randomized controlled trials to improve ultrafiltration and volume status in patients with PD, though not convincingly to reduce blood pressure (Davies, 2003). It has also been shown to improve glycemic control, decrease weight gain, and lessen glucose-induced lipid abnormalities (Cho, 2013; Goossen, 2020; Paniagua, 2009). There is some evidence of better long-term preservation of peritoneal membrane function (Davies, 2005) and of decreased technique failure in patients with diabetes (Takatori, 2011). The disadvantages are its extra cost and occasional skin reactions.

b. **Amino acid–based solutions.** These are used for nutritional supplementation as they are largely absorbed by the end of a 4- to 6-hour dwell. Studies have shown them to be modestly effective in nutritionally compromised patients (Li, 2003). They are reasonably effective osmotically (comparable to the 1.36% glucose solution) but can be used only once daily because in larger amounts they tend to cause acidosis, as well as a rise in the blood urea. These side effects can be addressed with oral alkali therapy and more dialysis, respectively. They are not widely used and are unavailable in many countries.

c. ***Other solutions.*** There is great interest in finding alternative osmotic agents for PD solutions, given the apparent local and systemic effects of glucose. Use of agents such as xylitol, glycerol, and carnitine has been reported in research studies, but none is available commercially.

6. **Sterility and trace metals.** The preparation of PD solutions is carefully regulated to ensure that the final product is bacteriologically safe and has very low concentrations of trace metals.

7. **Dialysis solution temperature.** PD solutions are usually warmed to body temperature prior to inflow. They can be instilled at room temperature, but uncomfortable lowering of the body temperature and shivering can result. The best warming method is to use a heating pad or special oven. Microwave ovens are frequently used, but this is not recommended by most manufacturers because “hot spots” may be produced during heating, in particular, in the transfer sets. Risks to the patient include overheating of the dialysis solution, as this can chemically alter the dextrose and may cause discomfort on instillation. Also, accidental boiling of the solution in a confined space may cause an explosion. Heating methods that involve immersing the PD solution container completely in water are also not recommended

because contamination can result.

B. Transfer sets. The PD solution bag is connected to the patient's peritoneal catheter by a length of plastic tubing called a "transfer set" (also sometimes called a "giving set"). There are three major types of transfer sets, each requiring a different method of performing the CAPD exchange. For the purpose of discussion, we will refer to them as the straight transfer set, the Y transfer set, and the double-bag system. Note that some transfer sets are connected to the peritoneal catheter via a short extension or adapter tubing (see what follows).

1. **Straight transfer set.** This system is now rarely used because it is associated with high rates of peritonitis. However, a brief description is helpful in understanding how more modern systems have evolved.

   Once every several months, the transfer set is changed. Extended-life transfer set tubing allows patients to dialyze for 6 months between transfer set changes.

   a. **Design.** The straight transfer set is a simple plastic tube. One end connects to the peritoneal catheter and the other end to the dialysis solution bag. All exchanges are performed by making and subsequently breaking the connection between the transfer set and the bag. This connection typically involves a spike or a Luer lock.

   b. **Exchange procedure.** Dialysis is performed as follows:
      1. Dialysis solution is instilled by gravity.
      2. The empty bag and transfer set are rolled up and stored in a pouch carried on the patient's body.
      3. Dwell time is typically 4 to 8 hours.
      4. The bag is unrolled and placed on the floor. The dialysate is drained into the bag. The bag is then disconnected from the transfer set and discarded.
      5. A new bag is attached to the transfer set using a spike or Luer lock.
      6. Fresh dialysis solution is instilled.

2. **The Y set** (Figure 20.2). The Y set was developed to free patients from the requirement to remain attached to the transfer set and empty bag between exchanges. Early studies revealed a more important benefit—a peritonitis rate significantly lower than that with the straight set. This is thought to be due to the flush-before-fill procedure used to prime the tubing. Bacteria that may be introduced during the connection procedure are washed out of the Y set into the empty drainage bag rather than into the patient, as happens with the straight set. Also, because the tubing and bags are disconnected from the patient between exchanges, less mechanical stress may be placed on the catheter exit site and tunnel. This may result in fewer episodes of minor trauma to the catheter exit site and tunnel, and therefore to fewer exit site and tunnel infections and associated peritonitis. Because of this lower peritonitis rate and the convenience of allowing the patient to disconnect between exchanges, Y-set systems increasingly displaced the straight system as the transfer set of choice from the mid-1980s onward.

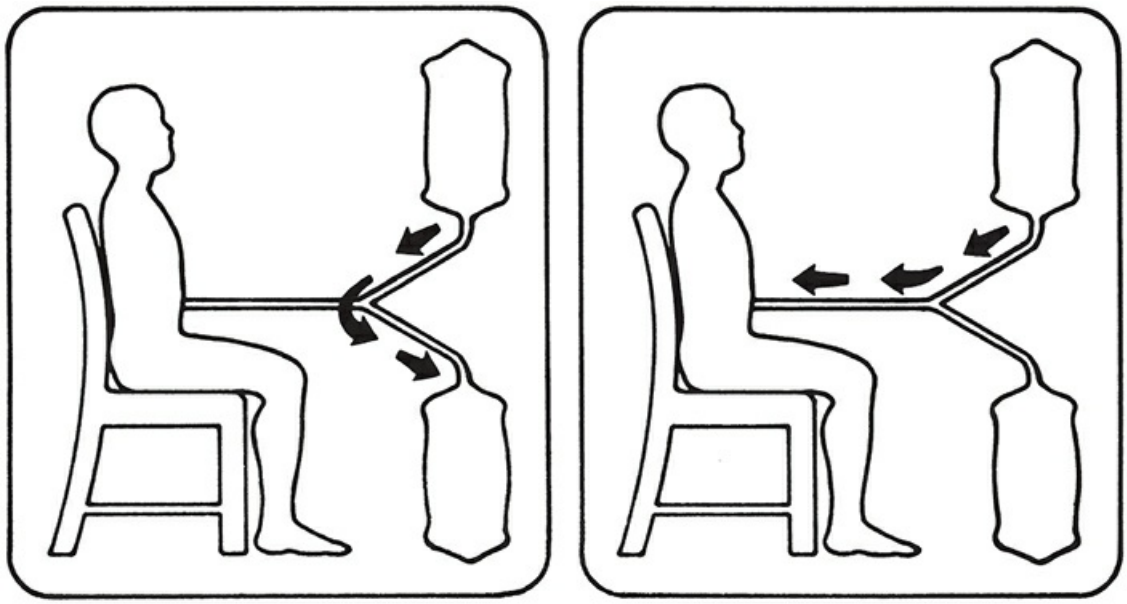


FIGURE 20.2: Y-set system using flush-before-fill. A. A small volume of fresh dialysis solution is drained directly into the drainage bag (either before or just after drainage of the abdomen). This act washes away any air or bacteria that may be present in the afferent limb of the Y. B. Fresh solution is introduced through the rinsed transfer set. With the preattached double-bag system, the purpose of the "flush-before-fill" step is solely to flush out any air in the tubing.

a. **Design.** This is a Y-shaped piece of tubing that is attached by its stem to the patient's catheter or extension tubing at the time of each solution exchange. During the exchange, the afferent and efferent limbs of the Y are attached to a bag of fresh PD solution and to a drain bag, respectively. In some cases, the drain bag is the empty solution bag that was used in the previous exchange. Most Y sets are not connected directly to the catheter but rather to a short (15-24 cm) adapter or extension tubing inserted between the catheter and the stem of the Y set. This adapter/extension tubing is sometimes confusingly called a transfer set, but in this chapter, that term is reserved for the tubing that connects the solution bag and drain bag to the extension tubing and catheter. The adapter/extension tubing avoids the need for, and the risk of damage associated with, repeated clamping of the catheter.

b. **Exchange procedure**
   1. **Spike/lock:** The fresh bag of PD solution is attached to the afferent limb of the Y set via a spike or Luer lock.
   2. **Connect:** The stem of the Y set is connected to the extension tubing.
   3. **Drain:** The stem and efferent limb of the Y are unclamped, and the spent dialysate is drained from the peritoneal cavity into the drain bag.
   4. **Flush:** With the stem of the Y set clamped, approximately 100 mL of fresh solution is flushed from the new bag through the afferent limb of the Y into the efferent limb and so into the drain bag.
   5. **Fill:** The efferent limb is clamped and the stem unclamped, and the peritoneal cavity is filled from the new bag of PD solution.

6. **Disconnect:** The Y set is then disconnected from the adapter/extension tubing.

3. **Preattached double-bag Y-set systems**

a. **Design.** These systems are a variant of the Y set in which the solution bag comes preattached to the afferent limb of the Y, obviating the need for any spike or Luer lock connection. The drain bag is similarly preattached to the efferent limb, and the only connection the patient needs to make is between the transfer set and the adapter/extension tubing. A flush-before-fill step is still performed, but the purpose is only to flush out residual air and not to prevent peritoneal cavity contamination, as this is no longer relevant in the absence of a need to make a transfer set–to–solution bag connection.

These are now by far the most popular systems because of their ease of use and because of evidence that they are associated with even lower rates of peritonitis than the standard Y sets (Kiernan, 1995).

b. **Exchange procedure**

1. **Connect:** The patient connects the new transfer set to the adapter/extension tubing.
2. **Drain:** The stem and efferent limb are unclamped, and spent dialysate is drained from the peritoneal cavity into the drain bag.
3. **Flush:** The stem is clamped, and the afferent limb of the Y is opened by breaking a "frangible" in the tubing. Then 100 mL of PD solution is flushed through from the fill bag to the drain bag to remove residual air from the tubing.
4. **Fill:** The efferent limb is clamped, the stem is unclamped, and fresh PD solution is run into the peritoneal cavity.
5. **Disconnect:** All limbs are clamped, and the transfer set is disconnected from the extension tubing.

C. Various connectors for PD. Over the years, a number of connectors and associated devices have been developed and marketed in an attempt to reduce the possibility of bacterial contamination while making either the catheter–to–transfer set or the transfer set–to–solution bag connections.

1. **Catheter–to–transfer set (or adapter/extension tubing–to–transfer set) connection**

a. **Catheter connector.** Early in the history of CAPD, simple, plastic, plug-in connectors were used at the catheter–to–transfer set junction. Cracking of the plastic connector and accidental disconnection were frequent events that often led to peritonitis. A special Luer lock connector made of titanium was developed to prevent such problems and has become standard. Titanium was chosen for its light weight and resistance to electrolyte-containing solutions. Designed for easier handling and a tighter connection, the new product functioned very well. Catheter–to–transfer set connectors constructed from more durable plastics are also available.

b. **Quick connect–disconnect systems.** With the advent of the disconnect Y sets and double bags, the need arose for an easy yet sterile connection at the catheter–to–transfer set joint (or adapter/extension tubing–to–transfer set joint). A number of connector designs for this purpose are now available. Typically,

they include a “Luer Lock”–type mechanism with a recessed orifice and an iodine-impregnated cap to minimize the risk of contamination. A more sophisticated device is the “Stay Safe” device from FMC, which regulates the fill and drain cycles as well as making the connection to the adapter tubing.

2. **Transfer set–to–solution bag connection.** With the advent of double-bag systems, technologies to facilitate the connection between the transfer set and the PD solution bag are less relevant. However, some of them are still used, and a brief mention will be made of them.
    a. **Spike-and-port design.** The spike-and-port design is the oldest and simplest system used to connect the transfer set to the PD solution bag. It is operated by pushing a spike located at the end of the transfer set into a port on the solution bag.
    b. **Easy-lock connectors.** Spiking the solution bag is difficult for many patients because it requires reasonably good vision, depth and sensory perception, and strength. Mistakes can result in contamination and subsequent peritonitis. The spike has thus been replaced in many transfer sets by a Luer lock– or screw-type system, resulting in easier insertion. A modified form contains a recessed fluid pathway to prevent accidental contamination, a reservoir that can be filled with an antiseptic solution (eg, povidone-iodine), and a silicon O-ring to provide a tight seal.

II. AUTOMATED PERITONEAL DIALYSIS.

APD, using a cycler, is now at least as widely used as CAPD across the world, and in many countries, including the United States, Canada, Australia, and most of Europe, the majority of patients with PD are treated this way (Roumeliotis, 2021). APD is traditionally divided into APD with a day dwell, also known as continuous cycling peritoneal dialysis (CCPD), and “day dry” APD, also known as nocturnal intermittent peritoneal dialysis (NIPD), although the combination of cycler therapy at night with multiple daytime exchanges is also commonly used (see what follows) (Figure 20.3). In APD with a day dwell, the patient carries PD solution in the abdominal cavity throughout the day but performs no exchanges and is not attached to a transfer set. At bedtime, the patient hooks up to the cycler, which drains and refills the abdomen with solution, 3 or more times in the course of the night. In the morning, the patient, with the last dwell remaining in the abdomen, disconnects from the cycler and is free to go about daily activities. In “day dry” APD, the patient drains out fully at the end of the cycling period, and so the abdomen is “dry” all day. Because of the absence of a long-duration day dwell, clearances are generally lower on day dry APD, but its use may be indicated as part of an incremental PD approach if there is a good residual renal function (see Chapter 23) or if there are mechanical contraindications to walking about with solution in the abdominal cavity (eg, leaks, hernias, back pain).

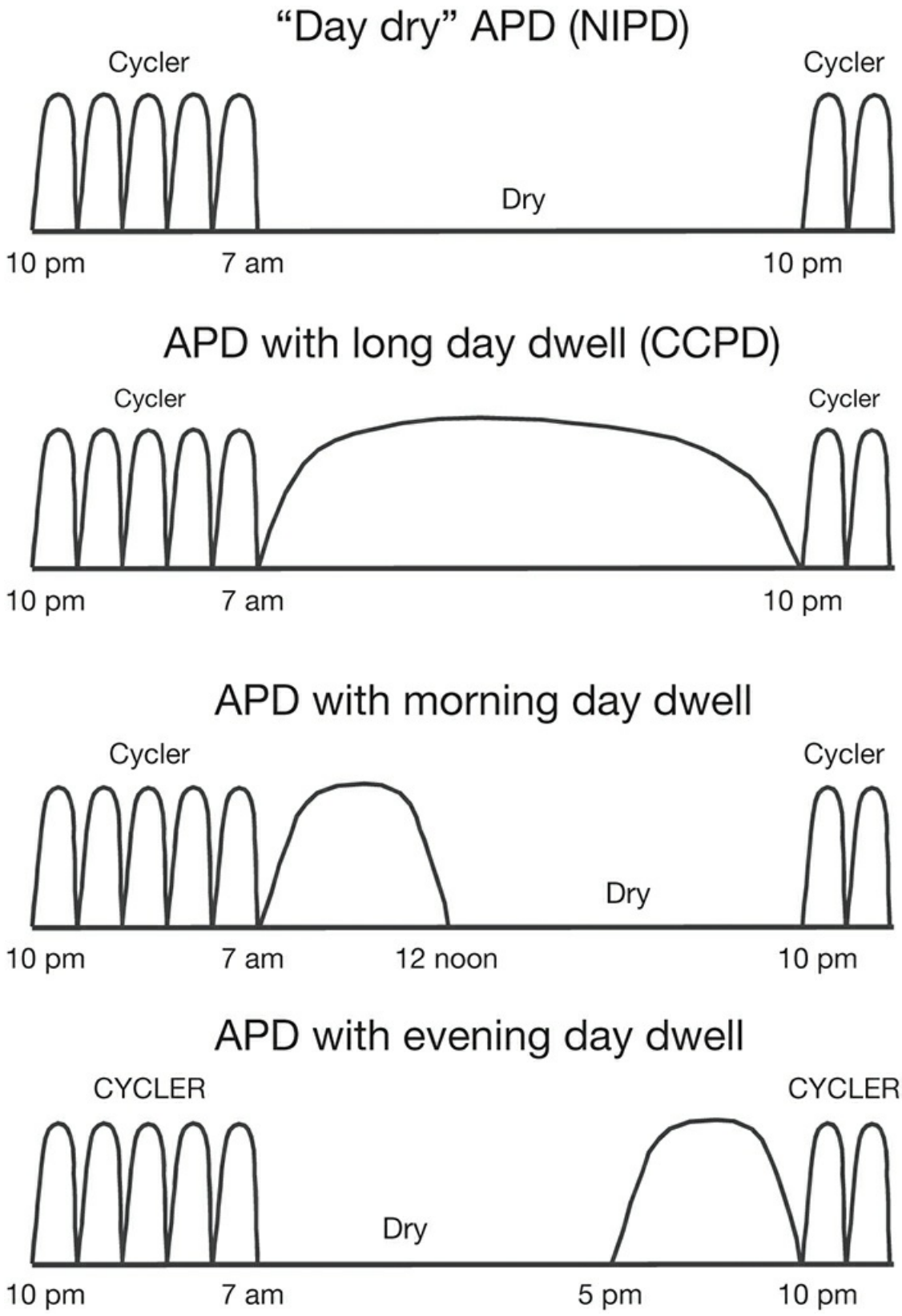


FIGURE 20.3: Visual representation of common CAPD, APD, and hybrid prescriptions. APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis.

A. Cyclers. These are machines that automatically cycle dialysis solution into and out of the abdominal cavity. Contemporary cyclers are not gravity dependent but instead use hydraulic pumps to deliver the solution from 3-, 5-, or 6-L bags to a "fill bag" and from there into the abdomen. The solution in the fill bag is warmed before inflow. With the aid of pressure alarms, clamps, and timers, inflow, dwell, and outflow of solution are regulated and overfilling is prevented.

Contemporary cycler models are small and light enough to pack in a large suitcase and carry on trips. Advanced design and computer technology make them simple to set up and operate. The patient typically sets only the start time, volume of solution to be used, dwell volume, and length of dialysis or stop time desired. The cycler calculates the timing of the exchanges, measures the volume of ultrafiltrate, and optimizes drain and inflow time by measuring flow rates. The cycler changes from drain to fill when the flow slows down rather than waiting for a preset time. It also tests to determine whether flow has stopped because of obstruction. Some models incorporate "smart cards," which can be used to program the cycler prescription and to record the actual prescription delivered to the patient.

More recent models such as Baxter's "Amia" or FMC's "Sleep Safe Harmony" and its newer "Versi-PD" cycler have interactive large color touch screens with animations and voice guidance. They also have remote patient monitoring technology platforms such as Baxter's "Share Source" and FMC's "Kinexus," which allow the PD unit to monitor treatment data including fluid removal and prescription adherence. These platforms are also being incorporated into the previous generation of less expensive cyclers such as Baxter's "Claria Homechoice Pro" and FMC's "Liberty," which are still widely used. More recently, FMC has introduced the "Silencia" cycler, which operates relatively silently and has softer alarms to improve sleep quality (Torres, 2023). Studies on these technological advances have been of variable quality and have shown inconsistent results (El Shamy 2022; Nygard, 2022). However, a recent large cluster randomized controlled trial from Mexico has demonstrated significant patient outcome benefits for remote patient monitoring in APD (Paniagua, 2024).

An extremely useful feature is the ability to draw dialysis solution from a separate solution container for the last instillation in the morning, called the "last bag option." This last inflow, which will be in place throughout the day, may require a higher dextrose concentration than the other exchanges. More often, nowadays, the last bag option is used to deliver an alternative solution such as icodextrin for the long day dwell.

Typically, patients spend 7 to 10 hours a night cycling. Dwell volumes range from 1.5 to 3.0 L, and the number of cycles usually varies from 3 to 10 per night. It is often possible to use a larger fill volume during APD compared with CAPD because of the lower intraperitoneal pressure in the recumbent position. A larger fill volume will increase clearance as well as ultrafiltration (owing to slower glucose absorption). The total amount of fluid used is typically between 8 and 18 L.

B. Dialysis solution. PD solution for APD is the same as that used for CAPD. Most cyclers are fed by a tube containing a multipronged manifold that can attach to as many as eight dialysis solution bags simultaneously to provide sufficient solution for the night. The total number of bags required, and thus the cost, can be reduced by using larger bags holding 3, 5, or 6 L of dialysis solution, although lifting these can be a

problem for older and frailer patients. Because some cyclers can be fed from two or more bags simultaneously, with an appropriate selection of the dextrose concentrations of the solutions being hung, a number of intermediate dextrose concentrations (eg, between those commercially available) can easily be delivered. Low GDP solutions (both lactate-based and bicarbonate-lactate-based solutions) are available in large-volume bags suitable for APD, whereas pure bicarbonate solution is not. Amino acids are occasionally used during APD to provide nutritional support and to reduce glucose exposure. However, the fractional absorption of the amino acids in the bag is much lower because of the much shorter cycle duration during APD compared with CAPD. Icodextrin solution is not usually prescribed for delivery by cycler, except as a "last bag option."

C. APD connections

1. **Transfer sets.** One set of plastic tubing serves to interconnect several solution bags to the cycler and to connect the cycler to the patient. Shorter, simpler, and less expensive solution delivery sets are constantly being developed.
2. **Catheter–to–transfer set connection.** The catheter–to–transfer set connection must be made every night and broken every morning. Previously, many patients had a standard Luer lock connector at the end of the peritoneal catheter. The procedure for connecting the catheter connector to the transfer set was tedious because it required sterile procedure and a lengthy antiseptic scrub. This older connector method has largely been replaced by new, quick connect–disconnect systems that require no manual disinfection and are therefore much easier to use. Most of these systems also may fit CAPD transfer sets, allowing patients with APD to use the CAPD method whenever desired (eg, when traveling).
3. **Transfer set–to–solution bag connections.** The standard spike-and-port or, more often, Luer lock connections are used to connect the multipronged transfer set to the dialysis solution bags. It is ironic that this step, which has largely disappeared from CAPD with the dominance of double bags, has become commonplace again with the growth in use of APD. In order to minimize the risk of contamination, the newer cyclers allow for a flush option after this connection has been made. The same connection technologies used to assist patients with CAPD with visual impairment, arthritis, or neuropathy can also assist patients with APD in making the transfer set–to–container connections.

D. Tidal peritoneal dialysis (TPD).

This variant of APD was designed to optimize solute clearance by leaving a significant volume of dialysis solution in the peritoneal cavity throughout the dialysis session. It was thought that this would allow diffusive clearance to continue throughout the drain and fill portions of the cycling period. Initially, the peritoneal cavity is filled with a volume of solution selected to be as large as possible without causing discomfort. The volume used depends on patient size and habitus, but is typically 2 to 3 L. When TPD was introduced, a 50% tidal volume was common; for example, if 2 L is being used, the next fill volume (the tidal volume) is 1 L, the next drain volume is about 1 L, and so on. Clearances with TPD have been disappointing and, with usual solution volumes, are no better than those with similar amounts of solution delivered by conventional cycling. Clearance benefits may be seen with high-volume TPD where solution volumes are greater than 20 L, but these are not widely used because of high cost and inconvenience. Today, the commonest indications

for TPD are to avoid low-drain alarms in patients with poor catheter function or to avoid drain pain in patients who experience discomfort at the end of the drain phase (Blake, 2014b). With this in mind, cyclers allow individualization of the tidal volume, and most commonly it is set to about 75% to 85%. TPD cycles are quite short, usually totaling less than 60 minutes, with dwell times for the replacement aliquot being only 10 to 40 minutes. The peritoneal cavity is drained completely at the end of the dialysis session but can also be drained every third or fourth cycle in order to avoid cumulative ultrafiltration leading to a progressively greater dwell volume. At the end of the cycler session, a day dwell can be left in or drained with the peritoneal cavity left day dry. The FMC "Harmony" cycler has an additional feature in that it adjusts the flow rate in response to changes in intraperitoneal pressure in order to maximize drain volume efficiently.

1. **Technical problems.** Classical high-volume TPD has a number of technical problems, making it difficult to recommend for routine use. Therefore, mainly, low-volume TPD is currently used.
   a. **Peritoneal catheter.** For classical high-volume TPD, the peritoneal catheter must have excellent inflow and drain characteristics, as flow must be 180 to 200 mL/min during the drain phase. In contrast, low-volume TPD is often used to avoid alarms from low drain when the catheter function is poor.
   b. **Cost.** In adults, the advantages of TPD in terms of clearance are seen only with 20 to 30 L of solution per treatment, and this is very expensive.
   c. **Ultrafiltration computations.** The ultrafiltration volume must be calculated and added to the drain volume with each exchange; otherwise, the intra-abdominal volume will become progressively larger. TPD is best performed with newer cyclers that have been modified so that the outflow volume can be set to trigger a change to dialysate inflow mode. When the preset outflow volume is reached (eg, 1.5 L), the machine switches immediately to inflow and infuses a fresh 1.5 L of dialysis solution. This system is quite different from that in most early cyclers, in which inflow/outflow cycles were regulated only by preset timers, not by volume.
   d. ***Overfill.*** The risk of overfill of the peritoneal cavity with consequent symptoms of raised intra-abdominal pressure is greater with TPD than conventional APD, perhaps because TPD is often used when catheter function is suboptimal (Cižman, 2014). Some cyclers have safety settings in place to ensure full drainage of the day dwell before cycling is initiated and to ensure ultrafiltrate does not progressively accumulate during cycling (Blake, 2014a).

III. **APD WITH DAYTIME EXCHANGES.** Even APD with a day dwell does not provide adequate clearances for some patients once residual renal function is lost. Additional exchanges and day dwells may be required (see Chapter 23). These dwells improve clearance, as the typical 14- to 16-hour, single-day dwell in APD does not provide significant additional clearance after the first 4 to 6 hours. These additional day exchanges improve ultrafiltration as the single-day dwell is often too long for effective net fluid removal, particularly with dextrose solutions. In fact, in many patients, especially higher transporters, a single dextrose day dwell can result in significant net fluid resorption. Additional day exchanges can be done manually using standard CAPD transfer sets, but this

is relatively expensive in terms of solution and tubing costs and may be inconvenient for patients.

A popular alternative strategy involves using the cycler tubing to deliver the additional exchange(s). The patient returns to the cycler in the afternoon or evening, reattaches to the transfer set, drains the dialysate that has been in the peritoneal cavity since that morning, and then refills from the large-volume solution bags (3-5 L) that will be used to provide solution for cycling that night. The patient then detaches from the transfer set but is able to reattach to the same tubing later to commence cycling that night. This is made possible by a modification of the transfer set that allows serial connections and disconnections to be performed or by simply using "caps" to protect the respective endings of the transfer set and adapter tubing while disconnected. This strategy, which has been described as using the cycler as a "docking station," can be easily performed with contemporary cyclers, and is less costly because no additional transfer set is required and because the solution can be drawn from more economical, large-volume solution bags. It has the additional advantage that it can be set up for the patient in advance by a relative or a helper. However, for the working patient, the requirement to return to the cycler during the noncycling period may be a disadvantage, and in such cases, a manual CAPD-type exchange may be preferred.

In some patients, a second day dwell is not required for clearance reasons, but a single long day dwell leads to net fluid resorption. In these cases, the cycler tubing can be used to drain the day dwell early without any subsequent fill (Figure 20.3). A common alternative strategy in this setting is to use icodextrin solution, which maintains an adequate oncotic gradient even during 16-hour day dwells.

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21 Peritoneal Dialysis Catheters: Placement and Care

Arsh K. Jain, Matthew J. Oliver, and John H. Crabtree

Peritoneal dialysis (PD) as a modality of kidney replacement therapy depends on reliable access to the peritoneal cavity. This access is achieved by implanting a catheter across the abdominal wall into the peritoneal space to serve as a controlled cutaneoperitoneal fistula for infusion and drainage of dialysate. A successful peritoneal access should provide optimal flow, durability, and resistance to infectious and mechanical complications.

I. PD CATHETERS

A. Conventional catheters.

The predominantly used PD catheters are illustrated in Figure 21.1. Most of the catheters used worldwide have two Dacron (polyester) cuffs, with straight or coiled intraperitoneal tips. The intercuff segment is either straight or preformed into a bent shape to facilitate a downward direction of the catheter at the exit site (Figure 21.1A, B). The technique of catheter insertion is more important than catheter type, as no difference in functionality has been convincingly demonstrated among different catheter designs. Although commonly used catheters are also available with single Dacron cuffs, it is widely believed that double-cuff catheters are superior in preventing catheter infection–related peritonitis by impeding pericatheter entry of organisms.

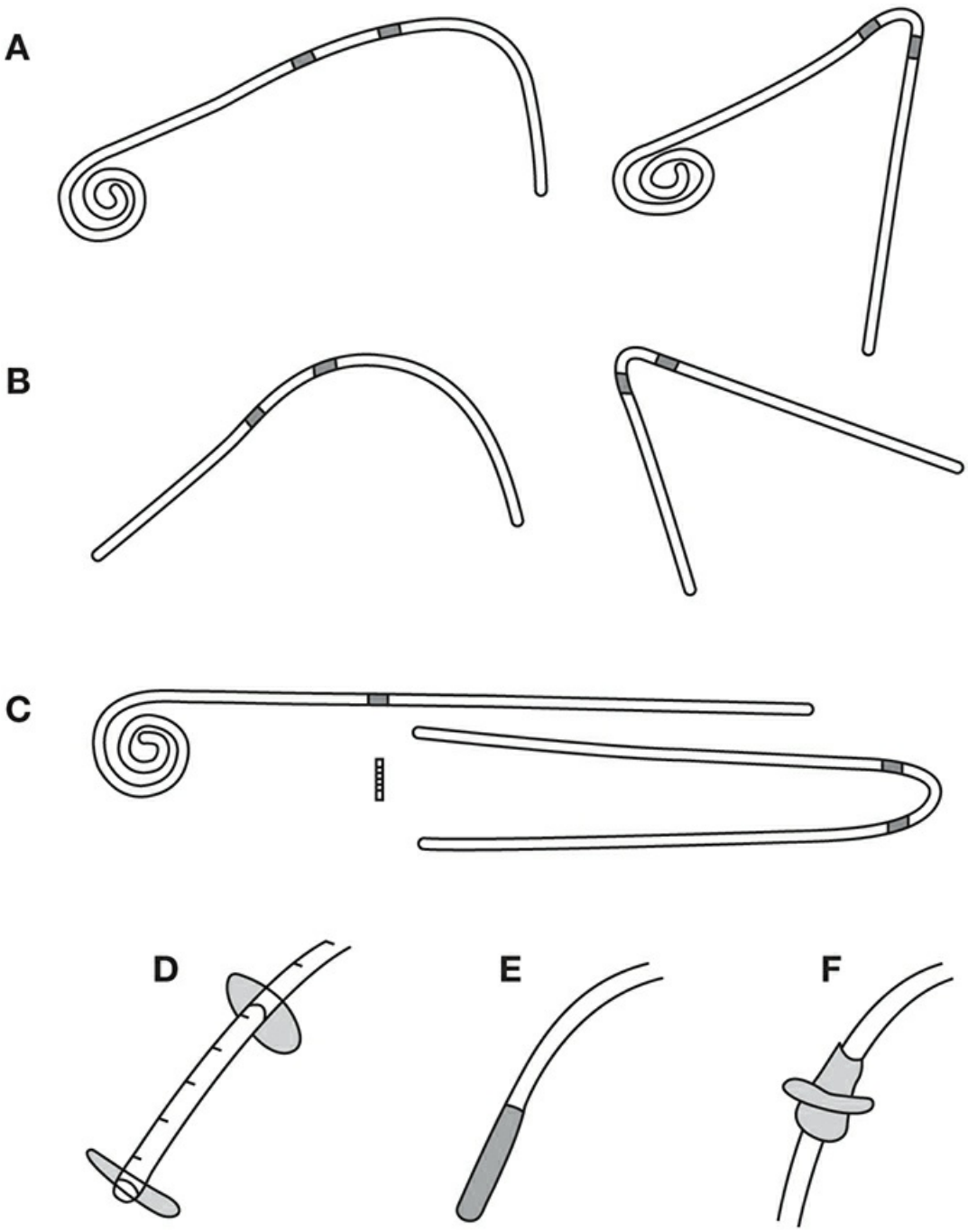


FIGURE 21.1: Commonly used peritoneal catheters and alternative design features. A. Catheters with coiled-tip, two-cuff, and straight or preformed arc bend in the intercuff segment. B. Catheters with straight-tip, two-cuff, and straight or preformed arc bend in the intercuff segment. C. Extended catheter with coiled-tip, one-cuff abdominal catheter, two-cuff extension catheter with preformed arc bend in the intercuff segment, and titanium connector. D. Toronto Western straight-tip catheter with silicone disks. E. Di Paolo straight-tip catheter with tungsten weight. F. Missouri catheter with Dacron flange and silicone bead below and adjoining the deep cuff.

B. Extended catheters. An "extended catheter" is comprised of a one-cuff abdominal catheter segment attached via a double-barbed titanium connector to a subcutaneous extension segment having one or two cuffs (Figure 21.1C). The extended catheter permits remote location of the exit site to the upper chest, upper abdomen, or back

region. The abdominal catheter segment can be placed by any insertion method. The subcutaneous extension catheter is implanted using a vascular tunneling rod or a similar device supplied by the catheter manufacturer.

C. Alternative catheter designs. Modifications of conventional catheter designs have been made to address problems with tissue attachment, tip migration, and pericatheter leaks. The Oreopoulos-Zellerman (Toronto Western) variation of the straight-tipped catheter includes the addition of two silicone disks to the intraperitoneal end of the tubing as an attempt to hold the bowel and omentum away from the side holes at the catheter tip (Figure 21.1D). The Di Paolo catheter is designed to discourage catheter tip migration by adding a tungsten weight to the end of the tubing to promote gravitational self-location to the pelvis (Figure 21.1E). The Oreopoulos-Zellerman and Missouri catheters have a Dacron flange adjacent to a silicone bead mounted below and contiguous with the deep cuff (Figure 21.1F). The flange and bead are attached at a 45° angle on the Missouri version. Suturing the peritoneum between the flange and bead and stitching the flange to the posterior rectus sheath was designed to reduce the occurrence of pericatheter leaks. Mounting the flange and bead at a 45° angle was intended to keep the catheter tip oriented toward the pelvis. However, none of these alternative configurations have been convincingly shown to have any benefit over the conventional designs presented in Figure 21.1A and B. Not all implantation approaches can be used to place these unconventional catheters, and removal is often more difficult. Some of these variants are not universally available and are generally more expensive than conventional catheters.

D. Specific catheter features. Currently, most PD catheters are constructed of silicone rubber, a material well recognized for its biocompatibility and biodurability. Although limited in international availability, some catheters are comprised of polyurethane. Historically, polyurethane catheters have been prone to soften and rupture from chronic exposure to certain topical antibiotic ointments and creams commonly used for chronic catheter exit-site prophylaxis. Excessive amounts of gentamicin cream application have been reported to cause similar damage to silicone catheters, but that appears to be a rare complication.

Figure 21.2 depicts a peritoneal catheter showing its relationship to abdominal wall structures. The deep Dacron cuff is preferably implanted in the muscle to provide for firm tissue ingrowth and fixation of the catheter. The superficial cuff is positioned in the subcutaneous tissues 2 to 4 cm from the exit site. When properly positioned, the superficial cuff not only serves as an effective barrier to entry of cutaneous debris and bacteria into the subcutaneous tunnel, it also limits the in and out piston-like motion of the catheter through the exit site that can drive these contaminants deep into the tunnel, disrupt the fine granulation tissue lining the tunnel, and initiate an exit site and/or tunnel infection.

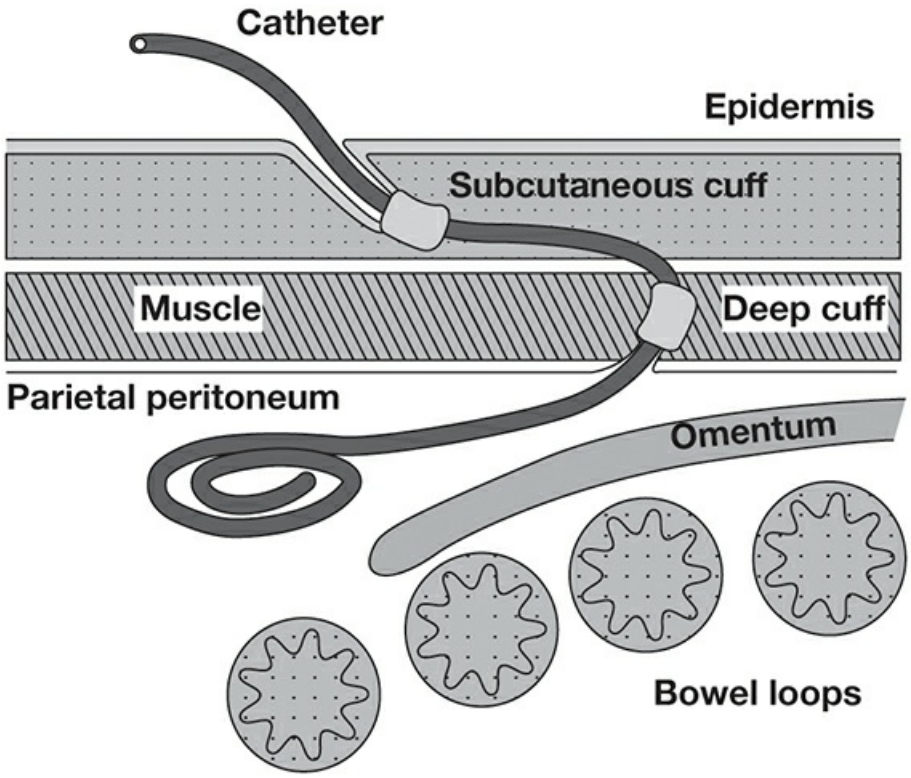


FIGURE 21.2: Schematic of a coiled-tip peritoneal catheter showing its proper relationship to adjacent anatomic structures.

The intraperitoneal segment of the catheter tubing has an end hole and numerous side holes. All recently manufactured catheters incorporate a white radiopaque stripe along the longitudinal axis of the tubing, which enables radiographic visualization. The stripe can also serve as a guide during the implantation of the catheter to prevent accidental twisting or kinking of the catheter tubing. The majority of adult catheters have a 2.6-mm internal bore. One catheter brand possesses a 3.5-mm bore and can be identified by its blue radiopaque stripe. Although in vitro flow rates of the larger bore catheter are faster, this has not been so apparent in the in vivo state. The theory that solute clearances may be improved with the larger bore catheter as a result of shorter exchange times enabling longer cumulative dwell periods has not been studied. It is important to recognize catheter bore size in order to prevent inadvertent interchange of replacement catheter adapters that can result in a loose fit and accidental separation.

II. CATHETER SELECTION

A. Patient factors influencing catheter selection. Patients come in all sizes and shapes with a variety of medical conditions; therefore, it is somewhat naive to expect that one catheter type should fit all. Choice of catheter type should take into consideration the patient's belt line, obesity, skin creases and folds, presence of scars, chronic skin conditions, incontinence, physical limitations, bathing habits, and occupation. A basic inventory of several catheter types is required to enable customization of the peritoneal access to the specific needs of the patient and to afford maximum flexibility in exit-site location. Figure 21.3 illustrates how a basic catheter

inventory might be applied. Patients who wear their belt lines above the umbilicus are often best served with a catheter with a preformed arc bend in the intercuff segment that allows the exit site to emerge below the belt line. Patients who wear their belt lines below the umbilicus are usually best fitted with a catheter having a straight intercuff segment that is bent to produce a laterally directed exit site emerging above the belt line. Individuals who have large rotund abdomens, severe obesity, drooping skin folds, intestinal stomas, gastrostomy tubes, urinary or fecal incontinence, yeast intertrigo, or desire to take deep tub baths are ideal candidates for extended catheters, which enable upper abdominal or presternal exit sites.

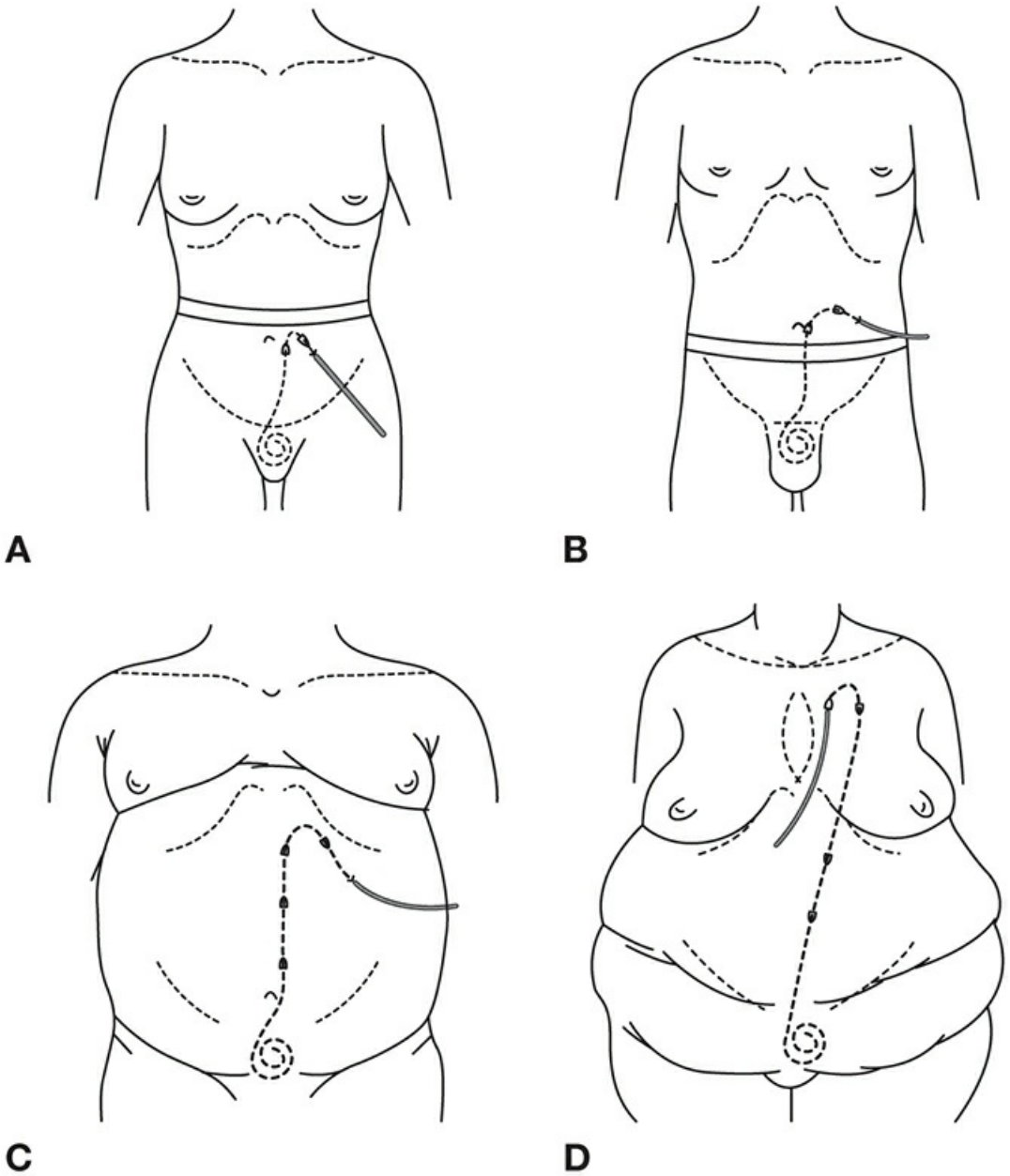


FIGURE 21.3: Depicted are practical applications of a basic catheter inventory. A. Preformed arc bend catheter with downwardly directed exit site emerging below a high-lying belt line. B. Straight intercuff segment catheter with laterally directed exit site emerging above a low-lying belt line. C. Extended catheter with upper abdominal exit site for

an obese rotund abdomen, lower abdominal skin folds, or incontinence. D. Extended catheter with upper chest exit site for severe obesity, multiple abdominal skin folds, intestinal stomas, or incontinence.

B. Stencil-based preoperative mapping. Some catheter manufacturers include marking stencils (Figure 21.4). Properly constructed stencils contain critical catheter design information, including the distance between the deep cuff and the coil at the intraperitoneal end, suggested subcutaneous tunnel configurations, and recommended exit-site locations relative to the position of the superficial cuff. Additional features of a well-designed stencil permit its precise orientation on the trunk region according to fixed anatomic landmarks, such as the pubic symphysis and the anatomic midline of the torso. Stencils permit accurate and reproducible association of the catheter design elements to these anatomic landmarks to help determine the best catheter style and insertion site that will produce optimal pelvic position of the coil at the intraperitoneal catheter end and ideal exit-site location.

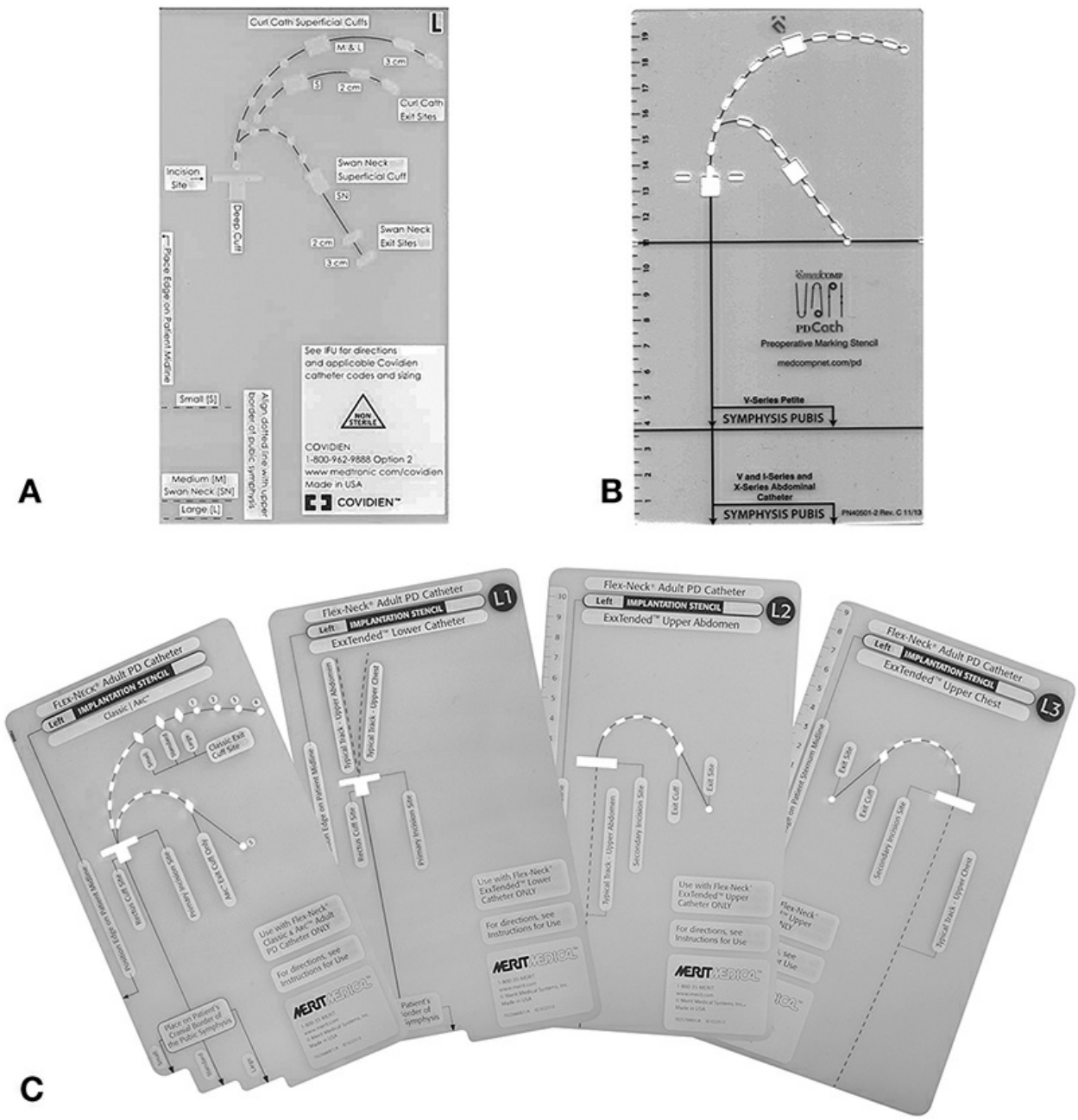


FIGURE 21.4: Commercially available stencils for most common peritoneal dialysis catheter types. A. Preoperative Catheter Stencil, Ritus (Medtronic, Mansfield, MA, USA). B. Preoperative Marking Stencil Pack (Medical Components, Inc., Harleysville, PA, USA). C. Merit Medical Flex-Neck Peritoneal Dialysis Catheter Implantation Stencils (Merit Medical Systems, Inc., South Jordan, UT, USA). (Reprinted from Crabtree JH, Hathaway PB. Patient selection and planning for image-guided peritoneal dialysis catheter placement. *Semin Intervent Radiol*. 2022;39:32-39 with permission from Thieme.)

Figure 21.5 shows the use of the stencil for lower abdominal, upper abdominal, and chest catheter exit-site locations. The stencil should initially be used during a preoperative evaluation where the patient can be examined fully clothed and in supine, sitting, and/or standing positions. The stencil can also be used at the time of the catheter insertion procedure to mark and/or verify the markings made during the preoperative

examination. During the preoperative mapping session in which the most appropriate catheter design is selected, only the exit-site cutouts need to be marked. At the time of the procedure, the entire pattern including incision marks, tunnel track, cuff, and exit-site cutouts are marked.

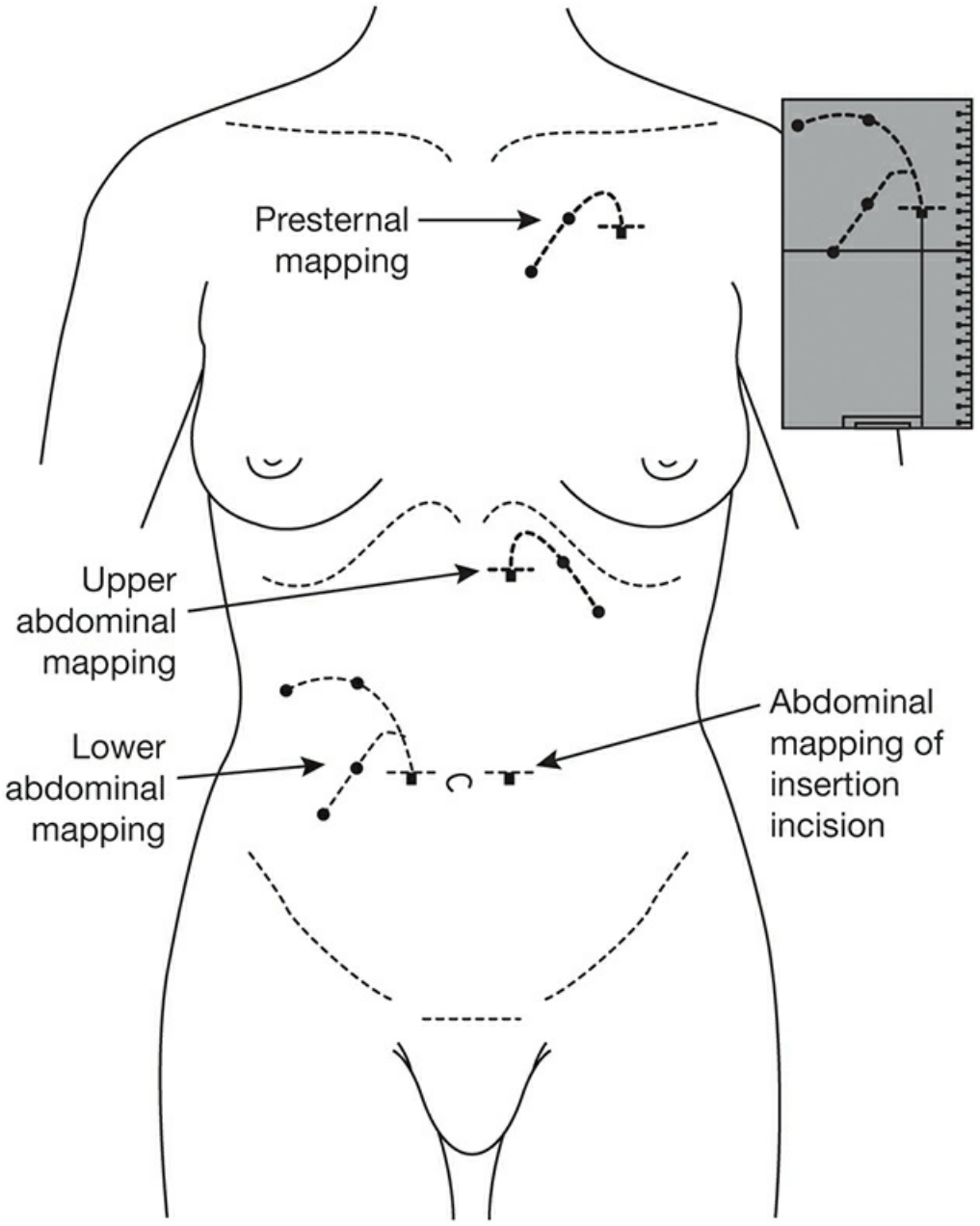


FIGURE 21.5: Shown is stencil-based preoperative mapping for standard abdominal and extended catheters to select the most appropriate device type and insertion site that produces both the ideal pelvic position of the catheter tip and exit-site location based on patient-specific anatomic features.

During the preoperative examination, the stencil is used to mark the potential exit sites of the catheter while the patient is supine. The patient then assumes a sitting or standing position, and the marked exit sites are checked to see which is best visible to

the patient and does not conflict with the belt line, skin creases, or apices of bulging skin folds. If none of the marked exit sites for a conventional abdominal catheter are satisfactory, the stencil is then used to map out either upper abdominal or presternal exit-site locations.

III. CATHETER PLACEMENT PROCEDURES

A. Best practices. Best practices for preoperative preparation and peritoneal catheter placement are listed in Tables 21.1 and 21.2. Adherence to a number of details is required to ensure the best opportunity for creating successful long-term peritoneal access. Omission of any one of these best practices can lead to the failure of the peritoneal catheter. It is recognized that some implantation techniques do not incorporate all of these best practices. Examples are percutaneous needle-guidewire approaches performed through the midline or positioning of the deep cuff above the level of the fascia.

TABLE 21.1 Best Practices in Patient Preparation

- Preoperative assessment to select the most appropriate catheter type and exit-site location
- Bowel prep the day before surgery: osmotic laxative (eg, polyethylene glycol solution), enema, or stimulant suppository
- Shower on the day of surgery with chlorhexidine soap wash of the abdomen/chest
- Removal of body hair in the preoperative holding area, preferably with electric clippers
- Empty the bladder before the procedure; otherwise, a Foley catheter should be inserted.
- Single preoperative dose of prophylactic antibiotic to provide antistaphylococcal coverage

TABLE 21.2 Best Practices in Procedure Performance

- Operative personnel are attired in cap, mask, and sterile gown and gloves.
- Surgical site is prepped with chlorhexidine-gluconate scrub, povidone-iodine (gel or scrub), or other suitable antiseptic agent and sterile drapes applied around the surgical field.
- Peritoneal catheter is rinsed and flushed with saline, and the air is squeezed out of the Dacron cuffs by rolling the submerged cuffs between fingers.
- Paramedian insertion of the catheter through the body of the rectus muscle
- Deep catheter cuff positioned within or below the rectus muscle
- Pelvic location of the catheter tip
- Catheter flow test performed to confirm acceptable function
- Skin exit site directed lateral or downward (not upward)
- Subcutaneous tunneling instrument should not exceed the diameter of the catheter.
- Exit site should be the smallest skin hole possible that allows passage of the catheter.
- Position subcutaneous cuff 2-4 cm from the exit site.
- No catheter anchoring sutures at the exit site
- Attach transfer (extension) set at the time of procedure.
- Exit site protected and catheter immobilized by nonocclusive dressing

B. Catheter placement approaches. Methods for insertion of peritoneal catheters include placement by percutaneous needle-guidewire technique (with or without image guidance), peritoneoscopic approach (Y-TEC procedure), open surgical dissection, and laparoscopic implantation. The implantation technique may include extending the catheter to a remote exit-site location and/or embedding the external limb of the catheter tubing under the skin with delayed externalization when initiation of dialysis is needed. An overview of each of the implantation approaches will be presented.

1. **Percutaneous needle-guidewire technique.** Placement of catheters by blind percutaneous puncture is performed using a modification of the Seldinger technique. The convenience of this approach is that it can be performed at the bedside under local anesthesia using prepackaged self-contained kits that include the dialysis catheter. The abdomen is prefilled with 1.5 to 2 L of dialysis solution instilled with an 18G introducer needle inserted through a 1.5- to 2-cm infraumbilical or paramedian incision. Alternatively, a Veress needle (Veress needles are described in the laparoscopic insertion section below) may be used to perform the prefill. A guidewire is passed through the needle into the peritoneal cavity and directed toward the pelvis. The needle is withdrawn. A dilator with an overlying peel-away sheath is advanced through the fascia over the guidewire. The dilator is removed from the sheath, leaving the guidewire in place. Alternatively, both the dilator and guidewire are removed. Either over the guidewire or using an intraluminal stiffening stylet, the dialysis catheter is directed through the sheath toward the pelvis. If using a stiffening stylet, the assembly is advanced through the peel-away sheath, periodically withdrawing the stylet as the catheter is pushed forward. As the deep catheter cuff advances, the sheath is peeled away. The deep cuff is advanced to the level of the fascia. The guidewire or stylet is withdrawn from the catheter. After testing the flow function, the catheter is then tunneled subcutaneously to the selected exit site.

   The addition of image guidance to the percutaneous approach improves the safety and reliability of catheter placement. Ultrasonography can be used to safely direct the needle entry into the peritoneal cavity, avoiding the inferior epigastric blood vessels in the rectus sheath. Fluoroscopy permits confirmation of needle entry into the peritoneal cavity by observing the flow of injected contrast solution around loops of the bowel. The true pelvis is identified by contrast pooling in the most dependent location. The guidewire is inserted through the needle and directed to the pelvis under fluoroscopic control. The catheter is advanced over the guidewire to this site. The remainder of the procedure is as described for blind placement. Although the radiopaque tubing stripe permits fluoroscopic imaging of the final catheter configuration, the proximity of adhesions or omentum cannot be assessed. Percutaneous guidewire placement techniques usually leave the deep catheter cuff external to the fascia.
2. **Peritoneoscopic approach (Y-TEC procedure).** The Y-TEC procedure (Merit Medical Systems, South Jordan, UT) is a proprietary peritoneoscopic technique of peritoneal catheter placement. A 2.5-mm trocar with an overlying plastic sleeve is inserted percutaneously into the peritoneal cavity through a paramedian incision. The obturator of the trocar is removed, permitting insertion of a 2.2-mm laparoscope to confirm peritoneal entry. The scope is withdrawn, and 0.6 to 1.5 L of room air is pumped into the abdomen with a syringe or hand bulb. The scope is reinserted, and the overlying cannula and plastic sleeve are visually directed into an identified clear area within the peritoneal cavity. The scope and cannula are withdrawn, leaving the expandable plastic sleeve to serve as a conduit for blind insertion of the catheter over a stylet into the identified clear area. The plastic sleeve is withdrawn, and the deep cuff is pushed into the rectus sheath. After testing the flow function, the catheter is tunneled subcutaneously to the selected exit site.

   The peritoneoscopic approach is performed primarily by interventional

nephrologists. The equipment is expensive to purchase and maintain, provides limited intraperitoneal visualization, and is only suitable for this single application. The peritoneoscopic technique has been largely abandoned by interventional nephrologists in favor of percutaneous and open dissection approaches.

3. **Open surgical dissection.** A paramedian incision is made through the skin, subcutaneous tissues, and anterior rectus sheath. The underlying muscle fibers are split to expose the posterior rectus sheath. A small hole is made through the posterior sheath and peritoneum to enter the peritoneal cavity. A purse-string suture is placed around the opening. The catheter, usually straightened over an internal stylet, is advanced through the peritoneal incision toward the pelvis. Despite being an open procedure, the catheter is advanced mostly by feel, therefore, blindly, into the peritoneal cavity. The stylet is partially withdrawn as the catheter is advanced until the deep cuff abuts the posterior fascia. After satisfactory placement has been achieved, the stylet is completely withdrawn and the purse-string suture is tied. Encouraging the catheter tip to remain oriented toward the pelvis is achieved with a short rectus sheath tunnel by obliquely passing the catheter through the rectus sheath in a craniocaudal direction. This is accomplished by exiting the catheter tubing through the anterior rectus sheath at least 2.5 cm cranial to the level of the purse-string suture and deep cuff location. An additional purse string is placed around the catheter at the point where it emerges from the anterior rectus sheath. Attention to detail in the placement of the purse-string sutures and repair of the anterior fascia is imperative to prevent pericatheter leak and hernia. The catheter is tunneled subcutaneously to the selected exit site following a satisfactory test of flow function.
4. **Laparoscopic.** Laparoscopy provides a minimally invasive approach with complete visualization of the peritoneal cavity during the catheter implantation procedure. The advantage of laparoscopic catheter placement over other approaches is the ability to proactively employ adjunctive procedures that significantly improve catheter outcomes. Laparoscopically guided rectus sheath tunneling places the catheter in a long musculofascial tunnel oriented toward the pelvis and substantially reduces catheter tip migration. Observed redundant omentum that lies in juxtaposition to the catheter tip can be displaced from the pelvis into the upper abdomen and fixed to the abdominal wall (omentopexy). Compartmentalizing adhesions that may affect the completeness of dialysate drainage can be divided. Intraperitoneal structures that siphon up to the catheter tip during the intraoperative irrigation test can be laparoscopically resected, including epiploic appendices of the sigmoid colon, vermiform appendix, and uterine tubes. Previously unsuspected abdominal wall hernias can be identified and repaired at the time of the catheter implantation procedure.

   Through a lateral abdominal wall puncture site remote from the point of intended catheter insertion, the abdomen is insufflated with carbon dioxide gas through a Veress needle to create a pneumoperitoneum that provides an intraperitoneal working space. A Veress needle is a spring-loaded needle with a blunt-tipped inner cannula that is pushed inside a sharp-tipped outer cannula during penetration of the abdominal wall. The blunt inner cannula springs forward upon entry into the peritoneal space to guard the sharp tip outer cannula, preventing visceral injury. A laparoscopic port and laparoscope are inserted. Alternatively, the

surgeon can initially use an optical view trocar port device in combination with the laparoscope to observe passage of the trocar through the abdominal wall layers into the peritoneal cavity. Upon entry, the inner trocar is removed, gas is insufflated, and the laparoscope is inserted. Under laparoscopic guidance, the catheter is introduced through an incision at the planned insertion site and placed in a long rectus sheath tunnel oriented toward the pelvis, usually through the use of a port device that created the tunnel. The catheter tip is directed into the true pelvis under visual control. The deep cuff of the catheter is positioned in the rectus muscle just below the anterior fascial sheath. A purse-string fascial suture is placed around the catheter at the level of the anterior sheath to minimize the risk of pericatheter leak. The pneumoperitoneum is released, but the laparoscopic ports are left in place until a test irrigation of the catheter demonstrates successful flow. After any indicated adjunctive procedures are completed, the laparoscopic ports are removed and the catheter is tunneled subcutaneously to the selected exit site.

5. **Special access procedure**
   a. **Extended catheters.** The abdominal segment of two-piece extended catheters can be implanted by any of the aforementioned insertion techniques. A secondary incision is made in the vicinity of the planned upper abdominal, presternal, or back exit site. A marking stencil is invaluable in helping to choose the optimal locations for the secondary incision and exit site. The measured distance between the abdominal insertion incision and the secondary incision is used to calculate how much tubing length will be trimmed from one or both of the catheter segments in order to correctly span the distance. The trimmed catheters are joined with a titanium connector, and the linked catheter segments are tunneled on the surface of the fascia from the abdominal insertion site to the remote secondary incision with a tunneling rod. The extension catheter is then passed from the secondary incision through the exit site using a stylet to complete the procedure.
   b. **Catheter embedding procedure.** The catheter is implanted in advance of intended use and allowed to “mature” in the subcutaneous bed until the start of dialysis (Figure 21.6). The catheter is allowed to heal in the sterile environment of the subcutaneous space without the potential contamination from the presence of an exit wound. Firm tissue ingrowth into the cuffs and the absence of biofilm formation have been speculated to reduce catheter infection–related peritonitis. Another important attribute of catheter embedding is greater patient acceptance of earlier commitment to PD by catheter placement ahead of time. The patient is not burdened with catheter maintenance until dialysis is needed. The need for insertion of vascular catheters and temporary hemodialysis can be avoided in patients previously implanted with an embedded catheter. When needed, the catheter is simply exteriorized and the patient begins dialysis with full volumes, obviating the need for a break-in period. The embedding technique permits more efficient surgical scheduling of catheter implantation as a nonurgent procedure and helps to reduce stress on operating room access. Disadvantages of the catheter embedding strategy include the need for two procedures (implantation and exteriorization) as opposed to one and the possibility of futile placement in the event of preemptive kidney transplant, lack of progression in chronic kidney

disease, development of incapacity for self-care, or changed modality choice.

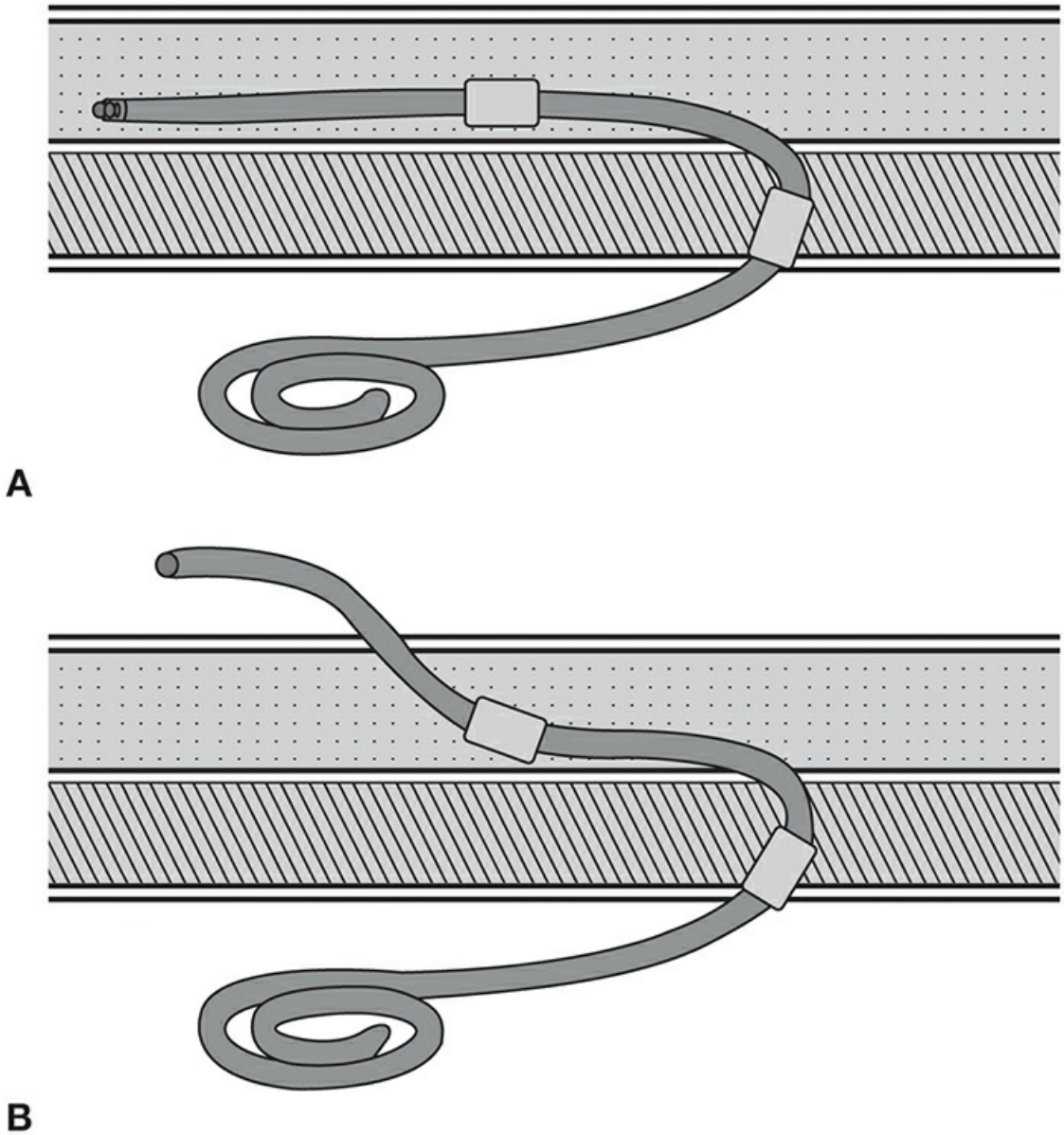


FIGURE 21.6: Illustrated is the embedded catheter strategy. A. External limb of the catheter tubing is embedded under the skin at the time of catheter placement. B. External limb of the catheter is externalized when time to initiate dialysis.

Catheter embedding can be incorporated into any of the implantation approaches using any catheter device. The catheter is temporarily externalized through the future skin exit site prior to embedment. The exit-site scar serves as a landmark to know where to come back to for externalization. After acceptable flow function of the catheter is confirmed, the tubing is flushed with heparin, plugged, and buried in the subcutaneous tissue. To minimize the risk of hematoma or seroma and to facilitate subsequent externalization, the catheter should be embedded in a linear or curvilinear subcutaneous track using a

tunneling stylet as opposed to curling the tubing into a subcutaneous pocket. Embedding should not be performed if the anticipated need for dialysis is less than 4 weeks. Externalization of embedded catheters is an office procedure. Catheters have been embedded for months to years, with an 85% to 93% immediate function rate upon externalization. Overall, 94% to 99% are successfully used for dialysis after radiologic or laparoscopic revision of nonfunctioning catheters.

IV. CATHETER CARE. Postoperative management of primarily externalized catheters will vary depending on whether they are used immediately or if a 2-week delay is to be prescribed to allow for wound healing and firm tissue ingrowth of the cuffs.

A. Catheter irrigation. Catheters that are not used immediately should undergo irrigation with 0.5 to 1.0 L of solution (ideally dialysate) within 3 to 7 days following insertion to wash out the blood and fibrinous debris. If the effluent is particularly bloody, irrigation is repeated until signs of clearing are evident. To assure patency, it is reasonable to consider repeated weekly irrigation until such time that dialysis is instituted. Heparin added to the irrigant (1,000 units/L) is helpful in preventing fibrin plugging of the catheter during the early postoperative period.

B. Postoperative catheter immobilization and dressings. Since no catheter anchoring stitches are used, it is important to immobilize the catheter on the abdominal wall. Immobilization can be achieved with gauze and sterile adhesive strips applied with or without medical tincture adhesive. A nonocclusive barrier dressing of sufficient size to protect the exit site and surgical wounds and to further immobilize the catheter should be applied at the time of the placement procedure. In addition, the transfer set should be secured to the abdominal wall to prevent tugging on the catheter at the exit site. In the case of urgent start, the transfer set can be secured outside the nonocclusive barrier dressing to ensure easy access for starting dialysis immediately. As long as the dressings are clean and intact and the exit site appears stable, dressings are changed on a weekly basis until such time that the patient is instructed in the protocol for chronic exit-site care.

C. Long-term catheter and exit-site care. Patients should limit themselves to nonstrenuous activities for 4 to 6 weeks following catheter placement to permit good wound healing. If exit-site healing is uncomplicated, most patients are able to resume showering in 3 to 4 weeks. This usually coincides with the implementation of the chronic exit-site care routine. Most exit-site care protocols involve daily cleansing with nonirritating, nontoxic, antiseptic agents and the application of a prophylactic antibiotic ointment or cream. Sterile dressings over the exit site are encouraged. Tub bathing and swimming with immersion of the exit site are discouraged. Centers that permit swimming usually restrict the activity to properly chlorinated private pools or ocean water. Consider using an ostomy appliance or similar device to cover the exit site and catheter during swimming and to perform routine exit-site care after the activity. Patients should be reminded that the catheter is a “lifeline” and advised to consider the consequences of risking exposure of their peritoneal access to potential contamination during swimming.

D. Embedded catheter care. Patients who undergo catheter embedment may resume showering after 48 hours. Avoidance of strenuous activities is required for 4 to 6 weeks

following catheter placement to permit good wound healing.

Externalization of embedded catheters is a clinical procedure performed using a sterile technique in a suitable treatment room under local anesthesia. If an appropriate embedding technique was performed, the catheter tubing should be easily palpable at the incision scar created during the procedure while the catheter was temporarily externalized at the future exit site. In equivocal cases, ultrasound examination can be employed to identify the catheter tubing at the correct distance from the superficial cuff. Care is exercised in anesthetizing the skin and making the incision to avoid damaging the catheter. Hemostat dissection is used to identify and deliver the catheter from the embedment track. The plugged end of the tubing is amputated, the catheter adapter is inserted, the transfer set is attached, and flow is tested. The catheter may require brisk push-pull saline irrigation with a 20-mL syringe to dislodge fibrin debris. Unsatisfactory flow should be managed as described below. Exit-site care following externalization of embedded catheters is the same as that described for primarily externalized catheters.

V. CATHETER BREAK-IN PROCEDURES.

There is no evidence-based approach for initiating patients onto PD. The following are some considerations:

A. Catheter irrigation.

Performance of postoperative irrigation (flushing) when immediate use of the catheter is not anticipated is discussed below.

B. Nonurgent start.

When possible, exchanges should be delayed for 2 or more weeks after catheter insertion to allow for healing and prevent leakage. Either chronic ambulatory PD or automated PD can be initiated at that time. The dwell volume can be increased over the course of weeks. For patients treated with automated PD, leaving the patient with no last fill for a number of weeks may help reduce the risk of leaks. Although the catheter is healing, it is suggested that the patient limit physical activities for 4 to 6 weeks, especially activities that could increase intra-abdominal pressure.

C. Urgent start.

A growing body of literature suggests that starting patients immediately (<2 weeks after catheter insertion) on PD is feasible. Although this approach may be associated with a higher risk of leak, there does not appear to be a concomitant increase in peritonitis. Furthermore, an urgent start on PD provides an alternative for those patients who would otherwise initiate therapy on hemodialysis with a central venous catheter. Catheters implanted by open dissection or laparoscopically can be used immediately postinsertion, provided that a tight seal was created at the peritoneal or fascial entry points to prevent leaks. Percutaneously inserted catheters can also be used immediately; however, because of the increased risk of a leak, the feasibility of this strategy should be assessed according to the historical experience of the center.

No standard dialysis prescription exists for patients starting PD urgently; however, most have described an incremental approach. Such an approach might consist of initiating exchanges with approximately 1 L volumes and increasing the amount by 250 to 500 mL/wk. Commencing therapy with the patient in the supine position will minimize the risks of dialysate leaks from increased intra-abdominal pressure. It has been demonstrated that when surgically placed catheters are appropriately secured, full-volume exchanges can be started immediately. As with nonurgent catheters, patients should be advised to reduce physical activity for about 4 to 6 weeks after insertion to allow for proper healing.

VI. ACUTE OPERATIVE COMPLICATIONS

A. Preperitoneal placement. During percutaneous catheter insertion, if the introducer needle, guidewire, or peel-away sheath fails to enter the peritoneal cavity, the catheter may be inadvertently advanced into the preperitoneal space. Dialysis solution inflow will be slow and often painful. Outflow will be minimal, and the effluent may become blood tinged. If this occurs, drain as much fluid as possible, remove the catheter and start over.

B. Blood-tinged dialysis effluent. In addition to preperitoneal catheter placement, blood-tinged outflow can result from injury of a blood vessel in the abdominal wall or mesentery. The return will usually clear with continued dialysis.

C. Serious complications. Grossly bloody effluent, fall in hematocrit, or signs of shock signify large blood vessel injury. Urgent laparotomy is usually required. Unexplained polyuria and glycosuria suggest entry into the urinary bladder. If the needle or catheter has entered the bowel, the instillation of dialysate will be accompanied by pain and/or an urgent need to defecate. In case of suspected bowel entry with a small-bore needle, it is sometimes possible to merely remove the needle and observe the patient carefully while treating with intravenous antibiotics. Catheter insertion should be delayed a few days until it is certain that there are no complications as a result of penetrating the bowel. Unrecognized placement of the catheter into the bowel may be heralded by feces or gas in the effluent or watery diarrhea having high glucose content. Surgical intervention is often required, and appropriate consultation should be obtained. If surgical exploration is planned, it is helpful to leave the catheter in place so that the site of perforation can be more easily identified.

VII. COMPLICATIONS OF PERITONEAL CATHETERS.

Mechanical and infectious complications are the two most common reasons for interruption of dialysis therapy and loss of the peritoneal catheter. Early and appropriate interventions can allow successful resumption of dialysis, avoid removal of the catheter, or, in the event of catheter loss, minimize the time before return to PD.

A. Mechanical complications. Mechanical complications of the catheter include pericatheter leaks, infusion and drain pain, flow restriction, and catheter cuff extrusion through the exit site.

1. **Pericatheter leak.** This complication is usually related to catheter implantation technique, timing of initiation of dialysis, and strength of abdominal wall tissues. When dialysis is initiated, subcutaneous leakage may occur at the catheter insertion site and usually manifests itself as fluid appearing through the incision or at the exit site. Questionable leaks can be verified by a positive glucose dipstick indicating a high glucose concentration of the seeping fluid. Delaying initiation of dialysis for 14 days or more following catheter placement minimizes the risk of developing a leak. Temporarily discontinuing dialysis for 1 to 3 weeks may result in sealing of an early leak. Dramatic early leaks may indicate purse-string suture failure, if one was placed at the time of insertion, or technical error in wound repair, and demands immediate exploration. Leakage through the exit site or insertion incision leaves the patient prone to tunnel infection and peritonitis. Prophylactic antibiotic therapy should be prescribed. Persistent leaks warrant catheter replacement.

   Late pericatheter leaks may be caused by pericatheter hernia or occult tunnel

infections with the separation of the cuffs from the surrounding tissues. The occurrence of pericatheter hernia is largely influenced by the location and degree of fixation of the deep cuff. At the parietal peritoneal surface, the mesothelium reflects along the surface of the catheter to reach the deep cuff. If the deep cuff was placed outside of the muscle wall or the cuff shifts outward because of weak midline fascial attachments, then the peritoneal lining actually extends above the fascial layer, creating the potential for a pseudohernia and pericatheter leak. If the abdominal wall is weak, the track may dilate and develop a true hernia. Most late leaks and pericatheter hernias are best managed by catheter replacement. Late leaks may also occur with accidental forceful tugging on the PD catheter. During manipulation procedures for catheter tip malposition, excessive torsion of the tubing can result in a leak. These leaks may seal with a rest period of 1 to 3 weeks.

2. **Infusion pain.** Pain during dialysate infusion is usually observed in new patients initiating dialysis and is often transient in nature, spontaneously disappearing over several weeks. Persistent infusion pain is commonly associated with the acidity of conventional lactate-buffered dialysis solutions (pH 5.2-5.5). Use of bicarbonate/lactate-buffered dialysis solutions (pH 7.0-7.4) can eliminate this pain. If buffered solutions are not available, manual addition of sodium bicarbonate 8.4% solution to each dialysis bag (5 mL/L) may be used to treat acid-related infusion pain. Alternatively, a 1% or 2% lidocaine solution added to the dialysate (5 mL/L) may be tried to assuage infusion discomfort.

   Other causes of dialysate-related pain include hypertonic glucose solutions, aged dialysis solution, overdistention of the abdomen, or extremes in dialysate temperature. Catheter malposition with the tip against the abdominal wall, tube restriction by attached tissues and adhesions, or bowel wrapping can produce both inflow and outflow pain.

   Slower infusion rates and incomplete drainage (tidal PD) may diminish flow pain; however, transluminal catheter manipulation or laparoscopic exploration/repositioning may be considered if the pain is persistent or also associated with flow restriction.

3. **Drain pain.** Pain during outflow is common, especially toward the end of the drain, and is especially frequent in the early days after initiation of dialysis (Aga, 2023). As the intraperitoneal structures siphon up to the catheter tip during the drain, it causes the catheter to bump up against the exquisitely sensitive parietal peritoneum. The pain is frequently experienced in the genital or anorectal region. Drain pain is more frequently a problem with automated PD due to hydraulic suction on the peritoneal lining. Catheters implanted too low on the abdominal wall can wedge tubing into the deep pelvis, resulting in drain pain from early collapse of pelvic viscera around the catheter tip. Similarly, constipation with crowding of the bowel around the catheter in the pelvis can cause or contribute to the severity of the symptoms. The drain pain sometimes resolves with time or with the treatment of associated constipation. If persistent, it can be managed by avoiding complete drainage of the peritoneal effluent. In cycler patients, this can be achieved by performing tidal PD. In resistant cases of drain pain, transluminal catheter manipulation or laparoscopic exploration/repositioning should be considered for flow pain that is persistent or also accompanied by flow restriction. Irremediable

drain pain will require catheter replacement. Preoperative stencil-assisted mapping, as described in the early parts of this chapter, assists in the selection of the new catheter insertion site that will result in the optimal pelvic position of the catheter tip to minimize the occurrence of drain pain.

4. **Flow restriction.** Catheter flow restriction can occur with inflow or outflow of dialysate, but the latter is more common. If catheter flow is restricted in both directions, it is more likely to be caused by a kink in the catheter or occlusion of the catheter lumen with fibrin. Outflow failure often signals the catheter is wrapped in omentum or encased in adhesions in association with other abdominal structures such as small or large bowel, epiploic appendages, vermiform appendix, or uterine tubes. Catheter tip migration out of the pelvis (above the level of the iliac crest) is usually, but not always, accompanied by flow restriction.

   Flow restriction can result in frequent alarms during cycler use, lost dwell time, and incomplete drainage of the abdomen. Patients can be assessed in the home dialysis unit by performing a catheter flush to determine the extent of the flow restriction. Evaluation and treatment for the common causes of flow dysfunction are as follows:

   a. **Constipation.** The most common cause of outflow dysfunction is constipation. Distended rectosigmoid colon may block the catheter side holes or displace the catheter tip into a position of poor drainage function. Abdominal radiography is helpful to look for a fecal-filled colon and catheter displacement. Constipation is treated with oral administration of an emollient, such as lactulose, 30 mL every 2 hours until the desired effect is achieved. Polyethylene glycol solution, 2 L, ingested over a period of 4 to 6 hours is usually effective in persistent cases. Stimulant laxatives such as bisacodyl and saline enemas are reserved for refractory cases since chemical and mechanical irritation of the colonic mucosa have been associated with transmural migration of bacteria and development of peritonitis.
   b. **Urinary retention.** Extrinsic bladder compression on the catheter due to urinary retention occurs less frequently. Causes of urinary retention include bladder outlet obstruction, neurogenic bladder, medications, and pelvic organ prolapse. Urinary retention can be assessed by determining postvoid residual urine volume by ultrasound or catheterization. Consider bladder distention as the cause of catheter flow restriction if postvoid residual urine volume is greater than or equal to 50 mL Urologic referral is appropriate for positive findings.
   c. **Tubing kink.** Mechanical kinking of the catheter tubing is usually accompanied by two-way obstruction. Radiographs of the abdomen with anterior and cross-table lateral views of the abdomen are often helpful in identifying a kink in the catheter tubing. Lateral chest x-ray is used to examine for a tubing kink in a presternal catheter. The radiology department should be instructed to perform the radiographs with the patient's arms down at the side to avoid missing kinks that may straighten out if the patient's arms are positioned overhead. Catheter revision or replacement will be required if a kink is discovered.
   d. **Fibrin strands and plugs.** Heparin should be added to the dialysate whenever fibrin strands or plugs are visible in the effluent. Heparin is more useful prophylactically than therapeutically, preventing the formation of fibrin

clots and extension of existing clots. Once outflow obstruction has occurred, irrigation of the catheter with heparin is often unsuccessful in recovering function.

If flow function is not restored with heparin, then thrombolytic therapy with tissue plasminogen activator (tPA) may be attempted. Failure to dislodge intraluminal debris by brisk irrigation of the catheter with saline is followed by instillation of tPA using the protocol described in Table 21.3. If catheter obstruction is due to a fibrin clot, recovery of flow function with tPA has a high likelihood of success. Because of cost considerations, the dose of tPA (used in a dilution of 1 mg/mL) has been based on the calculated volume of the catheter assembly; however, no adverse consequences have been documented for catheter overfill or repeated administration.

TABLE 21.3 Tissue Plasminogen Activator (tPA) Protocol for Thrombolysis of Obstructed Peritoneal Dialysis Catheters

Total Volume of Catheter and Transfer Set Assembly

Adult Catheter Size				
Internal Diameter (cm)	Length (cm)	Catheter Volume (cm^3)[a]	Total Volume With Baxter Transfer Set (cm^3)[b]	Total Volume With Fresenius Extension Set (cm^3)[b]
0.26[c]	42	2.2	4.2	4.7
0.26[c]	57	3.0	5.0	5.5
0.26[c]	62	3.3	5.3	5.8
0.35[d]	62	6.0	8.0	8.5

Procedure:

1. Aspirate contents of the catheter to remove any povidone-iodine from the transfer set.
2. Slowly but steadily instill 110% calculated volume of tPA (1 mg/mL) into the catheter.
3. Allow tPA to remain in catheter for 60 minutes.
4. Aspirate tPA from catheter.
5. With a 60-mL syringe, briskly irrigate the catheter with saline to determine patency and to dislodge any fibrin clots.
6. Repeat the process if the catheter remains obstructed.

[a]Volume = $\pi r^2 h$; $\pi = 3.14$, r = radius of catheter bore, h = height (length) of tube; cm^3 = mL.

[b]Baxter 6-inch transfer set = 2 cm^3; Fresenius 12-inch extension set = 2.5 cm^3.

[c]Internal diameter of conventional Tenckhoff catheters.

[d]Internal diameter of Flex-Neck catheter.

e. Catheter manipulation for outflow failure. If treatment of constipation and fibrinolytic therapy are not successful in restoring drainage function, and if urinary retention and tubing kinks have been excluded, the catheter may be obstructed by omentum or other adherent intraperitoneal structures and will require intervention in an attempt to restore function. Interventions to resolve catheter obstruction are most commonly performed using radiologic and laparoscopic techniques.

1. Radiologic intervention. Fluoroscopic guidewire manipulation can be used to redirect displaced catheters, mobilize tips if stuck to adhesions or

wrapped in omentum, and to mechanically clear obstructed lumens using guidewires or brushes. Prior imaging of the abdomen may indicate tip migration, increasing the likelihood that manipulation may improve function. Stiff guidewire manipulation of catheters with a swan neck bend can be difficult. Rectus sheath tunneling may also limit the ability to move the catheter tip. Forceful straightening of the subcutaneous tunnel can produce trauma and lead to infection or pericatheter leaks. Transluminal manipulation is not practical for extended catheters because of the long tubing length.

A preprocedure dose of prophylactic antibiotics to provide antistaphylococcal coverage is advisable (eg, cefazolin or clindamycin). Particular attention must be given to antiseptic preparation of the catheter tubing in addition to creating a sterile surgical field for the procedure. The transfer set is disconnected and discarded. After catheter manipulation is performed, restoration of flow function is checked by syringe irrigation. In some cases, the success of moving the catheter tip and improving catheter flow is limited. Studies find that short-term clinical success of manipulation, defined as a functioning catheter at 30 days following the procedure, ranges from 62% to 82%. Long-term success is lower at 31% to 61%, and often PD catheters will have to undergo a repeat manipulation or laparoscopic intervention.

Failure rates may be higher in patients who had an antecedent history of abdominopelvic surgery or peritonitis, suggesting that adhesions play a major factor in technical failures.

2. **Laparoscopic intervention.** Laparoscopy has become an invaluable method of evaluating and resolving catheter flow obstruction. Because laparoscopy can reliably identify the source of flow dysfunction and provide a means for definitive treatment, it is often considered the next step in the management sequence after initial correctable causes for obstruction have been excluded. The dialysis catheter frequently can be used to perform the initial gas insufflation of the abdomen since most catheter obstructions represent outflow problems. Alternatively, a Veress needle is used for insufflation or the initial laparoscopic port is placed by direct cut-down on the peritoneum. Laparoscopic exploration is performed to identify the source of obstruction. Additional laparoscopic ports for the introduction of operating instruments may be required depending on the findings.

Omental attachment or wrapping of the catheter coil with displacement of the tubing out of the pelvis is a common cause of outflow dysfunction. Omental entrapment is relieved by using laparoscopic grasping forceps to strip the omentum from the catheter. The omentum is sutured in the upper abdominal region (omentopexy) to keep it away from the catheter. If adhesions are present, adhesiolysis may be performed or the catheter is pulled free of the adhesions if they are not too extensive. If the lumen is occluded, the catheter tip may be temporarily exteriorized through one of the laparoscopic ports to facilitate the removal of residual intraluminal tissue debris and flushing of the catheter.

Catheter tip migration to a position of poor drainage function is frequently caused by shape-memory resiliency forces of a straight catheter bent into a configuration that imposes excessive stress on the tubing. Simply repositioning the catheter will be followed by a recurrence of the migration in a high percentage of

cases. Laparoscopic suturing of the catheter tip to a pelvic structure has an unacceptable rate of failure due to erosion of the suture. A more reliable approach is to laparoscopically place a suture sling through the abdominal wall in the suprapubic region and around the catheter. A sling will maintain the catheter toward the pelvis, will not erode through the abdominal wall, or hinder catheter removal if required at a later date.

Redundant epiploic appendices of the sigmoid colon and uterine fimbria may siphon up to the catheter coil and produce obstruction. Laparoscopic resection of the involved epiploic appendices and uterine tube prevents recurrence.

In some cases, the surgeon will determine the original PD catheter was not ideally placed or was poorly positioned and will elect to replace the catheter. Rates of refractory catheter nonfunction in excess of 15% suggest a need for the team to review insertion procedures.

5. **Cuff extrusion through the exit site.** Erosion of the superficial cuff through the exit site can result from positioning the cuff too close (<2 cm) to the exit wound during catheter placement. In addition, excessive bending of the catheter with a straight intercuff segment to produce a downward exit direction can induce mechanical stresses on the tubing. In combination with close proximity of the cuff to the exit site, the shape-memory forces of a catheter bent into this configuration can lead to the tube straightening over time with migration of the superficial cuff toward and extruding through the exit site. Another cause for superficial cuff erosion that can eventually result in the extrusion of the entire catheter is outer displacement of the tubing due to poor location and fixation of the deep cuff. Finally, exit-site infection extending to the superficial cuff may cause it to separate from the surrounding tissues and extrude through the exit site.

   An extruded cuff becomes a reservoir of bacteria within the vicinity of the exit wound. Exacerbated by daily wetting of the cuff during routine exit-site care, the presence of this bacterial-laden cuff interferes with maintaining acceptable exit-site hygiene.

   Using a scalpel blade applied parallel to the cuff surface, the cuff can be shaved in repetitive slices until all of the cuff material is removed. The blade should be changed often to ensure ease in performing the shave without applying undue pressure on the tubing. Extra care should be taken when shaving the cuff from 3.5-mm internal bore catheters (identified by the blue radiopaque stripe), as this thin-walled tubing can be easily damaged.

B. Catheter infection and management. Details of antibiotic treatment for catheter infections are discussed in Chapter 25. The eventual outcome of a chronic exit-site infection with superficial cuff involvement is a tunnel abscess or progression of the tunnel infection to the peritoneal cavity, producing concurrent peritonitis. Early recognition of chronic exit-site and tunnel infection is essential to provide the best opportunity for catheter salvage.

1. **Exit-site and tunnel infection.** Exit-site infection presents as redness, swelling, and tenderness at the exit site. With tunnel involvement, the signs of infection extend along the subcutaneous course of the catheter. In most cases, exit-site and tunnel infections are accompanied by purulent discharge from the exit site. In chronic smoldering cases, the exit-site skin is loose around the catheter, granulation

tissue is present at the skin exit sinus, and purulent material can be expressed through the exit orifice with pressure over the subcutaneous cuff or stroking the skin over the tunnel toward the exit site while gently tugging on the catheter. As long as the infection has not extended to the deep cuff, it is possible to resolve the problem without losing the catheter or interrupting therapy. Ultrasonography of the catheter tunnel is a useful preoperative tool to evaluate for deep cuff involvement, especially in patients who are obese where physical signs are often unreliable. Patients found to have infection involving the deep cuff on ultrasonography should undergo catheter removal. Moreover, patients with concurrent peritonitis are not candidates for catheter salvage procedures, as peritonitis suggests that transmural spread of the infection has already occurred.

a. Unroofing-cuff shaving. Unroofing the skin and subcutaneous tissue overlying the infected catheter tunnel permits drainage of pus, debridement of granulation tissue, and shaving of the superficial cuff. The catheter, including the shaved tubing segment, is directed out of the medial aspect of the incision and stabilized in this position by securing it to the adjacent skin with sterile adhesive strips. The wound is left open with the performance of wet-to-dry dressing changes (once or twice daily) with saline-soaked gauze and allowed to heal by secondary intention. Depending on the magnitude of the infection, the procedure can be performed in the treatment room or operating room under local or general anesthesia. The primary advantage of the unroofing-cuff shaving procedure is that dialysis is not interrupted.

b. Catheter splicing. An alternative surgical treatment approach for chronic exit-site infection that has not extended beyond the superficial cuff is replacement of the infected external tubing segment by catheter splicing. The procedure is contraindicated if ultrasonography demonstrates fluid around the superficial cuff and intercuff tubing segment. In the absence of ultrasonographic signs of infection in the intercuff segment, catheter splicing may be the preferred salvage procedure for a badly chosen exit-site location that was placed in an infection-prone area, such as within a skin crease, on the apex of a floppy skin fold, or under the belt line. In this circumstance, performing only an unroofing-cuff shaving procedure may still result in an exit-site location that is predisposed to infection. The spliced catheter segment can be routed to a more stable exit-site location including the upper abdomen or chest region. Since the procedure requires more extensive dissection and tunneling, it is best performed in the operating room under local or general anesthesia.

After skin preparation, the infected exit site is isolated from the primary surgical field during draping and managed in the final step to prevent contamination of the new catheter and wound. An incision is made through the previous insertion site scar to expose the uninvolved intercuff segment of the catheter at the level of the fascia. The catheter is divided in the intercuff segment to preserve a 2.5-cm stump on the deep cuff side. A single- or double-cuff catheter with or without a preformed intercuff arc bend may be selected for the splicing segment. After trimming the new catheter to an appropriate length, the segment is joined to the stump of the deep cuff end of the original catheter with a double-barbed titanium connector. The external segment of the spliced catheter

is tunneled to a suitable exit location remote from the infected exit site. The wound is closed, and dressings are applied. In the final step, the external part of the old catheter is removed and the wound is debrided and packed open with saline wet-to-dry dressings. Antibiotics are continued for 2 to 4 weeks until the infected wound is healed. PD can be resumed immediately after the procedure.

c. **Simultaneous catheter insertion and removal.** An alternative to unroofing-cuff shaving or splicing is simultaneous catheter insertion and removal. This option is indicated when the exit-site location is unsatisfactory, and the flow function of the existing catheter is suboptimal. The new catheter should be inserted first on the opposite side of the abdomen followed by removal of the infected catheter with care to avoid cross contamination of wounds.

2. **Catheter infection–related peritonitis.** Progression of an exit-site and tunnel infection to the deep cuff can lead to concurrent peritonitis. Rarely, peritonitis can lead to chronic deep cuff infection and proceed in a retrograde fashion to manifest initially as a tunnel infection. Ultrasonography can be helpful in evaluating deep cuff involvement. Catheter infection–related peritonitis is best managed by catheter removal. Antibiotic treatment for peritonitis is discussed in Chapter 25. Reinsertion of the dialysis catheter can be performed as early as 2 to 3 weeks after completion of antibiotic therapy and resolution of peritoneal symptoms.

VIII. CATHETER REMOVAL AND SECONDARY EMBEDDING

A. Catheter removal. Since firm tissue ingrowth of the Dacron cuffs will have occurred by 2 to 3 weeks, chronic catheters in place for a longer period have traditionally required removal by surgical dissection in the operating room or suitable procedure room, especially if the deep cuff was positioned in the muscle layer. Fascial defects require suture repair to prevent an abdominal wall hernia or leak, especially if a new catheter is replaced simultaneously or as a staged procedure.

Although less frequently practiced, catheter removal can be performed by the “pull technique.” The external part of the catheter is grasped and, with steady gentle traction, the catheter is avulsed from the abdominal wall. The Dacron cuffs shear off the tubing during extraction and are retained in the tissues. The “pull technique” can be performed in the clinic or procedure room with or without local anesthesia or sedation. Infection of the retained cuff material necessitating later excision, almost always the superficial cuff, has been reported in about 3% of cases. Consequently, when the procedure is performed for chronic exit-site infection with superficial cuff involvement, it is recommended to open up the exit site sufficiently to allow removal of the cuff. In cases of tunnel abscess requiring open drainage or catheter infection with peritonitis where the deep cuff is involved, surgical removal of the catheter and cuffs is the preferred procedure. Tubing breaks during the “pull technique” have been infrequent as long as steady smooth traction is performed. The procedure is not indicated for two-piece extended catheters (Figure 21.1E) due to the separation of the tubing at the titanium connector. In addition, the procedure should not be used for certain alternative catheter types (Figure 21.1D and F).

B. Secondary embedding of chronic catheters. On occasion, catheter removal is performed because patients regain sufficient renal function to discontinue dialysis, but recovery is not expected to be permanent. An alternative to removing the catheter is

secondary embedding. The inconvenience and cost of catheter maintenance can be eliminated for the interim by secondary embedding while still preserving a readily available peritoneal access that can be immediately employed. This approach avoids complications of new catheter placement, such as flow dysfunction and pericatheter leak, and also avoids the necessity of possible future central venous catheter placement for urgent hemodialysis.

The procedure performed is similar to catheter splicing except that the spliced external segment is embedded. After skin preparation, the existing exit site and catheter are isolated from the primary surgical field during draping and managed in the final step to prevent contamination of the spliced catheter and wounds. An incision is made through the previous insertion site scar to expose the intercuff segment of the catheter. The catheter is divided in the intercuff segment to preserve at least a 2.5-cm stump on the deep cuff side. A single- or double-cuff catheter with or without a preformed intercuff arc bend may be selected for the splicing segment. After trimming the new catheter to an appropriate length, the segment is joined to the stump of the deep cuff end of the former catheter with a double-barbed titanium connector. The external segment of the spliced catheter is temporarily externalized at the new exit site, flushed with heparin, plugged, and then tunneled into a subcutaneous bed, as described earlier for embedded catheters. After the wounds are closed and protected, the remaining external segment of the former catheter is removed and the old exit-site wound is excised and closed.

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22 Peritoneal Dialysis for the Treatment of Acute Kidney Injury

Daniela Ponce, André Luis Balbi, and Fredric O. Finkelstein

Peritoneal dialysis (PD) was the first successfully used modality of renal replacement therapy in patients with acute kidney injury (AKI). However, its use progressively declined after 1970 due to the greater convenience of acute hemodialysis, and it is now predominantly practiced in developing countries because of its lower cost and minimal infrastructure requirements. Two meta-analyses suggest outcomes equivalent to those with hemodialysis in AKI (Chionh, 2010; Liu, 2017).

I. INDICATIONS

A. Advantages. PD offers several advantages over hemodialysis in AKI. It is technically simpler, with minimal infrastructure requirements and often lower cost. It may be the better option for the patient with difficult vascular access. Solute and water removal is gradual, with less potential for the development of disequilibrium syndrome, cardiovascular stress, and abrupt reductions in blood pressure. These potential benefits may, in turn, reduce the risk of renal and cardiac ischemia, fluid and electrolyte imbalance, and intracranial fluid shifts. No extracorporeal circulation is required, thus reducing the potential proinflammatory changes that can occur with the exposure of blood to synthetic tubing and membranes. Taken together, these factors could potentially be beneficial in permitting more rapid recovery of renal function.

Besides the classical indications (volume overload, electrolyte disorders, uremic symptoms, or acid-base disturbances), acute PD can also be used to maintain volume control in patients with congestive heart failure, functional class IV, to control hyper- or hypothermia, and to treat necrotizing pancreatitis with peritoneal lavage. Acute PD is increasingly being used in cases of advanced chronic kidney disease (CKD) presenting urgently with uremia or fluid overload, a scenario described as “urgent start PD” (Ghaffari, 2013b).

In the setting of natural disasters such as earthquakes and pandemics, when multiple victims may develop AKI and when damage to infrastructure makes access to power, clean water, and facilities for water treatment challenging, acute PD can be an important and life-saving renal replacement modality.

During the COVID-19 pandemic, the number of patients needing renal replacement therapy for AKI increased dramatically, and, in many centers, continuous and intermittent hemodialysis capacities were overwhelmed. In those scenarios, acute PD was an important alternative to the usual extracorporeal treatment modalities (Caplin, 2020; Chen, 2021; Rizo-Topete, 2021).

Table 22.1 outlines the advantages and disadvantages of PD for treating patients with AKI.

TABLE 22.1 Advantages and Disadvantages of PD for Treating Patients With AKI

Advantages	Disadvantages
Simple to initiate	Needs an intact peritoneal cavity with adequate peritoneal clearance capacity
Can be initiated anywhere	Adequacy may be of concern in hypercatabolic patients.
No need for highly skilled personnel	May not be adequate for patients with severe acute pulmonary edema or life-threatening hyperkalemia
No need for vascular access	Ultrafiltration and clearance cannot be exactly predicted.
No need for expensive equipment	Infection (peritonitis) can occur.
No exposure of blood to plastic	The standard buffer used is lactate.
No need for anticoagulation	Concern about protein losses
Minimum blood loss	Can aggravate hyperglycemia
Possible less negative impact on recovery of renal function	Can impair respiratory mechanics
May be of special benefit in selected patients (children, or patients with heart failure, hemodynamic instability, bleeding diathesis)	
Is a form of continuous kidney replacement therapy	

AKI, acute kidney injury; PD, peritoneal dialysis.

B. Limitations. PD is relatively contraindicated in patients with recent abdominal surgery, large abdominal hernias, adynamic ileus, intra-abdominal adhesions, peritoneal fibrosis, or peritonitis. Since volume and solute removal are slow and at times unpredictable, PD may not be as safe and efficient as extracorporeal blood purification techniques for the treatment of certain emergencies, such as acute pulmonary edema, life-threatening hyperkalemia, and drug overdoses. The ability of PD to achieve adequate doses in hypercatabolic AKI has been a subject of controversy. Some authors have expressed concern over PD adequacy in these situations (Phu, 2002). However, there are also reports of positive outcomes associated with PD in patients with hypercatabolic AKI, especially when intensive PD regimens were used (Chitalia, 2002).

PD increases intra-abdominal pressure, which may lead to impaired diaphragm mobilization, decreasing pulmonary compliance and ventilation, and this may cause or worsen respiratory failure. However, patients undergoing PD generally maintain their vital capacity and respiratory volume, and PD is seldom the cause of ventilation impairment in patients without pulmonary disease. Another possible limitation of PD in AKI is that associated protein losses may aggravate malnutrition. Protein supplementation, either enteral or parenteral (1.5 g/kg/d), has been recommended for patients with AKI undergoing PD in whom poor nutrition is a concern.

The high glucose concentrations in peritoneal dialysate may cause hyperglycemia, even in nondiabetic patients. This is usually correctable through intravenous, subcutaneous, or intraperitoneal administration of insulin.

Older studies reported a high frequency of peritonitis. However, with better catheter implantation techniques, improved connectology, and automated methods, the incidence has been reduced and the risk is similar to the incidence of infections with extracorporeal blood purification for AKI (Ponce, 2013).

II. TECHNICAL ASPECTS

A. Peritoneal access. Safe and efficient access to the peritoneal cavity is a crucial factor for PD success. For many years, bedside insertion of a rigid catheter using a trocar was

the standard technique to access the peritoneal cavity for acute PD. This technique is still used routinely in many parts of the world, but its use has declined with the introduction of simple procedures for the insertion of a flexible, cuffed Tenckhoff catheter, which provides optimal access for PD. Depending on availability, a single- or double-cuff Tenckhoff catheter—either straight or swan neck—can be used in AKI. The advantages of a Tenckhoff catheter over the rigid catheter include a lower incidence of leakage; a larger diameter lumen; and side holes resulting in better dialysate flow rates, less obstruction, and a decreased incidence of peritonitis. Furthermore, rigid catheters need to be removed after 3 to 5 days, while flexible, cuffed catheters can be left in indefinitely, and if the patient does not recover renal function, the catheter may be used for chronic dialysis. It may be necessary to use alternative catheters with a rigid stylet, or even improvised options such as nasogastric tubes or surgical drains, in resource-poor environments where flexible, cuffed catheters are not available or are too costly.

Tenckhoff catheters can be inserted under local anesthesia at the bedside, in a designated treatment room, or in a surgical theater. Prophylactic antibiotics should be administered. In a patient with previous abdominal surgery, laparoscopic or open technique is preferred, and this will usually require an operating room and a surgeon. In patients without previous surgery, no method of insertion has been proven to be superior. Rather, the method of implantation should be based on the local availability of skills, equipment, and consumables. Bedside insertion utilizes a modified Seldinger approach with a guidewire and “peel-away” sheath and is practiced by many nephrologists. It is recommended that ultrasound guidance be used. The procedure should be done using sterile technique under strict aseptic conditions, and the catheter should be tunneled (Cullis, 2021). This is a blind procedure, and therefore this method should be avoided, if possible, in patients who have a midline surgical scar or a history to suggest intra-abdominal adhesions. For more details of catheter insertion methods, see Chapter 21.

B. PD solutions. Commercially prepared PD solutions are optimal because they have the advantage of minimizing the risks of errors in mixing fluids and of contamination and because their instillation incorporates standardized and generally accepted connectology. Where these are not available because of logistical problems or costs, locally prepared fluids can be used, but sterile production and mixing of solutions as well as the use of sterile connection devices are imperative. Recent studies have suggested that in lower resource settings, peritonitis rates are not higher with locally prepared compared to commercially made solutions (Palmer, 2018). Such locally prepared PD fluids can be produced from physiologic intravenous fluids by adding glucose and bicarbonate.

The composition of standard PD solutions is shown in Table 20.1. Other commercial intravenous solutions that can relatively easily be converted into PD fluids include Ringer lactate, Hartmann solutions, half-normal saline, and Plasmalyte B. Standard PD solutions generally use lactate as a buffer, and this is converted to bicarbonate mainly through liver and muscle pyruvate dehydrogenase enzymes. In critically ill patients with AKI, such as those with shock, poor tissue perfusion states, liver failure, and so on, there may be impaired conversion of lactate to bicarbonate, which can aggravate metabolic acidosis. In such patients, bicarbonate-containing PD solutions are preferable (Cullis, 2021). One small study randomized 20 patients with

AKI to treatment with either lactate- or bicarbonate-based PD and showed that bicarbonate PD solution allowed better correction of metabolic acidosis and was associated with greater hemodynamic stability (Bai, 2010). However, the study was not powered to show a mortality difference, and if bicarbonate solutions are not available, lactate solutions should still be used (Cullis, 2021).

C. PD modalities. The process of dialysate instillation and removal can be automated with a PD cycler. The advantage of this system is that it can be set up by a trained staff member to reduce the risk of complications. It reduces nursing time as all cycles are automatic, and there is some suggestion that peritonitis is less likely. Automated cyclers have been used extensively to perform PD in AKI, particularly when high-volume peritoneal dialysis (HVPD) is used. However, in a resource-poor setting, cyclers may be unavailable.

The choice of the type of PD to be utilized should be based on the experience of the medical and nursing team, available resources, the safety and efficacy of the technique, and the needs of the individual patient. An illustration of various techniques applicable to AKI is provided in Figure 22.1 and Table 22.2.

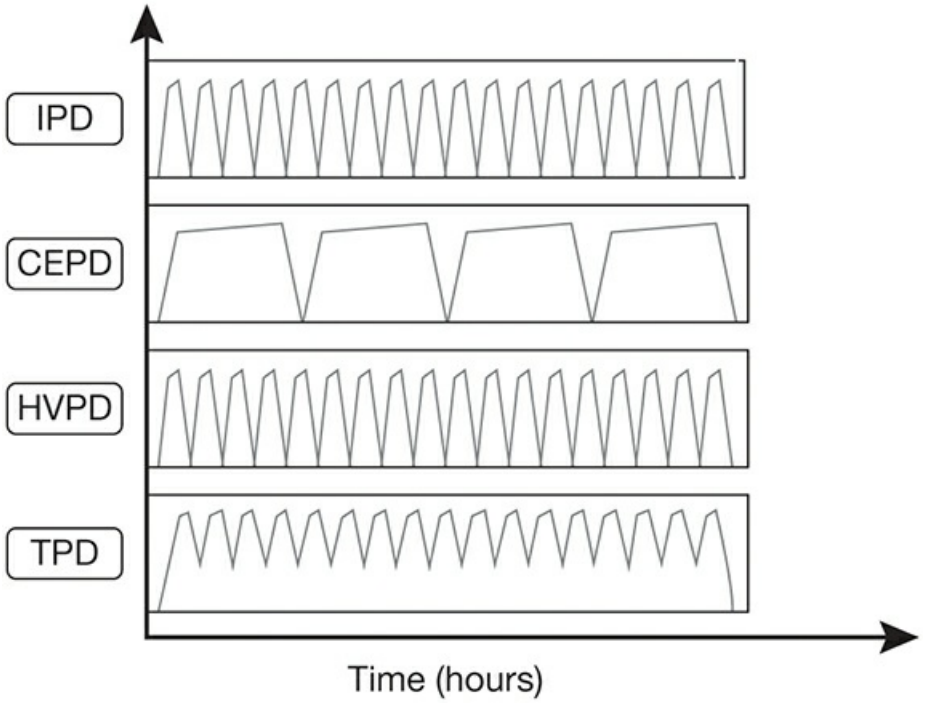


FIGURE 22.1: Illustration of the techniques of peritoneal dialysis (PD) used for patients with acute kidney injury. CEPD, continuous equilibrated PD; HVPD, high-volume PD; IPD, intermittent PD; TDP, tidal PD.

TABLE 22.2 Different Types of Peritoneal Dialysis (PD) and Selected Features

PD Types	Urea Clearance (mL/min)	Dwell Time (min)	Volume/ Cycle	Total Volume (L)	Session Duration(h)	Sessions per Week	Weekly *Kt/V*
IPD	12-20	30-60	2 L	30-48	24	2-5	—
CEPD	10-15	180-300	2 L	8-16	24	7	1.8-2.1
TIDAL	10-15	10-30	2 L fill	12-30	18-24	7	Variable
HVPD	15-20	35-60	2 L	36-44	24	7	3.5-3.8

CEPD, continuous equilibrated peritoneal dialysis; HVPD, high-volume peritoneal dialysis; IPD, intermittent peritoneal dialysis.

1. **Intermittent PD.** This is the PD technique that historically has been most frequently used in AKI, and it is still the most common, being routinely practiced in many parts of the world. Patients are treated for 48 to 72 hours, or occasionally longer, with rapid instillation and drainage of fluid and a dwell time of 30 to 60 minutes. A trocar-style PD catheter is traditionally used and removed after the dialysis treatment is completed, but Tenckhoff catheters can be left in and are a better option when available as they avoid interruption of dialysis, which limits small-solute clearance and might be inadequate in hypercatabolic, critically ill patients with AKI. Modeling suggests that intermittent PD can deliver appropriate amounts of dialysis in a broad range of clinical circumstances, depending on the degree of residual renal function (Guest, 2012).
2. **Continuous equilibrated PD.** This type of PD is similar to continuous ambulatory peritoneal dialysis (CAPD). A dwell time of 2 to 6 hours is typical, and continuous equilibrated PD can be performed manually or with a cycler. Several reports of patients successfully treated by this method can be found from the 1980s onward. The clearance of small molecules and fluid removal with this methodology depend on the frequency and volume of exchanges and need to be determined based on the clinical status of the patient.
3. **Tidal PD.** This is performed with a dedicated cycler. In tidal PD, an initial large infusion of PD solution is followed by drainage of a portion of the dwell volume, typically 50% to 75% of the initial volume, which is then replaced with fresh solution, restoring the initial intraperitoneal volume at each cycle. Tidal PD may result in higher small-molecular-weight (MW)-solute clearances than continuous equilibrated PD, though not all studies have found this. Tidal PD also may reduce the frequency of pain on the drainage of dialysate from the abdomen.
4. **HVPD.** HVPD is a continuous modality designed to achieve high small-MW-solute clearances. It requires an automated cycler and a Tenckhoff catheter. Each day the total volume of PD solution delivered ranges from 36 to 44 L, with a 30- to 50-minute dwell time. The efficacy of HVPD has been tested in several prospective studies involving seriously ill patients with AKI in Brazil. A weekly $_{Kt}/_{V}$ of 3.8 ± 0.6 can be delivered, and the mortality rate is similar to that in patients with AKI treated with intermittent or extended daily hemodialysis (Gabriel, 2008; Ponce, 2024).

III. PRESCRIBING AND DOSING ACUTE PD.

The most appropriate prescription and dose for PD in the management of patients with AKI is poorly defined because there are only a

limited number of trials available to compare treatment modalities; the studies that have been done have methodologic flaws, and the dose of dialysis used has varied widely (Chionh, 2010).

Where resources permit and where a cuffed catheter can be placed, using HVPD targeting a *Kt*/*V* urea of 0.5 daily (3.5 weekly) is associated with outcomes comparable to that of daily hemodialysis; targeting higher doses does not appear to improve outcome (Gabriel, 2008). A review of the literature suggests that such a high dose may not be necessary for many patients with AKI and that targeting a daily *Kt*/*V* of 0.3 (2.1 weekly) with a modified continuous equilibrated PD approach may be adequate for many patients (Cionh, 2010). This may be particularly helpful in developing countries where resources are limited, costs are critical, and AKI is more often caused by infections, volume contraction, an obstetrical problem, and so on, rather than complex postsurgical complications with multiorgan failure.

During the initial 24 hours of therapy, the cycler dwell time needs to be dictated by the clinical circumstances of the patient. Short cycle times (every 1-2 hours) with dwell volumes of 1.5 or 2 L may be necessary to correct hyperkalemia, fluid overload, or metabolic acidosis. Thereafter, the cycle time can be increased but generally not beyond 4 to 6 hours. Ultrafiltration is regulated by adjusting the dextrose concentration of the solution and by shortening the cycler dwell time.

A. How to prescribe acute PD. As the dialysis requirements of a patient may change from day to day, it is prudent to write PD orders for only 24 hours at a time, reassessing and altering the prescription as indicated. A standardized form for acute PD prescriptions is helpful in assuring that the specifications of the procedure are complete and clear for the nursing staff responsible for its delivery (Table 22.3).

TABLE 22.3 Acute Peritoneal Dialysis Sample Orders

A. Nursing orders:

1. Dialysis to run _____ hours
2. Exchange volume: _____ L
3. Warm dialysis fluid to 37 °C
4. Exchange time: Inflow 10 min
   Dwell _____ min
   Outflow 20 min or as long as fluid drains freely
   DO NOT LEAVE FLUID IN ABDOMEN
5. Strict intake and output to be kept on fluid intake–output record
6. Dialysate balance to be recorded on peritoneal dialysis record
7. Dialysis fluid running balance to be maintained at: _____ L
8. Dialysate solution: _____%
9. Additives to dialysate: Medication dose frequency
   _____ _____/2 L q exchange **or** × _____ _____exchanges
   _____ _____/2 L q exchange **or** × _____ _____exchanges
10. Heparin: 1,000 units/2 L q exchange: yes/no
11. Turn and position patient p.r.n. for optimum outflow.
12. Vital signs q _____ hours
13. Catheter care and dressing change every day
14. Withdraw 15 mL dialysis fluid from the catheter port every morning during dialysis and send for cell count with differential, and culture and sensitivity: yes/no.

B. Blood draw orders:

1. BUN, creatinine, HCO_3, Na, K, Cl, and glucose 8 AM and 6 PM each day during dialysis

C. Notify physician immediately for:

1. Poor dialysate flow
2. Severe abdominal pain or distention
3. Bright red blood or cloudy dialysate drain
4. Dialysate leak or purulent drainage around the catheter exit site
5. Blood pressure of < _____ mm Hg systolic
6. Respiration rate of > _____/min or severe shortness of breath
7. Temperature of > _____ °C
8. Two consecutive positive exchanges
9. Single positive exchange balance (dialysate-IN – dialysate-OUT) of ≥1,000 mL
10. If negative balance exceeds _____ L over _____ hours

BUN, blood urea nitrogen.

1. **Exchange volume.** The choice of exchange volume is dictated primarily by the size of the peritoneal cavity. An average-sized adult can usually tolerate 2-L exchanges, but in smaller patients, those with pulmonary disease, and those with abdominal wall or inguinal hernias, the volume should be reduced. Although initiating acute PD with a 2-L exchange volume is standard, some centers prefer to start with smaller volumes (1-1.5 L) for the first few exchanges to minimize the risk of leaks. Otherwise, the exchange volume should not be reduced without good reason, as this leads to lower clearances. In large or very catabolic patients, an exchange volume of 2.5 to 3 L may be helpful to augment the efficiency of dialysis.
2. **Exchange time.** This is the combined time required for inflow, dwell, and drain. If the aim is to maximize small-solute clearance, the exchange time should be relatively short at about 1 to 2 hours, but in continuous equilibrated PD, longer times are routine.
   a. **Inflow time.** Inflow is by gravity or hydraulically pumped with a cycler and usually requires about 5 to 10 minutes (200-300 mL/min). Inflow time is dictated by the volume to be infused and, with manual systems, the height of the dialysis solution above the patient's abdomen. It may be prolonged due to kinking of the tubing or increased inflow resistance by intra-abdominal tissues in close proximity to the catheter tip. On initiation of acute PD, some patients may experience pain or cramping with inflow of PD solution. This may result from the hypertonic and acidic nature of the PD fluid and often improves with time but, when severe, may be relieved by slowing the dialysate inflow rate for several exchanges. Otherwise, inflow time should be kept to a minimum to maximize dialysis efficiency. Cold PD solution can result in discomfort and hypothermia, so the solution should be warmed to 37 °C before infusion.
   b. **Dwell time.** The dwell period is the time during which the total exchange volume is present in the peritoneal cavity (ie, the time from the end of inflow to the beginning of outflow). When initiating PD in acutely ill and catabolic patients, the usual dwell time is 30 minutes to achieve an exchange time of 60 minutes. With a 2-L exchange volume, as much as 48 L of fluid can be exchanged daily. Given a peritoneal membrane with average transport characteristics, the urea concentration in the drained dialysate will be approximately 50% to 60% of that in the plasma (D/P urea ratio of 0.5-0.6 at 1 hour). Thus, with an aggressive dialysis exchange rate of 2 L/h, the plasma urea

clearance could approximate 24 to 29 L/d (0.5-0.6 × 48 L/d) or 168 to 202 L/wk. If the patient is not very catabolic, a longer dwell time (eg, 1.5-6 hours) can often be used. With a 4-hour exchange time (dwell time 3.5 hours), the dialysate urea concentration is, on average, 90% of that in the plasma (D/P urea ratio of 0.9 at 4 hours). This leads to a plasma urea clearance of at least 11 L/d (0.9 × 12 L/d) or 77 L/wk. Assuming an ultrafiltration rate of 1 L/d, this would add 6.3 L of clearance per week, giving a total urea clearance of 83 L/wk. In terms of weekly *Kt*/*V* urea, the weekly clearance of 83 L is the ($K \times t$) term. For a 70-kg male patient with a *V* of 42 L, weekly ($K \times t$)/*V* would be 83/42 or about 2.0.

   c. **Outflow time.** Outflow of spent dialysate is by gravity and usually requires 20 to 30 minutes. Outflow time depends on the total volume to be drained, the resistance to outflow, and, with manual methods, the difference in height between the patient's abdomen and the drainage bag. In many patients, particularly those with large abdomens, the first exchange may not drain completely (often only 1-1.5 L is retrieved) due to initial filling of poorly draining areas of the abdomen. As long as marked abdominal distension is not present, a second exchange of 2 L can be cautiously instilled. Subsequent drainage usually proceeds normally.

3. **Choosing the dialysis solution dextrose concentration**

   a. **Standard 1.5% dextrose (glucose monohydrate).** This concentration of dextrose (~1,360 mg glucose/dL [75 mmol/L]) will, in general, exert an osmotic force sufficient to remove 50 to 150 mL fluid/h (although this may vary from patient to patient) when using a 2-L exchange volume and a 60-minute exchange time. This ultrafiltration rate could translate into fluid removal of 1.2 to 3.6 L/d.

   b. **Higher concentrations of dextrose.** Greater fluid removal can be achieved with higher dextrose concentrations. A 4.25% dextrose solution can result in an ultrafiltration rate of 300 to 400 mL/h. Acutely, this degree of fluid removal can be required for the treatment of congestive heart failure or marked volume overload. However, continued use of the 4.25% solution could theoretically result in the removal of 7.2 to 9.6 L/d and cause marked hypernatremia. In practice, this degree of fluid removal is rarely required. Available dextrose solutions (ie, 1.5%, 2.5%, or 4.25% exchanges) can be adjusted to provide the level of ultrafiltration desired. Once the patient is euvolemic, one can resume using a 1.5% solution for all exchanges.

4. **Practical aspects of how to prescribe PD for patients with AKI.** During the initial 48 hours, the duration of the cycle needs to be determined based on the clinical circumstances. Short cycle times (every 1-2 hours) and a high frequency of exchanges may be necessary in the first 24 to 48 hours to correct hyperkalemia, fluid overload, and/or metabolic acidosis.

   a. **AKI with pulmonary edema.** Among patients with AKI who have pulmonary edema, we optimize ultrafiltration using PD by gradually altering the dextrose concentration of the dialysate and the cycle length, as tolerated.

      Ultrafiltration can be increased by raising the concentration of dextrose and/or shortening the cycle duration. We typically initiate PD with a 2.5% dextrose solution and modify the prescription (to a higher or lower dextrose concentration) depending on the evolving ultrafiltration goals in the setting of

AKI. Among patients who are hemodynamically unstable, we use the 1.5% dextrose solution with frequent exchanges to slow down ultrafiltration. Even with 1.5% dextrose solutions, frequent exchanges, such as hourly, can lead to ultrafiltration rates of 100 mL/h.

Dialysis solutions with higher dextrose concentrations can be substituted based on the ultrafiltration requirements and the patient's hemodynamic parameters. With a standard regimen, such as a 2-L exchange volume and 1-hour dwell time, the following approximate amounts of fluid can be removed over a 24-hour period:

- 2.5 L with 1.5% dextrose
- 4.5 L with 2.5% dextrose
- 8.5 L with 4.25% dextrose

One practical way to achieve adequate fluid removal is to alternate by mixing and matching low- and high-dextrose concentration solutions. Among patients receiving manual PD, this entails manually alternating bags of different dextrose concentrations, whereas for patients on automated PD, bags of varying dextrose concentrations get mixed when sequenced one after another.

b. AKI with hyperkalemia or uremic symptoms. Among patients who have severe hyperkalemia, metabolic acidosis, or uremic symptoms, short and frequent cycles are usually necessary to achieve metabolic control. HVPD or tidal PD are preferred in such situations.

PD is initiated with either a 1.5% or 2.5% dextrose solution, at the rate of one cycle per hour for the first 24 to 48 hours using exchange volume ranges of 20 to 40 mL/kg for a total dialysate volume of 32 to 48 L.

As an example, in a 60-kg woman with anuric AKI, a typical initial prescription would be:

- Session duration = 24 hours
- Number of cycles = 16
- Dwell time = 1 hour
- Inflow volume = 2 L (33 mL/kg)
- Total dialysate = 32.4 L
- Inflow time = 10 minutes
- Outflow time = 20 minutes

We then modify the prescription (to a higher or lower total volume, exchange volume, and dwell time) depending on the evolving metabolic goals in the setting of AKI.

5. Subsequent prescription. Patients who have improvement in their hyperkalemia, metabolic acidosis, uremic symptoms, and/or hypervolemia can be transitioned to a less intense PD prescription until there is sufficient return of native kidney function.

a. Subsequent prescription for all patients. The prescription is then altered by increasing the cycle length to 4 to 6 hours to match the metabolic needs of the patient. Among patients who are euvolemic, the volume status can generally be maintained with a 1.5% dextrose dialysate. As the native kidney function begins to return with associated improvement in metabolic and volume control, the

number of cycles is gradually tapered until the native kidney function recovers enough for the patient to discontinue PD.

As an example, in a 60-kg woman with anuric AKI who has had initial improvement in volume and metabolic control, a typical prescription would be:

- Session duration = 24 hours
- Number of cycles = 6
- Dwell time = 3.5 hours
- Inflow volume = 2 L (33 mL/kg)
- Total dialysate = 12 L
- Inflow time = 10 minutes
- Outflow time = 20 minutes

6. **Dialysis solution additives.** When injecting any additive into PD solution bags, a sterile technique must be followed in order to prevent bacterial contamination of the dialysis solution and peritonitis.
   a. **Potassium.** Standard PD solutions contain no potassium (K). In general, after the initial exchanges, serum K concentrations are within the normal range, unless the patient is very catabolic. In fact, losses of K can be high in acute PD. Such removal may cause serious K depletion and cardiovascular instability. This can be prevented or corrected by adding K to the dialysis solution. Serum K should be measured at least daily, and when it is less than 4 mmol/L, 4.0 to 5 mmol/L of potassium can be added to the PD solutions to minimize the risk of hypokalemia (Gabriel, 2008).
   b. **Heparin.** Sluggish dialysate flow from catheter obstruction by fibrin or blood clots may occur in acute PD, often as a result of the slight bleeding that may accompany catheter insertion or irritation of the peritoneum by the catheter. Heparin (500-1,000 units/L) added to the dialysis solution can be helpful in preventing or treating this problem. Because heparin is absorbed minimally through the peritoneum, there is no increased risk of bleeding.
   c. **Insulin.** Because glucose is absorbed from the dialysis solution, supplemental insulin administration may be required for the patient with diabetes undergoing acute PD. Insulin can be given subcutaneously or intravenously, or regular insulin may be added to the PD solution before infusion. The blood glucose level must be monitored closely, and the dose of insulin tailored to the needs of the patient. The following starting doses of regular insulin can be added to the PD solution:

      - 4 to 5 units/L to a 1.5% dextrose bag
      - 5 to 7 units/L to a 2.5% dextrose bag
      - 7 to 10 units/L to a 4.5% dextrose bag

   d. **Antibiotics.** Intraperitoneal administration of antibiotics is an efficient route for treating peritonitis. In general, antibiotics should not be given intraperitoneally to treat systemic infections, but this can be done in special circumstances.

B. How to measure dose in acute PD. It is important to ensure that acute PD is delivering an adequate amount of dialysis for the patient with AKI. Adequacy is generally assessed by measuring the Kt/V urea delivered by the PD. This is done by measuring the urea concentration in representative samples of dialysate and plasma in

order to calculate a D/P ratio for urea. This is multiplied by the total daily dialysate drain volume and divided by the estimated volume of distribution of urea using anthropometric equations for total body water, such as the Watson equation (see Chapter 23). However, patients with AKI often are fluid overloaded, and urea distribution volume often will be considerably higher than predicted by such equations.

C. Role of *Kt/V*. Some centers modify the prescription using $_{Kt}/_{V}$ in addition to clinical and laboratory assessment, while others rely on clinical and laboratory assessment alone. When $_{Kt}/_{V}$ is used, the International Society of Peritoneal Dialysis guidelines state that a weekly $_{Kt}/_{V}$ goal of 3.5 is recommended, when resources permit. However, a lower weekly $_{Kt}/_{V}$ of 2.1 is sufficient for many patients. A weekly $_{Kt}/_{V}$ urea of 3.5 can be targeted in the first 48 hours for catabolic patients with marked hyperkalemia or uremic symptoms, and 2.1 thereafter, provided that there is improvement in metabolic control (Cullis, 2021; Parapiboon and Jamratpan, 2017; Ponce, 2013).

MEASUREMENT OF DELIVERED *Kt/V*

$$Kt/V = \text{clearance of urea} \times \frac{\text{time}}{\text{volume of distribution of urea}}$$

$$= \frac{\text{mean dialysate urea nitrogen (mg/dL)}}{\text{mean serum urea nitrogen (mg/dL)}}$$

$$\times \frac{\text{drained 24-hour volume in mL}}{\text{estimated volume of distribution of urea (mL)}}$$

This is multiplied by 7 to yield the weekly *Kt/V* urea.

IV. COMPLICATIONS.

A number of problems may arise during the course of acute PD. These include mechanical, infectious, technical, and metabolic problems.

A. Mechanical complications. Incomplete drainage may lead to "overfill," which is a progressive intraperitoneal accumulation of dialysate, with attendant discomfort, distention, and even respiratory compromise. Catheter-related problems resulting in poor drainage are the main cause of this, although intra-abdominal adhesions or bowel distention can contribute. The drainage cycle should be monitored to make sure that the patient is emptying completely during the allowed drainage period. Mechanical problems occur in up to 10% of patients undergoing acute PD.

B. Peritonitis. Peritonitis rates have ranged from 4% to 41% during acute PD treatment in different studies. This occurs most often after 48 hours and is more common with open- than with closed-drainage systems. Although infections from gram-positive organisms dominate, there is a high incidence of gram-negative or fungal-related peritonitis in acute PD. This may be a reflection of the severity of illness in patients requiring acute PD as well as predisposing factors, such as the prolonged use of multiple antibiotics.

C. Hyperglycemia. The amount of glucose absorbed during PD varies significantly between patients due to differences in peritoneal membrane permeability and the concentrations of dextrose used. Fast transporters absorb glucose more quickly. Among patients undergoing CAPD with four exchanges per day, 60% to 80% of the glucose

instilled is absorbed. In a study of 31 patients with AKI treated with HVPD, the absorption of glucose was about 35% of that instilled during treatment (Góes, 2013). In order to avoid or reduce hyperglycemia in patients treated with PD, glucose absorption from dialysate should be taken into consideration when calculating total energy intake. Additionally, when hyperglycemia is detected, frequent blood glucose monitoring (approximately every 6 hours) should be performed, and intravenous, subcutaneous, and/or intraperitoneal administration of insulin should be considered. In studies of patients undergoing HVPD, glucose levels were well maintained between 130 and 170 mg/dL (7.2 and 9.4 mmol/L) using both intravenous and intraperitoneal insulin.

D. **Hypernatremia.** Due to the low sieving coefficient for sodium, which is related to water passage via aquaporin channels, the ultrafiltrate generated in PD during the early part of the dwell has a sodium concentration of approximately 70 mmol/L. Increased losses of water associated with frequent hypertonic exchanges can therefore lead to hypernatremia. Intravenous replacement of losses with hypotonic fluids or replacing half of the losses with 5% dextrose water prevents the development of hypernatremia.

E. **Hypoalbuminemia.** With the frequent exchanges utilized in acute PD, protein loss via the dialysate can be as high as 10 to 20 g/d and up to twice this amount if peritonitis develops. Oral or parenteral hyperalimentation should be considered in patients for whom malnutrition is deemed a problem. In general, protein losses through dialysis should not limit the use of PD in patients with AKI.

F. **Hypotension secondary to rapid volume removal.** Removal of volume by ultrafiltration, especially when an intensive (frequent exchanges with higher glucose concentrations) PD schedule is used, can result in severe hypovolemia-related hypotension. BP needs to be closely monitored, especially during the first 24 hours of acute PD, and an appropriate stop order should be in place to re-evaluate the PD prescription if hypotension is observed.

V. OUTCOMES WITH PD FOR AKI.

Interest in PD for AKI is increasing, and the safety of PD for AKI is increasing. PD can be successfully used to treat AKI and has efficacy and survival comparable with hemodialysis or continuous kidney replacement therapy (CKRT). In a 2017 Cochrane review of six trials involving 484 patients with AKI, patients who were treated with PD were comparable to those treated with extracorporeal modalities (hemodialysis, prolonged hemodialysis, or CKRT). There were no differences in all-cause mortality, kidney function recovery, or infectious complications (Liu, 2017).

In a subsequent trial, 125 critically ill patients with AKI were randomly assigned to high-volume tidal PD or CKRT. At 28 days, patients treated with PD had a higher rate of survival (70% vs 47%) and of kidney function recovery (60% vs 37%) and a shorter median length of intensive care unit stay (9 vs 19 days; Al-Hwiesh, 2018).

VI. “URGENT START” PD.

Urgent start PD has increasingly been used in the past decade. It is a strategy where people with advanced CKD who urgently and unexpectedly need dialysis due to uremia or fluid overload are treated urgently with PD rather than the more standard approach with hemodialysis. The aim is to increase the use of PD and to avoid the need for two accesses in the patient. While some define urgent start PD as dialysis when using a peritoneal catheter within 2 weeks of insertion, “true” urgent start is where the catheter is used within 48 to 72 hours (Blake, 2018; Duan, 2024; Ghaffari, 2013b).

A successful urgent start PD program requires a number of components (Ghaffari, 2013a). First, there needs to be prompt access to Tenckhoff catheter placement by a surgeon, nephrologist, or radiologist. Second, there needs to be a willingness of nephrologists in the center to alter their previous practice and consider the urgent start PD option in patients with CKD who present acutely with uremia or fluid overload. Third, there needs to be an ability to carry out some form of low-volume acute PD, typically delivered by a cycler with the patient in the supine position, in a ward setting for at least a few days to control acute uremia and fluid overload. Fourth, there needs to be a willingness and ability to train the patient in the PD unit at short notice once initial clinical stabilization on PD has occurred. Otherwise, an unacceptably long inpatient admission while waiting for a training spot would result. These requirements mean that an urgent PD program will only work if there is flexibility and cooperation between the hospital ward and PD unit staff and physicians, with overall leadership from an enthusiastic nephrologist.

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23 Prescription of Maintenance Peritoneal Dialysis

Peter G. Blake and John T. Daugirdas

The prescription of maintenance peritoneal dialysis (PD) involves a number of elements. Initially, there is the choice of PD modality between continuous ambulatory PD (CAPD) and cycler or automated PD (APD) and their variants. Then there is the selection of a specific prescription based on clearance, ultrafiltration, and nutritional/metabolic requirements. The term "adequacy" has historically been used in this context but is usually used to refer specifically to the quantity of clearance delivered. The new preferred term endorsed by the "Kidney Disease: Improving Global Outcomes" (KDIGO) initiative and by the International Society of Peritoneal Dialysis (ISPD) in its new Practice Recommendations is "High-Quality Goal-Directed" PD and takes into account not only clearance but volume status, residual renal function preservation, nutrition, symptoms, treatment burden, and quality of life (Brown, 2020; Chan, 2019; Manera, 2019). The US Kidney Disease Outcomes Quality Initiative (KDOQI) endorsed a specific urea clearance target in 2006, which US Medicare continues to define as a requirement for full funding, but in a recent commentary, KDOQI broadly endorsed the new ISPD recommendations (KDOQI, 2006; Teitelbaum, 2021). Please review Chapters 19 (Physiology) and 20 (Equipment) at this time, as many concepts discussed in those chapters will not be repeated here.

I. CHOICE OF A PD TREATMENT MODALITY (TABLE 23.1 AND FIGURE 23.1)

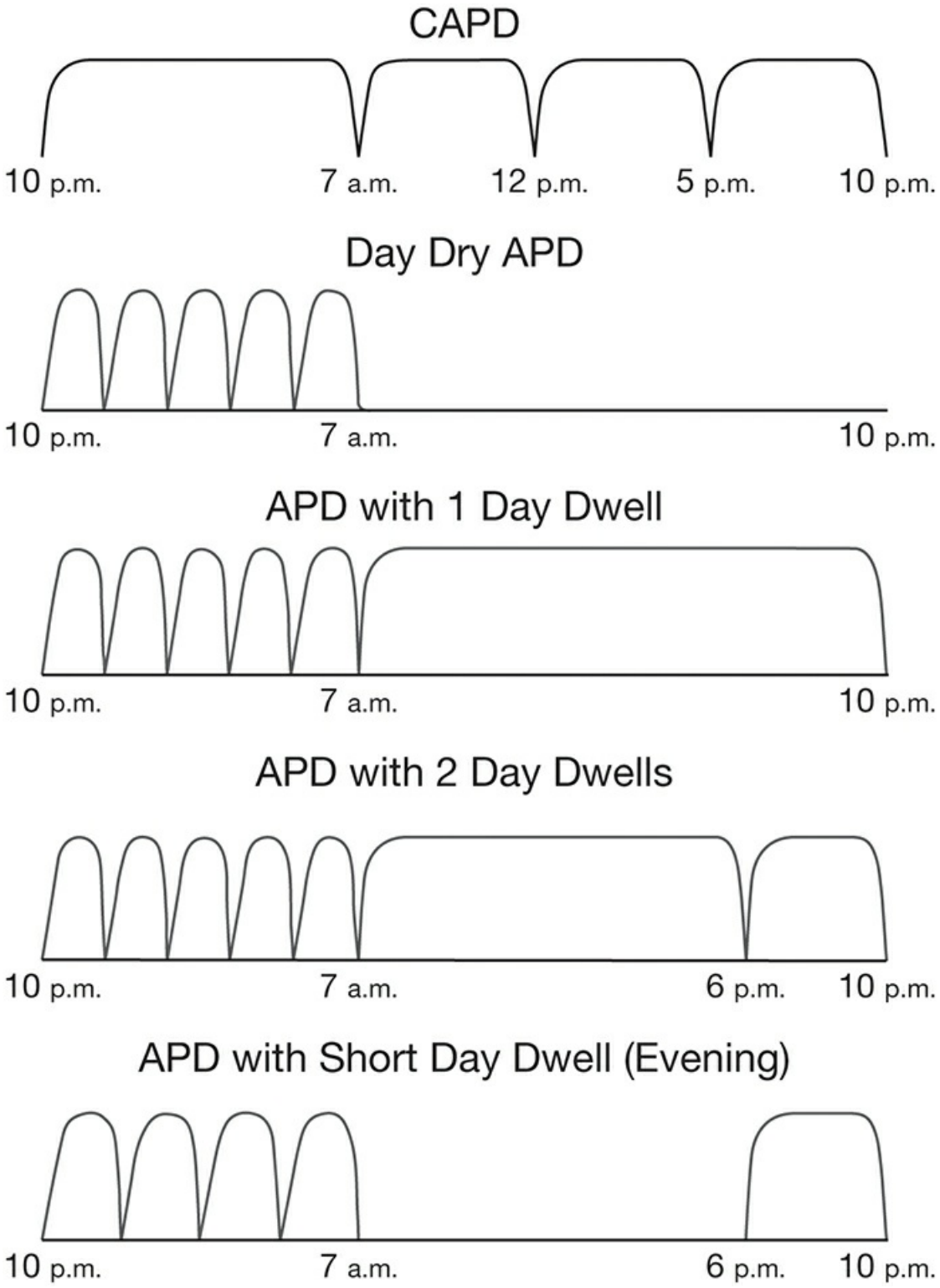


FIGURE 23.1: Diagrammatic representation of various CAPD and APD prescriptions. APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis.

TABLE

23.1 Comparison of Typical CAPD and APD Prescriptions

	CAPD	APD With Day Dwell	APD Without Day Dwell
PD solution used (L/wk)	56-72	70-120	84-120
Dialysis time (h/wk)	168	168	70
Time on machine (h/wk)	0	63-70	63-70
Number of procedures/wk	28	14	14
Kt/V urea/wk	1.5-2.4	1.5-2.6	1.2-2.0
CrCl (L/wk)	40-70	40-70	25-50

APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis.

A. Modalities of PD

1. **CAPD.** The simplicity of CAPD, the ease of doing it at home, its relatively low cost, and the associated freedom from dialysis machinery have combined to make it a popular chronic PD modality. CAPD provides continuous therapy and a steady physiologic state. Control of body fluid volume can usually be achieved, and normalization of blood pressure is possible in many patients.

   The principal disadvantage of CAPD for many patients is the requirement for multiple procedural sessions (usually four per day), each taking up 30 to 40 minutes of patient time. While these can be done away from home, the requirement for sterility and access to supplies usually means that the patient has to be at home, and so this may constrain daily activities somewhat. Frequency of procedures may also be an issue where relatives or other caregivers are carrying out the exchanges for the patient. Other factors are limitations on dwell volumes due to increased intraperitoneal pressure and a limited range of solute clearance. Episodes of peritonitis occurring as often as once every 12 months were a significant disadvantage in the past; however, with improved transfer sets and connecting devices, such occurrences have been markedly reduced and successful programs report rates of less than one peritonitis episode every 3 years.

2. **APD.** This has become very popular over the past 25 years and, in most wealthier countries, is being used in the majority of patients undergoing PD. The main advantage of APD, compared with CAPD, is the lesser number of on-off procedures required each day—typically two versus four for CAPD—and none during the daytime. Connections and preparation of equipment usually take place in the privacy of the home. APD is an attractive treatment option for active individuals who would be inconvenienced by the interruptions in daily routine that are required with CAPD. APD is also the therapy of choice for most patients who require assistance in carrying out their dialysis (eg, children, dependent older adults, and nursing home residents).

   The main disadvantages of APD relative to CAPD are the need for the patient to be connected to a cycler for 8 to 9 hours daily, the greater cost, and the slightly greater complexity.

   APD has classically been divided into APD with a day dwell, often called continuous cycling PD (CCPD), and “day dry” APD (Figure 23.1), often called nocturnal intermittent PD. These modalities have already been described in Chapters 19 and 20.

An alternative form of APD is tidal PD. This modality uses an initial fill volume followed by partial drainage at periodic intervals (Fernando and Finkelstein, 2006). The principal purpose of tidal PD was to enhance the clearance of small solutes by avoiding the normal loss of dialysis time associated with inflow and drainage. In terms of clearance, the advantage of tidal PD over standard APD is not seen unless very large quantities of dialysis solution are used. The main use of tidal PD nowadays is to minimize drain pain during nighttime cycling. The disadvantage of high-volume tidal PD is increased cost and complexity, and it is not widely used (Demetriou, 2006).

3. **CAPD or APD: Which modality to choose?** This decision should take into consideration both patient preferences and the need to provide a medically optimal PD prescription. Patient preferences may be based on lifestyle, employment, place of residence, ability to perform the modalities, comfort with cycler technology, and the degree of family and social support. In the past, peritoneal solute transfer rate (PSTR), as measured in a peritoneal equilibration test, and its influence on clearance and fluid removal were thought to be critical in choosing between CAPD and the different types of APD, but there is now an increasing sense that these aspects were somewhat overstated and that lifestyle factors should be given more emphasis, especially when residual renal function is still substantial. However, there is evidence that people with fast PSTR do better with APD (Johnson, 2010).

   APD was once thought to be better than CAPD for managing volume status. However, the phenomenon of sodium sieving (see Chapter 24) is more apparent with the short dwell times of APD, and this, along with the risk of net fluid resorption with long day dwells, has led to concerns about the adequacy of sodium removal with APD. One study suggests less salt removal and a higher prevalence of systolic hypertension with APD than with CAPD, but this was not a randomized trial, and there is no consensus that these findings are generalizable (Rodriguez-Carmona, 2004). Salt and water removal require close attention on both CAPD and APD, but there is insufficient evidence to justify it being a factor in initial modality selection.

   The risk of peritonitis is another medical factor that may arise when deciding between CAPD and the variants of APD. One randomized trial done over three decades ago showed less peritonitis on APD, but both modalities have changed since then, and there is now no consensus that one or the other is more likely to predispose to peritonitis (de Fijter, 1994).

   A third consideration is cost. CAPD generally is cheaper than APD. Dialysis programs have to deal with financial constraints, and in some settings, patients may have to bear some or all of the costs.

II. CHOICE OF A PRESCRIPTION

A. Clearance targets

1. **Weekly *Kt / V* urea.** Clearance targets in PD are mostly set in terms of weekly urea clearance (*Kt*) normalized to the patient's estimated urea distribution volume (*V*). KDOQI guidelines from 2006 proposed a *Kt*/*V* urea target of at least 1.7 weekly. However, the weakness of the evidence for this has increasingly been emphasized. Higher clearance targets were not supported by the landmark large

randomized Adequacy of Peritoneal Dialysis in Mexico (ADEMEX) trial (Paniagua, 2002), which found no difference in outcomes between patients assigned to receive a higher versus lower dose of PD—a weekly *Kt*/*V* of 2.1 versus 1.6, respectively. A similar trial from Hong Kong (Lo, 2003) also failed to find a convincing benefit for higher doses of PD. Given the lack of validation of specific clearance targets in these trials, the new ISPD recommendations suggest that an individualized approach to clearance should be negotiated with patients through shared decision-making and should be set in the context of other factors including goals of care, treatment burden, and quality of life (Brown, 2020; Manera, 2019). In general, many PD practitioners would still wish to achieve a weekly *Kt*/*V* over 1.7 in relatively younger healthier patients who are transplant candidates or who have substantial life expectancy but are willing to accept lower values in older frailer patients who seem to be doing reasonably well, who do not appear to be clinically uremic, and who might not wish to have a greater treatment burden (Blake and Brown, 2020; Maliha, 2023). This reflects the fact that increasing peritoneal clearance in patients undergoing PD can be arduous in that it may require more daily procedures, greater dwell volumes, and consequently more interference with quality of life, which patients value highly, and that this trade-off may not be justified given the lack of evidence of resulting improved outcomes (Manera, 2019).

2. **Weekly creatinine clearance (CrCl) per 1.73 m^2.** Previous guidelines set a weekly CrCl target in addition to the *Kt*/*V* urea target. The creatinine target was normalized to 1.73 m^2 body surface area (BSA) and was in the range of 60/1.73 m^2 L/wk. The idea of setting a separate creatinine target was to model a uremic toxin that had a slightly higher molecular weight than urea (113 vs 60 Da) and that was not so rapidly removed by diffusion. Most current guidelines no longer recommend a minimum level of weekly CrCl, as such targets have not been shown to be of any additional value over urea-based *Kt*/*V* targets. However, they do reflect clearance of slightly larger molecules than urea, and so some European, but not US, guidelines have suggested an additional CrCl target of 45 to 50/1.73 m^2 L/wk (Dombros, 2005; Woodrow, 2017). These targets have not recently been updated, however.
3. **Should residual kidney function be counted in the clearance target?** Greater residual kidney clearance has repeatedly been shown to be associated with superior patient survival; in contrast, no similar survival effect for peritoneal clearance has been shown, at least within the range of prescriptions in typical clinical use (Churchill, 1996). KDOQI, Canadian, and European guidelines, however, all recommend that peritoneal and residual kidney clearances can be added together to achieve a desired urea or creatinine-based target.
4. **Same *Kt*/*V* target for CAPD and APD.** The previous idea that target clearances for APD should be higher than those for CAPD, because APD is somewhat more intermittent, is now thought to be unjustified and to introduce unnecessary complexity.

B. Measurement of clearance (Table 23.2). Both *Kt*/*V* urea and CrCl/1.73 m^2 in PD comprise a peritoneal and a residual kidney component. Residual kidney function lasts longer in PD than in hemodialysis and accounts for a greater proportion of total clearance.

TABLE

23.2 Formulas for Calculating Clearance Indices in Peritoneal Dialysis

Kt /V:

Kt = Total ***Kt*** = peritoneal ***Kt*** + renal ***Kt***

Peritoneal ***Kt*** = 24-h dialysate urea nitrogen content/serum urea nitrogen

Renal ***Kt*** = 24-h urine urea nitrogen content/serum urea nitrogen

***V* (by Watson formula):**

$V = 2.447 - 0.09516A + 0.1704H + 0.3362W$ (in males)

$V = -2.097 + 0.1069H + 0.2466W$ (in females)

where A = age (y); H = height (cm), and W = weight (kg)[a]

CrCl:

CrCl = total **CrCl** corrected for 1.73 m^2 BSA Total **CrCl** = peritoneal **CrCl** + renal **CrCl**

Peritoneal **CrCl** = 24-h dialysate creatinine content/serum creatinine

Renal **CrCl**[b] = 0.5 (24-h urine creatinine content/serum creatinine + 24-h urine urea nitrogen content/serum urea nitrogen)

BSA (DuBois formula):

$BSA\ (m^2) = 0.007184 \times W^{0.425} \times H^{0.725}$

where BSA = body surface area (m^2), W = weight (kg)[a], and H = height (cm)

[a]Anthropometric (median standard or ideal body weight as per Appendix B) instead of actual body weight may be used for calculation of ***V*** or BSA.

[b]For PD adequacy purposes, renal "CrCl" is the average of the urinary creatinine and urea creatinine clearances.

1. **Measurement of weekly *Kt/V* urea.** Peritoneal *Kt*/*V* is calculated by collecting 24-hour dialysate effluent and measuring its urea content. This is then divided by the average serum urea level for the same 24-hour period to give a clearance term, *Kt* (Table 23.3). The timing of the serum urea sample is not critical in CAPD because it is relatively constant at all times. In APD, blood urea is not quite so constant throughout the day; ideally, therefore, it is best to take a measurement in the middle of the noncycling daytime period, which is typically between 11:00 AM and 5:00 PM and is thought to represent approximately the average blood urea levels for the day.

TABLE 23.3 Examples of Clearance Calculations in CAPD and APD

1. A 50-year-old man weighing 66 kg has no residual renal function. He is on CAPD with four 2.5-L exchanges daily, and his net UF is 1.5 L. His *V* by the Watson formula is 36 L, and his BSA by the DuBois formula is 1.66 m^2. Serum urea nitrogen is 70 mg/dL (25 mmol/L), and serum creatinine is 10 mg/dL (884 mcmol/L). The urea nitrogen and creatinine (after correction for glucose) levels in the 24-h dialysate collection are 63 mg/dL (22.5 mmol/L) and 6.5 mg/dL (575 mcmol/L), respectively. Calculate his *Kt*/*V* and CrCl.

Kt urea/d = 24-h drain volume × D/P urea = 11.5 L × 63/70 = 10.35 L/d.

Daily *Kt*/*V* = 10.35 L/36 L = 0.288

Weekly *Kt*/*V* = 0.288 × 7 = 2.02

Creatinine clearance per day = 24-h drain volume × D/P creatinine = 11.5 L × 6.5/10 = 7.48 L/d.

Corrected for 1.73 m^2 BSA = 7.48 × 1.73/1.66 = 7.80 L/d.

Weekly CrCl/1.73 m^2 = 7.8 × 7 = 55 L/wk.

2. A 48-year-old woman on APD weighs 63 kg and does five 2.4-L cycles nightly plus a 6-h 2-L day dwell. Her *V* by Watson is 32 L, and her BSA by DuBois is 1.60 m^2. Her 24-h dialysate drain volume is 15 L, indicating 1-L net UF. Her pooled dialysate collection has a urea nitrogen level of 48 mg/dL (17.1 mmol/L) and a creatinine level (after correction for glucose) of 4.5 mg/dL (398 mcmol/L). Her mid-afternoon serum urea nitrogen is 65

mg/dL (23.2 mmol/L), and serum creatinine is 9 mg/dL (796 mcmol/L). Her urinary urea and creatinine clearance are 2 and 4 mL/min, respectively.

Calculate her total weekly *Kt*/*V* and creatinine clearance.

Peritoneal *Kt* = daily drain volume × D/P urea = 15 L × 48/65 = 11.1 L.

Peritoneal *Kt*/*V* = 11.1 L/32 L = 0.35/d = 2.45/wk.

Renal urea clearance = renal *Kt* urea = 2 mL/min = 20 L/wk.

Renal *Kt*/*V* = 20/32 = 0.63/wk.

Total *Kt*/*V* = peritoneal plus renal *Kt*/*V* = 2.45 + 0.63 = 3.08/wk

Peritoneal creatinine clearance = daily drain volume × D/P creatinine = 15 L × 4.5/9 = 7.5 L.

Corrected for 1.73 m^2 BSA = 7.5 × 1.73/1.60 = 8.1 L/d = 57 L/wk.

Renal creatinine clearance (for this purpose) = mean of renal urea and renal creatinine clearance = mean of 2 and 4 mL/min = 3 mL/min = 30 L/wk. Corrected for 1.73 m^2 BSA = 30 × 1.73/1.60 = 32.4 L/wk.

Total creatinine clearance/1.73 m^2 = 57 + 32.4 = 89.4 L/wk.

APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; D/P, dialysate/plasma; UF, ultrafiltration.

Residual renal $_{Kt}$ urea is calculated in the same way using a 24-hour collection of urine. The peritoneal and renal $_{Kt}$ terms are then added to give the total $_{Kt}$ per day, and this value is normalized to $_{V}$, which represents total body water. It is recommended that $_{V}$ be estimated using one of the standard formulas for total body water, such as those of Watson or Hume-Weyers. These are based on the patient's age, sex, height, and weight (Table 23.2). This then gives a daily value for $_{Kt}/_{V}$ urea, which needs to be multiplied by 7 to give a weekly value. It is recommended that $_{V}$ be calculated using the patient's ideal or standard body weight rather than from actual body weight. This makes it easier to achieve targets in patients who are obese and is appropriate, in that body fat has a low water content and it is not thought that clearance requirements should rise in proportion to obesity. Conversely, wasted malnourished patients will require more dialysis to achieve targets if clearance is corrected to $_{V}$ based on their standard or ideal body weight. These weights are calculated from anthropometric values, as described in Appendix B, and then the standard or ideal body weight value should be used in the Watson equation to calculate the value for an adjusted $_{V}$.

2. **Measurement of weekly CrCl/1.73 m^2.** The measurement of CrCl is similar to that of $_{Kt}/_{V}$ (Tables 23.2 and 23.3). Again, the peritoneal component is calculated by measuring the creatinine content of a 24-hour collection of dialysate effluent, and this is then divided by the serum creatinine. The way that renal CrCl is added to the peritoneal component differs from the procedure for $_{Kt}/_{V}$ urea. Residual renal CrCl is known to markedly overestimate true glomerular filtration rate in patients undergoing dialysis; therefore, it is conventional to add the average of the urinary urea and creatinine clearances to the peritoneal clearance to give the total CrCl. The total daily "creatinine clearance" is then normalized to 1.73 m^2 BSA, with BSA estimated using the formula of DuBois or Gehan and George (see Appendix B). This daily clearance value is then multiplied by 7 to give a weekly CrCl/1.73 m^2. Normalization to standard or ideal body weight can be done in the same way as for $_{Kt}/_{V}$ urea, where the weight from Appendix B is used to calculate an adjusted BSA value.

3. **Analytical problem in measuring creatinine in the glucose-containing dialysate.** The high glucose levels found in dialysate artifactually elevate the measurement of creatinine in some biochemical assays, and each laboratory should make a correction for this based on its own experience. This may be done by spiking unused bags of dialysis solution containing various dextrose concentrations with a known amount of creatinine and then performing the assay, enabling the derivation of the appropriate correction factor.
4. **Frequency of measurements.** It was recommended by KDOQI in 2006 that in patients undergoing PD, $_{Kt}/_{V}$ urea should be measured within 1 month of initiating PD and every 4 months subsequently, as well as after every significant change in the PD prescription or in the patient's clinical status. Urinary clearance should be measured every 2 months if an incremental approach to PD dialysis is being used. Some will find these requirements unduly onerous, and a compromise in more stable patients who have been achieving their targets would be to measure clearances every 6 months.

C. Nonprescription determinants of clearance (Table 23.4). The total weekly *Kt*/*V* urea achieved on standard PD prescriptions typically ranges from as little as 1.2 to as much as 3.0 a week. Similarly, CrCl/1.73 m^2 can range from as little as 30 L/wk to as much as 150 L/wk. The major source of this variation is residual kidney function.

TABLE 23.4 Factors Determining Clearance in Patients Undergoing Peritoneal Dialysis

1. **Nonprescription factors:**
   - Residual renal function
   - Body size
   - Peritoneal transport characteristics
2. **Prescription factors:**
   - a. **CAPD:**
     - Dwell volume
     - Frequency of exchanges
     - Tonicity of dialysis solution
   - b. **APD:**
     - Number of day dwells
     - Volume of day dwells
     - Tonicity (glucose concentration) of day dwells
     - Time on cycler
     - Cycle frequency
     - Cycler dwell volumes
     - Tonicity of cycler solution

APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis.

1. **Residual kidney function.** This can easily account for as much as 50% of total clearance at the initiation of PD. There is some evidence from randomized controlled trials that residual renal clearance can be preserved in patients on CAPD by treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (Li, 2003b). It is always wise to minimize exposure to potentially nephrotoxic agents, including aminoglycosides, radiocontrast dyes, and nonsteroidal anti-inflammatory drugs. Episodes of volume depletion should be avoided. It has

been suggested that the preservation of residual function is better in CAPD than in APD, but this is not a consistent finding.

2. **Peritoneal solute transfer rate (PSTR).** This is an important determinant of clearances, especially in APD, where the short-duration cycles limit solute equilibration between serum and dialysate to a greater degree than is the case for the longer-duration dwells in CAPD. PSTR is measured using the peritoneal equilibration test as discussed in Chapter 19. In general, patients with slow PSTR achieve greater clearances with high-volume, long-duration dwells, whereas those with rapid PSTR do well with short-duration dwells. However, these differences are less pronounced for urea as compared to creatinine because the lower molecular weight of urea leads to relatively rapid diffusion, even with slow PSTR. PSTR status is a determinant of patient and technique survival on CAPD, with patients with slow PSTR doing best despite clearances that tend to be lower than those that their rapid PSTR counterparts achieve. It is likely that this is partly due to the importance of ultrafiltration and its interaction with cardiovascular morbidity.
3. **Body size.** Given that clearance indices are normalized to BSA or total body water, this is an important determinant. When standard or ideal body weight, rather than actual body weight, is used to calculate an adjusted *V* and an adjusted BSA, the impact of actual weight will be lessened. While large body size makes it harder to achieve higher clearance targets, there is controversy about whether larger patients have worse outcomes.

D. Prescription strategies to achieve clearance targets in maintenance PD

1. **Patient-centered PD prescription.** Before further discussing PD prescription strategies in detail, it should be noted that present guidelines strongly advocate for input from the person being treated with PD and from their families when prescription changes are being planned. Some strategies will suit some patients better than others, and quality of life can be adversely affected if this is not taken into account. Shared decision-making needs to occur. Some patients may choose to refuse prescription changes, and in these situations, sensitive discussions will be required, taking into account the limited evidence for higher clearances (Blake and Brown, 2020; Brown, 2020).
2. **Incremental versus maximal PD prescription.** There are two distinct approaches to the initial prescription of PD when clearance targets are being considered. The incremental approach, which has become particularly popular in recent times, advocates that PD should only be used to make up the difference between residual renal clearances and targeted clearances. Thus, patients may initially require only two or three CAPD exchanges daily or a low-volume, “day dry” APD prescription or even a day-per-week-off dialysis. The alternative is the so-called maximal approach in which patients are at the outset, given a sufficient prescription to meet their targets with PD alone. This approach considers residual kidney function as a temporary bonus that inevitably deteriorates with time.

   The definition of incremental PD is that (1) the prescription be less than the standard or full-dose PD prescription. (2) The initial peritoneal clearance is less than the individualized clearance goal for the patient, but the combined peritoneal plus kidney clearance achieves that goal. (3) The clear intention is to increase the peritoneal clearance as required to achieve the target if and when residual kidney

clearance declines (Blake, 2020).

The advantages of the incremental approach are that it reduces the patient's initial treatment burden, may decrease total glucose exposure and risk of peritonitis, insofar as fewer procedures are required, and is less costly. A disadvantage is that it requires regular monitoring of residual kidney function to ensure that the total clearance achieved does not fall below target levels.

The incremental approach has been evaluated in a randomized trial of CAPD only. That study compared outcomes in 69 patients randomized to a standard 4 × 2 L prescription versus 70 patients randomized to 3 × 2 L, with a fourth dwell added if clearance targets were not achieved. There was no difference in outcome after 2 years of follow-up except for a lower time to first peritonitis rate in the incremental group and no signal of harm. This suggests that the incremental approach is safe as well as less onerous (Yan, 2017). Other data show no difference in residual renal function decline with an incremental approach (Hayat, 2023). Multiple observational studies have shown no signal of harm with incremental APD or CAPD (Blake, 2020; Cheetham, 2023).

3. **CAPD.** The typical initial full-dose CAPD prescription is 4 × 2 L daily. Some centers will start with 4 × 2.5 L in larger patients, especially if residual renal function is low. Those using an incremental CAPD approach often start with 3 × 2 L daily or 3 to 4 × 1.5 L daily depending on patient preference, body size, and degree of residual renal function. In Hong Kong, where mean body weight is less than in Western countries, good results have been reported using 3 × 2 L initially in almost all patients. When icodextrin is available, some centers use it routinely for the nocturnal dwell, but it is more expensive, and others use it only in patients with high PSTR or in those in whom fluid resorption at night becomes a clinical problem.

   If a clearance measurement is unexpectedly low, it should be repeated as there is significant variation and potential for error. If appropriate clearance targets are not being achieved, a prescription change needs to be considered, especially if the patient has symptoms suggestive of uremia. The choice of strategy should take into account the increment in clearance required, the patient's PSTR status, volume and nutritional/metabolic considerations, and, perhaps most importantly, the likely effect on lifestyle for the patient and for any caregivers, as a disruptive prescription may lead to worsening of symptoms and quality of life, nonadherence and burnout, with consequent technique failure.

   To increase peritoneal Kt/V in patients undergoing CAPD, there are three options (Table 23.4): increase the dwell volumes, increase the frequency of daily exchanges, and/or increase dialysis solution tonicity, thereby augmenting ultrafiltration. Another alternative is to switch to APD.

   a. **Increasing the dwell volumes.** This increases clearance because the total volume of solution delivered daily rises, and on being drained, the larger dwell volume has only a small decrease in urea and creatinine equilibration. In larger patients, for example, a switch from 4 × 2 L to 4 × 2.5 L CAPD involves an approximately 25% increase in instilled volume and will typically raise peritoneal Kt/V by 18% to 20%. However, in smaller patients, and especially when 3-L dwell volumes are used, there may be a greater falloff in equilibration and the percentage increase in clearance is reduced. To achieve a weekly Kt/V of

1.7 on CAPD in larger (>75 kg) patients with anuria, typically at least 2.5-L dwell volumes are required. The main disadvantage of increasing dwell volumes is that some patients may complain of back pain, abdominal distention, and even shortness of breath. Studies show only a small increase in the risk of hernias and leaks with the associated rise in intraperitoneal pressure. This rise in pressure may also impair ultrafiltration somewhat, but this effect is partly offset by the longer persistence of the glucose osmotic gradient when higher volumes are used.

b. **Increasing the frequency of daily exchanges.** Increasing the number of CAPD exchanges from 3 to 4 or from 4 to 5 per day generally does not have a major effect on urea equilibration, which remains at approximately 85% to 90% in patients with average PSTR characteristics. In the case of five exchanges daily, the amount of urea equilibration of the drained dialysate may be reduced if the exchanges are not well spaced, with less than a 4-hour dwell time. Also, with five daily exchanges, even if well-spaced out, there will be a noticeable drop in creatinine concentration in the drained effluent because the equilibration curve for creatinine is typically still rising 4 to 5 hours after the dwell commences. Thus, increasing the frequency of exchanges is less effective than increasing dwell volumes where CrCl is concerned.

   An additional disadvantage of increasing the frequency of exchanges to 5 daily is that it may interfere with a patient's lifestyle and increase treatment burden, leading to nonadherence or "burnout." Also, the use of five exchanges per day is 25% more costly than four per day, whereas 2.5-L bags of dialysis solution are not usually much more expensive than the 2.0-L size.

c. **Increasing the glucose concentration of the dialysis solutions.** This strategy increases both ultrafiltration and clearance. It is rarely used because there are concerns that it leads to a higher incidence of hyperglycemia, hyperlipidemia, obesity, and long-term peritoneal membrane damage.

4. **APD.** The initial APD prescription is quite variable across centers. In centers using full prescription APD, a typical starting volume delivered by the cycler is 6 to 10 L daily plus one or two day dwells. Some use up to 15 L daily delivered by the cycler with one day dwell, but this is expensive and uncommon. Typical cycler time is 8 to 10 hours, and dwell volumes on the cycler are usually 2 L or, in larger patients, 2.5 L.

   Centers using an incremental approach may start without a day dwell—so-called day dry APD, and/or they may use lower solution volumes on the cycler or shorter cycler times or they may give the patient 1 or 2 days off per week. Again, this should depend on the patient's individualized clearance goal, body size, residual renal function, and particular wishes established through shared decision-making.

   In those prescribed a single day dwell, the duration may be shortened to avoid fluid resorption, especially in those with rapid PSTR, leaving the patient "dry" for part of the day. Alternatively, in this situation, a second dwell may be prescribed. If icodextrin is available, some centers will use it routinely for the day dwell, while others will prescribe it only in those with fast PSTR, in those who have fluid resorption, and/or in those in whom there are metabolic concerns about excess glucose absorption, for example, patients with diabetes or patients who are obese.

Peritoneal clearance in APD can be increased using a number of different strategies (Table 23.4). In order of usefulness, these are as follows:

a. **Adding day dwells.** In "day dry" patients, the best way to increase clearance is to add a day dwell. This raises both *Kt*/*V* and CrCl, but the effect on CrCl is greater because creatinine equilibration is more dependent on longer dwell times. Typically, adding a day dwell to a "day dry" patient undergoing APD will increase daily peritoneal *Kt*/*V* and CrCl by 25% to 50%, respectively, and so this is very cost effective. Further increases in clearance can be achieved by adding a second day dwell. The added second day dwell can be done by reattaching to the cycler—sometimes called the "docking-station" approach, or if it suits the patient better, by using manual CAPD tubing. Day dwell volumes can be titrated to maximize clearance while minimizing mechanical symptoms. The two day dwell strategy does have the disadvantage of requiring the patient to do procedures in the daytime, which increases treatment burden, but it is often the preferred and most cost-effective strategy to increase clearance.
b. **Increasing frequency of cycles.** In general, doing more frequent cycles with APD increases clearances because it maximizes the concentration gradient between blood and dialysate (Demetriou, 2006). However, when the number of cycles exceeds 6 to 9 per 9-hour treatment, a large proportion of the dialysis session is spent draining and filling, and further increments in clearance become minimal. The benefit of more frequent cycles tends to be higher in those with rapid PSTR and is higher for urea than for creatinine clearance. It may also be influenced by catheter function. Maintaining a small amount of dialysate in the peritoneum constantly (ie, using tidal PD) can be used to help support clearance during high-frequency cycling but with conventional APD it has no such effect and is mainly used to avoid drain pain.
c. **Increase dwell volumes on cycler.** This increases clearance in APD, just as in CAPD. Because patients are supine during cycling, they can usually tolerate larger dwell volumes more easily. Greater clearances will be achieved if the same total amount of dialysis solution is delivered in a smaller number of aliquots (ie, 4 × 2.5 L per session is better than 5 × 2 L per session) though the increase in clearance is modest.
d. **Time on cycler.** In general, the longer the time the patient spends on APD, the better the clearance because individual dwell times are longer, allowing more complete equilibration between dialysate and blood. However, this may not be in accord with the patient's quality of life and sleep, and 9 hours is usually the maximum tolerated.
e. **Increasing dialysis solution glucose concentration.** As in CAPD, clearance can be augmented in APD by increasing dialysis solution glucose levels, which increases daytime or nighttime ultrafiltration, but concerns about glucose-related complications limit the usefulness of this approach.

E. Empirical versus modeled approach. One decision when prescribing PD is whether to use commercially available software programs for modeling appropriate prescriptions or whether to proceed in an empirical manner. The modeled approach involves collecting patient anthropometric data, measuring PSTR, and quantifying residual renal function. It also typically involves the collection of 24-hour dialysate

effluent to make particular calculations about peritoneal fluid removal and absorption. The computer program uses the data to predict, with reasonable accuracy, the clearances that will be achieved with various potential prescriptions. The program can also suggest appropriate prescriptions to achieve the desired clearances. With this approach, the actual clearances still have to be measured as sometimes there is a discrepancy between the modeled and actual clearances achieved.

The alternative approach is empirical, in which the physician uses knowledge of the patient's size, residual renal function, and PSTR to choose a reasonable prescription. This is then tested, clearances are assessed, and the prescription is adjusted if necessary. The modeled approach has the advantage that it may involve less trial and error and so results in earlier identification of an appropriate prescription for the patient, with consequent decreases in cost as well as inconvenience to the patient. The empirical method has a theoretical advantage in that it focuses the physician's attention on the patient rather than on purely numerical data. In practice, a combination of both approaches is frequently used, with the modeled approach being of particular use in complex cases and in patients on APD.

F. Prescription pitfalls in PD. There are a number of common pitfalls that physicians face in attempting to achieve adequate clearances and fluid removal on PD.

1. **Loss of residual renal function.** A common problem is that residual renal function is not monitored closely enough and drops to a very low level without the physician being aware. Thus, the patient is left on an inadequate prescription for a significant period of time. This is best avoided by measuring residual kidney clearance every 2 to 3 months or by adopting a maximal prescription approach that gives sufficient peritoneal clearance independent of residual function.

   The amount of daily urine volume correlates with residual kidney urea and creatinine clearance, although the relationship does have considerable variability. Although residual kidney solute concentration cannot be predicted from urine volume alone, a marked drop in daily urine volume is very often associated with a fall in residual kidney solute clearance. For this reason, simply querying the patient on a regular basis regarding the usual volume of urine made per day can be a useful prompt that a repeat measure of residual kidney function may be indicated.

2. **Nonadherence.** A patient undergoing maintenance PD may sometimes appear uremic or have unexpectedly high levels of urea and potassium in blood despite measured clearances that exceed recommended targets. A strong possibility here is nonadherence. On the day that collections are performed, the patient is fully compliant with the prescription and appears to have excellent clearances. On other days, however, the patient is omitting exchanges or shortening time on the cycler. In CAPD, there is no single test that identifies this particular problem, and a high index of suspicion is required. In APD, newer cyclers that record delivered doses of PD make it easier to identify this problem. There are a number of patterns of nonadherence in patients undergoing PD that should be considered (Bernardini, 2000). These include:
   - **a.** Skipping CAPD exchanges
   - **b.** Inadequate spacing of CAPD exchanges
   - **c.** Reducing the dwell volume of CAPD exchanges by flushing fresh dialysis solution directly into the drain bag

   d. Skipping cycler treatments
   e. Shortening of cycler time in APD
   f. Skipping or shortening day dwells in APD
3. **High serum creatinine despite good clearances.** This is a common scenario. The patient has a $_{Kt}/_{V}$ urea above 1.7 per week, but the serum creatinine is over 12 to −16 mg/dL (about 1,000-1,500 mcmol/L). There are a number of possibilities here. One is nonadherence to the prescription. If this is the case, blood urea and potassium would also be high. A second possibility is that this is an example of discordance between $_{Kt}/_{V}$, which is high, and CrCl, which is low. This is most often seen once residual renal function fades away in slow PSTR patients or in those on APD with no day dwell. This can be confirmed by measuring the CrCl. The third possibility, also common, is that the serum creatinine is markedly elevated, not because of particularly low clearance but rather because of high creatinine generation, indicating a higher percentage of lean body mass. This can be demonstrated by measuring CrCl and showing it to be at or above 45-50 L/wk/1.73 m^2, suggesting that the percentage of lean body mass is high relative to what might be predicted. Such patients are not necessarily overtly muscular and indeed may be somewhat thin. Identification of this situation is helpful because patients with high creatinine generation or percentage of lean body mass have a good prognosis on PD, and it would be a mistake for the elevated serum creatinine to trigger a diagnosis of inadequate clearance and a switch to hemodialysis.
4. **“Day dry” APD in patients with anuria.** Some patients, even when their residual function is lost, can achieve a $_{Kt}/_{V}$ urea above 1.7 per week with prescriptions that leave them “dry” for all or most of the day. Such patients are typically smaller in body size and have rapid PSTR. This creates concern because while $_{Kt}/_{V}$ is above target, middle-molecule clearance in the absence of residual kidney function is dependent on dialysis time and so, while not routinely measured, will be low. There is no recommended target for middle-molecule clearance in either peritoneal or hemodialysis and no high-level clinical evidence that middle-molecule clearance is important. However, there has always been a viewpoint that it may matter and that middle-molecule clearance in patients with anuria may be better in CAPD or APD with day dwells because they are continuous modalities compared to day dry APD. There is no definite answer to this question, but it should at least be kept in mind when prescribing “day dry” APD in patients with anuria.
5. **Inappropriate switch from CAPD to APD.** It is sometimes presumed that APD is a panacea for inadequate dialysis on CAPD, but the problem can actually become worse on APD if prescriptions are inappropriate. This is especially true in those with slow PSTR, who are unlikely to achieve higher clearances on APD than on CAPD unless two day dwells are prescribed. Also, a patient who has the same *Kt*/*V* urea after a switch from CAPD to APD will typically have a lower CrCl.
6. **Inadequate attention to fluid removal.** Fluid removal is frequently neglected in prescriptions for PD. Prescriptions that yield good clearances may not give sufficient ultrafiltration to control volume status. This is particularly true in those with rapid PSTR, especially if long dwells that result in net fluid resorption are used. The use of icodextrin for the long dwell in both CAPD and APD and the prescription of two day dwells in APD are strategies that may be useful.

III. GLUCOSE-SPARING STRATEGIES.

There has long been concern about the harmful consequences of exposure to the hypertonic glucose in PD solutions (Holmes and Mujais, 2006). There is strong evidence that cumulative glucose exposure leads to deterioration in peritoneal membrane function with a decline in ultrafiltration. There is also awareness that systemic absorption of glucose may aggravate or induce hyperglycemia, hyperinsulinemia, obesity, and hyperlipidemia. Glucose-sparing strategies can be divided into the following categories:

A. General strategies.

These are approaches to lessen the need for high amounts of ultrafiltration and hypertonic glucose. They include (1) salt and water restriction, (2) prescription of high-dose loop diuretics to maintain higher urine volumes, (3) any intervention that preserves residual renal function (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, avoidance of nephrotoxic medications, contrast exposure, and volume depletion), and (4) revising target weight upward to avoid inappropriate use of hypertonic glucose when body weight gain occurs due to an increase in body fat mass.

B. Nonglucose dialysis solution strategies.

These involve the substitution of dialysis solutions containing icodextrin or amino acids for those containing glucose (Li, 2013; Paniagua, 2009).

While avoidance of hypertonic glucose is central to glucose-sparing strategies, a balance needs to be kept between minimizing excess glucose exposure and avoiding hypervolemia.

IV. ASSISTED PD.

If a patient is unable to do their own PD reliably and safely, their PD prescription cannot be provided without assistance. Frequently, this assistance comes from family members or, in some settings, from domestic workers or privately paid caregivers. However, these options are not always available and, in an increasing number of countries or regions, there are formal “Assisted PD” programs (Malho Guedes, 2023). These are now defined as assistance with PD procedures funded by health care systems and performed in the home by health care professionals, trained laypersons, or even paid family members (Oliver, 2024).

The support provided can be temporary or permanent and may include the performance of the PD exchanges, set up of cyclers, or help with weighing, blood pressure measurements, and choice of solution strengths. The overall aim is to increase accessibility to PD for people who could not do it independently and also to improve retention of patients on the modality and lessen patient and family caregiver “burnout.” A position paper on this topic has recently been provided by the ISPD (Oliver, 2024).

V. NUTRITIONAL ISSUES IN PD.

Nutritional status in patients undergoing PD has been repeatedly shown to predict patient survival and other outcomes. It is recommended that indicators of nutrition be routinely monitored to identify high-risk patients and target them for appropriate interventions.

A. Nutritional indices

1. **Normalized protein nitrogen appearance (nPNA).** This is easily measured using the same 24-hour collections of dialysate and urine required to calculate *Kt*/*V*. The rationale is that, in a steady state, nitrogen excretion is proportional to protein intake. A variety of formulas have been derived to estimate nPNA from nitrogen and

protein excretion. One reliable formula is that developed by Bergström (1998) (see Table 23.5 for formula and sample calculation). Previously, nPNA estimates were normalized using actual body weight, but this can lead to misleadingly high nPNA values in wasted malnourished patients and inappropriately low values in patients who are obese. Normalization to desirable or ideal weight based on anthropometric tables is now preferred. The recommended target nPNA for patients undergoing PD is 1.2 g/kg/d, but this may be unnecessarily high for many patients who often can achieve nitrogen balance at lower intakes. A falling nPNA or a level less than 0.8 g/kg/d should be a cause for concern, especially if accompanied by other evidence of poor nutrition.

TABLE 23.5 Calculation of Normalized Protein Nitrogen Appearance With Example

Bergström formulas:

1. PNA (g/d) = 20.1 + 7.5 UNA (g/d)

or

2. PNA (g/d) = 15.1 + 6.95 UNA (g/d) + dialysate protein losses (g/d)

UNA (g/d) = urinary urea losses (g/d) + dialysate urea losses (g/d)

Use formula (1) if dialysate protein losses are unknown and formula (2) if they are known.

Normalization of PNA to body weight gives nPNA. Actual body weight, if used, can give a misleadingly high value in malnourished patients and a misleadingly low one in patients who are obese.

Normalization to standard body weight based on anthropometric tables is preferable.

Example:

A 60-kg man on CAPD 4 × 2.5 L daily has 24-h dialysate effluent volume of 12 L which contains 58.3 mg/dL urea nitrogen so that total content = 12 × 58.3 × 10 = 7,000 mg = 7 g of urea nitrogen.

The 24-h urine has a 500-mL volume and contains 560 mg/dL = 2,800 mg = 2.8 g of urea nitrogen.

Total UNA = 7 + 2.8 = 9.8 g/d.

Dialysate protein losses are measured at 8 g/d.

Thus:

PNA = 15.1 + 6.95 (9.8) + 8 = 91.2 g/d.

nPNA based on actual weight = 91.2/60 = 1.52 g/kg/d.

Patient has lost weight, however, and anthropometric tables suggest that his standard weight is 72 kg.

nPNA based on this weight is 91.2/72 = 1.27 g/kg/d.

PNA, protein nitrogen appearance; UNA, urea nitrogen appearance.

2. **Caloric intake.** This is sometimes neglected in patients undergoing dialysis because it cannot be as easily measured as protein intake. In PD, caloric intake is a combination of dietary intake plus calories in the glucose absorbed from the dialysis solution.

   The suggested target is 35 kcal/kg/d; typically, 10% to 30% of this will come from dialysis solution glucose, with the exact amount absorbed depending on dialysis solution glucose concentration dwell time, and volume of solution used, as well as on the patient's PSTR characteristics, which influence the percentage of instilled glucose absorbed. Measurement of energy intake requires dietary assessment plus quantification of the glucose absorbed. The latter can be calculated directly by subtracting the amount of glucose in the effluent from the amount present in the source dialysis solution.
3. **Serum albumin.** This is one of the strongest predictors of patient survival in PD.

Serum albumin in this population is much more than a nutritional marker, as it is influenced by the PSTR status, which influences dialysate albumin losses, and by the presence of systemic illness or inflammation, as judged by the serum levels of acute-phase reactants such as C-reactive protein. Compared with the above factors, dietary protein intake has only a minor effect on serum albumin.

4. **Subjective global assessment (SGA).** This simple clinical tool is easily used at the bedside, promotes history taking and physical examination, and has been shown to predict patient outcome. The SGA is described in more detail in Chapter 29.
5. **Creatinine excretion.** The total creatinine content measured in the same 24-hour urine and dialysate collections done to calculate clearance can be used to estimate lean body mass (Keshaviah, 1995). These estimates of creatinine excretion are predictive of patient outcome, and a low or falling value identifies a patient who is at risk.

B. Treatment of malnutrition. This is reviewed in Chapter 29.

1. **Amino acid–containing dialysis solution.** Intraperitoneal amino acids have long been studied and are available in some countries, though not in many others including the United States. They are typically administered as one 2-L dwell given during the daytime either on CAPD or on APD, using the "last bag option." About 85% of the amino acid content of the bag will be absorbed if it is left in place for 6 hours. Food should be ingested at the time of the dwell to maximize utilization of the absorbed amino acids. This strategy does improve nitrogen balance, but there is little evidence of a dramatic effect on important clinical outcomes. The best randomized study to date suggests that intraperitoneal amino acids are associated with better long-term maintenance of nutritional indices, particularly in women, but no study has been large enough to detect any beneficial effect on the quality or quantity of life (Li, 2003a).

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24 Volume Status and Fluid Overload in Peritoneal Dialysis

Neil Boudville and Peter G. Blake

Fluid overload in patients undergoing peritoneal dialysis (PD) can manifest clinically as generalized edema, pulmonary edema, and hypertension. It causes left ventricular hypertrophy and is a major contributor to cardiovascular disease, the leading cause of death in all patients undergoing dialysis. It is also associated with hypoalbuminemia, malnutrition, inflammation, and atherosclerosis (Demirci, 2011). Volume overload is common in patients undergoing PD and is associated with increased mortality and a higher risk of transfer to hemodialysis, especially in patients on long-term PD (Ateş, 2001; Van Biesen, 2019).

I. ASSESSMENT OF FLUID STATUS. This is based primarily on clinical examination, which gives at best a crude estimation. The target body weight or "dry weight" for PD is the weight that gives a well-tolerated normotensive, edema-free state, and, just as in hemodialysis, it is determined by trial and error. Since patients undergoing PD tend to be seen less frequently than those on hemodialysis, there is a risk that this process will be more protracted and less well done. It requires frequent clinical reassessment of patients.

Alternative methods of assessing volume status include bioimpedance, serum levels of brain natriuretic peptide (BNP), and ultrasound of the inferior vena cava or of the lungs. Bioimpedance analysis can be done with relatively simple devices and involves the attachment of electrodes and application of low-voltage currents. This allows extracellular and intracellular fluid volumes to be estimated. It is being used clinically in some centers but without high-grade evidence to justify it (Tan, 2016; Tian, 2020). Serum BNP levels are in clinical use and are predictive of patient outcomes, but do not reliably distinguish fluid overload from cardiac injury (Lee, 2006). Lung ultrasound is being widely studied in patients undergoing dialysis, but its routine clinical use has not yet been validated (Alexandrou, 2022).

II. MECHANISMS OF FLUID OVERLOAD. Fluid overload in a patient undergoing PD may reflect any combination of inappropriate prescription, nonadherence to PD, dietary salt excess, heart failure, loss of residual renal function, mechanical problems such as catheter dysfunction and peritoneal leaks, and peritoneal membrane dysfunction. Awareness that any one factor alone may not explain volume overload in an individual patient undergoing PD is important, and one should avoid thoughtlessly attributing all fluid overload to membrane-related ultrafiltration failure (UFF).

III. DIAGNOSIS OF PERITONEAL MEMBRANE DYSFUNCTION AND UFF. Background information for this section is contained in Chapter 19. UFF is defined as fluid overload in association with a 4-hour ultrafiltration (UF) volume or UF capacity of less than 400 mL in a modified peritoneal equilibration test (PET; see Figure 19.7). The modified

PET uses a 4.25% dialysate dwell instead of the usual 2.5% bag used in the standard PET (described in Chapter 19). With the standard PET, a UF volume or capacity less than 100 mL suggests UFF. UFF should not be diagnosed if the UF volume exceeds these cut-off points or if there is no clinical evidence of significant volume overload. *UFF should also not be diagnosed until catheter malfunction and leaks have been excluded.* UF volume greater than 400 mL in the modified PET implies normal peritoneal membrane function, and, if fluid overload is present, closer attention needs to be paid to nonmembrane causes such as catheter dysfunction or occult leaks as listed in Table 24.1. Recently, it has been suggested that the term "ultrafiltration dysfunction" be used instead of UFF on the grounds that UF is a continuum rather than a binary finding and that it can vary substantially in the same patient, due in part to measurement issues (Morelle, 2021a).

TABLE 24.1 Causes of Fluid Overload in Patients Undergoing PD

Inappropriate bag selection
Inappropriate prescription for membrane transport status
Long, dextrose-containing daytime or nocturnal dwells
Failure to optimize APD regimen for transport status
Failure to use icodextrin-containing solutions
Noncompliance with PD prescription
Noncompliance with salt and water restriction
Loss of residual renal function
Abdominal leak
Catheter malfunction
Poor blood glucose control
Peritoneal membrane dysfunction

APD, automated peritoneal dialysis; PD, peritoneal dialysis.

If UFF is diagnosed, the next step is to review the peritoneal solute transfer characteristics of the patient using the results of the modified 4.25% PET or the standard PET, as the results are very similar. There are three possibilities.

A. Fast peritoneal solute transfer rate (PSTR) with UFF (type I). In this situation, the dialysate glucose concentration falls quickly after infusion because of rapid absorption, resulting in a loss of the concentration gradient that drives fluid removal. This is the most common cause and is often called type I UFF. It typically develops after 3 or more years on PD. It is believed to reflect an increase in the effective peritoneal surface area consequent to the increased membrane vascularity that often occurs with time on PD. This occurs to a greater extent in some patients than in others. Typically, the equilibration ratio for creatinine between dialysate and plasma (D/P Creatinine) at 4 hours as measured by the PET is greater than 0.8 in these cases. Many of these patients also have progressive peritoneal fibrosis, which contributes additionally to the decrease in UF volume (Davies, 2005, 2016). Some patients have a relatively fast PSTR from the time they initiate PD, but most do not have early UFF. Causes of this initial fast PSTR include peritoneal inflammation with the generation of higher levels of intraperitoneal interleukin-6 in response to PD solutions. This may in part be genetically determined, but it is also more frequent in patients who are older or those with diabetes (Siddique, 2015). Causes of a marked rise in PSTR with time include cumulative exposure of the membrane to high glucose loads (Davies, 2001).

More biocompatible normal pH PD solutions do not protect against this process, but substitution of icodextrin for glucose does (Davies, 2005; Htay, 2018). Cumulative episodes of peritonitis may also contribute, and type I UFF may also occur transiently in patients with acute peritonitis during and after the episode owing to acute inflammation of the membrane.

B. Slow PSTR with UFF (type II). This group of patients has reduced small solute clearance and reduced fluid removal. The D/P creatinine is less than 0.5. This is also called type II UFF and is much less common. It reflects decreased membrane surface area and is most often due to adhesions and scarring after severe peritonitis or other intra-abdominal complications. It is difficult to maintain these patients on PD unless they have significant residual renal function.

C. UFF with PSTR in the normal range (so-called high-average and low-average transporters). Careful consideration once again should be made to exclude mechanical causes of poor fluid removal in this group. If these are excluded, this is often called type III UFF. Causes include the following:

1. **Increased lymphatic absorption:** Lymphatic absorption of peritoneal fluid is the cause in some patients. This can be quantified by measuring the disappearance rate of dextran 70 from the peritoneal cavity, but this is rarely done in clinical practice, and the diagnosis tends to be one of exclusion.
2. **Aquaporin dysfunction.** A similar pattern can be seen with the increasingly recognized condition of aquaporin dysfunction. One variant is due to a particular aquaporin promoter genotype found in over 10% of patients undergoing incident PD in a recent international study, and this is associated with significantly lower UF capacity, less free water transport, and worse outcomes on PD (Morelle, 2021b). Aquaporin dysfunction can be diagnosed by measuring the "sodium dip," which is the change in dialysate sodium concentration between 0 and 60 minutes of a 2-L dialysis dwell with 4.25% glucose. Why does the dialysate sodium fall during the early part of a dwell? When dialysate glucose levels are high, osmotically driven UF occurs primarily via aquaporin channels, which transport water but not sodium. The result is an early lowering in the dialysate sodium concentration by 5 to 10 mmol/L with a 4.25% glucose dwell. This leads to a sodium gradient between blood and dialysate, and sodium diffusion brings the dialysate sodium level up again as the dwell proceeds (Figure 19.7). If aquaporin-mediated water transport is impaired, the initial fall in dialysate sodium will not occur with 4.25% dwells and there will be a less than 5 mmol/L difference between the dialysate sodium levels at time 0 and 60 minutes (Ni, 2006; Smit, 2004).
3. **Progressive peritoneal fibrosis.** The pattern of decreased UF, low free water transport, and decreased sodium dip can also be acquired in a subset of patients undergoing long-term PD and has been attributed to severe progressive peritoneal fibrosis rather than to aquaporin dysfunction. In these cases, however, there is usually also a fast PSTR, but the loss in UF is disproportionately greater than can be accounted for by the PSTR alone (Davies, 2005; Krediet, 2022). It is important to distinguish progressive peritoneal fibrosis from encapsulating peritoneal sclerosis, which is a much more serious condition that develops in a small minority of people with progressive peritoneal fibrosis (see Chapter 26).

It should be noted that different causes of UF dysfunction can coexist in the

same patient and can be further aggravated by mechanical problems such as catheter dysfunction.

IV. PREVENTION AND MANAGEMENT OF FLUID OVERLOAD.

Often, multiple causes of volume overload coexist in an individual patient undergoing PD. For example, there may be some UFF but also excess dietary salt intake or poor glucose control. Optimal management may therefore require multiple therapeutic and preventive strategies (Brown, 2020).

A. General measures

1. **Sodium and fluid restriction.** It is important that patients receive education on sodium and fluid restriction, especially when residual renal function declines. An intake of less than 2.3 g (100 mmol) of sodium per day is recommended for those with difficult hypertension or volume control problems (Ateş, 2001).
2. **Patient education on when to use higher-strength glucose solutions.** Patients are usually taught to choose or titrate PD solution glucose concentrations in order to best achieve the target body weight. Underuse of hypertonic solutions may contribute to fluid overload. However, regular selection of high-concentration glucose solutions should not be the preferred method of fluid volume control over sodium restriction. Overuse of high-concentration glucose solutions may adversely affect peritoneal membrane function, increasing glucose absorption, worsening blood glucose and lipid control, and promoting obesity. A balance needs to be found, and this requires careful regular clinical attention using physical examination but also looking at urine output. Peritoneal ultrafiltration targets are sometimes suggested, but this may be problematic in older, frailer, nutritionally compromised patients who restrict their intake and may be at risk of volume depletion (Sharma, 2003). New technology involving a hypertonic glucose infusion during continuous ambulatory peritoneal dialysis (CAPD) dwells to maintain a constant osmotic gradient has been reported to achieve sustained ultrafiltration with less glucose absorption, but this requires further research (Davies, 2023; Heimbürger, 2024).
3. **Frequent clinical assessment.** Patients need to be assessed regularly and have their target weight reviewed. In patients undergoing PD, there is an early tendency to weight gain, likely due to glucose absorption, so the target weight may need to be adjusted to avoid excess use of hypertonic glucose in an attempt to reach an unrealistic weight. Later in the course of PD, as urine volume declines, there is an increased rate of fluid overload, and the clinician needs to be aware of this and intervene accordingly. No single test is reliable to detect this, and clinical examination plus trial and error remains the best approach.
4. **Management of heart failure.** See the section below.
5. **Good blood glucose control.** This will help maintain the glucose concentration gradient across the peritoneal membrane required for fluid removal.
6. **Preserving residual renal function.** This is important for both clearance and fluid removal. There is clinical trial evidence in patients undergoing PD that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers preserve residual renal function, in terms of both clearance and urine volume (Li, 2004; Liu, 2017). Use of high-dose loop diuretics in patients with residual renal function, with or without metolazone, will also increase urine volume and sodium

and fluid removal (Medcalf, 2001). Avoidance of nephrotoxins and of intravascular depletion both serve to protect residual renal function. Biocompatible PD solutions based on double-pouched bag technology have low glucose degradation product content, and a large randomized trial suggested that these are associated with better preservation of residual renal function (Htay, 2017; Johnson, 2012); however, there is a concern that this is, at least partly, mediated by a higher PSTR and less ultrafiltration with these solutions (Blake, 2012; Htay, 2018).

7. **Abdominal leaks.** See Chapter 26.
8. **Catheter malfunction.** See Chapter 21.
9. **Preservation of peritoneal membrane function.** Reduction in episodes of peritonitis and avoidance of excessive exposure to high-glucose-concentration PD fluid will help to preserve long-term peritoneal membrane function. Randomized trials looking at "biocompatible" PD solutions with low glucose degradation product levels have not shown that these preserve membrane function better than conventional PD solutions (Htay, 2018).

B. Management of UFF

1. **High PSTR status (UFF type I).** Short dwell times are required to maintain the dialysate glucose concentration gradient, so automated peritoneal dialysis (APD), programmed for short 1.0- to 1.5-hour dwells, may be best. Long-duration glucose-containing dwells in CAPD and APD should be avoided. In APD, short glucose day dwells can be used. However, icodextrin is a more attractive approach for long dwells in both CAPD and APD.
    a. **Icodextrin.** This is a carbohydrate polymer used instead of glucose, to produce an oncotic concentration gradient for ultrafiltration. It is discussed in Chapter 19. It is not absorbed across the membrane, although it does slowly get taken up by the lymphatics. Accordingly, a concentration gradient is maintained throughout a long dwell, allowing ongoing ultrafiltration. Icodextrin is ideal for the 14- to 16-hour day dwell in APD and for the long nocturnal dwell in CAPD. The use of icodextrin has been shown to improve volume status (Davies, 2003; Goossen, 2020) and to prolong technique survival substantially in patients with UFF and high PSTR status (Takatori, 2011).
    b. **Resting the peritoneum.** There have been documented cases of improved peritoneal membrane function in type I UFF following a temporary cessation of PD. The mechanism for this is unclear but may involve the resolution of increased vascularity with time off PD.
2. **UFF with low transport status.** These patients are unlikely to do much better on APD than CAPD or with icodextrin. Generally, transfer to hemodialysis is required.
3. **UFF with average transport status.** There is no specific method to either reduce lymphatic absorption or to correct impaired aquaporin function. Generally, this type of UFF is managed by salt and water restriction, diuretics, and general measures to increase total ultrafiltration to compensate for the volume reabsorbed. This approach may include shortening dwell times and using icodextrin for long dwells. Icodextrin may be particularly useful in aquaporin deficiency as the ultrafiltration it induces occurs almost exclusively via the non-aquaporin small pores. If these measures are not effective, a switch to hemodialysis is recommended (Morelle, 2021a).

V. PD AND HEART FAILURE

A. Management. A high proportion of all people on maintenance dialysis, including PD, have a history of heart failure, and this can exacerbate the challenges of managing their volume status and increase their risk of hospitalization and mortality (Roehm, 2020). A key point in their management is that they should, if possible, receive the same medications that have been shown to improve outcomes in heart failure with reduced ejection fraction in people not on dialysis. These include loop diuretics, β-blockers, and renin-angiotensin-aldosterone system antagonists, including spironolactone. The roles of the combined valsartan-sacubitril medication and of sodium-glucose cotransporter-2 inhibitors in people on dialysis are less clear at present. Evidence is even more uncertain for those on dialysis with heart failure and preserved ejection fraction. Mineralocorticoid receptor antagonists and sodium-glucose cotransporter-2 inhibitors have been shown to have benefits in people not on dialysis. The former can be used cautiously in people on dialysis, but there is no published experience with the latter. Renin-angiotensin system inhibitors and β-blockers are unproven in this type of heart failure but are often used anyway in people on dialysis for other reasons such as hypertension and residual renal function preservation. For all these medications, people on dialysis were not included in the pivotal randomized controlled heart failure trials, so the evidence for their use is suboptimal (Roehm, 2020). Nephrologists caring for these patients need to balance risks and benefits but should not be too nihilistic, as untreated mortality is high.

B. PD for heart failure. People with severe diuretic-resistant heart failure who do not have advanced stage 5 chronic kidney disease are sometimes treated with PD to remove fluid. Some success has been reported in uncontrolled studies, but there is no successfully completed randomized trial (Dukka, 2019; Papasotiriou, 2022). Typical PD prescriptions used in these situations are one long icodextrin dwell daily, with or without additional hypertonic glucose dwells, two long icodextrin dwells daily—although this is “off label” use of this agent, and day dry APD (Papasotiriou, 2022). Very rapid cycling is not ideal, as sodium sieving will result in less salt than water removal.

VI. GLUCOSE-SPARING STRATEGIES.

At the level of the peritoneal membrane, there has been evidence from laboratory studies that hypertonic glucose exposure leads to neovascularization of the membrane and a pattern analogous to UFF with high transport status. Clinical studies have shown that patients undergoing long-term PD exposed to more hypertonic glucose are more likely to develop fast transport characteristics than those who receive less glucose (Davies, 2001). Systemically, glucose loading may also be harmful, as detailed in Chapter 27. This has led to a greater emphasis on strategies to minimize glucose exposure. Essentially, this involves the use of less hypertonic glucose (Johnson, 2012; Li, 2013). At first, such an approach might be expected to lead to less ultrafiltration and to a greater risk of fluid overload. It is possible, however, to find a balance between glucose sparing and volume control. Effective glucose-sparing strategies include salt and water restriction, the use of loop diuretics to maintain volume, and the use of renin-angiotensin system inhibitors to preserve residual renal function (Li, 2003; Medcalf, 2001). Icodextrin allows the reduction of daily glucose exposure, and there are studies suggesting more stable long-term membrane function with this solution (Davies, 2005). Intraperitoneal amino

acids, where available, can also be substituted for one daily dextrose dwell.

VII. HYPERTENSION AND HYPOTENSION IN PD

A. Hypertension. Hypertension is common in patients undergoing PD, and antihypertensive medication requirements tend to increase with the duration on PD, especially when residual renal function is lost (Ortega and Materson, 2011). There are however no clear evidence-based blood pressure targets for patients undergoing PD. This is because the association between blood pressure and clinical outcomes is complex due to the confounding association of low blood pressure with cardiac and other comorbidities (Wang, 2020). In general, most clinicians would however treat systolic blood pressures that are consistently over 150 mm Hg.

1. **Management.** This should focus initially on volume control, although it is increasingly appreciated that long-standing systolic hypertension in older patients may not always be responsive to this approach, and care must be taken to avoid volume depletion that may cause a decline in residual renal function (Wang, 2020). Volume control includes salt restriction, appropriate PD solution strengths, and the use of loop diuretics. Antihypertensives, other than cardioprotective agents, should be introduced if volume control alone is unsuccessful. Preference should be given to agents that have a beneficial effect on urine volume or residual renal function, such as loop diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. The choice of agent in many patients may be driven by coexisting medical conditions such as ischemic heart disease.
2. **Sodium removal and hypertension using APD.** Sodium removal is a little less in APD because the short duration of the cycled dwells means that dialysate is drained while sodium levels are still low due to sodium sieving and before sodium diffusion has had a chance to correct this (Rodriguez-Carmona, 2004). Concerns have been raised, but studies to date have not consistently shown a difference in blood pressure control between patients on CAPD and APD (Boudville, 2007).

B. Hypotension. Hypotension is not uncommon in patients undergoing PD, with one cohort study (Malliara, 2002) detecting it in 13% of patients. The cause of hypotension is sometimes unclear, but approximately 20% of cases are secondary to heart failure. An additional 40% may be due to hypovolemia, and it is important to recognize this as the hypotension in these patients typically responds to volume repletion and residual renal function may improve as well. Patients with hypotension due to cardiac causes and cases in which no cause can be identified have a poor prognosis, with a high mortality rate. Agents such as midodrine and fludrocortisone have been used but with no proven long-term benefit. New-onset hypotension may represent developing sepsis or acute cardiac injury.

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25 Peritonitis and Exit-Site Infection

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I. PERITONITIS

A. Incidence.

Peritonitis remains the Achilles heel of peritoneal dialysis (PD). Peritonitis is a "contributing factor" to 16% of deaths on PD. Furthermore, peritonitis is the most common cause of treatment failure, accounting for nearly 30% of the cases. Peritonitis rates should be reported as the number of episodes per patient-year. Every PD program should monitor the peritonitis rate at least yearly (Li, 2022). The latest targets recommended by the International Society for Peritoneal Dialysis (ISPD) for overall peritonitis rate should be no more than 0.40 episodes per year at risk, and the percentage of patients free of peritonitis per unit time should be targeted at greater than 80% per year (Li, 2022). In addition to the overall peritonitis rate, organism-specific and culture-negative peritonitis rates, antimicrobial susceptibilities of the infecting organisms and peritonitis outcomes should be monitored. The incidence of peritonitis in patients undergoing continuous ambulatory peritoneal dialysis (CAPD) during the 1980s and early 1990s averaged 1.1 to 1.3 episodes per patient-year in the United States. With improved patient training, PD delivery systems, and prophylactic measures, the rate of peritonitis has fallen worldwide. Many centers now report a peritonitis rate of 0.2 to 0.6 episodes per patient-year at risk (Li, 2022). The introduction of the Y-set and double-bag disconnect systems has substantially reduced the incidence of peritonitis, particularly episodes caused by gram-positive organisms (Li, 2002; Monteón, 1998). The same flush before fill methodology used in CAPD Y sets can also be used effectively in automated peritoneal dialysis (APD). Peritonitis rates with APD and CAPD are not substantially different. Patients on APD going "dry" during the day (ie, no daytime dwell) may have a decreased risk of infection compared with those with a day dwell.

B. Pathogenesis

1. Pathways of infection

a. Intraluminal. The most common direct cause of peritonitis is touch contamination, that is, errors in technique in making or breaking a transfer set-to-bag or catheter-to-transfer set connection. As a result, bacteria gain access to the peritoneal cavity via the catheter lumen. Typically, the organisms are coagulase-negative staphylococci or diphtheroids.

b. Periluminal. Bacteria present on the skin surface can enter the peritoneal cavity via the peritoneal catheter tract. Common organisms involved are *Staphylococcus aureus* or *Pseudomonas* species.

c. Bowel source. Bacteria of intestinal origin can enter the peritoneal cavity by migrating across the bowel wall. This is the usual mechanism of peritonitis episodes associated with diarrhea or gastrointestinal endoscopy. Typical organisms involved are *Escherichia coli* and other *Enterobacteriaceae* species.

d. Hematogenous. Peritonitis is occasionally caused by bacteria spreading from a distant site via the bloodstream. Typical organisms here are streptococci and

staphylococci.

e. **Transvaginal.** Ascending infection from the vagina via the uterine tubes is uncommon. Some *Candida* peritonitis may occur by this route.

2. **Role of host defenses.** The peritoneal leukocytes are critical in combating bacteria that have entered the peritoneal cavity. A number of factors are now known to alter their efficacy in phagocytizing and killing invading bacteria.

a. **Dialysis solution pH and osmolality.** Standard PD solutions have a pH of around 5 and an osmolality of 1.3 to 1.8 times of normal plasma. The unphysiologic conditions inhibit the ability of peritoneal leukocytes to phagocytize and kill bacteria. High osmolality, low pH, and lactate anion combine to inhibit superoxide generation. The new generation of "biocompatible" PD solutions with normal pH may reduce the peritonitis rate, but published data are not consistent (Cho, 2014; Htay, 2018).

b. **Dialysis solution calcium.** The antimicrobial actions of peritoneal macrophages are enhanced by both calcium and cholecalciferol. The use of PD solutions with a calcium concentration of 1.25 mM (2.5 mEq/L) may benefit adynamic bone disease and vascular calcification but may be associated with an increased risk of *Staphylococcus epidermidis* peritonitis although the evidence is controversial.

C. Etiology. With appropriate culture techniques, the causative organism can be isolated from the PD effluent in over 90% of cases. The responsible pathogen is usually a bacterium, but fungal peritonitis occurs occasionally (Table 25.1).

TABLE 25.1 Frequency of Organisms Isolated in PD-Related Peritonitis

Organisms Identified	Percentage (%)
Gram-positive organisms	**40-50**
Staphylococcus aureus	11-12
Coagulase-negative staphylococcal species	12-30
Gram-negative organisms	**20-30**
Pseudomonas species	12-15
Escherichia coli	6-10
Fungi	2-4
Mycobacterium	~1
Polymicrobial growth	**~10**
Culture negative	**~15**

PD, peritoneal dialysis.

D. Diagnosis. At least two of the following three findings should be present: (a) symptoms and signs of peritoneal inflammation, (b) cloudy peritoneal fluid with an elevated PD effluent leukocyte count (>100/mcL or 100 × 10^6/L) with neutrophil predominance (>50%), and (c) demonstration of bacteria in the PD effluent by Gram stain or culture.

1. **Symptoms and signs.** The most common symptom is abdominal pain, but it is sometimes mild. Other symptoms include nausea, vomiting, and diarrhea (Table

25.2). In older adults or patients with diabetes, abdominal pain may be absent, and the only clinical features may be hypotension and systemic sepsis. On the other hand, abdominal pain in patients undergoing PD can be caused by problems unrelated to peritonitis.

TABLE 25.2 Symptoms and Signs of Peritonitis

	Incidence (%)
Symptoms	
Abdominal pain	95
Nausea and vomiting	30
Feverish sensation	30
Chills	20
Constipation or diarrhea	15
Signs	
Cloudy peritoneal fluid	99
Abdominal tenderness	80
Rebound tenderness	10-50[a]
Fever	33
Blood leukocytosis	25

[a]Highly variable, depending on the severity of the infection and the amount of time elapsed between onset and medical evaluation.

2. **PD effluent**
   a. **Cloudiness of PD effluent.** The PD effluent generally becomes cloudy when the leukocyte count exceeds 50 to 100/mcL (50-100 × 10^6/L). In most patients, sudden onset of cloudy fluid together with abdominal symptoms is sufficient evidence of peritonitis, and antimicrobial therapy should be initiated. However, cloudy PD effluent may be due to other causes (eg, fibrin, blood, or, rarely, malignancy or chyle) rather than to an increase in the leukocyte count. Occasionally, PD effluent drained after a prolonged dwell period (eg, after the daytime dwell in APD) may appear cloudy. On the other hand, a relatively translucent PD effluent does not completely exclude peritonitis.
   b. **Importance of performing a differential leukocyte count.** Peritonitis is usually associated with an increase in the absolute number and percentage of neutrophils in the PD effluent. Occasionally, a high PD effluent leukocyte count may be caused by an increase in monocytes or eosinophils. These cases are not peritonitis and do not require antimicrobial treatment. For this reason, one should perform a differential cell count on the PD effluent sample.
   c. **Obtaining the specimen**
      1. **Patients undergoing CAPD.** After disconnecting the drain bag full of PD effluent, the bag is inverted several times to mix its contents. A sample (7 mL) is aspirated from the port of the drain bag and transferred to a tube containing ethylenediamine tetraacetic acid (EDTA).

2. **Patients undergoing APD.** For patients using a daytime dwell, a PD effluent cell count can be obtained by draining the abdomen and then obtaining the sample from the drainage bag. In those who are "day dry," there may be some residual fluid present in the abdomen at the time the patient is seen. In these cases, the PD effluent sample can be obtained directly via the peritoneal catheter. After careful cleaning of the catheter with povidone-iodine, a syringe is attached using a meticulous sterile technique, and 2 to 3 mL of fluid in the catheter lumen is withdrawn and discarded. The peritoneal fluid sample (7 mL) is then withdrawn from the catheter using a second syringe. The sample is injected into a tube containing EDTA. If insufficient fluid is obtained in this manner, one can infuse 1 L of dialysis solution and drain the abdomen, obtaining a sample from the effluent. Although the absolute PD effluent cell count will be lower in this diluted specimen, the differential count will be similar to that in a sample obtained directly via the catheter.
3. **Storage time.** Morphologic identification of the various cell types can be difficult in effluent samples stored for more than 3 to 5 hours prior to injection into the EDTA-containing sample tube.

d. **Effluent nucleated cell counts.** The normal absolute nucleated cell count in the PD effluent is usually less than 50 and often less than 10 cells/mcL. In patients undergoing APD with a "dry day," the nucleated cell count may be much higher even without peritonitis, especially in specimens taken directly via the catheter when the effluent volume is small. Normally, the peritoneal leukocytes are mainly mononuclear cells (monocytes, macrophages, and occasional lymphocytes), and the percentage of neutrophils does not exceed 15%. A value greater than 50% suggests peritonitis. The percentage of neutrophils is also usually raised in fungal and mycobacterial peritonitis. The percentage of neutrophils in the PD effluent is occasionally elevated in the absence of peritonitis, for example, in patients with infectious diarrhea, active colitis, appendicitis, acute diverticulitis, pelvic inflammatory disease, and in women who are menstruating, ovulating, or following a pelvic examination.
    1. **PD effluent monocytosis.** If there is persistent peritoneal fluid monocytosis or lymphocytosis, mycobacterial peritonitis should be considered. PD effluent monocytosis may also occur in conjunction with peritoneal fluid eosinophilia.
    2. **PD effluent eosinophilia.** PD effluent eosinophilia occurs most often soon after PD catheter insertion. The irritant effect of air (eg, introduced at the time of laparotomy) and plasticizers leached into the peritoneum from PD solution containers and tubing are the suspected causes. In such cases, eosinophilia often resolves spontaneously within 2 to 6 weeks. Less commonly, PD effluent eosinophilia can also occur during the treatment phase of bacterial peritonitis, in association with fungal or parasitic infections of the peritoneum, and in sterile peritonitis in patients newly started with icodextrin PD solution.
e. **Gram stain.** Gram stain of the PD effluent sediment is useful but positive in less than half of cases of culture-proven peritonitis. A Gram stain is also useful

for making the diagnosis of fungal peritonitis.

f. **Culture of PD effluent.** The yield of obtaining positive PD effluent cultures in patients suspected to have peritonitis depends on the culture technique. Culture-negative peritonitis should not be over 15% of episodes.
   1. **Storage.** PD effluent should be cultured promptly even though infected effluent kept at room temperature or refrigerated often grows the causative organisms on subsequent culture. If immediate delivery to the laboratory is not possible, the inoculated culture bottles should ideally be incubated at 37 °C.
   2. **Sample volume.** Bedside inoculation of 5 to 10 mL effluent into two (aerobic and anaerobic) blood culture bottles has a reasonable sensitivity. A higher volume of PD effluent (eg, 50 mL) further increases the likelihood of a positive culture: the effluent sample should be centrifuged (eg, at 3,000*g* for 15 minutes) to concentrate the organisms. The supernatant is decanted off, and the pellet is resuspended in 3 to 5 mL of sterile saline and inoculated into standard blood culture media.
   3. **Time to positive cultures.** Seventy percent to 90% of PD effluent samples from patients with peritonitis yield positive cultures for the causative organisms within 24 to 48 hours. More time may be needed for fastidious organisms.
   4. **False-positive culture results.** With very sensitive culture techniques, about 7% of cultures may be positive in patients without clinical peritonitis. It is therefore important to consider the clinical presentation and PD effluent leukocyte count when making a treatment decision.

3. **Other considerations**
   a. **Blood culture.** Routine blood cultures are not necessary unless a patient appears septic or an acute surgical abdominal condition is suspected.
   b. **Consideration of secondary peritonitis.** In a small but significant proportion of patients with peritonitis, there is a serious underlying intra-abdominal disease (eg, perforated peptic ulcer, pancreatitis, appendicitis, or diverticulitis). The presence of PD solution in the abdomen may mask local tenderness. If there is any suspicion of a perforated abdominal viscus, a chest radiograph should be obtained. The presence of free intraperitoneal (IP) air on an upright chest radiograph is unusual in patients undergoing CAPD unless there has been a recent laparotomy or transfer set change. Otherwise, free IP air may suggest a perforated viscus. However, free IP air may be present in patients undergoing cycler APD.
   c. **Consideration of acute pancreatitis.** If acute pancreatitis is suspected, serum total amylase level should be checked, and a level more than 3 times the upper limit of normal supports the diagnosis. PD effluent amylase level is not a sensitive indicator of pancreatitis, but an effluent amylase level greater than 100 units/dL remains suggestive of pancreatitis or other intra-abdominal catastrophe. In patients undergoing PD using icodextrin-based PD solutions, the measurement of lipase is superior to amylase for the diagnosis of acute pancreatitis.

E. Treatment

1. **Initial management**
   a. **Hospital admission.** Most of the patients with peritonitis can be managed as outpatients. The decision to hospitalize a patient depends on a variety of factors, including patient reliability, severity of peritonitis, and the treatment schedule chosen.
   b. **Empirical antimicrobial therapy.** Empirical antibiotics should be started once a clinical diagnosis of peritonitis has been made and appropriate specimens have been collected for microbiologic studies. The empirical antibiotic regimen used should cover both gram-positive and gram-negative organisms. Vancomycin or a first-generation cephalosporin such as cefazolin or cephalothin can be used in combination with a third-generation cephalosporin such as ceftazidime or an aminoglycoside. Recent evidence suggests cefepime monotherapy, a fourth-generation cephalosporin, may be an acceptable alternative for empirical antibiotic regimens (Li, 2022). Each PD center should decide on a center-specific empiric antibiotic regimen, depending on the local spectrum of bacteriologic causes and antibiotic sensitivities. For gram-positive coverage, the dosage of IP cefazolin should be increased by 25% in patients with substantial residual renal function (Manley, 1999). For patients who are allergic to penicillin, and for gram-positive bacteria resistant to methicillin, vancomycin should be the agent of choice; alternatives include linezolid, daptomycin, and clindamycin. Ciprofloxacin alone is not recommended for gram-positive infections. For gram-negative coverage, aminoglycosides should be avoided in patients with substantial residual renal function because of the risk of nephrotoxicity (Shemin, 1999). Table 25.3 lists sample prescriptions based on the use of cefazolin in combination with ceftazidime for the empirical treatment of peritonitis.

TABLE 25.3 Sample Regimen for Initial Empirical Antibiotic Treatment of Peritonitis

CAPD (continuous dosing method)

1. Drain the abdomen and obtain cell count and culture from the drainage bag. Change the transfer set.
2. Loading dose: Infuse 2-L dialysis solution containing:
   1,000 mg ceftazidime
   1,000 mg cefazolin
   1,000 units heparin
   Allow to dwell 3-4 h. In patients who appear septic, administer loading doses IV rather than IP.
3. Continue regular CAPD schedule, using normal exchange volume if tolerated. Add 125 mg/L ceftazidime, 125 mg/L cefazolin, and 500-1,000 units/L heparin to each dialysis solution bag.

CAPD (intermittent dosing method)

1. Drain the abdomen and obtain cell count and culture from the drainage bag. Change the transfer set.
2. Loading dose: as the continuous dosing method.
3. Continue regular CAPD schedule, using normal exchange volume if tolerated. Administer ceftazidime 1,000 mg and cefazolin 1,000 mg into each nocturnal exchange. If fibrin or blood is in dialysate, add heparin to every exchange.

APD: see text.

APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; IP, intraperitoneal; IV, intravenous

c. Route of administration and schedule for antimicrobial drugs

1. **IP versus intravenous (IV) therapy.** IP administration of antibiotics is preferred to IV for treating peritonitis. IV antibiotics, however, should be used when there is clinical evidence of systemic sepsis.
2. **Loading dose.** Many antibiotics require a loading dose when given IP (Table 25.4). If the patient is septic, an IV loading dose should be used. If a patient is in substantial pain and cannot tolerate the usual exchange volume, the IP loading dose can be administered in a smaller volume of dialysis solution (eg, 1 L). For patients undergoing APD, the loading dose can be given IV, but it can also be instilled via a peritoneal dwell that is then left in place for at least 4 hours.

TABLE 25.4 Intraperitoneal Dosing Recommendation for Treatment of Peritonitis[a]

	Intermittent One Exchange Daily, Dwell at Least 6 H	Continuous
Aminoglycosides		
Amikacin	2 mg/kg	Not advised
Gentamicin, netilmicin, or tobramycin	0.6 mg/kg	Not advised
Cephalosporins		
Cefazolin	15 mg/kg (long dwell) 20 mg/kg (short dwell)	LD 500 mg/L, MD 125 mg/L
Cefepime	1,000 mg	LD 500 mg/L, MD 125 mg/L
Ceftazidime	1,000-1,500 mg (long dwell) 20 mg/kg (short dwell)	LD 500 mg/L, MD 125 mg/L
Others		
Ciprofloxacin	No data	MD 50 mg/L
Daptomycin	300 mg	LD 100 mg/L, MD 20 mg/L
Linezolid	Oral 200 to 300 mg q.d.	
Meropenem	500 mg daily (long dwell) 1,000 mg (short dwell)	MD 125 mg/L
Piperacillin/tazobactam	No data	LD 4 g/0.5 g, MD 1 g/0.125 g
Vancomycin	15-30 mg/kg every 5-7 d for CAPD 15 mg/kg every 4 d for APD	LD 20-25 mg/kg, MD 25 mg/L
Antifungals		
Fluconazole	150-200 mg every 24-48 h (Oral route is preferred.)	No data
Voriconazole	2.5 mg/kg (Oral route is preferred.)	No data

LD, loading dose; MD, maintenance dose.

[a]Dosing of drugs with renal clearance in patients with residual renal function (defined as >100 mL/day urine output): dose should be empirically increased by 25%.

Adapted from: Li PK, et al. ISPD peritonitis guideline recommendations: 2022 update on prevention and treatment. *Perit Dial Int*. 2022;42:110-153.

3. **Maintenance dose.** After the loading dose if needed, the CAPD or APD

schedule is continued with maintenance doses of IP antimicrobials (Table 25.4). Maintenance antibiotics in patients undergoing CAPD can be administered on a continuous (ie, every bag of PD solution) or intermittent (ie, once daily) dosing schedule. For patients on APD, antibiotics can be administered once daily in the daytime dwell. For patients on a day dry APD schedule, temporary conversion to a CAPD regimen may be considered, but this may be a problem for patients, especially if they are being treated at home. Alternatively, a low-volume daytime dwell (eg, 1 L) could be temporarily added. Because of increased cycler clearance of antibiotics, doses need to be higher in patients who remain on APD during the treatment of peritonitis (Manley and Bailie, 2002).

4. **Antimicrobial dosing guidelines.** Suggested loading and maintenance IP doses for commonly used antimicrobial drugs are listed in Table 25.4. For many antibiotics, continuous and intermittent IP dosing are both feasible. For continuous dosing, the same dose of antibiotic is added to each dialysis solution bag. Alternatively, a larger dose is added to one bag only, every 12 or 24 hours (or, in the case of vancomycin, every 4-5 days). For aminoglycosides, single daily dosing should be used because of better efficacy and potentially less toxicity. For cephalosporins, trough concentrations of antibiotic may be low if it is given once daily, especially in patients with residual renal function (Fielding, 2002; Low, 1996). In general, continuous dosing is preferred for cephalosporins, but intermittent dosing is also widely used.
5. **Stability of antibiotics in dialysis solutions.** Vancomycin, aminoglycosides, and cephalosporins can be mixed in the same dialysis solution bag. However, aminoglycosides are incompatible with penicillin. Vancomycin (25 mg/L) is stable in dialysis solution stored at room temperature for 28 days, although high ambient temperatures will reduce the duration of stability. Gentamicin (8 mg/L) is stable for 14 days, but the duration of stability is reduced when it is mixed with heparin. Cefazolin (500 mg/L) is stable for at least 8 days at room temperature or for 14 days if refrigerated, and the addition of heparin does not affect the stability. Ceftazidime is less stable; concentrations of 125 mg/L are stable for 4 days at room temperature or 7 days if refrigerated, and concentrations of 200 mg/L are stable for 10 days if refrigerated (So, 2022).

d. Other adjunctive treatment

1. **Heparin.** Peritonitis is often associated with fibrinous clots in the PD effluent, and the risk of catheter obstruction is high. Most centers add heparin (500-1,000 units/L) to the dialysis solution until PD effluent clears up and fibrinous clots are no longer visible.
2. **Antifungal prophylaxis.** Since the majority of fungal peritonitis episodes are preceded by courses of antibiotics, prophylaxis of fungal peritonitis with oral nystatin or fluconazole during antibiotic therapy may prevent fungal (especially *Candida* species) peritonitis (Campbell, 2017; Li, 2022).

e. Other common problems

1. **Acute changes in peritoneal permeability.** During peritonitis, the

permeability of the peritoneum to water, glucose, and proteins is increased. Rapid glucose absorption from the dialysis solution reduces the amount of ultrafiltration and can result in fluid overload. Higher dialysis solution glucose levels and shorter dwell times may be needed to maintain adequate ultrafiltration. Because glucose absorption is more rapid during peritonitis, hyperglycemia may develop in patients with diabetes unless glucose values are monitored and insulin doses are titrated. Short-term use of an icodextrin-based regimen may facilitate ultrafiltration and prevent fluid overload during peritonitis. Protein losses during peritonitis are temporarily increased.

2. **Constipation.** Constipation is a common complaint during peritonitis episodes, and constipation may itself be a risk factor for developing peritonitis, in addition to its impact on poor drainage of dialysate. If constipation is present, calcium-containing phosphate binders, which can cause or worsen constipation, should be temporarily discontinued.
3. **Contamination without peritonitis.** After wet contamination of the PD system, the incubation period for most organisms is about 12 to 48 hours. If a break in sterile technique has occurred, it is advisable to institute antimicrobial therapy promptly in order to prevent peritonitis. The transfer set should be changed, and the peritoneal cavity flushed with dialysis solution containing an antistaphylococcal antibiotic. A short (1- to 2-day) course of oral antimicrobial therapy (eg, ciprofloxacin) may also be given.

2. **Modification of antibiotic regimen.** With effective treatment, the patient should begin to improve within 48 hours; the total nucleated cell count and percentage of neutrophils in the PD effluent should begin to decrease. Visual inspection of the effluent is often sufficient, but it is advisable to repeat PD effluent cell count (and probably culture) 2 to 3 days after antibiotic treatment. Isolation of causative bacteria and determination of their antimicrobial sensitivity can generally be obtained within 2 to 3 days. Longer growth periods may be needed for fastidious organisms. Once the Gram stain, microbiologic culture, or antibiotic sensitivity results become available, the empirical antibiotic should be modified accordingly.
   a. **Gram-positive organism identified.** If a gram-positive organism is identified, the antibiotic for gram-positive coverage should be continued, and that for gram-negative coverage should be stopped. First-generation cephalosporins (eg, cefazolin) are preferred to vancomycin if the bacteria isolated are methicillin sensitive so as to avoid the emergence of vancomycin-resistant organisms. Many *S. epidermidis*–like organisms reported to be resistant to first-generation cephalosporins are sensitive to the levels achieved in the peritoneal cavity, and there is often no need to change the antibiotic regimen if the patient is clinically responding to treatment. If an *Enterococcus* sp. is identified, vancomycin should be used unless there is vancomycin resistance.
      1. **Duration of therapy.** For coagulase-negative *Staphylococcus* and *Streptococcus* peritonitis, antimicrobial therapy should be continued for a total of 14 days if patient improvement is prompt. Peritonitis episodes caused by *S. aureus* or *Enterococcus spp.* require antimicrobials for 3 weeks. A 5-day course of rifampin could be considered an adjunct for the prevention of relapse or repeat *S. aureus* peritonitis, but rifampin induces cytochrome P450

(CYP3A4) and potential drug interaction should be considered. *S. aureus* peritonitis with concurrent exit-site or tunnel infection is less likely to respond to antibiotic therapy without catheter removal.

2. **Nasal carriage of *S. aureus*.** Patients who develop *S. aureus* peritonitis are usually nasal carriers of this organism, and they need to be tested for this. Eradication of nasal carriage may help prevent further peritoneal infections. This can be accomplished with intranasal mupirocin (bid for 5 days every 4 weeks) or oral rifampin (300 mg bid for 5 days every 3 months). Eradication of the nasal carrier state should be documented by repeating a culture test.

b. **Gram-negative organism identified.** If a single non-*Pseudomonas* gram-negative organism is identified, the antibiotic for gram-negative coverage should be continued, and that for the coverage of gram-positive bacteria should be stopped. A single appropriate antibiotic is usually sufficient for treatment, but some centers prefer to use two agents. If a *Pseudomonas* sp. is recovered, treatment with two antibiotics is necessary, which usually comprises an aminoglycoside and a third-generation cephalosporin or semisynthetic penicillin with anti-*Pseudomonas* activity (eg, piperacillin). It should be noted that semisynthetic penicillin can inactivate aminoglycosides in vitro, and IP co-administration should be avoided. Other possible alternatives are fluoroquinolone, aztreonam, carbapenem, and trimethoprim-sulfamethoxazole. Fluoroquinolones have the advantage that effective dialysate levels can be achieved with PO dosing, but their concurrent administration with phosphate-binding antacids (including calcium salts, sevelamer, and lanthanum carbonate) should be avoided to ensure adequate absorption. It is important to note that gram-negative organisms (especially *Pseudomonas* sp.) are difficult to eradicate; the risk of relapsing peritonitis is high, and catheter removal is often needed. Gram-negative peritonitis may sometimes be a sign of unsuspected intra-abdominal pathology.

1. **Duration of therapy.** If the initial response to antibiotic therapy is prompt, gram-negative peritonitis should be treated with appropriate antibiotics for 3 weeks. If the PD catheter is removed, appropriate antibiotics should be continued for 2 weeks after catheter removal.
2. **Aminoglycoside toxicity.** Intermittent IP gentamicin given once daily (rather than continuous dosage in every PD exchange) should be used, and a loading dose is generally not required. The duration of aminoglycoside treatment should not be over 3 weeks because of the risk of ototoxicity (Lui, 2005a). Predose serum aminoglycoside levels may be monitored to avoid inadvertent toxicity, but the optimal schedule of monitoring is not well defined.
3. **Second-line agents.** Resistance to third-generation cephalosporins and gentamicin is increasingly common. Carbapenems, semisynthetic penicillin, newer cephalosporins, newly developed fluoroquinolones, and aztreonam are potential second-line agents, depending on the spectrum of antibiotic resistance as well as local availability.

c. **Polymicrobial peritonitis.** Most peritonitis episodes caused by multiple gram-positive organisms respond to antibiotic therapy. About 60% of these

episodes resolve without catheter removal (Szeto, 2002b). In contrast, if multiple enteric organisms are grown, particularly in association with anaerobic bacteria, the presence of an intra-abdominal surgical problem must be considered. Perforated diverticulum, tubo-ovarian abscess, cholecystitis, appendicitis, perforated ulcer, and pancreatitis should all be included in the differential diagnosis. The risk of mortality is increased (Kern, 2002). For adequate antibiotic coverage, triple agents that target gram-positive, gram-negative, and anaerobic organisms (eg, IP aminoglycoside, IP vancomycin, and PO or IV metronidazole) are usually needed. A surgical evaluation should be obtained, and management must be individualized.

d. **Culture-negative peritonitis.** If the culture results are negative at 24 hours, then the most likely explanation is that a bacterial infection was present but that the responsible organisms failed to grow in the culture sample. The clinical response to antibiotic therapy should be assessed. If the response is satisfactory, discontinuation of the gram-negative coverage (ie, ceftazidime or aminoglycoside) or continuation of the two empirical antibiotics for 14 days are both valid options. The decision probably depends on the local prevalence of gram-negative peritonitis. If the response to antibiotics is not satisfactory, the PD effluent should be cultured again with special techniques to look for unusual organisms, including mycobacteria and fungi. If a dialysis program has a rate of culture-negative peritonitis greater than 15%, the method of sample handling and culture should be reviewed.

e. **Mycobacterial peritonitis.** Infection with *Mycobacterium* $_{tuberculosis}$ or with nontuberculous mycobacteria (Fung, 2022) sometimes presents as culture-negative peritonitis because the time to a positive culture is exceptionally long. When mycobacterial peritonitis is suspected, the diagnostic yield can be improved by culturing the sediment after centrifugation of a large volume of effluent (50-100 mL) using a solid medium (such as Lowenstein-Jensen agar) and a fluid medium (Septi-Chek, BACTEC, etc). Treatment of tuberculous peritonitis consists of a multiple-drug regimen (usually isoniazid, rifampin, levofloxacin, and pyrazinamide). Removal of the PD catheter is usually not required. Streptomycin and ethambutol are generally not recommended in patients undergoing dialysis (Ling, 2023).

f. **Fungal peritonitis.** Fungal peritonitis is a serious complication and should be strongly suspected in patients with recent antibiotic treatment for bacterial peritonitis. Other predisposing factors include diabetes, immunosuppression (eg, immunosuppressive therapy, HIV infection), malnutrition, and low serum albumin levels. *Candida sp.* is the most prevalent species identified, but many types of fungi can be responsible. The ISPD recommendation is prompt removal of the catheter as soon as fungi are identified by Gram stain or culture (Li, 2022), together with treatment for at least 14 days with antifungal agents after catheter removal. In some patients, a new catheter can be inserted later, provided that at least 2 weeks have elapsed since all clinical evidence of peritonitis has subsided. Although fluconazole and amphotericin B are recommended as antifungal agents, echinocandins (eg, caspofungin, anidulafungin, and micafungin) are effective and less toxic alternatives for *Candida* peritonitis,

while voriconazole and posaconazole are valuable alternatives when filamentous fungi are identified. The recommended dosages of these agents are listed in Table 25.5. Flucytosine used to be an important adjunct to fluconazole and amphotericin B, but it is expensive and its availability is limited in many countries.

TABLE 25.5 Systemic Antibiotic Dosing Recommendation for Treatment of Peritonitis and Catheter-Related Infections

Drug	Dosing
Antibacterial	
Amoxicillin	PO 250-500 mg BID
Amoxicillin/clavulanate	PO 875 mg/125 mg BID
Cephalexin	PO 500 mg BID to TID
Ciprofloxacin	PO 500-750 mg daily (750 mg BID for CCPD)
Clarithromycin	PO 500 mg loading, then 250 mg BID
Clindamycin	PO 300-450 mg TID
Cloxacillin/flucloxacillin	PO 500 mg QID
Ertapenem	IV 500 mg daily
Levofloxacin	PO 250 mg daily or 500 mg every 48 h
Linezolid	PO or IV 600 mg BID
Metronidazole	400 mg TID
Moxifloxacin	400 mg daily
Rifampicin	450 mg daily for weight <50 kg; 600 mg daily for weight≥50 kg
Trimethoprim-sulfamethoxazole	PO 160 mg/800 mg BID
Antifungal	
Amphotericin B desoxycholate	IV 0.75-1.0 mg/kg/d over 4-6 h
Amphotericin B liposomal	IV 3-5 mg/kg/d
Anidulafungin	IV 200 mg loading, then 100 mg daily
Caspofungin	IV 70 mg loading
Fluconazole	PO 200 mg loading, then 100 mg daily
Micafungin	IV 100 mg daily
Posaconazole	PO 300 mg every 12 h for two doses as loading, then 300 mg daily
Voriconazole	PO 200 mg every 12 h

BID, two times a day; CCPD, continuous cycling peritoneal dialysis; IV, intravenous; PO, orally; QID, four times a day; TID, three times a day.

3. **Refractory, relapsing, recurrent, and repeat peritonitis.** The definitions of refractory, relapsing, recurrent, and repeat peritonitis episodes are summarized in Table 25.6. It is important to note that relapsing episodes should not be counted as another peritonitis when calculating peritonitis rates, while recurrent and repeat episodes should be counted. Previous studies suggest that relapsing and recurrent peritonitis episodes are caused by a different spectrum of bacteria and probably represent two distinct clinical entities (Szeto, 2009). Notably, recurrent peritonitis

episodes have a worse prognosis than relapsing ones. Although repeat peritonitis episodes generally have a satisfactory response to antibiotics, they have a substantial risk of recurring with further relapsing or repeat peritonitis (Szeto, 2011).

TABLE 25.6 Terminology for Peritonitis

Refractory: Peritonitis episode with persistently cloudy bags or persistent dialysis effluent leukocyte count >100 × 10^9/L after 5 d of appropriate antibiotic therapy
Relapsing: Peritonitis episode that occurs within 4 wk of completion of therapy of a prior episode with the same organism or one sterile (culture-negative) episode (ie, specific organism followed by the same organism, culture negative followed by a specific organism, or specific organism followed by culture-negative)
Recurrent: Peritonitis episode that occurs within 4 wk of completion of therapy of a prior episode but with a different organism
Repeat: Peritonitis episode that occurs more than 4 wk after completion of therapy of a prior episode with the same organism

Adapted from: Li PK, et al. ISPD peritonitis guideline recommendations: 2022 update on prevention and treatment. *Perit Dial Int*. 2022;42:110-153.

4. **Removal of the PD catheter.** In general, catheter removal is carried out in order to reduce patient morbidity and preserve the peritoneal membrane. In particular, PD catheters should be removed in cases of refractory peritonitis, relapsing peritonitis, refractory exit-site or tunnel infection (see below), or fungal peritonitis. Catheter removal may also be considered for repeat peritonitis, nontuberculous mycobacterial peritonitis, and peritonitis episodes caused by multiple enteric organisms. If an intra-abdominal surgical problem is suspected, additional imaging (eg, ultrasound or computed tomography) is indicated and, if confirmed, these patients require surgical consultation for exploration or drainage and not just simple catheter removal. After catheter removal, antibiotics should be continued for at least 2 weeks. If reinsertion of a new catheter is attempted, it should be performed at least 2 weeks after removal of the original catheter and complete resolution of peritoneal symptoms. Resumption of PD is possible in approximately one-half of patients but may necessitate a change in dialysis prescription to achieve adequate dialysis and ultrafiltration (Szeto, 2002a).
5. **Fibrinolytic agents.** Streptokinase and urokinase have been used by some investigators in the treatment of refractory or relapsing peritonitis. These agents are used in an attempt to release bacteria entrapped in fibrin within the peritoneum or along the catheter, thus making it possible to eradicate the infection. Controlled studies have not proved this approach to be effective compared with catheter removal and replacement (Williams, 1989).
6. **Prophylactic antibiotics.** Prophylactic antibiotic use does not prevent peritonitis; this is probably true even for patients with exit-site infections. However, short-term prophylactic systemic antibiotics may be beneficial in the following settings: (a) before catheter placement (vancomycin or cefazolin); (b) to prevent bacteremia during invasive procedures, such as dental procedures (amoxicillin 2 g) or colonoscopy, colonoscopic polypectomy, hysteroscopy, or cholecystectomy (ampicillin plus an aminoglycoside); and (c) after an accidental contamination.
7. **Primary prevention of peritonitis.** There are a few simple and effective

strategies to prevent peritonitis episodes in patients undergoing PD. Systemic prophylactic antibiotics should be administered immediately prior to the insertion of a PD catheter. Antibiotic prophylaxis should also be used prior to colonoscopy, invasive gynecologic procedures, and probably upper gastrointestinal endoscopy that require complicated interventions. Disconnect systems with a "flush before fill" design should always be given for CAPD. In stable patients undergoing PD, good exit-site care is the most important practice to prevent peritonitis (see the following section). Hypokalemia is associated with an increased risk of enteric peritonitis, and therefore, if present, should be corrected. There is no specific catheter design, number of cuffs, or choice of dialysis solution that effectively reduces the risk of peritonitis. Training methods have a substantial influence on the risk of PD infections, and training should follow standard guidelines (Chow, 2023b; Figueiredo, 2016); each PD program should consult the standard ISPD guidelines to prepare the trainer and develop a specific curriculum.

8. **Secondary prevention.** In addition to antifungal prophylaxis during antibiotic therapy, specific efforts should be made for secondary prevention. For each peritonitis episode, a root cause analysis should be done to determine the etiology, and, whenever possible, an intervention directed against any reversible risk factor should be made to prevent another episode. Identification of etiology may involve a review of the patient's technique. Retraining should be considered following peritonitis caused by technical problems, as well as following changes in dexterity, vision, or mental acuity.

II. CATHETER-RELATED INFECTIONS.

Exit-site infection is defined as the presence of purulent discharge, with or without erythema of the skin at the catheter-epidermal interface. Tunnel infection is defined as the presence of clinical inflammation (erythema, tenderness, swelling, or inflammation) with or without ultrasonographic evidence of fluid collection along the catheter tunnel. Erythema alone without purulent discharge may or may not represent infection (Chow, 2023b).

A. Incidence.

The incidence of exit-site infections is approximately 0.5 to 1.0 episode per patient-year on PD. Approximately one-fifth of peritonitis episodes are temporally associated with exit-site or tunnel infections (Piraino, 2005).

B. Etiology and pathogenesis.

Catheter-related infections are predominantly caused by *S. aureus* or *P. aeruginosa. S. epidermidis* is the causative organism in less than 20% of patients. Approximately 45% of patients with *S. aureus* catheter-related infections are nasal carriers, which is also associated with subsequent peritonitis (Luzar, 1990a, b). Eradication of the carrier state is helpful in preventing recurrence of catheter-related infections and the development of peritonitis.

C. Therapy.

When the diagnosis of catheter-related infection is made on clinical grounds, empirical antibiotic treatment can be started once the purulent discharge has been sent for Gram stain and bacterial culture. The exit site should be cleansed at least daily during catheter-related infection. An oral antistaphylococcal penicillin (eg, cloxacillin) or first-generation cephalosporin are appropriate choices unless the patient has a history of *Pseudomonas* infection. Therapy can subsequently be modified according to the results of Gram stain and culture. If the patient has a history of *Pseudomonas* infection or if gram-negative organisms are identified on Gram stain or culture, an oral

fluoroquinolone is an appropriate choice. For borderline cases (eg, exit-site erythema alone), topical treatment with hypertonic saline, hydrogen peroxide, or mupirocin 2% ointment is usually sufficient. Mupirocin ointment should not be used with polyurethane catheters (eg, many catheters made by Vas-Cath or the Cruz catheter from Corpak) because the polyethylene glycol in mupirocin ointment will degrade the polyurethane and destroy the catheter. Ciprofloxacin otologic solution can be used with polyurethane catheters, but its efficacy in treating exit-site infection is unknown (Montenegro, 2000).

Table 25.5 lists appropriate oral antimicrobial doses for the treatment of catheter-related infections. If there is no improvement after 1 week of antibiotic treatment, the use of a second-line antibiotic (eg, IP vancomycin, ceftazidime, or aminoglycoside) should be considered. Occult tunnel infection is common in patients who present with simple exit-site infection. Ultrasound examination of the catheter tunnel is helpful in detecting asymptomatic inflammation or fluid collection along the tunnel, in monitoring the response to antibiotic treatment and in predicting the risk of recurrence (Vychytil, 1999). Exit-site infection should be treated with at least 2 weeks of effective antibiotics. However, exit-site infection caused by *Pseudomonas* species or tunnel infection should be treated for at least 3 weeks (Szeto, 2017). Refractory catheter-related infection is defined as failure to respond after 3 weeks of effective antibiotic therapy. Catheter removal should be considered, and simultaneous reinsertion of a new catheter with a new exit site under antibiotic coverage is often possible (Lui, 2005b). Other catheter-preserving surgical approaches (eg, de-roofing, outer-cuff shaving, or catheter diversion procedures) are possible alternatives, but they depend on the availability of local expertise. Catheter removal should be performed if exit-site infection progresses despite antimicrobial treatment or occurs simultaneously with peritonitis, and reinsertion of a PD catheter should be performed at least 2 weeks after catheter removal and complete resolution of peritoneal symptoms. Catheter removal is also needed in most cases of fungal or nontuberculous mycobacterial catheter-related infections (Fung, 2022).

D. Prevention. The primary objective of preventing catheter-related infections is to prevent the subsequent development of peritonitis. Before the insertion of PD catheters, screening for nasal *S. aureus* carriage is valuable. If nasal carriage of *S. aureus* is found, eradication by topical nasal application of mupirocin (2% ointment twice daily for 5 days) is often effective. Other approaches to *S. aureus* eradication (eg, oral rifampin or trimethoprim-sulfamethoxazole) are possible, but adverse effects are more common. Prophylactic antibiotics should be administered immediately before catheter insertion. No specific catheter design or technique of catheter placement has been demonstrated to be superior to others for the prevention of catheter-related infections. PD training should be conducted by nursing staff with the appropriate qualifications and experience, and the latest ISPD recommendations should be followed (Chow, 2023b).

For stable patients undergoing PD, the most important and effective means of preventing catheter-related infection is the daily topical application of antibiotic cream or ointment to the catheter exit site. Mupirocin ointment is most commonly used and has the best evidence. Resistance with long-term use is usually not a major concern (Szeto, 2017). Gentamicin cream is an effective alternative (Bernardini, 2005) and has the advantage of preventing *S. aureus* infections as well as *P. aeruginosa* and other gram-negative catheter infections. The exit site should be cleansed at least twice weekly and every time after a shower. It should be covered during swimming (Bennett, 2022). No

cleansing agent has been shown to be superior with respect to preventing catheter-related infections.

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26 Hernias, Leaks, and Encapsulating Peritoneal Sclerosis

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The instillation of dialysis fluid into the peritoneal cavity is accompanied by an increase in intra-abdominal pressure (IAP). The two principal determinants of its magnitude are dialysate volume and the position of the patient during the dwell. The supine position is associated with the lowest IAP for a given dialysate volume; sitting is associated with the highest. Furthermore, actions such as coughing, bending, or straining at stool transiently increase IAP. The increased IAP can lead to a variety of mechanical complications.

I. HERNIA FORMATION

A. Incidence and etiologic factors.

The incidence and prevalence of hernias are difficult to assess. Hernias can be asymptomatic and may be missed on cursory examination. It has been suggested that as many as 10% to 20% of patients may develop a hernia at some time on peritoneal dialysis (PD).

Potential risk factors are listed in Table 26.1 and include large dialysate volumes and activities that involve isometric straining or the Valsalva maneuver. Deconditioning of the musculature of the abdominal wall increases wall tension and predisposes to hernia formation.

TABLE 26.1 Potential Risk Factors for Hernia Formation

Large dialysate volumes
Sitting position
Isometric exercise
Valsalva maneuver (eg, coughing, straining at stool)
Recent abdominal surgery
Pericatheter leak or hematoma
Obesity
Deconditioning
Multiparity
Congenital anatomic defects

B. Types of hernia.

Many different types of hernia have been described in patients undergoing PD. These are listed in Table 26.2.

TABLE 26.2 Types of Hernias Reported in Patients Undergoing Peritoneal Dialysis

Ventral

Epigastric
Pericatheter
Umbilical
Inguinal (direct and indirect)
Femoral
Foramen of Morgagni
Cystocele
Spigelian
Richter
Enterocele

Indirect inguinal hernias are the result of bowel and/or dialysate tracking through the processus vaginalis, which in some individuals has remained patent rather than undergoing normal obliteration during fetal development. It is much more common in males. In boys, it is very likely that if one processus vaginalis is patent (causing inguinal hernia), then the other side is also patent, and repair should be done bilaterally.

C. Diagnosis. As mentioned previously, hernias can be clinically occult. To better detect them, it is often useful to have the patient stand and "bear down," as this increases IAP and makes a hernia more obvious. Pericatheter hernias need to be differentiated from masses caused by a hematoma, seroma, or abscess. Ultrasonography can distinguish the solid-appearing hernia from the fluid collections characterizing these other conditions. The scrotal fullness of an indirect inguinal hernia has in its differential diagnosis hydrocele (fluid/dialysate entering the scrotum through a patent processus vaginalis) and intrinsic scrotal or testicular pathology.

Delineation of a hernia can be aided by dye-assisted computed tomography (CT). First, 100 mL of iohexol 300 is added to a 2-L bag of dialysate, which is then instilled into the peritoneal cavity. **It is important that the patient then be as active and ambulatory as possible for the next 2 hours to facilitate the pressure-driven entry of dye into any hernia sacs.** CT scanning is then performed. In the case of inguinal hernias, it is important that the genitalia be scanned. The CT scan can indicate whether scrotal edema is the result of fluid tracking along a patent processus vaginalis or along the anterior abdominal wall (see below). This procedure can also help delineate an abdominal wall hernia from isolated leaks. In other types of hernia, such as umbilical hernia, CT scanning may not be necessary because the diagnosis is usually obvious.

Magnetic resonance imaging (MRI) may be useful in the diagnosis of abdominal wall and genital leaks, and it may be helpful in patients with allergy to conventional radiocontrast dye. The dialysate itself looks bright white on the MRI images, and gadolinium is not required.

D. Treatment. Small hernias, especially umbilical hernias, pose the greatest risk of incarceration or strangulation of bowel. These should be repaired surgically. The patient should be warned that if a hernia stops being reducible, and especially if it becomes tender, medical consultation should be sought immediately. **Any patient presenting with peritonitis should be examined for the presence of small strangulated hernias, as these can lead to transmural leakage of bacteria and peritonitis.** Large hernias can also be repaired surgically, as can cystocele and enterocele. Uterine prolapse (not really a hernia) can sometimes be managed with a pessary, but ultimately hysterectomy may be necessary.

After surgical repair of a hernia, IAP must be kept as low as possible to facilitate

healing. If the patient has significant residual kidney function (eg, glomerular filtration rate [GFR] 5 mL/min or more), it may be possible to stop dialysis altogether for several days and then recommence with small volumes (eg, 1 L). The patient should be monitored for the development of uremic symptoms or hyperkalemia while off dialysis. If automated peritoneal dialysis (APD) is available, the patient can dialyze supine and hence with lower IAP. If there is little or no renal function, low-volume PD should be started postoperatively. An alternative is to hemodialyze the patient until some degree of wound healing has occurred (2-3 weeks).

Options for the patient with recurrent hernias include a reduction in physical activity that increases IAP, more frequent dialysis exchanges with lower volumes, or transfer to hemodialysis.

If the patient refuses surgery or is too frail to have it, mechanical support of the hernia can be effected with a corset or truss. The patient should be warned about the symptoms of incarceration and strangulation.

II. ABDOMINAL WALL AND PERICATHETER LEAK. The precise incidence of these complications is also unknown, but they are less common than hernias. Risk factors are similar to those outlined in Table 26.1. Poor surgical technique may play a role in the development of pericatheter leak.

A. Diagnosis. Abdominal wall leak may be difficult to diagnose clinically. It may be mistaken for ultrafiltration failure if dialysate returns are less than the instilled volume (see Chapter 24). Weight gain is common as the dialysate accumulates in the tissues of the abdominal wall. The diagnosis should be considered when there are decreased effluent volumes, weight gain, protuberant abdomen, and absence of generalized edema. The patient should stand during the examination, as this may reveal asymmetry of the abdomen. The abdominal wall itself may have a “boggy” look, with deep impressions made by waist bands, dialysate tubing, and so on, because of the subcutaneous edema.

Pericatheter leak is usually diagnosed by wetness (dialysate) on the exit-site dressing. A urine dipstick placed on the wet part should test strongly positive for glucose. Diagnosis can be proven using contrast CT scanning.

B. Treatment. Pericatheter leak usually occurs as a postoperative complication of catheter implantation. The patient should be drained, and PD stopped for at least 24 to 48 hours. The longer the patient can be left off PD, the greater the chance that the leak will seal itself. If necessary, the patient should receive hemodialysis, and PD can be recommenced several days later. In most cases, the leak seals spontaneously. If the leak persists for more than 30 days, the catheter should be removed and reinserted at another site, and special care should be taken in catheter implantation. Long-term transplant patients may be at particular risk if their immunotherapy includes corticosteroids or sirolimus, as these drugs may impair wound healing. There is no evidence for or against antibiotic prophylaxis for pericatheter leaks, but it should be used if infection is suspected.

In contrast to pericatheter leaks, abdominal wall leaks can occur early or late. APD in the supine position usually allows the dialysate accumulation to resolve. If the leak is the result of disruption of abdominal wall integrity, the patient should be converted to a day dry APD regimen or to hemodialysis. Sometimes, the abdominal wall defect heals after a transient course of day dry APD. Sometimes surgical repair is feasible.

Vaginal leaks can also occur. Other leaks can be due to dissection of dialysate through fascial defects and require patients to convert to day dry APD or hemodialysis.

III. GENITAL EDEMA

A. Pathogenesis. Dialysate can reach the genitalia by two routes: One is by traveling down a patent processus vaginalis to the *tunica vaginalis*, resulting in hydrocele. In this first route, the dialysate can also dissect through the walls of the *tunica vaginalis*, causing edema of the scrotal (or, less commonly, labial) wall itself. The second route is through a defect in the abdominal wall, often associated with the catheter tract. In this instance, the dialysate tracks inferiorly along the abdominal wall. This leads to edema of the foreskin, scrotum, or mons pubis.

B. Diagnosis. This complication is often painful and distressing to the patient who will be quick to bring it to medical attention. CT peritoneography should be performed to distinguish which route has led to the genital swelling (ie, anterior abdominal wall or processus vaginalis). Alternatively, 3 to 5 mCi of technetium-labeled albumin colloid can be injected into the dialysate and infused into the patient, and the route of leakage traced by scintigraphy.

C. Treatment. PD should be temporarily stopped. Bed rest and scrotal elevation are helpful. Depending on the need, temporary APD with low volumes and with the patient supine can often be used without causing reaccumulation of genital edema. If necessary, hemodialysis can be used temporarily.

A leak via a patent processus vaginalis can be repaired surgically. If the leak is through the anterior abdominal wall, replacement of the catheter may be required. APD in the supine position with low volume or no day dwell may decrease the chance of a recurrent leak.

IV. RESPIRATORY COMPLICATIONS

A. Hydrothorax. Under the influence of raised IAP, dialysate can travel from the peritoneal to the pleural cavity, leading to a pleural effusion composed of dialysis effluent. This complication is termed hydrothorax.

1. **Incidence and etiologic factors.** The incidence of hydrothorax is unknown because the pleural effusion may be small and asymptomatic. It is less common than hernia.

   There are defects in the hemidiaphragm that allow passage of dialysate. These defects may be congenital, in which case hydrothorax can occur with the first dialysis exchange, or acquired, in which case hydrothorax can be a late complication. Hydrothorax occurs almost exclusively on the right side, probably because the left hemidiaphragm is mostly covered by the heart and pericardium.

2. **Diagnosis.** Symptoms of hydrothorax range from asymptomatic pleural effusion to severe shortness of breath. Acute shortness of breath at the beginning of PD therapy should suggest this diagnosis. Thoracentesis can be done for diagnosis and/or to relieve symptoms. The most diagnostic feature of the pleural fluid is a very high glucose level, although this is often not found. It is otherwise typically transudative, with variable numbers of leukocytes.

   Radionuclide scanning with technetium may be helpful. Technetium-labeled albumin colloid (5 mCi) is added to a dialysate bag, which is then infused into the

patient. Posterior views are taken at 0, 10, 20, and 30 minutes and an anterior view at 30 minutes. It is important that the patient be ambulatory while the instilled tracer is dwelling to increase IAP and flux into the pleural cavity. Late (2-3 hours) views may be necessary if the movement of the tracer into the pleural cavity is not detected by γ-camera in earlier shots. CT scanning with intraperitoneal dye can also be used.

3. **Treatment.** If there are respiratory symptoms, PD should be stopped immediately. Thoracentesis may be necessary; in which case, the diagnosis can be made by measuring glucose in the pleural fluid.

   Definitive treatment entails repair of defects in the hemidiaphragm or obliteration of the pleural space (pleurodesis). Rarely, the dialysate itself acts as an irritant in the pleural cavity and causes pleurodesis, so that PD can be resumed 1 to 2 weeks later. APD with low IAP (small volumes, supine position) can sometimes be carried out without recurrence. The movement of fluid into the pleural space is pressure driven, so leaving the patient in the supine position is helpful. Surgical options for the treatment of hydrothorax are listed in Table 26.3.

TABLE 26.3 Surgical Options for Treatment of Hydrothorax

Pleurodesis
Talc
Oxytetracycline
Autologous blood
Aprotinin-fibrin glue
Repair of hemidiaphragm
Oversewing defects
Reinforcement with patches

B. Altered mechanics of breathing. Pulmonary function is unchanged with PD, except for a mildly decreased functional residual capacity. Arterial oxygenation has been observed to decrease slightly and transiently with the start of PD.

PD does not worsen respiratory symptoms in patients with obstructive pulmonary disease. The tonic stretch placed on the diaphragm by the raised IAP may actually facilitate the mechanics of breathing in these patients.

V. BACK PAIN

A. Pathogenesis. The presence of dialysate in the peritoneal cavity both raises IAP and swings the body's center of gravity forward, producing lordotic stress on the lumbar vertebrae and paraspinal muscles. In predisposed individuals, the altered spinal mechanics can lead to exacerbation of sciatica or posterior facet symptoms. Lax anterior abdominal musculature will exacerbate this effect.

B. Treatment. Bed rest and analgesia (avoiding nonsteroidal anti-inflammatory drugs if the patient has residual kidney function) are important when symptoms are acute. Some patients benefit from the performance of more frequent exchanges with smaller dialysate volumes. If possible, APD with a small or no day dwell is advisable for these patients because dialyzing supine removes the lordotic stress on the lumbar spine. Ideally, the patient should undertake abdomen and back strengthening exercises, but this is not always feasible.

VI. OVERFILL.

Overfill is defined as a clinical event in which symptoms of raised IAP occur acutely in association with a very high dwell volume to fill volume ratio. It is most likely to be significant if the ratio exceeds 2.0, for example, a 4-L end-dwell volume in a patient whose fill volume is 2 L. Symptoms typically include acute abdominal discomfort or shortness of breath. Most episodes result from situations where dialysis solution volume is infused without adequate drainage of the previous dwell volume. This may be accidental, but more often it is associated with poor catheter outflow function. A large volume of ultrafiltrate may also contribute. Significant overfill is more common in children, in patients on APD, especially when tidal prescriptions are being used, and in those in whom minimum drain alarms are turned off. Newer cyclers make it more difficult to initiate cycling without a complete drain of the day dwell and also have precautions in place to drain cumulative ultrafiltrate. Asymptomatic overfill episodes are probably quite common. Rarely, deaths have been associated with severe overfill.

VII. ENCAPSULATING PERITONEAL SCLEROSIS (EPS)

A. Incidence and etiologic factors.

EPS is a rare but devastating complication of long-term PD that has been reported to occur in 1% to 3% of patients. There is an early inflammatory phase associated with vague abdominal discomfort, a change to a rapid transport status, bloody effluent, and signs of inflammation, including anemia and elevated C-reactive protein. The inflammatory phase can progress, either with or without a "second hit" such as peritonitis, to a sclerosing phase where a fibrotic cocoon slowly encapsulates the small bowel. In this second phase, the patient typically shows weight loss and recurrent bowel obstruction, and some deteriorate rapidly. However, a subset of patients with EPS follows a more indolent course and may survive for years.

The strongest risk factor for EPS is the duration of PD therapy. Although the overall incidence is low, it becomes significant after 5 years and even more so after 10 years. Young age at onset of PD is also an independent risk factor. Patients who have transitioned to hemodialysis or renal transplant remain vulnerable.

There is no reliable association of EPS with the type or number of episodes of PD peritonitis or with the type or strength of PD solutions used. Patients with underlying autoimmune/inflammatory diseases such as lupus or vasculitis may be predisposed.

B. Diagnosis and treatment.

The inflammatory phase of EPS should be considered when a long-term PD patient presents with new bloody effluent, inflow or outflow pain, or generalized abdominal discomfort. The sclerosing phase is suggested by recurrent bowel obstruction. As mentioned, the patient may no longer be on PD. Inflammatory markers may be elevated. If the patient is still on PD, loss of sodium sieving (see Chapter 24) appears to be associated with the development of EPS.

Imaging is helpful in the sclerosing phase, during which cocooning of the bowel is seen, in conjunction with thickening, tethering, enhancement, and calcification of the peritoneal membrane. **Thickening of the peritoneal membrane is seen in any long-term PD patient and, by itself, is not diagnostic of EPS.** Regular CT surveillance of long-term patients has not been shown to be helpful.

The inflammatory phase of EPS is best treated with modest doses of corticosteroid. Infective causes should be ruled out before contemplating this therapy. The duration of treatment is unclear and could be titrated to the symptoms. Some studies have suggested

the addition of mycophenolate mofetil, tamoxifen, or mTor inhibitors for their antifibrotic effects. As in any sclerosing condition, there is a better therapeutic window during the inflammatory phase than when extensive scar formation has already occurred.

It is not clear whether the patient should be transitioned to hemodialysis. On the one hand, it reduces continuing exposure to the process that led to the EPS. On the other hand, leaving the abdomen dry stops the "washout" of inflammatory mediators that PD affords.

In the patient with an established abdominal cocoon and recurrent bowel obstruction, surgery may be necessary. It is very important to consult a surgeon who is familiar with the operative approach to this kind of patient, as the risk of bowel tear, fecal peritonitis, and operative mortality are all high.

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27 Metabolic, Acid-Base, and Electrolyte Aspects of Peritoneal Dialysis

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Although peritoneal dialysis (PD) provides effective control of many of the diverse consequences of uremia, the therapy itself has unique effects on several metabolic parameters that may be potentially important for the health of patients with end-stage kidney disease.

I. HYPERGLYCEMIA. With PD, ultrafiltration is induced by exerting either crystalloidal osmotic or oncotic pressure across the peritoneal barrier. This is typically achieved with PD solutions that contain supraphysiologic concentrations of glucose; some prescriptions also include once-daily treatment with either icodextrin or amino acid–based dialysis solution. Each of these substances is absorbed during the course of the PD dwell, leading to systemic metabolic effects. Treatment with glucose- or icodextrin-based PD solutions results in a daily absorption of 50 to 150 g of carbohydrates. The amount of carbohydrate absorbed is higher with greater use of more hypertonic solutions and in individuals with faster peritoneal solute transfer rates. Absorbed icodextrin is metabolized, not to glucose but to a variety of oligosaccharides and to the disaccharide maltose (Moberly, 2002).

In some individuals with diabetes mellitus, carbohydrate absorption results in poorer glycemic control and requires adjustments in diabetes therapy. These may include an increase in total daily insulin dose or initiation of insulin or other glucose-lowering therapy for individuals who did not previously need such treatment. Hence, it is imperative to increase the intensity of home glucose monitoring in patients with diabetes for the first few weeks after initiating PD or whenever the prescribed tonicity of glucose-based dialysate is increased. Worse glycemic control is associated with worse outcomes in patients undergoing PD, but it is unclear whether this is mere association or true cause and effect (Duong, 2011). Indeed, there are no published randomized trials that have definitely shown a beneficial impact of improved glycemic control on clinically meaningful outcomes for patients with diabetes treated with PD. There are limited data to determine how much PD increases the incidence of new-onset diabetes, but two studies from China suggest that between 5% and 8% of nondiabetic patients develop new-onset diabetes or impaired glucose tolerance within 5 years of starting PD (Dong, 2016; Szeto, 2007). Therefore, blood glucose levels should also be measured every 1 to 3 months in nondiabetic patients undergoing PD. Of note, being obese or overweight appears to be a significant risk factor for the development of new-onset diabetes among patients undergoing incident PD (Than, 2022).

Just as glucose-based dialysis solutions may worsen glycemic control, glucose-sparing regimens may improve it. These glucose-sparing regimens generally comprise the substitution of one glucose-based exchange with icodextrin; the greater ultrafiltration with

icodextrin during the long dwell may allow for the use of lower concentrations of glucose for the other dwells. Substituting a second glucose-based exchange with amino acid dialysate allows for further reduction in systemic glucose absorption, as shown in the multicountry IMPENDIA randomized clinical trial (Li, 2013). Despite clearly demonstrated lower peritoneal glucose absorption with icodextrin-based PD regimens, a recently published meta-analysis of randomized trials failed to demonstrate that this directly translated into changes in fasting plasma glucose or hemoglobin A_{1c} levels (Goossen, 2020). Notwithstanding these results, the use of glucose-sparing regimens should still be considered in individuals with diabetes treated with PD when there is difficulty in achieving glycemic control.

II. **WEIGHT GAIN.** The effects of increased body weight in PD are complex. In patients undergoing hemodialysis, increased body weight is associated with better survival, but the evidence is conflicting in patients undergoing PD, with one study of patients undergoing incident PD in Spain showing no association between obesity and all-cause mortality (Quero, 2021). In observational studies, higher body mass index in patients undergoing PD may be associated with a faster decline in residual kidney function and greater peritonitis-related hospitalization (Obi, 2018). Patients often gain weight after initiation of dialysis irrespective of modality; this generally reflects gain in fat rather than in lean body mass. This weight gain is, at least in part, a result of increased dietary energy and protein intake following the amelioration of uremic anorexia with initiation of dialysis. In patients treated with PD, some of the weight gain is attributed to obligatory systemic carbohydrate absorption. However, large head-to-head comparisons do not support the notion that patients treated with PD are more likely to gain significant weight when compared with individuals treated with hemodialysis. Replacing glucose with icodextrin for the long day dwell in automated PD (APD) or for the night dwell in continuous ambulatory PD (CAPD) results in smaller gains in body weight, but this could reflect differences in total body water rather than body fat. Limited evidence suggests that the sites for deposition of excess body fat differ by dialysis modality, with a greater gain in visceral fat in patients undergoing PD; the clinical relevance of this is unclear (Choi, 2011). Despite this uncertainty, it is prudent to limit exposure to more hypertonic glucose dialysis solutions in order to avoid excessive weight gain.

III. **PERITONEAL PROTEIN LOSS.** During PD, proteins in the blood—primarily albumin—move into the dialysate down their concentration gradient across the peritoneal barrier and are lost as the dialysate is drained. The daily peritoneal protein loss with PD averages 6 to 8 g and is substantially increased during episodes of peritonitis. As a result of this obligatory daily loss, serum albumin may decrease in patients starting treatment with PD and is often lower in patients undergoing PD compared with individuals undergoing hemodialysis.

This daily peritoneal protein loss is generally not modifiable, and its clinical relevance remains unclear. Evidence associating the higher daily peritoneal protein loss with all-cause mortality, cardiovascular events, or protein-energy wasting is, at best, inconsistent (Balafa, 2011). Moreover, the lower serum albumin in patients treated with PD does not seem to put these patients at any higher risk than patients undergoing hemodialysis. All these considerations suggest that PD can be safely continued in patients who are otherwise well

but have modest decrements in serum albumin levels with the therapy.

IV. LIPID ABNORMALITIES. Dyslipidemia is highly prevalent in patients undergoing maintenance dialysis and reflects the net effects of the uremic state, underlying causes of kidney disease (eg, diabetic nephropathy, other proteinuric kidney diseases), and any potential disparate effects of the dialysis modality. The obligatory carbohydrate absorption and peritoneal protein loss with PD can adversely influence the lipid profile. The lipid abnormalities described in patients undergoing PD include increases in total and low-density cholesterol, triglycerides, lipoprotein (a), and apolipoprotein B (Cheng, 2024; Prichard, 2006).

The contribution of lipid abnormalities to the high cardiovascular risk in patients treated with PD is presently unknown. The Study of Heart and Renal Protection (SHARP) is the only clinical trial examining the impact of lipid lowering on cardiovascular events and mortality that has included patients undergoing PD; of the 9,270 enrolled participants, 496 were undergoing PD at the time of enrollment. Although treatment with simvastatin/ezetimibe was associated with fewer cardiovascular events in this clinical trial, there was no significant effect on either all-cause or cardiovascular mortality (Baigent, 2011). Specifically, there was no significant difference in outcomes in the subgroup treated with PD. This trial suggests that the clinical benefit from lipid lowering may not be as large in patients with kidney disease, including those undergoing PD, as in the general population. It is important to note, however, that several studies have demonstrated a higher risk of acute pancreatitis in patients undergoing PD, and thus treatment of severe hypertriglyceridemia may be warranted to reduce this risk (Wang, 2018).

Limited data indicate that drug therapies are as effective in improving dyslipidemia in patients treated with PD as in the general population. Some studies have also examined whether modifications in the PD prescription can improve lipid abnormalities. Substituting one glucose-based exchange with icodextrin has been shown to have a modest effect on serum total cholesterol. In the IMPENDIA trial, a glucose-sparing regimen that included one exchange each with icodextrin and amino acid–based PD solution resulted in a significant decrease in both serum triglycerides and apolipoprotein B (Li, 2013). Such modifications to the PD regimen may be considered in selected individuals for the treatment of these lipid abnormalities.

V. HYPOKALEMIA/HYPERKALEMIA. In all, 10% to 30% of patients treated with PD are reported to have low serum potassium levels. There are several potential reasons for this high prevalence of hypokalemia. These include greater potassium removal with dialysis since PD solutions have no added potassium, inadequate dietary intake, transcellular shift induced by insulin released in response to the obligatory glucose absorption, kidney losses in patients treated with diuretics, and gastrointestinal losses with the use of laxatives (Zanger, 2010).

Observational studies have demonstrated that hypokalemia is associated with a higher risk for PD-related peritonitis and a greater risk for all-cause, cardiovascular, and infection-related mortality in patients undergoing PD (Davies, 2020). In a recent multicenter clinical trial of patients with hypokalemia undergoing PD in Thailand, protocol-based potassium supplementation to maintain serum potassium 4 to 5 mEq/L decreased the risk of peritonitis compared to the strategy of reactive supplementation whenever serum potassium was less

than 3.5 mEq/L (Pichitporn, 2022). Oral administration of potassium supplements is probably the easiest and safest way to correct hypokalemia. Although intraperitoneal administration of injectable potassium chloride can correct hypokalemia, it exposes patients to a higher risk of peritonitis from touch contamination. Although mineralocorticoid receptor antagonists such as spironolactone appear to be safe in patients undergoing PD and may prevent cardiac hypertrophy, it has not been conclusively demonstrated that these agents reduce the incidence of PD-associated hypokalemia (Ito, 2014). Significant hyperkalemia is uncommon in PD and is typically related to nonadherence to the PD prescription. Of note, the use of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) is not associated with a greater risk of hyperkalemia in patients undergoing PD (Ribeiro, 2017).

VI. METABOLIC ACIDOSIS. Progressive loss of excretory function in chronic kidney disease is associated with reduced acid excretion by the kidneys. Hence, metabolic acidosis is frequently present in patients at the time of starting dialysis. Conventional glucose- and icodextrin-based PD solutions contain lactate as the buffer. During treatment with such solutions, bicarbonate enters the peritoneal cavity and is removed with each exchange, while lactate is absorbed systemically. The absorbed lactate is metabolized to bicarbonate, and this corrects the uremic metabolic acidosis. Bicarbonate-based PD solutions are available commercially in some parts of the world; in patients treated with these solutions, the systemic absorption of bicarbonate is responsible for the correction of metabolic acidosis.

Regardless of the buffer used, PD provides a more complete correction of metabolic acidosis than thrice-weekly in-center hemodialysis. Yet the correction remains incomplete in a significant minority of patients undergoing PD. There is evidence that uncorrected metabolic acidosis contributes to protein-energy wasting and osteopenia. Observational studies have also demonstrated a higher risk for all-cause or cardiovascular mortality in patients with persistently low serum bicarbonate levels undergoing PD (Vashistha, 2013). These data argue for the treatment of persistent metabolic acidosis in patients undergoing PD.

A number of clinical trials have tested the clinical benefits of treating metabolic acidosis in patients undergoing PD (Stein, 1997; Szeto, 2003). Such treatment is associated with higher net positive nitrogen balance, significant weight gain, an increase in mid-arm circumference, and a reduction in hospitalizations. Whether treatment of metabolic acidosis has any effect on the risk of death of patients undergoing maintenance dialysis is unknown. In patients undergoing PD, oral administration of sodium bicarbonate is the most effective way to correct metabolic acidosis and should be used to achieve a serum bicarbonate level of at least 22 mmol/L.

VII. HYPONATREMIA/HYPERNATREMIA. Hyponatremia is quite common in patients undergoing PD, with an estimated prevalence of 11% to 26% (Rhee, 2019). Translocational hyponatremia (due to movement of sodium-poor fluid from cells to extracellular fluid) can occur due to hyperglycemia, with the serum sodium falling about 1.3 mmol/L for each 6 mmol/L rise in blood glucose. Icodextrin causes a 2 to 3 mmol/L fall in serum sodium by the same mechanism due to metabolites in the circulation, but this is typically an iso-osmolar hyponatremia. However, icodextrin-induced hyperosmolar hyponatremia has been

described in patients and is likely due to higher circulating metabolite levels due either to twice-daily use or to higher rates of absorption or metabolism (de Fijter, 2024). Dilutional hyponatremia in patients undergoing dialysis is generally thought to reflect excessive water intake, but recent studies in PD suggest it is more often a marker of decreased intracellular mass and is associated with weight loss, potassium depletion, and protein-energy wasting (Dimitriadis, 2014). Hyponatremia should therefore be an indication for nutritional assessment of the patient. Rarely, hyponatremia can be factitious when serum sodium is measured by flame photometry in the presence of severe hypertriglyceridemia.

Although less common than hyponatremia, hypernatremia is also associated with PD therapy. In patients treated with PD, fluid is removed either through aquaporins or through small pores in the peritoneal capillaries (see Chapter 19). The relative contribution of aquaporins to fluid removal is greatest early in the course of a PD dwell, and this is not associated with any concomitant removal of sodium or other solutes. APD prescriptions with short dwell times, particularly with hypertonic dialysate, have the potential therefore to remove more water relative to sodium, and this can result in hypernatremia. One recent observational study of over 4,600 patients undergoing incident PD in the United States found that 4% of patients had hypernatremia (defined as sodium ≥144 mEq/L) at baseline (Ravel, 2017). In contrast to hyponatremia, hypernatremia was not associated with a higher mortality risk in this study. However, hypernatremia can induce thirst and stimulate greater fluid intake, and it is prudent to avoid frequent exchanges with hypertonic dialysate when prescribing PD.

VIII. ABNORMALITIES IN MINERAL METABOLISM. For a discussion of the full range of abnormalities in mineral metabolism, see Chapter 34. The discussion here is limited to issues specific to PD. Studies done several decades ago indicated that patients treated with PD were significantly more likely to have adynamic bone disease than individuals undergoing maintenance hemodialysis. Small and relatively low-quality studies indicated that this risk could be ameliorated with the use of low-calcium dialysate (2.5 mEq/L [1.25 mM]). The overwhelming majority of patients are now treated with low-calcium PD solutions, and there is increasing use of phosphate binders that do not contain elemental calcium, so the situation has changed. Despite this, many patients undergoing PD still have positive calcium balance (Davenport, 2023). Studies of bone microarchitecture using high-resolution quantitative computed tomography (CT) have demonstrated that patients undergoing PD have low bone mineral density and impaired bone microarchitecture compared to healthy controls, although not to the same degree seen in patients undergoing hemodialysis (Pelletier, 2012).

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PART IV

Clinical Problem Areas

28 Psychosocial Issues

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Patients with end-stage kidney disease (ESKD) are affected by numerous psychosocial stressors. These include the effects of illness and treatment, functional limitations and sexual dysfunction, dietary restrictions, time constraints, and fear of death. In addition, there may be marital conflict, strained interpersonal relationships with family and administrative or medical personnel, and socioeconomic concerns regarding the costs of treatment and unemployment.

Approximately 10% of patients with ESKD who are hospitalized have an underlying psychiatric disorder. Hospitalization rates for psychiatric disorders in ESKD are high relative to other chronically ill patients and are associated with increased mortality compared to hospitalizations without an underlying psychiatric diagnosis. Common problems include depression, dementia and delirium, psychosis, personality and anxiety disorders, and substance abuse.

I. DEPRESSION.

Depression is arguably the most common, as well as the most important, problem because of the risk of resulting noncompliance with the dialysis and/or medication regimen and the risk of suicide. Depression may be widely underdiagnosed and untreated in patients with ESKD. According to the most recent version of the *Diagnostic and Statistical Manual for Mental Disorder*, Fifth edition (DSM 5), a major depressive disorder should be diagnosed if, during a period of at least 2 weeks, a patient experiences depressed mood nearly every day or loss of interest/pleasure in usual activities and at least four of the following additional symptoms: (a) significant weight loss or weight gain or appetite disturbance; (b) change in sleep pattern, including insomnia or hypersomnia; (c) psychomotor agitation or retardation; (d) fatigue; (e) feelings of worthlessness or excessive guilt; (f) decreased concentration; or (g) recurring thoughts of death or suicide. The last criterion, (g), is probably the most specific, as some of the others are associated with uremia itself.

Different investigators have estimated that depression occurs in as many as 10% to 50% of patients undergoing dialysis. Screening tools include the Beck Depression Inventory (BDI), Patient Health Questionnaire (PHQ-9), and the Hamilton Rating Scale for Depression. In patients with no underlying medical problems, a BDI score less than 9 suggests no or minimal depression, 10 to 18 indicates mild to moderate depression, 19 to 29 moderate to severe depression, and greater than 30 severe depression. In patients with ESKD undergoing hemodialysis, the recommended cutoff scores for depression are higher, with BDI scores greater than 14 to 16 indicating significant disease. The PHQ-9 is widely used throughout medicine, is closely aligned with DSM criteria, and is available for use free of charge.

Screening for underlying depression in the dialysis population is an important element of the treatment plan. Depressive affect can influence medical outcomes in several ways. In addition to the risk of suicide, depression may lead to poor compliance with the dialysis prescription, abnormal immunologic function, or anorexia and poor nutritional status.

Depressive affect has also been linked to a higher incidence of peritonitis. Whether depression independently increases mortality risk is controversial. Some studies have suggested that baseline depressive symptomatology is associated with increased mortality, even after multiple medical risk factors have been accounted for in analyses.

Patients with ESKD can display suicidal behavior differently from patients with other chronic illnesses. The rate of suicide in patients with ESKD undergoing hemodialysis is higher than in the general US population. Important risk factors include a previous history of mental illness, recent hospitalization, age more than 75 years, male gender, White or Asian race, and alcohol or drug dependence. Patients with ESKD presumably can commit or attempt suicide more easily, either through noncompliance with their medical regimen or by manipulating their dialysis access sites.

A. Treatment options. Treatment options for depression include pharmacotherapy, psychotherapy, including cognitive behavioral therapy, and electroconvulsive therapy. Unfortunately, there are limited data on the effects of antidepressants in patients with ESKD, since these patients are often excluded from many of the large clinical trials. The ASCEND study (A Trial of Sertraline vs. Cognitive Behavioral Therapy for End-stage Renal Disease Patients with Depression) was a multicenter, parallel-group, open-label randomized trial that evaluated the impact of sertraline versus cognitive behavioral therapy for patients with ESKD treated with hemodialysis from 41 dialysis facilities. In all, 120 patients were randomized to cognitive behavioral therapy versus sertraline. Depressive symptoms improved in both groups and were "modestly" better with sertraline compared to cognitive behavioral therapy after 12 weeks. However, there was an increased number of adverse events seen in the sertraline arm compared to those who received cognitive behavioral therapy.

1. Pharmacotherapy

a. Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs). Treatment with SSRIs should be continued for at least 4 to 6 weeks before deciding whether there has been a therapeutic benefit. If efficacy is not achieved, then a switch to another antidepressant of the same class or a different class is a reasonable step. SSRIs are advantageous because they typically cause fewer anticholinergic symptoms than TCAs and are not associated with cardiac conduction abnormalities. Furthermore, TCAs can cause death if taken in large doses and hence pose a potential suicide risk. However, there is a potential for increased bleeding in patients taking SSRIs, which may be relevant to patients with ESKD and preexisting qualitative platelet defects from uremia. SSRIs may also worsen nausea and vomiting, which are common symptoms in the patient population undergoing dialysis.

Typically, SSRIs are cleared by the liver and are highly protein bound. It has been recommended that the dose of SSRI in patients with ESKD should be reduced to two-thirds of the usual amount. Selected SSRIs may have the additional benefit of reducing postural and intradialytic hypotension through effects on vascular tone. Fluoxetine and sertraline are the best studied medications in this family. A dose of 20 mg of fluoxetine daily is usually well tolerated, although data are limited to the short term. Sertraline doses up to 200 mg daily were used in the ASCEND trial. Other medications in this same family include paroxetine and citalopram.

b. **Selective norepinephrine reuptake inhibitors (SNRIs).** Venlafaxine and bupropion hydrochloride are examples of a different class of antidepressants called SNRIs. The SNRIs should be used with caution in patients with ESKD since these drugs are primarily renally excreted. Bupropion has active metabolites that are almost completely removed by the kidney. These metabolites may accumulate in patients undergoing dialysis, predisposing them to developing seizures.

c. **Monoamine oxidase inhibitors (MAOIs).** MAOIs have numerous side effects and should be avoided if possible in patients with ESKD because of their potential to cause hypotension.

2. **Nonpharmacologic options.** There are several forms of psychotherapy (cognitive behavioral therapy, interpersonal, supportive, and group therapy) that might be effective in managing psychological distress. There are few data on such treatments in patients with chronic kidney disease (CKD). Individual psychotherapy (cognitive-behavioral, interpersonal, and supportive) is useful when the patient has identified that there is a problem and has accepted encouragement from the clinician to seek treatment. A randomized crossover trial of 65 patients undergoing hemodialysis showed significant improvements in depression scores as measured by the BDI II and the Hamilton Depression Rating Scale in those patients who received cognitive behavioral therapy. With cognitive behavioral therapy, there was also an improvement in quality-of-life scores and a reduction in interdialytic weight gain.

   Denial is common and is a way of coping with uncomfortable thoughts or feelings related to being a "dialysis patient." When a patient is noncompliant with treatment, denial might play a part in such behavior. Such patients may benefit from psychiatric interventions. However, these patients may resist treatment, as the implication is that "there is something wrong" with them. Motivating a patient to accept these forms of therapy may be difficult. Introducing therapy as a stress management approach to living with ESKD might be one approach to ease the patient into appropriate treatment. Supportive psychotherapy in conjunction with pharmacologic treatment is important for decreasing the rate of relapse. Group therapy may also have a positive impact. One uncontrolled study showed participation in group therapy sessions at the dialysis unit was associated with increased patient survival. A recent study showed improvement in pain, fatigue, and depression symptoms as a result of cognitive behavioral therapy delivered to hemodialysis patients using telemedicine.

   a. **Electroconvulsive therapy** may be used for patients with severe refractory depression, provided that there are no contraindications.

   b. **Transcranial magnetic stimulation (rTMS).** A small study from Korea investigated the impact of rTMS as a treatment for patients with depression undergoing hemodialysis. There may be improvements in anxiety and somatization symptoms with this therapy. Further studies are needed to determine whether this will be an effective treatment option.

II. **DEMENTIA/DELIRIUM.** Neurocognitive disorders are common in patients with ESKD. Cognitive deficits may be related to underlying uremia or other coexistent underlying medical conditions, as described in more detail in Chapter 38. Physicians should initiate

discussions with the family about the cessation of dialysis in patients with progressive dementia. Withdrawal from dialysis is relatively common, especially in older patients or patients who fail to thrive. Advanced directives should be offered to patients at the initiation of renal replacement therapy, ideally before the onset of any disease that would impair their capacity for decision making. The guidelines regarding shared decision making endorsed by the U.S. Renal Physicians Association are a helpful resource.

III. ANXIETY AND BEHAVIOR DISORDERS. Anxiety disorders can be frequent in patients with ESKD and are associated with lower patient perception of quality of life (QOL), increased hospitalizations, and mortality. There was a 45% prevalence of anxiety disorders in a single-center study of 70 patients undergoing hemodialysis. Disruptive behavior directed toward the dialysis staff occurs in a minority of patients but nevertheless can be a disturbance to others in the dialysis unit. It is important to try to understand why the patient is angry and to explore potential solutions. Anxiety states should be treated through psychotherapy and behavioral techniques. Setting limits or establishing boundaries is paramount when hostility or aggression poses a threat of harm to the patient or to others. Hostility and aggressive behaviors might be manifestations of underlying psychiatric symptoms, such as paranoia, referential thinking, or even conditions associated with delirium. If doubt about a particular patient exists, consultation with a psychiatrist should be sought.

If these measures are not effective, short-acting benzodiazepines such as lorazepam or alprazolam may be prescribed for limited periods. These benzodiazepines are metabolized by the liver. Nevertheless, as with SSRIs, it is prudent to start with lower doses. The use of diazepam and chlordiazepoxide should be avoided in patients undergoing dialysis, owing to their metabolism to pharmacologically active metabolites and the association of their use with higher morbidity. Barbiturates should not be used in place of benzodiazepines, since the long-acting ones are removed by hemodialysis. For acutely agitated patients, antipsychotic medications, such as haloperidol, are sometimes required. Haloperidol is not renally cleared; therefore, no dose adjustment is usually necessary. Little is known about the effects of other atypical antipsychotics, such as risperidone or olanzapine, in this patient population. Gabapentin is currently used to treat anxiety, but it does not have U.S. Food and Drug Administration approval for this indication. Gabapentin is eliminated by renal excretion as an unchanged drug. In patients with ESKD, the plasma clearance of gabapentin is reduced and there is an increased risk of morbidity and mortality.

IV. BIPOLAR DISORDERS. Patients with ESKD and CKD with bipolar disorders requiring lithium should have serum lithium levels checked frequently. Lithium is cleared by dialysis; therefore, the dose should be given after each dialysis treatment. Valproic acid is another mood stabilizer sometimes used to treat bipolar disorder. Free serum levels of this drug have been observed to be elevated in patients with impaired renal function. Caution should be exercised in the administration of glucocorticoids to potential renal transplant patients with a history of psychosis, because of the risk of steroid-induced psychosis. Other steroid-sparing agents should be used if clinically feasible.

V. OTHER PSYCHOSOCIAL ISSUES IN THE POPULATION WITH ESKD

A. Marital issues. There have been only a few studies that assess marital relationships in

patients with ESKD. One study found that more than 50% of couples that included a patient with ESKD experienced marital discord. Marital conflict may be an important stressor for patients with ESKD. Marital conflict may be associated with a patient's perception of the burden of illness and the degree to which a patient does not adhere to the dialysis prescription. Marital satisfaction and conflict may be particularly salient for female patients. One study showed that female hemodialysis patients with higher levels of marital satisfaction had improved survival. Marital satisfaction was not associated with differential outcomes in men.

B. Sexual dysfunction. Patients with ESKD have a high prevalence of sexual dysfunction, owing to the effects of uremia, neuropathy, autonomic dysfunction, vascular disease, depression, and medications. Disturbances in the hypothalamic-pituitary-gonadal axis are also frequently encountered. Problems include decreased libido, erectile dysfunction, menstrual disorders, and infertility. Impotence is believed to occur in roughly 70% of men treated with dialysis, and men about to initiate dialysis should be counseled regarding the possibility of erectile dysfunction. This may lead to better communication with the physician and therefore reduce the possibility of depression. Women treated with dialysis commonly have disturbances in fertility and menstruation. Irregular menstrual cycles are common after the initiation of hemodialysis treatment. The most common menstrual disorder in women with ESKD is anovulation. For information about treatment, see Chapter 37.

C. Socioeconomic issues. More than half of patients with ESKD do not continue working after beginning renal replacement therapy. Those holding professional occupations may have greater flexibility in their work schedules and may be more likely to continue employment. Unemployment can have a significant psychological impact on the individual, possibly contributing to a greater likelihood of depression.

D. Rehabilitation. Exercise may play an important role in improving a patient's overall sense of well-being. Specially designed exercise programs are available for those with physical impairments, and these should be promoted at the dialysis center or during routine physician visits. Other therapeutic modalities to consider are stress reduction/relaxation exercises and biofeedback, which have been successfully used, especially in managing disruptive and unstable patients.

E. Quality of Life. It is essential for the medical staff and family to address the patient's perception of their quality of life. This is especially important when making decisions regarding the initiation or withdrawal of dialysis. Patients who rate their quality of life higher and have an increased sense of well-being may be more likely to comply with their dialysis prescription. There are several different scales that have been used to assess quality of life in patients with ESKD, including the SF-36, Illness Effects Questionnaire, Karnofsky Scale, Satisfaction with Life Scale, and the KD-QOL, or Kidney Disease Quality-of-Life Scale. These scales primarily consist of subjective measures. Therapy with erythropoietin has improved quality of life for patients undergoing dialysis. Patients with ESKD with successful renal transplants tend to rate their quality of life higher than those with failed transplants or those treated with dialysis. There have been several recent clinical trials that evaluated the impact of intensification of dialysis prescriptions on patients' perceptions of their quality of life. The Frequent Hemodialysis Network (FHN) evaluated the effect of intense dialysis 6 times weekly versus conventional 3 times weekly treatments on quality of life and

depression scores. Although there were few changes in many subdomain measures of quality of life, there were improvements in both the SF-36 and BDI scores in the 6 times weekly dialysis arm. Physicians should strongly consider the impact their medical decisions have on a patient's quality of life and discuss these issues in depth with patients and their families. In addition, patient satisfaction with care is an important aspect of quality of life that should be evaluated.

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29 Nutrition

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I. CAUSES OF PROTEIN-ENERGY WASTING IN PATIENT WITH CHRONIC KIDNEY DISEASE (CKD). Metabolic and nutritional derangements are common in patients with CKD, especially in patients on maintenance dialysis therapy (Ikizler, 2013). These derangements are called protein-energy wasting of CKD. Patients with this syndrome have increased rates of hospitalization and mortality (Kalantar-Zadeh, 2004). There are multiple etiologies of protein-energy wasting (Table 29.1), including decreased nutrient intake; metabolic derangements such as metabolic acidosis, dialysis-associated catabolism, uremic toxins; and comorbid medical conditions such as diabetes mellitus and cardiovascular disease (Carrero, 2013). Protein-energy wasting affects approximately one-quarter to one-half of patients undergoing hemodialysis and peritoneal dialysis (Carrero, 2018). The sequelae of protein-energy wasting in kidney disease are numerous and include malaise, fatigue, poor rehabilitation, impaired wound healing, increased susceptibility to infection, increased cardiovascular disease risk, and increased rates of hospitalization and mortality. In most instances, serum levels of inflammatory markers are increased, and numerous causes of chronic inflammation may be present. Proinflammatory cytokines can cause anorexia with suppression of nutrient intake (Torres, 2022). Chronic inflammation also is associated with cytokine-mediated hypermetabolism and resistance to anabolic actions of insulin leading to increased net protein catabolism (Siew, 2010). Disruption of the growth hormone and insulin-like growth factor-1 axis leads to decreased protein synthesis.

TABLE 29.1 Causes of Kidney Disease Wasting

Decreased nutritional intake
Overzealous dietary restrictions
Delayed gastric emptying and diarrhea
Intercurrent illnesses and hospitalizations
Decrease in food intake on hemodialysis days
Medications causing dyspepsia (phosphate binders, iron preparations)
Suppression of oral intake by peritoneal dialysate glucose load
Inadequate dialysis
Monetary restrictions Inability to prepare or acquire food due to physical limitations Poor dentition or severe gum disease Neurologic disorders that impair eating/swallowing
Depression
Altered sense of taste

Increased losses
Gastrointestinal blood loss (100 mL blood = 14-17 g protein)
Intradialytic nitrogen losses (hemodialysis 6-8 g amino acid per procedure; peritoneal dialysis 8-10 g protein/day) Severe proteinuria (>8-10 g/d)
Increase in protein catabolism
Intercurrent illnesses and hospitalizations
Other medical comorbidities, including diabetes mellitus, cardiovascular disease, infection
Metabolic acidosis (promotes protein catabolism)
Catabolism associated with hemodialysis (due to activation of proinflammatory cytokines)
Dysfunction of the growth hormone-insulin growth factor endocrine axis Insulin resistance
Catabolic effects of other hormones (parathyroid hormone, cortisol, glucagon)

A. Obesity. Concern has focused primarily on wasting in patients with advanced CKD because the death rate increases steeply with evidence of skeletal muscle loss, weight that is below peer weight, or body mass index (BMI). There is, however, an increasing incidence of obesity among patients initiating maintenance dialysis therapy. Studies of the effect of obesity on survival in patients undergoing dialysis are difficult to interpret because of their observational nature, differences in analysis techniques and definitions of obesity, and confounding conditions (Stenvinkel, 2013). Exaggerated oxidative stress and inflammation are driven by increased adiposity in many settings, and BMI is strongly associated with biomarkers of these metabolic abnormalities in the general population as well as in patients with CKD, suggesting that obesity predisposes patients undergoing dialysis to an abnormal metabolic milieu.

II. NUTRITIONAL ASSESSMENT

A. Comprehensive nutritional assessment. A comprehensive nutritional assessment should be performed within 90 days of starting dialysis. This assessment should include, at a minimum, appetite assessment, a history of dietary intake, measurements of body weight and height, biochemical data, and nutrition-focused anthropometric values. A comprehensive nutritional assessment should be repeated annually or more often, based on clinical circumstances, in patients with CKD stages 3 to 5D (KDOQI 2020 Nutrition guideline, section 1.1).

B. Patient interview and physical examination. Symptoms of nausea, vomiting, and anorexia, as well as recent changes in body weight, should be carefully evaluated in an attempt to ascertain the cause. Nonuremic causes of changes in weight and/or food intake must be kept in mind, including severe congestive heart failure, diabetes mellitus, various gastrointestinal diseases, and depression. Phosphate binders or oral iron preparations can cause dyspepsia and other gastrointestinal symptoms.

C. Assessment of dietary energy and protein intake. Patient recall of food intake over 24 hours should ideally be determined on both dialysis and nondialysis days (Kopple, 2001). Intake on dialysis days typically is about 20% lower (Burrowes, 2003). Food frequency questionnaires (Kalantar-Zadeh, 2002) may also provide useful information.

D. **Normalized protein nitrogen appearance rate (nPNA).** Because most protein in the body is catabolized to urea, urea appearance or generation rate can be used to estimate the rate of protein nitrogen catabolism or appearance. In patients with relatively stable nitrogen balance, the nPNA will give a measure of protein intake. A common mistake, however, is to ignore the amount of urea being excreted by residual kidney function. If residual kidney urea excretion is not taken into account, the nPNA calculation will be artefactually low and can substantially underestimate protein intake.

E. **Nutritional screening tools:** A variety of screening tools are available, such as the Malnutrition Universal Screening Tool (MUST) and the Mini Nutritional Assessment (MNA). They each require a brief patient interview. Questions common to all screening tools include information about body weight changes within a given time frame, amount of food intake, and lack of appetite. Due to limited evidence, the 2020 Kidney Disease Outcome Quality Initiative (KDOQI) Nutrition guidelines do not recommend one screening tool over another.

F. **Nutritional assessment tools**

1. **Body composition**

   a. **Body weight and height.** The kg/m^2 calculation of BMI should be measured at the first visit and then monitored over time. Adjustments may be needed in patients with massive edema, ascites, or who harbor markedly enlarged polycystic organs. Weight should be monitored at least monthly.

      1. **Underweight.** A BMI of less than 18.5 kg/m^2 predicts a higher risk of mortality. A diagnosis of protein-energy wasting can be made when the BMI is less than 18 kg/m^2.
      2. **Overweight or obese.** In chronic patients undergoing hemodialysis, overweight (BMI of 25-29.9 kg/m^2) or obesity (BMI of 30 kg/m^2 or more) predicts a lower risk of mortality.
      3. **Change in postdialysis weight.** Once changes in fluid overload have been excluded, an increase in postdialysis weight over time most often is related to increases in body fat. A decrease in body weight over time is often associated with loss of lean body mass and is associated with a poor outcome.

   b. **Anthropometry.** Skinfold thickness measurements may be used to assess body fat when edema is not present. Waist circumference may be used to assess abdominal obesity. This measurement is limited in its ability to assess changes over time, however. The conicity index is another measure of abdominal fat mass. It has been used both to assess nutritional status and to predict the risk of mortality (Martins, 2023). This index is calculated from waist circumference, weight, and height according to the following formula:

$$\text{Conicity index} = \frac{\text{waist circumference (m)}}{0.109\sqrt{\frac{\text{weight (kg)}}{\text{height (m)}}}}$$

   c. **Bioimpedance.** Bioimpedance may be used to assess body composition. Bioimpedance analysis is based on the measurement of resistance and reactance when a constant alternating electrical current is applied to a patient. Empirical equations are used to predict total-body water from resistance and total-body cell

mass from the ratio of resistance to reactance or from its geometrical derivative, the phase angle. The phase angle correlates strongly with anthropometric measures of nutritional status and with serum albumin levels. For reproducibility, multifrequency instruments should be used to assess body composition and should be performed a minimum of 30 minutes after the end of a hemodialysis session to allow for redistribution of body fluids (Di Iorio, 2004; Ikizler, 2020). Low-phase angle measurements are associated with an increased risk of mortality (Chertow, 1997; Huang, 2020).

d. **Dual-energy x-ray absorptiometry (DEXA).** This test was developed to measure bone density but was later adapted to quantify soft tissue composition, including fat and fat-free mass. A DEXA scan takes only 6 to 15 minutes, involves minimal radiation exposure, and hence can be used serially to follow changes in body composition over time. DEXA remains the gold standard for measuring body composition despite being influenced by volume status.

e. **Creatinine kinetics.** Creatinine kinetics may be used to estimate muscle mass. The accuracy of this measurement may be reduced, however, with very high or very low dietary intake of meat and/or creatine supplements. A decrease in serum creatinine over time may be an indication of decreasing muscle mass. A special consideration is patients who are on maintenance dialysis following acute kidney injury (AKI) where a partial recovery of residual renal function may be the cause of a decreasing serum creatinine value. An increase in serum creatinine over time usually indicates either noncompliance with the dialysis treatment regimen or decreasing residual kidney creatinine clearance.

2. **Handgrip strength.** Handgrip strength may be used as an indicator of protein-energy status and functional status when baseline data (prior measures) are available for comparison (Silva, 2011). Handgrip strength is also useful in that it correlates with patient survival.

3. **Composite indices**

a. Subjective global assessment (SGA) is a clinical method for evaluating nutritional status that includes history, symptoms, and physical parameters. The history component focuses on five areas: (a) percentage of body weight lost in the previous 6 months; (b) food intake; (c) the presence of anorexia, nausea, vomiting, diarrhea, or abdominal pain; (d) functional capacity; and (e) metabolic demands in view of an underlying disease state. Physical parameters focus on the assessment of subcutaneous fat; muscle wasting in the temporal area, deltoids, and quadriceps; the presence of ankle or sacral edema; and the presence of ascites. The SGA has a good reproducibility and correlates strongly with outcomes (de Mutsert, 2009; Kwon, 2016).

b. Malnutrition Inflammation Score (MIS, Kalantar-Zadeh, 2001) uses a combination of 10 objective and subjective factors to assess nutritional status, each with four levels of severity, from normal (0) to very severe (3) to generate a score between 0 and 30. The MIS also correlates with patient outcomes (Rambod, 2009).

G. Laboratory and other tests

1. **Serum albumin.** Low levels are a strong predictor of mortality, and hospitalization risk rises dramatically and logarithmically as levels decline below

4.0 g/dL (40 g/L). The assay method used (bromocresol green vs bromocresol purple) can change results by as much as 20%. Serum albumin levels correlate modestly with other nutritional measures, and hypoalbuminemia may be due to a low nutrient intake, protein losses, increased catabolism, fluid overload, or some combination of these mechanisms.

2. **Serum prealbumin** levels may be elevated because of the interaction of prealbumin with retinol-binding protein and decreased renal clearance.
3. **C-reactive protein (CRP)** is an acute phase reactant that correlates negatively with albumin and other visceral protein concentrations. When serum levels of albumin or prealbumin are low, it is appropriate to check CRP levels to help uncover potential covert inflammation. CRP levels are highly variable among patients with end-stage kidney disease (ESKD), impacting their practical utility in cross-sectional analysis, but serial CRP measurements may provide valuable information.
4. **Serum transferrin** is low in almost all patients undergoing dialysis and is influenced by changes in iron stores, presence of inflammation, and changes in volume status; therefore, it is not a good indicator of nutritional status.
5. **Predialysis serum urea nitrogen (SUN).** The predialysis SUN level reflects the balance between urea generation and removal. Thus, a low SUN level could occur in a very well-dialyzed patient with good protein intake or in an inadequately dialyzed patient with poor protein intake. Also, a low SUN may reflect substantial residual kidney function or a markedly anabolic state (such as during rapid recovery from an intercurrent illness). Therefore, it is difficult to infer the level of protein intake from the SUN directly, especially if the amount of residual kidney urea clearance is not assessed concomitantly.

III. DIETARY REQUIREMENTS.

The recommended average levels of nutritional intake are listed in Table 29.2 and include recommendations that are generally consistent with the National Kidney Foundation's (NKF) KDOQI 2020 guidelines on nutrition.

TABLE 29.2 Daily Dietary Recommendations for Patients Undergoing Dialysis

Nutrient or Substance	
Protein (g/kg)	1.0-1.2[a,b]
Calories (sedentary, kcal/kg)	25-35[a,c]
Sodium	<100 mmol
Potassium	Adjust dietary intake to maintain potassium in the normal range.
Bicarbonate	Maintain a serum bicarbonate level of 24-26 mmol/L using, if needed, increased bicarbonate or a citric acid/sodium citrate solution supplementation.
Calcium	Adjust calcium intake (dietary calcium, calcium supplements, or calcium-based binders) with consideration of concurrent use of vitamin D analogs and calcimimetics in order to avoid hypercalcemia.
Phosphate	Adjust dietary phosphate intake to maintain serum phosphate levels in the normal range. When making decisions about phosphate restriction treatment, consider the bioavailability of

	phosphate sources (eg, animal, vegetable, additives).
Iron	See Chapter 32.
Vitamin A	No routine supplementation
Folate	Supplement to correct deficiency
Vitamin B_{12} (mg)	Supplement to correct deficiency
Vitamin C	Consider supplementation as needed to maintain an intake of at least 90 mg/d for men and 75 mg/d for women.
Vitamin E	No routine supplementation
Vitamin D	See Chapter 35.
Vitamin K	Consider avoiding supplementation in patients receiving medications that inhibit vitamin K activity such as warfarin.
Selenium	No routine supplementation
Zinc	No routine supplementation
Long-chain ω-3 Polyunsaturated fatty acids (LC n-3 PUFA)	Can use 1.3-4 g/d in HD to reduce triglycerides and LDL cholesterol levels and raise HDL levels Consider use in PD to improve the lipid profile (1.3-4 g/d).

HD, hemodialysis; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PD, peritoneal dialysis.

It is reasonable for the registered dietitian nutritionist (RDN) or an international equivalent to encourage eating a diet that meets the recommended dietary allowance (RDA) for adequate intake of all vitamins and minerals (OPINION).

[a]All intakes calculated on the basis of normalized body weight (ie, the average body weight of normal persons of the same age, height, and sex as the patient).

[b]For patients at risk of hyper- and/or hypoglycemia, higher levels of dietary protein intake may need to be considered to maintain glycemic control.

[c]Includes glucose absorbed from dialysis solutions.

A. Need for individualization. A "renal" diet has numerous restrictions, and so adherence to such a diet can be difficult and stressful. Prescribed diets should be individualized to help accommodate each patient's unique circumstances in terms of palatability, cost, comorbid medical conditions, and cultural eating habits. It is reasonable to assess factors beyond dietary intake (eg, medication use, knowledge, beliefs, attitudes, behavior, access to food, depression, and cognitive function) to effectively plan nutrition interventions. Specific nutritional issues in the patient with diabetes undergoing dialysis are discussed in Chapter 30. Too many restrictions should be avoided, as they may lead to poor intake and even to decreases in the serum albumin level. The nutritional recommendations need to be reinforced by all members of the health care team. Compliance should be assessed on a regular basis, even monthly at the initiation of dialysis or for those with a previous history of noncompliance.

B. Adequacy of dialysis. The delivery of a dialysis dose that is less than adequate can adversely affect appetite, nutrient intake, and measures of nutrition. Provision of adequate dialysis corrects subtle uremia and thus mitigates uremia-associated anorexia and may improve hypercatabolism as well. Having said this, in the Hemodialysis (HEMO) Study, there was no improvement in either protein or energy intake in patients randomized to high dose (single-pool $_{Kt/V}$ ~ 1.7) compared with patients randomized to standard-dose (single-pool $_{Kt/V}$ ~ 1.3) dialysis; weight declined similarly in both groups of patients, although the decreases in some anthropometric parameters were somewhat

less for patients assigned to the higher dialysis dose (Rocco, 2004). Assignment to the high-flux group had little measurable nutritional advantage. Despite anecdotal reports of marked nutritional improvement on patients changing from hemodialysis 3 times per week to a more frequent schedule, the two randomized Frequent Hemodialysis Network trials failed to find improvement in either serum albumin or lean body mass in patients assigned to more frequent short daily or long nocturnal therapy; however, patients with hypoalbuminemia were excluded from participation in either trial (Kaysen, 2012). Claims have also been made of nutritional improvement in patients receiving intermittent hemofiltration or hemodiafiltration, but the supportive evidence is also relatively weak.

C. Protein Intake. Patients undergoing hemodialysis and peritoneal dialysis should ingest 1.0 to 1.2 g of protein/kg/d. When scaling protein intake to body size, care must be taken to choose the appropriate measure of body weight (ideal body weight, usual, current, or adjusted) and BMI, based on the patient's health goals (KDOQI 2020 Nutrition guideline, section 3.0). Patients with diabetes mellitus who are at risk for hyperglycemia and/or hypoglycemia may need a higher level of dietary protein intake (DPI) in order to maintain glycemic control. Plant-based diets have been advocated for patients with kidney disease (Joshi, 2020). However, in patients undergoing dialysis, there is little evidence to recommend a particular mix of animal versus plant-based protein in regard to developing a daily protein intake prescription.

D. Energy

1. **Assessment of resting energy expenditure.** Achieving energy balance is critical so that protein-energy malnutrition and protein-energy wasting can be prevented or treated in susceptible persons.
   a. **Indirect calorimetry.** Indirect calorimetry is the gold standard method for determining resting energy expenditure.
   b. **Predictive energy equations.** If indirect calorimetry is not available, CKD-specific predictive energy equations may be used to estimate resting energy expenditure. Equations that have been compared with indirect calorimetry include the Maintenance Hemodialysis Equation, the Harris-Benedict equation, the Schofield Equation, and the Vilar equation. Predictive equations are less reliable at the extremes of BMI, where they would be most useful (Bailey, 2022).
2. **Energy intake.** In patients who are metabolically stable, an energy intake of 25 to 35 kcal/kg body weight per day should be prescribed. Individualized energy intake goals should take into account the patient's age, sex, level of physical activity, body composition, weight status goals, concurrent illness, presence of inflammation, and/or intercurrent illnesses (D'Alessandro, 2021; KDOQI Nutrition guideline, 2020, section 3.1).
   a. **Dialysis and energy intake.** Energy intake in patients undergoing peritoneal dialysis should take into account any calories provided by the absorption of glucose from the dialysis solution (Table 29.3). The amount of energy intake from dialysate depends on the percentage of dextrose used for each dwell, the length of each exchange, the volume of each dwell, the number of exchanges, and peritoneal membrane transport properties and is typically in the range from 300 to 400 kcal per day.

TABLE 29.3 Estimated Kilocalories from Absorbed Glucose as a Function of Instilled Volume in Patients undergoing CAPD and CCPD

Instilled Volume	%D Daytime	%D Overnight	kcal Absorbed
CAPD			
4 × 2.0 L	1.5% D	2.5% D	332
4 × 2.5 L	1.5% D	7.5% Icodextrin	187
4 × 2.5 L	1.5% D	2.5% D	386
4 × 3.0 L	1.5% D	2.5% D	432
CCPD[a]			
3 × 2.0 and 2.0	2.5% D	1.5% D	299
3 × 2.5 and 2.5	2.5% D	1.5% D	350
3 × 3.0 and 3.0	2.5% D	1.5% D	396
3 × 2.5 and 2.5 + 2.5	Both 1.5% D	1.5% D	342
3 × 2.5 and Ico	7.5% Icodextrin	1.5% D	144

CAPD, continuous ambulatory peritoneal dialysis; CCPD, continuous ambulatory peritoneal dialysis; D, % dextrose of instilled solution.

[a]CCPD using 9 hours overnight and three exchanges per night and a last-bag-fill for CCPD regimens 1, 2, 3, and 5. CCPD regimen 4 includes a last-bag-fill and midday exchange.

Adapted from Burkart J. Metabolic consequences of peritoneal dialysis. *Semin Dial*. 2004;17:498-504. These estimates do not take into account glucose losses during icodextrin dwells or kcal gained from the metabolism of polyglucose.

E. Sodium and water. Most excess fluid intake is driven by ingestion of excess sodium, and dietary counseling needs to educate patients and their families about the importance of limiting sodium. In some patients, there are substantial non–salt-driven causes of fluid ingestion as well, and these should be sought and corrected. Sodium intake should be restricted to less than 100 mmol/d (2.3 g/d) to reduce blood pressure and improve volume control.

1. **Patients undergoing peritoneal dialysis.** Although one can remove sodium-stimulated fluid ingestion using higher glucose dwells, this comes at the cost of glucose loading, with potentially adverse effects on the peritoneal membrane as well as on lipids and triglyceride levels. Therefore, a lower sodium intake is desirable.
2. **Anuric patients with ESKD.** Fluid intake generally should be limited to about 1.0 to 1.5 L/d. Additional fluid can be consumed in patients with residual renal function, with the amount based on the daily urine volume.

F. Potassium

1. **Peritoneal dialysis.** Hyperkalemia in anuric patients undergoing peritoneal dialysis is unusual because the dialysate contains no potassium. Patients undergoing peritoneal dialysis typically require only modest potassium restriction (4 g or 100 mmol/d) or no restriction at all. Some of these patients may actually require potassium supplementation, especially if nutrient intake is not optimal.
2. **Hemodialysis.** In patients undergoing hemodialysis with limited residual renal function, a lower intake of potassium (2 g or 50 mmol/d) is often required to prevent predialysis hyperkalemia. One small study found that dietary potassium intake had little impact on predialysis serum potassium levels in patients undergoing hemodialysis (Ramos, 2021), but then how would one explain the success in

lowering pre(hemo)dialysis serum potassium levels by prescribing agents that block gut potassium absorption, such as sodium zirconium cyclosilicate (Ni, 2023) or patiromer? An important issue that needs attention is to limit exposure to very low potassium (0 K or 1 K) hemodialysis solutions, as this has been associated with arrhythmias and an increased risk of sudden death (Dilaver, 2024).

G. Calcium and phosphate. The dietary intake of calcium and phosphate and the management of hyperphosphatemia are discussed in Chapter 34. The bioavailability of phosphate sources should be taken into consideration when developing a phosphate-restricted diet. Animal-based phosphate has a 40% to 60% absorption in the gastrointestinal tract while plant-based phosphate has only a 20% to 50% absorption. In contrast, phosphate additives contain inorganic phosphate and have a high degree of intestinal absorption.

H. Micronutrient intake and supplementation. Patients undergoing dialysis should be encouraged to eat a diet that meets the recommended dietary allowance (RDA) for adequate intake of all vitamins and minerals. Periodic dietary intake assessment should include queries regarding intake of micronutrient or multivitamin supplements. Vitamin deficiencies can be caused by poor intake, interference with absorption by drugs or uremia, altered metabolism, and losses to the dialysate.

Patients undergoing dialysis who have chronic inadequate dietary intake should be provided with multivitamin supplementation, including all water-soluble vitamins, to prevent or treat micronutrient deficiencies. If a multivitamin is prescribed, it should not contain fat-soluble vitamins such as vitamins A or E (see below). There is insufficient evidence to support routine supplementation; instead, supplementation should be individualized and based on clinical judgment.

1. **Folate.** Red blood cell folate levels reflect body stores over the past several months in patients undergoing dialysis, while plasma or serum folate levels reflect recent dietary absorption. Serum homocysteine, vitamin B_{12}, and folate level monitoring may be considered for patients who take certain medications such as methotrexate, nitrous oxide, 6-aziridine, phenytoin, carbamazepine, and oral contraceptives, or who have excessive alcohol intake, which can interfere with folate absorption. Patients older than 50 years of age may have an increased need for supplementation due to a higher prevalence of atrophic gastritis. Excessive folate intake can have deleterious effects since it can inhibit zinc absorption by forming a complex with zinc in the intestinal lumen.
2. **Vitamin B_{12}.** The use of supplemental vitamin B_{12} in patients with lower-range serum cobalamin levels to reduce erythropoietin-stimulating agent requirements is discussed in Chapter 32.
3. **Vitamin C.** Ascorbic acid supplementation should be limited to 60 to 100 mg/d, as higher doses can result in the accumulation of its metabolite, oxalate.
4. **Vitamin D.** Vitamin D supplementation in the form of cholecalciferol or ergocalciferol should be used to correct undesirably low levels of serum 25-hydroxyvitamin D, suggesting deficiency or insufficiency (Pilkey, 2023). A currently accepted usual range of serum 25-D levels in nondialysis subjects is 30 to 100 ng/mL (75-250 nmol/L). Whether there is a clinical benefit associated with moving patients from the lower end to the middle of this range is a matter of current study. Further information on the dosing of vitamin D is discussed in Chapter 34.

5. **Vitamins A and E.** Fat-soluble vitamins such as vitamins A and E are not routinely supplemented in patients undergoing dialysis due to the potential for accumulation, as neither hemodialysis nor peritoneal dialysis removes fat-soluble vitamins. Accumulation can lead to vitamin toxicity; thus, if supplementation is indicated, patients need to be monitored on a regular basis for possible toxicity. High levels of vitamin A can result in multiple, serious adverse effects in nonuremic individuals. Hypervitaminosis A in patients undergoing dialysis can cause anemia and abnormalities of lipid and calcium metabolism.
6. **Vitamin K.** Patients receiving anticoagulant medicines such as coumadin that are known to inhibit vitamin K activity should not receive vitamin K supplements. Although vitamin K levels are typically low in patients undergoing hemodialysis, there is a paucity of data on vitamin K supplementation in the dialysis population. Some small trials have suggested a benefit of supplementation in terms of vascular calcification and arterial stiffness and even for reduction in hemodialysis-related muscle cramps. To date, there is no consensus for a need for supplementation with either vitamin K1 or K2 (Roumeliotis, 2022).
7. **Minerals.** Supplementation of selenium or zinc is not recommended since there is little evidence that it improves nutritional, inflammatory, or micronutrient status (KDOQI 2020 Nutrition guideline, section 5.6).

IV. NUTRIENT REQUIREMENTS IN HOSPITALIZED PATIENTS WITH KIDNEY DISEASE

A. Energy requirements in hospitalized patients undergoing dialysis. The energy requirements of hospitalized patients undergoing dialysis are not well defined. Since the overall dietary intake of hospitalized patients is usually reduced, it is important to provide additional renal-specific nutritional supplementation in these patients. In other instances, one can follow recommendations for patients with AKI requiring dialysis who are estimated to have energy needs between 25 and 40 kcal/kg actual body weight. Higher levels of caloric intake have not been shown to be beneficial from a nutritional standpoint, worsen net nitrogen balance, and can cause hypercapnia, especially if patients have impaired pulmonary function. Indirect calorimetry should be used to determine actual energy requirements. In the absence of indirect calorimetry measurements, a simple method is to assume a baseline requirement of 25 or 35 kcal/kg actual body weight per day based on individual patient's clinical and demographic characteristics, and then multiply by adjustment factors that are relevant to the patient (Soop, 1989). Please refer to the European Society for Clinical Nutrition and Metabolism Guideline for additional guidance on clinical nutrition in hospitalized patients with kidney disease (Fiaccadori, 2021).

B. Protein requirements. In critical illness, amino acids are infused to help prevent protein breakdown, not to provide an additional source of calories; hence, they are not counted as part of the daily energy intake. The amino acid intake for patients with AKI or CKD undergoing either maintenance dialysis or one of the continuous renal replacement therapies during hospitalization should be in the range of 1.1 to 2.0 g/kg/d. There appears to be no benefit in using higher levels of protein supplementation, even in the face of very high nitrogen losses. When higher levels are given, there does not appear to be any additional improvement in nitrogen balance, and there is increased

formation of urea and other nitrogenous waste products.

C. Lipid requirements. In hospitalized patients requiring nutritional supplementation, energy requirements cannot usually be achieved by the administration of glucose infusions alone. The daily amount of glucose administered should not exceed 5 g/kg body weight, as supplementation above this level results in incomplete oxidation of glucose and conversion of glucose to fat. The balance of energy requirements is provided by lipids. Lipids have a high specific energy content as well as a low osmolality. The daily provision of 1.0 g/kg body weight or less usually prevents the development of an essential fatty acid deficiency while decreasing the risk of hypertriglyceridemia.

V. TREATMENT

A. General comments. Reversible causes of protein-energy wasting of CKD should be diligently pursued and corrected (see Figure 29.1 for a treatment algorithm developed by the International Society of Renal Nutrition and Metabolism). Inadequate dietary protein and energy intake is a major cause of protein-energy wasting of CKD (Carrero, 2013) and is often *secondary to anorexia.*

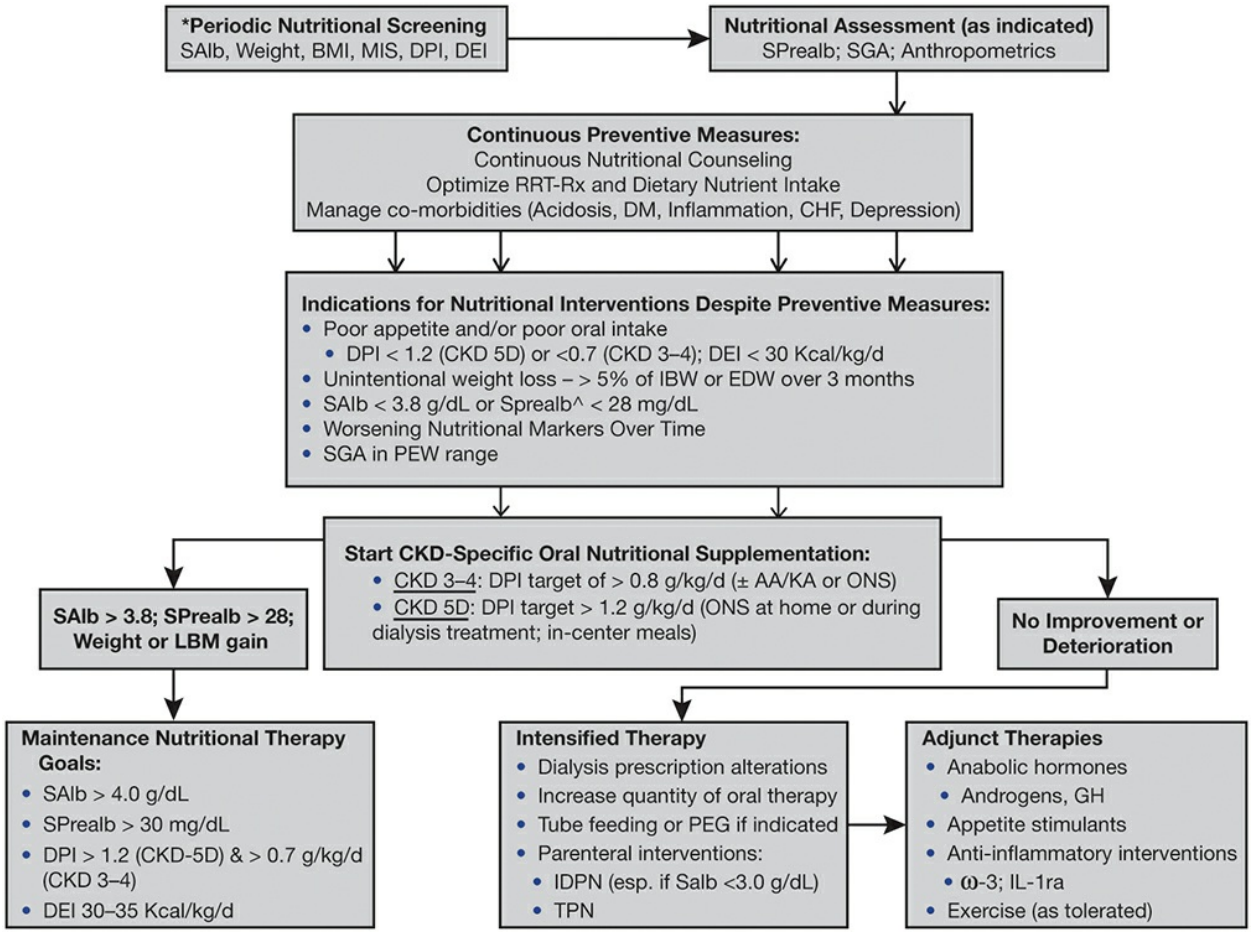


FIGURE 29.1: Algorithm for nutritional management and support in patients with chronic kidney disease (Ikizler, 2013). BMI, body mass index; CHF, congestive heart failure; CKD, chronic kidney disease; DEI, dietary energy intake; DM, diabetes mellitus; DPI, dietary protein intake; EDW, end-dialysis weight; GH, growth hormone; IBW, ideal

body weight; IDPN, intradialytic parenteral nutrition; MIS, malnutrition inflammation score; ONS, oral nutritional supplementation; PEG, percutaneous endoscopic gastrostomy; PEW, protein energy wasting; RRT, renal replacement therapy; SAlb, serum albumin; SPrealb, serum prealbumin; SGA, subjective global assessment; TPN, total parenteral nutrition.

Anorexia has many etiologies. The provision of adequate dialysis is a crucial first step in improving nutritional status; however, data on more frequent hemodialysis are mixed regarding the benefit of an increased dose of dialysis on nutritional parameters (Rocco, 2013). Other medical conditions, especially infection and inflammation, acidemia, intercurrent illness, and cardiovascular disease, should be identified and treated if possible. Metabolic acidosis promotes protein-energy wasting by increasing muscle protein catabolism and by stimulating the oxidation of essential amino acids. Thus, a goal bicarbonate level of 24 to 26 mmol/L in both patients undergoing hemodialysis and peritoneal dialysis is suggested for patients with protein-energy wasting (KDOQI Nutrition guideline 2020, section 6.1). Causes of inflammation, including the use of central venous catheters in hemodialysis, should be treated or eliminated if possible. Correction of gastrointestinal disturbances, including diabetic gastroparesis, colitis, and pancreatic insufficiency, may also improve nutritional status.

Other nutritional considerations include access to, and ability to prepare, food, ethnic and personal food preferences, and assessment for the need for or repair of dentures and/or bridges. Once reversible causes of poor nutritional status have been identified and corrected, intervention in the form of oral or parenteral supplements should be considered.

Constipation is a common and unappreciated complication in patients undergoing maintenance dialysis. It could be due to low fluid intake, sedentary lifestyle, low fiber intake, and medications such as calcium-containing phosphate binders, oral iron supplements, and a number of psychoactive medications that impair gut motility. Since some important putative uremic toxins are generated in the gut, constipation might increase and prolong their adverse impact. Avoidance of constipation is especially important in patients undergoing peritoneal dialysis, because stool in the colon can impede proper drainage of the instilled peritoneal dialysis solution. In patients undergoing peritoneal dialysis, constipation has also been associated with a higher risk of peritonitis. A toolkit to evaluate and guide the treatment of constipation has been developed based on expert consensus (Ng, 2022). Fiber in the diet can usually be increased without meaningfully impacting serum phosphate (Lambert, 2020; Tsai, 2023) and potassium levels, as long as binging on high-potassium fruits is avoided. The medication list should be reviewed, and the possibility of replacing constipation-inducing drugs with other drugs in the same class with less effects on gut motility should be considered. A limited number of studies also suggest that synbiotics could help constipation (Lydia, 2022). Acute constipation can be treated with lactulose (Lin, 2017) or polyethylene glycol.

B. When to initiate nutritional supplements. The International Society of Renal Nutrition and Metabolism has published recommendations for the nutritional management and support of patients with CKD (Ikizler, 2013). Once preventive and preliminary corrective approaches have failed, indications for the prescription of nutritional supplements include the following (Figure 29.1):

1. Poor appetite and/or poor oral intake

2. Dietary protein intake (DPI) less than 1.2 g/kg/d, dietary energy intake (DEI) less than 30 kcal/kg/d
3. Serum albumin level less than 3.8 g/dL (38 g/L) or (if patient is anuric) and serum prealbumin level less than 28 mg/dL (280 mg/L)
4. Unintentional weight loss greater than 5% of ideal body weight or postdialysis weight over 3 months
5. Worsening nutritional markers over time
6. SGA in the protein-energy wasting range

The initial nutritional supplementation should be CKD specific with a target dietary energy and protein intake as noted earlier. The goal serum albumin level is 3.8 g/dL (38 g/L) initially, with a long-term goal of greater than 4.0 g/dL (40 g/L).

Patients who do not show improvement with oral nutritional supplementation should have intensified therapy, which can include an increased quantity of oral nutritional supplementation, feeding via tube or percutaneous endoscopic gastrostomy or jejunostomy if indicated, and parenteral interventions. IDPN should be reserved for patients who cannot tolerate or do not respond to oral intake or the use of a feeding tube (KDOQI Nutrition guideline, 2020, section 4).

C. Oral supplements

1. **Oral protein-energy supplementation.** Oral protein-energy supplementation, for a minimum of 3 months, should be considered for either the prevention of or treatment of protein-energy wasting when dietary counseling alone is unsuccessful in achieving sufficient energy and protein intake.
2. **Oral amino acid supplementation.** Either amino acid or branched-chain amino acid supplementation in patients receiving either hemodialysis or peritoneal dialysis results in increased reported protein intake and nPNA.

D. Enteral supplements.

A trial of enteral tube feeding should be considered when both nutritional counseling and oral supplementation are insufficient to achieve adequate protein and energy intake. A number of different supplements specifically formulated for patients undergoing maintenance dialysis are available for either oral or enteral use. Other considerations in the choice of nutritional supplements include cost, palatability, and presence of lactose tolerance.

E. IDPN in patients undergoing hemodialysis

1. **Indications and benefits.** IDPN is indicated in an adequately dialyzed patient undergoing hemodialysis with protein-energy wasting who is unable to ingest or absorb sufficient food via the gastrointestinal tract. IDPN promotes protein anabolism in the acute setting. Since IDPN is only given during hemodialysis sessions, it cannot provide complete nutritional support. Therefore, IDPN should only be used if the combined intake of protein and energy from both oral/enteral and IDPN sources would be expected to provide sufficient protein and calories to support long-term nutritional needs. Otherwise, total parenteral nutrition (TPN) should be considered for nutritional support.
2. **Composition, infusion, and complications.** The IDPN solution is usually composed of an 8.5% amino acid solution mixed with 250 mL of 50% dextrose. It is infused into the venous drip chamber for the entire duration of the hemodialysis procedure. Additional energy can be provided by infusing a lipid emulsion; patients receiving lipids should be monitored closely for hypertriglyceridemia, changes in

liver function tests, or compromise of the reticuloendothelial system. A typical composition of IDPN solution is outlined in Table 29.4.

TABLE 29.4 Composition of a "Typical" Solution for Intradialytic Parenteral Nutrition

Component	Amount
50% dextrose (D-glucose)	125 g (250 mL)
8.5% crystalline amino acids (essential and nonessential)	42.5 g (500 mL)
20% lipids	50 g (250 mL)
Electrolytes	Sodium, phosphate, potassium sulfate, chloride, and magnesium with the amount per IDPN bag adjusted for serum electrolyte levels
Vitamins	See text and Table 29.2
Insulin, regular	Adjusted/blood glucose levels
Caloric content	
50% dextrose	425 kcal/treatment
20% lipid emulsion	500 kcal/treatment
Total	925 kcal/treatment

IDPN, intradialytic parenteral nutrition.

Painful arm cramps can occur when a high-osmolality IDPN solution is infused too rapidly (the dialysis session may need to be lengthened). Hypoglycemia can occur when a rapid infusion of glucose-containing IDPN solution is suddenly discontinued. Patients should consume some carbohydrates within the last 30 minutes of the IDPN infusion to prevent hypoglycemia. Likewise, if patients dialyze against a glucose-free dialysate, the IDPN should not be discontinued until the conclusion of the hemodialysis procedure.

3. **Potential risks of IDPN.** Hypo- and hyperglycemia, especially in patients with diabetes mellitus, should be anticipated and appropriately treated. Prolonged use of IDPN may lead to an increased risk of infections, abnormalities in lipid profile, and accumulation of fat tissue rather than muscle. When amino acids are given as part of IDPN, there typically will be about a 0.2 decline in the treatment *Kt/V* (McCann, 1999). This decline in *Kt/V* is thought to be due to a sudden increase in urea generation associated with amino acid infusion, which elevates the postdialysis SUN level.

F. TPN. TPN is used in patients with severe nutritional deficits who cannot receive adequate nutritional intake from oral supplements, intraperitoneal amino acids, or IDPN. General guidelines for the formulation of a typical TPN solution are outlined in Table 29.5.

TABLE 29.5 Composition of "Typical" Total Parenteral Nutrition (TPN) Solutions for Hospitalized Patients With Kidney Disease

Component	Amount
70% dextrose (D-glucose)	350 g (500 mL)
8.5% crystalline amino acids (essential and nonessential)	42.5 g (500 mL)

20% lipids or 10% lipids		100 g or 50 g (in 500 mL)
Electrolytes (general guidelines)[a]		
Sodium		40-80 mM
Chloride		25-35 mM
Potassium		<35 mmol/d
Acetate		35-40 mmol/d
Calcium		5 mmol/d
Phosphate		5-10 mmol/d
Magnesium		2-4 mmol/d
Iron		2 mg/d
Vitamins		See text and Table 29.2
Caloric content		
Solution		
Administration Rate	**40 mL/h or 960 mL/d**	**60 mL/h or 1,440 mL/d**
70% dextrose	762 kcal/d	1,142 kcal/d
20% lipid emulsion	640 kcal/d	960 kcal/d
Total	1,402 kcal/d	2,102 kcal/d
70% dextrose	762 kcal/d	1,142 kcal/d
10% lipid emulsion	352 kcal/d	528 kcal/d
Total	1,114 kcal/d	1,670 kcal/d

[a]The specific amount of electrolytes given should be modified based on the patient's clinical condition and serum concentration of electrolytes. The guidelines listed include electrolytes contributed by the infusion of amino acids. Use of a TPN sodium level of about 140 mmol/L will prevent hyponatremia but requires either daily dialysis or continuous renal replacement therapy for adequate volume control.

1. **Carbohydrates.** Approximately 50% to 70% of nonprotein calories in TPN are provided from glucose. Glucose is usually provided as 70% D-glucose to minimize the amount of fluid administered. The precise amount of D-glucose given is dependent on the calculated energy intake indicated for an individual patient. Each milliliter of 70% dextrose provides 2.38 kcal.
2. **Amino acids.** There is much controversy regarding the optimal mix of essential and nonessential amino acids used in TPN solutions. Some authors report that essential amino acids can be used more efficiently than larger quantities of essential and nonessential amino acids, whereas others report the development of nausea, vomiting, and metabolic acidosis when only essential amino acids are administered. Most commercial crystalline amino acid solutions provide a mix of essential and nonessential amino acids.
3. **Lipids.** Lipids can provide up to 50% of the nonprotein calories in TPN solutions. Lipid emulsions are usually available in 10% and 20% solutions; the latter provides 2.0 kcal/mL. Lipids should be given over a 12- to 24-hour period to decrease the risk of decreased functioning of the reticuloendothelial system. Some authors recommend decreasing the amount of lipids given by 50% if the patient is septic or at a high risk for sepsis. There is some controversy regarding the ratio of

polyunsaturated to saturated fatty acids that is preferable in acutely ill patients undergoing dialysis, with most authors recommending a ratio between 1.0 and 2.0. If patients develop marked hypertriglyceridemia, lipid infusions can be provided once or twice weekly instead of daily.

4. **Electrolytes.** The amount of sodium and chloride, the two principal ions, depends on whether continuous kidney replacement therapy (CKRT) or intermittent hemodialysis is being done. With CKRT, the TPN solutions, as well as most other infusates, should have a sodium level close to 140 mM. With intermittent hemodialysis, a lower TPN solution sodium level is often used (40-80 mM) in order to minimize the risk of causing volume overload and pulmonary edema. With SLED (sustained low-efficiency dialysis) given daily, higher TPN solution sodium concentrations often can be used to limit hyponatremia. Acetate, which is metabolized to bicarbonate, is traditionally added to TPN solutions when alkalinization of the serum is desired. The high glucose load plus the anabolism induced by TPN solutions can result in hypokalemia, hypophosphatemia, and hypomagnesemia owing to intracellular shifts of these ions. Therefore, blood levels of these electrolytes should be monitored frequently, and they should be added to the TPN solution or infused separately, as needed.
5. **Vitamins.** Little research has been performed on vitamin requirements in patients with AKI. In general, vitamin supplementation during TPN should be similar to that provided to patients undergoing maintenance dialysis (Table 29.2).
6. **Minerals and trace elements.** Iron should be supplemented to help provide for effective erythropoiesis. Zinc is sometimes given on the basis of some evidence that it accelerates wound healing. Other trace elements probably need not be supplemented unless the patient receives TPN for more than 3 weeks.

G. Intraperitoneal infusion of amino acids in patients undergoing peritoneal dialysis

1. **Indications and benefits.** Amino acid dialysate should be considered in patients undergoing peritoneal dialysis with protein-energy wasting who are unable to tolerate or are not suitable for oral nutritional supplements. Trials conducted using intraperitoneal amino acids have shown benefits only for intermediate markers of nutrition.
2. **Composition, infusion, and complications.** Usually, the amino acid dialysate solution consists of both essential and nonessential amino acids. It is given as the overnight exchange in patients undergoing continuous ambulatory peritoneal dialysis (CAPD) or as the long daytime dwell in patients undergoing continuous cycling peritoneal dialysis in order to maximize protein absorption. The osmotic effect of a 1.0% amino acid dialysate solution is similar to that of a 2.0% dextrose solution. Complications of utilizing amino acid dialysate solutions include anorexia, nausea, vomiting, and an increase in SUN levels, and are more common when patients receive two amino acid dialysate dwells per day versus one per day.

H. Adjuvant therapies and exercise.

Other therapies that have been suggested to improve nutritional status include growth hormone, anabolic steroids, exercise, appetite stimulants, and anti-inflammatory interventions. Evidence of the effectiveness of these interventions is weak and thus none of them are discussed in the KDOQI 2020 Nutrition guidelines.

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30 Diabetes

David J. Leehey and Monica Giles

More than 40% of all new patients starting dialysis in the United States have diabetes. Provision of maintenance dialysis for this group can be a challenging task. Morbidity and mortality are substantially higher in patients with diabetes maintained on dialysis than in their counterparts without diabetes, with cardiovascular disease and infection being the leading causes of death. The overall survival of patients with diabetes undergoing dialysis is approximately 5 years (U.S. Renal Data System [USRDS], 2022).

I. WHEN TO INITIATE DIALYSIS. Early referral to nephrologists of patients with diabetes with renal failure reportedly improves outcomes. The IDEAL (Initiating Dialysis Early and Late) study published in 2010 found no difference in survival between early or late initiation of dialysis (Cooper, 2010). As a result of the IDEAL trial and other observational studies, treatment guidelines changed on the timing of initiating dialysis. Current guidelines on initiating dialysis prioritize clinical signs/symptoms rather than estimated glomerular filtration rate (National Kidney Foundation, 2015). Specifically in patients with diabetes, studies found no difference in survival between early or late initiation of dialysis (Nacak, 2016).

II. HEMODIALYSIS (HD) VERSUS PERITONEAL DIALYSIS (PD). The potential problems with each form of dialysis are listed in Table 30.1. Long-term PD in patients with diabetes may complicate the control of blood glucose because altered glucose homeostasis is stressed further by the large amount of glucose administered via the dialysis solution. In addition, glucose absorption from the abdominal cavity decreases appetite. Many patients undergoing PD have difficulty ingesting the higher recommended amount of protein (1.2 g/kg daily). On the other hand, the incidence and severity of hypoglycemic episodes are reduced in continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD) compared with HD because of the constant or near-constant presence of glucose in the abdomen. Rates of infection (peritonitis, exit-site, and tunnel infections) and rates of catheter replacement are similar between patients on PD with or without diabetes. Administration of insulin intraperitoneally appears to slightly increase the risk of peritonitis in patients undergoing PD and, though appealing on physiologic grounds, is now uncommonly employed. With HD, coexisting blood vessel disease often hinders the creation of an adequate, long-lasting vascular access. The survival rates of both arteriovenous (AV) fistulas and grafts are substantially reduced in patients with diabetes. A small fraction of patients with diabetes develop severe ipsilateral hand ischemia after the creation of an AV fistula, which can lead to gangrene and the need for amputation; prompt ligation of the fistula is indicated in such instances. Because of autonomic nervous system dysfunction or cardiac diastolic dysfunction, patients with diabetes are at increased risk for hypotension during HD. Problems with vascular access and increased risk of hypotension may cause patients with diabetes to receive a lesser amount of dialysis (in terms of

fractional urea clearance [*Kt*/*V*]) than their counterparts who do not have diabetes.

TABLE 30.1 Dialysis Modalities for Patients With Diabetes

Modality	Advantages	Disadvantages
Hemodialysis	Very efficient Frequent medical follow-up (in-center) No protein loss to dialysate	May be poorly tolerated in patients with advanced cardiac disease Multiple arteriovenous access surgeries often required; risk of severe hand ischemia Relatively high incidence of hypotension during dialysis sessions Predialysis hyperkalemia Prone to hypoglycemia
Peritoneal dialysis	Good cardiovascular tolerance No need for arteriovenous access Good control of serum potassium Lower risk of hypoglycemia	Peritonitis, exit-site infection, and tunnel infection (however, risks are similar to those in nondiabetic patients undergoing dialysis) Protein loss into dialysate (may complicate the tendency to malnutrition) Increased intra-abdominal pressure effects (hernias, fluid leaks, etc) (though risks are similar to nondiabetic dialysis patients) Often needs a caregiver (eg, some blind patients)

Lower extremity amputations are frequent in patients with diabetes on either HD or PD. The rate of progression of retinopathy appears to be similar between patients treated with HD and PD. Although visual impairment impedes training for CAPD and makes it difficult for the patient to perform the exchange procedure properly, even blind patients with diabetes can be trained to perform CAPD without a helper. When properly instructed, their risk of developing peritonitis is only slightly greater than the risk in sighted patients with diabetes. A number of devices are available to help visually impaired patients connect the dialysis solution container to the peritoneal transfer set. APD is a better therapeutic choice for blind patients with diabetes because many APD schedules require the performance of only one “on” and one “off” procedure daily.

Earlier reports from the USRDS suggested that mortality is higher in patients with diabetes, and especially women, on PD than in those on HD. Patient selection biases and/or inadequate PD may have affected these observations. In a subsequent large analysis, mortality risk in patients with diabetes with no comorbidity was higher with HD than PD among younger patients but lower with HD than PD in older patients. In those with baseline comorbidity, mortality rates were lower with HD than PD in older patients, with no difference seen in younger patients (Vonesh, 2004). In another study, within 2 years of initiating dialysis, mortality risk was significantly lower in patients with diabetes undergoing PD in comparison to patients with diabetes undergoing HD (Lukowsky, 2013). These results are undoubtedly affected by selection biases. Comorbidity and malnutrition have much larger effects on mortality than the dialysis modality. Meticulous management and prevention of cardiovascular and infectious morbidity may lead to substantial improvement in patient survival.

III. DIET. Whatever the mode of dialysis therapy, patients with diabetes generally show evidence of wasting and malnutrition. Many factors contribute, including chronic inflammation, inadequate food intake, diabetic gastroparesis and enteropathy, and the catabolic stress associated with frequent intercurrent illness. In the event of serious illness,

patients with diabetes undergoing dialysis often require early and intensive nutritional support.

A. Routine dietary prescription. The diets advocated for patients undergoing HD and PD in Chapter 29 also apply to patients with diabetes. In an anuric patient with diabetes being treated with HD, the stringent sodium, potassium, and fluid restrictions described in Chapter 29 should be applied. Special effort should be made to limit the intake of simple sugars and saturated fats.

1. **Carbohydrates percentage.** The general recommendation for a diabetic diet is for 50% to 60% of the intake to be carbohydrates, with some interest in using an even lower carbohydrate diet in patients with diabetes (Arora and McFarlane, 2005). In patients undergoing PD, the glucose calories supplied from the PD regimen (usually around 400 kcal daily) should be subtracted from the dietary carbohydrate prescription, and perhaps in selected patients with hypertriglyceridemia, a focus on avoiding all high-glycemic-index carbohydrates might be of benefit.
2. **Dietary "glycotoxins" from advanced glycosylation end products (AGEs).** Levels of AGEs are increased in food cooked using dry heat technology such as frying, grilling, and baking. The modern Western diet is high in AGEs. Dietary AGE ingestion increases oxidative stress and inflammation. Through oxidative stress and inflammatory pathways, AGEs are involved in the pathogenesis of diabetic kidney disease by glomerular basement membrane thickening, mesangial expansion, podocyte apoptosis, and lipid accumulation in renal tubular epithelial cells (Wu, 2021). Any reason to additionally restrict food in patients with end-stage kidney disease (ESKD) should be done with caution, given the high prevalence of malnutrition; however, some attention to food preparation with a focus on minimizing formation of AGEs (minimization of deep frying, extensive heating) and reducing consumption of high AGE foods might be a consideration.

B. Diabetic gastroparesis and enteropathy. The diagnosis of diabetic gastroparesis is often made on the basis of symptoms of nausea, vomiting, abdominal pain, bloating, early satiety, and postprandial fullness. Esophagogastroduodenoscopy should be performed to exclude mechanical obstruction before symptoms are ascribed to gastroparesis alone. Scintigraphic measurement of gastric emptying is the criterion standard and most widely used diagnostic tool. However, scintigraphy exposes patients to radiation and is therefore not ideally suited for repeated investigations (to monitor the response to therapy). This problem can be overcome by gastric emptying breath tests (such as the octanoic acid breath test) or wireless motility capsule. Diabetic gastroparesis can be associated with poor food intake and unpredictable nutrient absorption; the result can be hypoglycemia alternating with hyperglycemia. In such patients, small, frequent (up to 6 times per day) low-fat, low nonsoluble fiber meals may improve symptoms. The pharmacologic treatment of gastroparesis in patients with diabetes undergoing dialysis is unsatisfactory. Metoclopramide and erythromycin are the only medications approved by the U.S. Food and Drug Administration (U.S. FDA) for gastroparesis. Metoclopramide is given in a small starting dose (5 mg before meals) with small increments until results are seen. This drug is associated with a high incidence of extrapyramidal complications in patients undergoing dialysis, particularly at higher doses, and its effects are often temporary. Other "prokinetic" gastrointestinal motility drugs, such as domperidone, motilin agonists, or ondansetron, may be tried.

Diabetic enteropathy results from functional impairment of the enteric nervous system and can result in disordered motility of the small bowel and the colon, resulting in either prolonged or shortened bowel transit times. Diabetic enteropathy with resulting diarrhea can complicate alimentation, causing debilitation, poor food intake, and hypoglycemia. Severe cases of diabetic enteropathy can be treated with a trial of broad-spectrum antimicrobials (eg, doxycycline in a dose of 50 or 100 mg daily) to combat bacterial overgrowth in the intestine. Loperamide hydrochloride (up to 10 mg daily) to decrease bowel motility is also useful.

IV. CONTROL OF BLOOD SUGAR

A. Alteration of insulin metabolism by chronic kidney disease (CKD).

In uremic patients (both those with and those without diabetes), both insulin secretion by the β cells of the pancreas and responsiveness of peripheral tissues (eg, muscle) to insulin are decreased (ie, there is increased insulin resistance). Insulin resistance occurs in almost all uremic patients and results in hyperglycemia. Hepatic glucose production and uptake appear to be normal in uremia, and skeletal muscle is the primary site of insulin resistance, probably via a postreceptor defect (Castellino, 1992). However, many of the actions of insulin are maintained in renal failure, including potassium uptake by the cells and inhibition of proteolysis.

The kidney is pivotal in insulin metabolism in healthy individuals. Insulin is freely filtered by the glomerulus, with 60% cleared via glomerular filtration and 40% by extraction from the peritubular vessels; less than 1% of filtered insulin is excreted in the urine unchanged. Approximately 6 to 8 units of insulin are degraded by the kidney each day, roughly 25% of the daily production of insulin by the pancreas. Renal metabolism is enhanced in patients with diabetes receiving exogenous insulin since injected insulin bypasses the liver and goes directly into the systemic circulation. The rate of insulin catabolism is decreased owing to decreased renal mass, and therefore the half-life of any insulin present in the circulation is prolonged. The reduction in insulin clearance is also mediated by a decline in hepatic metabolism. These abnormalities are only partially corrected after institution of maintenance dialysis therapy.

1. **Abnormal glucose tolerance tests in all patients undergoing dialysis.** The glucose tolerance test cannot be used to diagnose diabetes in patients undergoing dialysis because the rise in serum glucose concentration will be greater and more prolonged than normal in all patients undergoing dialysis due to uremia-induced insulin resistance. However, fasting serum glucose concentrations are normal in nondiabetic patients undergoing HD; a high level suggests the presence of diabetes. In patients undergoing PD, a true fasting state is never achieved owing to the constant absorption of glucose from the dialysis solution. In this group, unless peritonitis is present, the “fasting” serum glucose value rarely exceeds 160 mg/dL (8.9 mmol/L), even when using 4.25% dextrose dialysis solution; higher levels suggest that the patient has diabetes. In patients undergoing CAPD using icodextrin, serum glucose values may be spuriously overestimated by autoanalyzers that use the glucose dehydrogenase method of sample analysis (Tsai, 2010).
2. **Increased sensitivity to insulin.** Initiation of dialysis may result in improved insulin sensitivity because of improved uremia, acidosis, and phosphate metabolism. Furthermore, glucose metabolism is altered in HD through impaired clearance of

glucoregulatory hormones (insulin, glucagon, C-peptide). In patients with diabetes undergoing dialysis being treated with exogenous insulin, the importance of reduced insulin catabolism overrides the impact of insulin resistance; when exogenous insulin is administered, its effect may be intensified and prolonged. Thus, smaller-than-usual doses should be given. Bolus administration of moderately large intravenous doses (eg, 15 units of regular insulin), even when ketosis is present, can result in severe hypoglycemia. Hypoglycemia can also occur after administration of the longer-acting insulins, such as isophane insulin (also known as Neutral Protamine Hagedorn or NPH) and insulin glargine.

3. **Hyperglycemia.** The clinical presentation of hyperglycemia is modified when renal function is absent. Decreased glucose filtration and excretion by the kidneys may result in the development of severe hyperglycemia (serum glucose level >1,000 mg/dL [56 mmol/L]). However, severe hyperosmolality with accompanying alteration of mental status is unusual because of the absence of water loss induced by osmotic diuresis. Indeed, even extreme hyperglycemia is often asymptomatic in patients undergoing dialysis (Al-Kudsi, 1982). On occasion, manifestations can include thirst and signs of volume expansion such as weight gain and pulmonary edema. In rare cases, patients may present comatose due to neurologic manifestations of severe hypertonicity (Tzamaloukas, 2008). Diabetic ketoacidosis, frequently accompanied by severe hyperkalemia and coma, can develop in insulin-dependent patients undergoing dialysis. Management of hyperglycemia with or without ketoacidosis differs from that in patients without renal failure in that administration of large amounts of fluid is unnecessary and generally contraindicated. All clinical and laboratory abnormalities of hyperglycemia are corrected by insulin administration, which often is the only treatment needed. To manage severe hyperglycemia, one can administer a continuous infusion of low-dose regular insulin (starting at 0.05-0.10 units/kg/h) with close clinical monitoring and measurement of serum glucose and potassium concentrations at 2- to 3-hour intervals. Gradual correction of hyperglycemia (reduction rate of 50-75 mg/dL/h) is necessary to avoid cerebral edema (Dhatariya, 2020). If severe hyperkalemia is present, electrocardiography should be done. Emergency dialysis may be needed in patients with hyperglycemia and either severe pulmonary edema or life-threatening hyperkalemia that does not improve with insulin administration.
4. **Hypoglycemia.** Avoidance of hypoglycemia is often the rate-limiting step in obtaining good glucose control. Treatment for hypoglycemia can lead to rebound hyperglycemia and erratic glycemic control. There are many factors that contribute to hypoglycemia, including decreased caloric intake due to attendant anorexia, decreased insulin clearance, reduced renal gluconeogenesis due to the reduction in functioning renal mass, impaired release of the counterregulatory hormone epinephrine due to the autonomic neuropathy of renal failure, decreased hepatic metabolism of insulin, and decreased metabolism of drugs that might promote a reduction in the plasma glucose concentration, such as alcohol, propranolol, and other nonselective adrenergic blockers. Additionally, hypoglycemic unawareness and gastroparesis may increase the risk for hypoglycemia. In patients with diabetes, the HD solution should always contain 100 to 200 mg/dL glucose; if glucose is not added, severe hypoglycemia during or soon after the HD session can result

(Burmeister, 2012; Padmanabhan, 2018). The higher (200 mg/dL, 11 mM) dialysate glucose level may increase the frequency of hyperglycemia (Raimann, 2012), while not protecting against hypoglycemic episodes, so 100 mg/dL (5.5 mM) is the current standard.

B. Insulin therapy. Achieving and maintaining reasonable glucose control while avoiding hypoglycemia is the challenge in managing patients with diabetes on dialysis. HbA_{1c} levels less than 6.0% or greater than 8.0% are each associated with increased mortality risk (Ricks, 2012). Reasonable glycemic control in patients with diabetes on chronic dialysis is considered a fasting blood glucose below 140 mg/dL and a 1-hour postprandial value of less than 200 mg/dL with an HbA_{1c} between 7% and 8%. The HbA_{1c} target that is associated with the best outcome in patients undergoing dialysis has not been established (Kidney Disease Outcomes Quality Initiative [KDOQI] clinical practice guidelines, 2012). In patients undergoing dialysis, HbA_{1c} may overestimate or underestimate glycemic control as a result of several influencing factors such as iron deficiency anemia, metabolic acidosis, malnutrition, and erythropoietin. Glycated albumin and fructosamine measurements as alternative markers for glycemic control in dialysis have been proposed; however, the quality of supporting evidence remains limited.

Irreversibly and slowly formed compounds that are the result of nonenzymatic glycosylation of proteins, the so-called AGEs, alter the structure and function of vascular basement membranes, stimulate the production of growth factors, and alter the function of intracellular proteins. In patients undergoing PD, AGE deposition in the peritoneal membrane is associated with an increase in permeability and excessive protein losses in the dialysate (Nakamoto, 2002).

1. **Example using glargine and rapid-acting insulin.** As an example, a common weight-based dose might be 0.6 units/kg total daily dose of insulin (Murphy, 2009). Reducing this by 50% for ESKD changes this to 0.3 units/kg total daily dose of insulin (Baldwin, 2012). Of this, half should be given as basal insulin and half as mealtime bolus insulin. This would mean that 0.15 units/kg would be given in the morning as a basal dose, and then the remainder (0.15 units/kg) divided up by the number of meals, given as rapid-acting insulin; say 0.05 units/kg at breakfast, lunch, and supper. For a 70-kg patient, the total dose of insulin would be 70 kg × 0.3 units/kg = 21 units. Half of this, or approximately 10 units, would be given as the basal once-daily glargine, and the remaining 11 units would be given over the three daily meals, or 3 to 4 units of rapid-acting insulin per meal.
2. **Example using NPH plus a rapid-acting insulin.** When using NPH with rapid-acting insulin, the total daily dose would be the same (21 units), but two-thirds of the daily dose (or 14 units) should be given as NPH, with two-thirds of the NPH (9 units) given at breakfast and the remaining 5 units of NPH at bedtime. The non-NPH remainder of the total daily dose (7 units) would then be given as rapid-acting insulin, giving 3 units at breakfast and 4 units at dinner. A lunchtime dose of rapid-acting insulin is not needed, as the morning dose of NPH is peaking at this time and would cover this meal.
3. **Other insulin formulations.** Pharmacokinetics of insulin degludec are comparable at various levels of kidney function, including ESKD. Renal clearance of insulin degludec is negligible, and HD does not affect the clearance of degludec;

therefore, dose adjustments may not be necessary. Additionally, insulin degludec is associated with lower hypoglycemia risk in comparison to glargine and detemir insulins. In regard to concentrated U-300 glargine insulin, there are no studies to confirm the necessity of dose adjustments with HD initiation. In one study, administration of insulin detemir in patients with diabetes on dialysis was associated with lower glycemic variability and proinflammatory profiles in comparison to insulin glargine (Savu, 2016). Inhaled rapid-acting human insulin has not been studied in ESKD.

4. **Timing of mealtime insulin.** While mealtime insulin is generally given about 5 minutes before the meal, some patients prefer to take it just after the meal. This is somewhat safer in that it allows patients to reduce the insulin dose if the entire meal is not eaten. For example, if only 50% of the meal is eaten, only 50% of the dose is taken. Finer enhancements of the mealtime insulin dose include modification by carbohydrate counting (if the patient is willing to learn and implement this technique) and by addition to or subtraction from the mealtime insulin dose using a correction factor scale (if the patient is willing to check their glucose values before each meal).

   With both of the above regimens, a reasonable "correction dose" of rapid-acting insulin would be 1 extra unit of daily insulin for every 50 mg/dL glucose above target (eg, the target level might be 150 mg/dL for that patient).

5. **Glucose monitoring.** It is important that blood glucose levels be monitored closely and that individually appropriate dose adjustments in insulin therapy be made. Patients receiving insulin therapy at home should monitor their glucose levels at least twice daily, in the morning and at bedtime (American Diabetes Association [ADA], 2024). Continuous glucose monitoring (CGM) is useful for patients managed with insulin on dialysis. Since HbA_{1c} may be less reliable in patients on dialysis, CGM may provide a more accurate assessment of glycemic control and insulin needs. Further, in patients treated with insulin, the use of CGM may help prevent hypoglycemia and improve overall glycemic control. In patients with stage 3 to 5 CKD, observational data suggest that the use of CGM is associated with a reduced rate of hospitalizations (Hannah, 2024).

6. **Effect of HD on insulin dose.** HD has been shown to improve both tissue sensitivity to insulin and insulin secretory response to glucose (DeFronzo, 1978). The mechanism by which this occurs is unknown, but improved acid-base status may be contributing. When HD is initiated, the insulin requirement in any given patient may change, depending on the net balance between improved tissue sensitivity and improved hepatic insulin metabolism. One cannot readily predict insulin requirements in this setting, and careful observation of the patient is essential.

   In patients undergoing HD, several different insulin regimens can be used to achieve glycemic control. The glargine- and NPH-based regimens described earlier can be used as a starting point. Some experts feel that long-acting insulin preparations should be avoided, while others feel that such agents should be used, but there are no head-to-head comparisons of different regimens in patients undergoing dialysis.

   With regard to insulin therapy on dialysis versus nondialysis days, the usual

baseline dose is normally given, but the timing of mealtime doses is often changed when dialysis alters the times when food is consumed. Small studies demonstrated that in patients undergoing maintenance dialysis, a 25% reduction in basal insulin pre- and post-HD reduced hypoglycemic episodes (Singhsaku, 2019; Sobngwi, 2010). With insulin degludec, adjustments are not recommended with maintenance HD, which may make it preferable to other basal insulin formulations. Further, with maintenance HD, a 10% to 15% reduction in rapid-acting insulin dose closest to the dialysis session is suggested in the Joint British Diabetes Societies guidelines (Frankel, 2018).

7. **Effect of PD on insulin dose.** The glucose contained in peritoneal dialysate increases the need for blood glucose-lowering therapy, and more insulin is often required because of insulin resistance and the glucose load absorbed from the hypertonic dialysate. A 1.5% dextrose (glucose monohydrate, molecular weight [MW] 198) dialysate solution, for example, has a glucose (MW 180) concentration of 1,500 × (180/198) = 1,364 mg (76 mmol/L), well above that in the plasma. On the other hand, in some patients undergoing PD, less insulin can be required than anticipated owing to decreased carbohydrate intake and to prolongation of the duration of action of insulin resulting from reduced renal and hepatic insulin clearance.

   To help maintain near-normal glycemia during PD, blood glucose in patients treated with CAPD or APD can be controlled with intraperitoneal insulin, although this is now done only rarely. Use of the intraperitoneal route has the advantages of a continuous or nearly continuous presence of insulin, elimination of the need for injections, and a more physiologic route of insulin supply to the liver via the portal vein, mimicking the way that pancreatic insulin reaches the liver (Tzamaloukas, 1991). Disadvantages are the potential for bacterial contamination of dialysate during injection of insulin into the bags, need for somewhat higher daily total insulin doses due to losses of insulin with the spent dialysate, and, perhaps of greatest concern, the risk of peritoneal fibroblastic proliferation and hepatic subcapsular steatosis (Maxwell, 1991). If intraperitoneal insulin is used, it is recommended that a long, 3.8-cm (1.5 in) needle be used to ensure that the full dose of insulin is injected into the dialysis solution container rather than being trapped in the infusion port; the dialysis solution container should be inverted several times after injection to ensure proper mixing. For intraperitoneal insulin protocols, please refer to previous editions of this Handbook.

   It is important to remember that icodextrin and maltose, which are contained in some PD solutions, can interfere with, or cause falsely elevated glucose results with, some self-monitoring methods, possibly leading to inappropriate therapy (Firanek, 2014; Tsai, 2010).

8. **Use of an insulin infusion pump.** Patients on dialysis with insulin-requiring type 2 diabetes and type 1 diabetes may benefit from insulin pump therapy. Automated closed-loop delivery system treatment in patients with type 2 diabetes on HD resulted in 38% increased time in the target glycemic range in comparison to patients treated with subcutaneous insulin (Bally, 2019). In patients using insulin pump therapy, the insulin infusion may be shut off 1 hour or so prior to HD and resumed shortly after the dialysis session is completed (Atherton, 2004).

9. **Insulin regimens.** As noted above, it is recommended to reduce insulin doses by 50% for patients with eGFR less than 10 mL/min.

C. Oral hypoglycemic agents and noninsulin injectable agents. These agents are useful adjuncts in the treatment of patients with diabetes and are used by many nephrologists. Suggested agents and appropriate doses are listed in Table 30.2. Using data from USRDS from 2012 through 2017, insulin was the most prescribed antihyperglycemic agent, followed by sulfonylureas (SUs), dipeptidyl peptidase 4 inhibitors (DPP-4is), and thiazolidinediones. During this time period, use of DPP-4is increased. There also was a minimal increase in the use of glucagon-like peptide (GLP) receptor agonists, while the number of SU prescriptions decreased (Klein, 2022).

TABLE 30.2 Agents for Diabetes in Chronic Kidney Disease

Drug	Usual Nonuremic Dose	Dose for Patient Undergoing Dialysis (% of Nonuremic dose)
Insulins		
Short-acting		
Regular	0.2-1 units/kg/d SC b.i.d.–q.i.d.	Decrease dose (25%-50%)
Aspart	0.2-1 units/kg/d SC b.i.d.–q.i.d.	Decrease dose (25%-50%)
Glulisine	0.2-1 units/kg/d SC b.i.d.–q.i.d.	Decrease dose (25%-50%)
Intermediate-acting		
NPH	0.2-1 units/kg/d SC q24h–b.i.d.	Decrease dose (not defined)
Long-acting		
Glargine	0.1-1 units/kg/d SC q24h	Decrease dose (not defined)
Detemir	0.1-1 units/kg/d SC q24h	Decrease dose (not defined)
Degludec	0.1-1 units/kg/d SC q24h	Same (100%)
Sulfonylureas		
Glipizide	2.5-20 mg PO q24h–b.i.d.	2.5-10 mg PO q24h–b.i.d. (50%)
Glimepiride	1-8 mg PO q24h	1-4 mg PO q24h (50%)
Glyburide	1.25-10 mg PO q24h	Avoid in renal failure
Thiazolidinediones[a]		
Pioglitazone	15-45 mg PO q24h	Same (100%)
α-Glucosidase inhibitors		
Acarbose	50-100 mg PO t.i.d.	Avoid in renal failure.
Miglitol	50-100 mg PO t.i.d.	Avoid in renal failure.
Meglitinides		
Repaglinide	0.5-8 mg PO t.i.d.	0.5-4 mg PO t.i.d. (50%)
Nateglinide	60-120 mg PO t.i.d.	Avoid in renal failure.

Biguanides		
Metformin	500-2,000 mg PO q24h-b.i.d	Avoid in renal failure.
Amylin analog		
Pramlintide	30-120 mcg SC q.a.c.	Same (100%). No data on patients undergoing dialysis
SGLT-2 inhibitors		
Empagliflozin	10-25 mg PO q24h	Avoid in dialysis.
Dapagliflozin	5-10 mg PO q24h	Avoid in dialysis.
Ertugliflozin	5-15 mg PO q24h	Avoid in dialysis.
Canagliflozin	100-300 mg PO q24h	Avoid in dialysis.
DPP-4 inhibitors		
Sitagliptin	100 mg PO q24h	If eGFR ≥30 mL/min/1.73 m^2 and <50 mL/min/1.73 m^2, 50 mg (50%) If eGFR <30 mL/min/1.73 m^2, 25 mg (25%)
Saxagliptin	2.5-5 mg PO q24h	If eGFR <50 mL/min/1.73 m^2, 2.5 mg (50%)
Linagliptin	5 mg PO q24h	Same (100%)
Alogliptin	25 mg PO q24h	If eGFR ≥30 mL/min/1.73 m^2 and <50 mL/min/1.73 m^2, 12.5 mg (50%) If eGFR <30 mL/min/1.73 m^2, 6.25 mg (25%)
GLP-1 receptor agonists		
Exenatide	2 mg weekly SC 5-10 mcg b.i.d. SC	Avoid in renal failure.
Liraglutide	0.6-1.8 mg q24h SC	Same (100%)
Semaglutide	0.25-2 mg qweekly SC	Same (100%)
Semaglutide oral	3-14 mg PO q24h	Same (100%)
Dulaglutide	0.75-4.5 mg qweekly SC	Same (100%)
Tirzepatide[b]	2.5-15 mg qweekly SC	Limited data in dialysis

b.i.d., 2 times/d; DPP-4, dipeptidyl peptidase 4; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide 1; NPH, neutral protamine hagedorn; PO, by mouth; SGLT-2, sodium-glucose cotransporter 2; q.a.c., before meals; q.i.d., 4 times/d; q24h, daily; t.i.d., 3 times/d; SC, subcutaneously.

[a]May cause fluid retention in patients with chronic kidney disease not on dialysis.

[b]Dual GLP-1 RA and GIP.

1. **Sulfonylureas (SUs).** SUs are insulin secretagogues that bind to the SU receptor, a part of the potassium channel, on pancreatic β cells. They cause potassium channel closure with subsequent membrane depolarization, which, in turn, causes the opening of voltage-gated calcium channels. This allows for a sudden increase in intracellular calcium, which causes preformed insulin to be released from intracellular secretory granules. First-generation SUs (acetohexamide, chlorpropamide, tolazamide, and tolbutamide) are rarely used and should be avoided in ESKD. All second-generation SUs undergo hepatic metabolism with a variable percentage of renal excretion (Spiller, 2006). As GFR declines, clearance of SUs and their metabolites also decreases, resulting in a higher risk of hypoglycemia. Once GFR is less than 60 mL/min/1.73 m^2, glyburide should be avoided and glimepiride should be used with caution and discontinued once GFR is less than 30

mL/min/1.73 m^2. The metabolite of **glipizide** has little or no hypoglycemic activity and a short half-life of 2 to 4 hours. Therefore, even though its renal excretion is high (80%-85%), glipizide is the SU of choice in patients undergoing dialysis. However, SUs as a class show a relatively high incidence of hypoglycemia, plus many drugs frequently used in patients undergoing dialysis can either antagonize (phenytoin, nicotinic acid, diuretics) or enhance (salicylates, warfarin, ethanol) the hypoglycemic action of SUs. Another reason that SUs are not optimal in the ESKD population is that their mechanism of action (facilitating insulin release) presupposes that the individual being treated is still producing some endogenous insulin. In people with type 2 diabetes, endogenous insulin, assessed by C-peptide measurements, was highest in people with recently diagnosed disease and progressively decreased as the duration of diabetes increased (Duckworth, 2011). Since most people on dialysis will have had diabetes for a fairly long time, many will be producing little or no endogenous insulin and so will be unable to respond to SUs.

2. **Metformin.** Metformin, a member of the biguanide class, is perhaps the most widely used oral agent to treat type 2 diabetes in patients with normal renal function and has several distinct advantages. Metformin use is associated with a very low incidence of hypoglycemia, is body weight neutral, and has a favorable effect on serum lipids. Its mechanism of action is to acutely decrease hepatic glucose production by transiently inhibiting the respiratory enzyme chain in mitochondria. However, metformin has been associated with the rare complication of life-threatening lactic acidosis. The causation of this association is not completely clear, and acidosis is most commonly seen in patients with substantial comorbidity, and patients with markedly reduced renal function are at increased risk. Metformin is not metabolized, and 90% is excreted as an active drug by the kidneys (Spiller, 2006). Plasma metformin levels are thus substantially higher in patients with reduced creatinine clearance (Lipska, 2011). Metformin is contraindicated in patients with a GFR less than 30 mL/min/1.73 m^2. In patients with eGFR 30 to 44 mL/min/1.73 m^2, metformin dose should be reduced to a maximum of 1,000 mg/day. In patients with eGFR greater than 45 mL/min/1.73 m^2, the maximally tolerated dose is recommended. Metformin has been associated with the symptomatic development of vitamin B_{12} deficiency, and an argument can be made for monitoring serum B_{12} levels in patients taking the drug, especially in the higher dose range. Metformin at any dose should not be given to patients undergoing dialysis.
3. **α-Glycosidase inhibitors.** There are two α-glucosidase inhibitors available in the United States: acarbose and miglitol. They work by competitively and reversibly inhibiting gut enzymes that mediate the intestinal breakdown of oligosaccharides into simple sugars, thereby limiting their absorption. Postprandial glucose surges are reduced without stimulation of endogenous insulin, and, thus, the risk of hypoglycemia is relatively low. Little **acarbose** is absorbed, but it is extensively metabolized in the gut, and about one-third of the metabolites, some active, are absorbed (Reilly, 2010; Spiller, 2006). In patients with reduced renal function, the plasma levels of acarbose and its metabolites can increase. **Miglitol** is absorbed to a greater extent than acarbose. Miglitol is not metabolized and is excreted unchanged in the urine (Reilly, 2010; Spiller, 2006). Neither acarbose nor miglitol has been

well studied in patients in whom eGFR is less than 25 mL/min/1.73 m^2, and, in general, their use is not recommended in patients undergoing dialysis.

4. **Peroxisome proliferator-activated receptor (PPAR) agonists (thiazolidinediones).** PPAR-γ agonists include drugs such as rosiglitazone and pioglitazone. These drugs sensitize target tissues to insulin, increase glucose uptake in muscle and adipose tissue, and decrease hepatic glucose production. They may also have beneficial anti-inflammatory, vascular, and metabolic (hypolipidemic) effects. Furthermore, hypoglycemia risk is low.

   Pioglitazone is metabolized primarily by the liver. It has been found to be safe and effective as monotherapy and add-on therapy to other oral antidiabetic agents in patients on HD when studied up to 96 weeks (Abe, 2010). There is no need for dose reduction. Pioglitazone has been associated with bladder cancer. In the United States, it carries a warning to avoid use in patients with active bladder cancer and to consider risks versus benefits prior to initiating therapy in patients with a history of bladder cancer. Like pioglitazone, rosiglitazone is metabolized primarily by the liver. **Rosiglitazone** was effective at all degrees of renal function (Chapelsky, 2003). One group found an increase in interdialysis weight on rosiglitazone, but this study lacked a true control group (Chiang, 2007). There was no meaningful change in the pharmacokinetics of the drug in patients on HD, and there was no difference in plasma drug levels on dialysis compared with nondialysis days (Thompson-Culkin, 2002), suggesting no need for dosage adjustment because of altered renal function. However, in one study of patients on CAPD, the half-life of rosiglitazone was increased compared with healthy volunteers (Aramwit, 2008). In 2007, a review of a variety of sources of available data linked rosiglitazone with an increased risk of myocardial infarction and cardiovascular death, and its use has been restricted in the United States (Nissen and Wolsky, 2007). This restriction was partially lifted by the FDA in November 2013, but rosiglitazone remains suspended from the market in Europe and a number of other countries. Both pioglitazone and rosiglitazone have been associated with weight gain, bone loss, edema, and congestive heart failure in nonuremic patients; the mechanism is thought to be increased renal retention of sodium and water. Acute myopathy has been reported when thiazolidinediones were given in conjunction with fibrates.

5. **Meglitinides. Repaglinide** is a member of the meglitinide family of compounds and acts as an insulin secretagogue. It binds to the SU receptor and functions in a manner similar to the SUs, but it has an additional β-cell binding site and thus a different binding profile (Hatorp, 2002). It differs from the SUs in several ways. First, it has a much shorter duration of action with a half-life of 1 to 1.5 hours with somewhat less hypoglycemic risk than SUs. Second, it is eliminated almost entirely by hepatic metabolism with biliary or fecal excretion of mainly inactive metabolites. Only 8% is excreted in urine. Like SUs, it is highly protein bound. Several studies have examined the impact of renal disease on repaglinide pharmacokinetics (Hatorp, 2002; Marbury, 2000; Schumacher, 2001). In general, there is no impact with moderate renal disease. However, with more severe renal disease (GFR < 30 mL/min), the “area under the curve” of the plasma level of the drug was higher because of increased elimination half-life. Despite these findings, there was little difference in hypoglycemia, and repaglinide is not contraindicated in people with

renal disease but should be used with caution, starting at a low dose (0.5 mg once daily) and titrating upward slowly to a maximum dose of 2 mg with each meal (up to 4 times/d). Studies were not conducted in patients with eGFR less than 20 mL/min/1.73 m^2 or in patients with renal failure requiring dialysis. Like the SUs, repaglinide may not be effective if the individual being treated can no longer generate endogenous insulin.

In contrast to repaglinide, which has primarily fecal excretion, **nateglinide**, another meglitinide, is 90% excreted by the kidney, primarily as active metabolites (Reilly, 2010; Spiller, 2006). Use of nateglinide in patients on dialysis should thus be avoided or done with the greatest caution.

6. **GLP-1 receptor agonists.** There are five GLP-1 receptor agonists available, exenatide (which comes in both twice-per-day and once-per-week formulations), liraglutide, dulaglutide, lixisenatide, and semaglutide. GLP-1 is a naturally occurring gut peptide made and secreted by colonic L-cells in response to meals. It has multiple actions, including stimulation of endogenous insulin secretion, inhibition of endogenous glucagon secretion, delay of gastric emptying, and inhibition of appetite. The effects on insulin and glucagon are glucose dependent, that is, they occur only in the presence of hyperglycemia. These actions result in improved glucose control with little hypoglycemic risk (as monotherapy) and weight loss. Endogenous GLP-1 is rapidly degraded by dipeptidyl peptidase 4 (DPP-4). However, GLP-1 receptor agonists are degradation resistant and undergo little systemic metabolism. GLP-1 receptor agonists reduce albuminuria, slow eGFR decline, and reduce major adverse cardiovascular events in patients with type 2 diabetes. The most common side effects are nausea, vomiting, and diarrhea. Further, increased heart rate (~5 bpm) is seen with GLP-1 receptor agonists. GLP-1 receptor agonists are not recommended for patients at risk for thyroid C-cell tumors, pancreatic cancer, or pancreatitis.
    a. **Incretin mimetics. Exenatide** (long-acting release, immediate release) and **lixisenatide** are derived from exendin-4 (a peptide isolated from saliva of the Gila monster). They are excreted mainly by the kidneys. The half-life increases with decreasing renal function. Exenatide is generally well tolerated in mild and moderate renal insufficiency without dose adjustment, but not in subjects with ESKD (Linnebjerg, 2007). Its use is contraindicated for those with eGFR less than 30 mL/min/1.73 m^2 (eGFR < 45 mL/min/1.73 m^2 for long-acting release exenatide), including patients on maintenance dialysis. Caution is advised for people who have received kidney transplants.
    b. **Human GLP-1 analogues: Dulaglutide, semaglutide (injectable and oral), and liraglutide.** In contrast to incretin mimetics, human GLP-1 analogues have specific molecular characteristics (binding to albumin, immunoglobulin, and fatty acids) that prevent elimination through the kidneys. Therefore, they can be safely used in advanced kidney disease with an eGFR of 15 mL/min/1.73 m^2, including patients undergoing dialysis. No dose adjustment for CKD is required in US labeling; however, there are limited data with respect to use in patients on dialysis and caution is advised.
    c. **Tirzepatide** is a dual agonist glucose-dependent insulinotropic peptide (GIP)-GLP-1. Adding GIP is thought to potentiate the central effects of GLP-1-induced

food intake reduction. In clinical trials, it demonstrated significant weight and A_{1c} reduction in patients with type 2 diabetes. Most common side effects are nausea, vomiting, and diarrhea. Similar to GLP-1 receptor agonists, tirzepatide is not recommended for patients at risk for thyroid C-cell tumors, pancreatic cancer, or pancreatitis.

In pharmacokinetic studies, various degrees of renal impairment, including dialysis, did not result in clinically significant effects on tirzepatide pharmacokinetics. Therefore, dose adjustments may not be required for renal impairment (Urva, 2021). In patients with type 2 diabetes and high cardiovascular risk, in comparison to insulin glargine, tirzepatide reduced the rate of eGFR decline, albuminuria, and new onset micro- and macroalbuminuria (Heerspink, 2022). Future studies are needed to evaluate the safety and efficacy of tirzepatide use in patients with type 2 diabetes and CKD and in particular those requiring maintenance dialysis.

7. **Dipeptidyl peptidase-4 (DPP-4) inhibitors.** There are four DPP-4 inhibitors now available in the United States: sitagliptin, saxagliptin, linagliptin, and alogliptin. As a group, they act by inhibiting the enzyme (DPP-4), which rapidly degrades endogenous incretin hormones. The major incretin is GLP-1, a gut hormone that stimulates insulin, suppresses glucagon, delays gastric emptying, and decreases appetite.

Approximately 75% to 80% of an oral dose of **sitagliptin** is excreted unchanged in the urine, and sitagliptin levels markedly increase with declining renal function (Bergman, 2007). Because of this, it is recommended that the dose be adjusted on the basis of eGFR. A 100-mg daily dose can be given if eGFR is more than 50 mL/min/1.73 m^2. This dose should be reduced to 50 mg if eGFR falls below 50 mL/min/1.73 m^2 and to 25 mg daily if eGFR is below 30 mL/min/1.73 m^2 or if the patient is on dialysis (Arjona Ferreira, 2013). At these reduced doses, sitagliptin was similarly effective in improving glycemic control as glipizide with less severe hypoglycemia (0% vs 7.7%) in patients on dialysis. These findings confirm an earlier study in which hypoglycemia was much less common with sitagliptin (4.6% of the patients treated with sitagliptin compared with 23% of those treated with glipizide) (Chan, 2008). The fraction removed by HD is relatively small, 13% and 4%, for HD initiated 4 or 48 hours postdose, respectively, so that sitagliptin can be administered without regard to the timing of HD (Bergman, 2007).

Saxagliptin, the second DPP-4 inhibitor to reach the market, has a major active metabolite, 5-hydroxy saxagliptin, which is about half as potent as the parent compound (Boulton, 2011). About 75% is excreted in the urine; 24% is saxagliptin and 36% is 5-hydroxy saxagliptin and minor metabolites. Levels of saxagliptin and 5-hydroxy saxagliptin rise with the degree of renal impairment, with the metabolite rising to a greater degree than saxagliptin itself. Because of this, a dosage adjustment is advised. A full 5-mg dose of saxagliptin can be used if eGFR is greater than 50 mL/min/1.73 m^2, but the dose should be reduced to 2.5 mg daily for lower eGFR. Interestingly, in patients on HD, saxagliptin concentrations are slightly lower than in healthy subjects, but 5-hydroxy saxagliptin is much higher. It has been speculated that this may be due to the efficient removal of saxagliptin by HD. Because 4 hours of HD removes about 23% of saxagliptin, it should be given after

dialysis sessions. Saxagliptin was superior to placebo in improving glycemic control in those with moderate or severe renal insufficiency, but saxagliptin was no better than placebo in those with ESKD (Nowicki, 2011). The percentage of patients with hypoglycemic events was similar between those treated with saxagliptin (28%) and those treated with placebo (29%) (Nowicki, 2011).

The elimination of the third available DPP-4 inhibitor, **linagliptin**, is not dependent on the kidney. Renal excretion of unchanged linagliptin is less than 7%, and the degree of renal impairment does not affect linagliptin concentrations. Its 5-mg daily dose does not need to be adjusted in renal disease (Graefe-Mody, 2011).

About 10% to 20% of **alogliptin** is metabolized by the liver into compounds with little pharmacologic activity. Approximately 63% is excreted unchanged by the kidney. Alogliptin doses should be reduced by one-half of the standard dose (to 12.5 mg/d) for patients with eGFR between 30 and 50 mL/min/1.73 m^2 and by three-quarters (to 6.25 mg/d) in those with eGFR less than 30 mL/min/1.73 m^2 or ESKD requiring HD (Golightly, 2012).

Safety concerns have been raised with the incretin category of antidiabetic agents relating to a pancreatic safety signal associated with incretin-based medications. Large meta-analyses of DDP-4 inhibitors demonstrated no increased risk of pancreatic cancer; however, there was a small increased risk of pancreatitis (Pinto, 2018).

8. **Sodium-glucose cotransporter 2 inhibitors.** Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin are sodium-glucose cotransporter 2 inhibitors (SGLT-2i). These medications lower the renal threshold for glucose, cause osmotic diuresis by increasing urinary glucose excretion, and thereby decrease plasma glucose in patients with hyperglycemia. SGLT-2i also shifts metabolism from carbohydrate utilization to ketogenesis. Potential side effects include diabetic ketoacidosis, genital mycotic infections, volume depletion, and questionable risk of lower-limb amputations with canagliflozin.

   For patients with eGFR greater than or equal to 20 mL/min/1.73 m^2, canagliflozin, dapagliflozin, and empagliflozin reduce CKD progression, heart failure, and atherosclerotic cardiovascular disease risks in patients with and without diabetes and CKD. As a result of the cardiorenal benefits, SGLT-2is are strongly recommended in patients with CKD and type 2 diabetes. Safety and efficacy for people with eGFR less than 20 mL/min/1.73 m^2 is not established; therefore, initiation of SGLT-2i therapy is not recommended in this population outside of a clinical trial format. However, clinical experience has shown that these agents can be continued in patients already receiving them until such time as maintenance dialysis is required. There is no role for these agents in patients undergoing dialysis at the current time.

9. **Pramlintide.** Pramlintide is a synthetic analog of human amylin. Amylin is a naturally occurring hormone synthesized by pancreatic β cells that is cosecreted with insulin in response to food intake. Pramlintide, like amylin, prevents the postprandial rise in glucagon and increases satiety, thus decreasing caloric intake. Pramlintide also slows gastric emptying. It is metabolized mainly by the kidneys to an active metabolite. There is no need for dosage adjustment in patients with renal impairment down to an eGFR of 20 mL/min/1.73 m^2. There are few or no data on its

use in patients on dialysis.

V. HYPERKALEMIA. Hyperkalemia occurs commonly in patients with diabetes treated by maintenance HD. The causal factors include insulin deficiency and resistance (resulting in impaired potassium uptake by cells), aldosterone deficiency (resulting in impaired colonic and residual renal excretion), metabolic acidosis (resulting in increased proton-potassium exchange across cells), administration of other drugs that can cause hyperkalemia, intracellular to extracellular fluid shifts due to hyperglycemia (resulting in movement of water accompanied by potassium out of cells), and excesses in dietary potassium intake. Severe hyperkalemia is much less frequently found in patients with diabetes on maintenance PD. Treatment in patients with diabetes generally does not differ from that in the general dialysis population and is discussed in Chapters 10 and 11.

VI. CARDIOVASCULAR DISEASE AND HYPERTENSION

A. Hypertension. The incidence of hypertension is high in patients with diabetes undergoing dialysis. Control of high blood pressure is very important for the prevention of cardiovascular sequelae and deterioration of vision. Most patients with diabetes have volume-sensitive hypertension that can be controlled by appropriate sodium and fluid restriction and by removal of excess extracellular fluid by dialysis. The treatment of hypertension in patients with diabetes undergoing dialysis is similar to that for all such patients and is discussed in detail in Chapter 31.

B. Coronary artery disease. Despite the increased prevalence of patients with diabetes, outcomes of coronary artery bypass grafting have continuously improved in patients undergoing dialysis. Nonetheless, mortality rates remain almost 3-fold higher compared with non-ESKD patients (Parikh, 2010) (see Chapter 36).

C. Peripheral vascular disease. Patients with diabetes on dialysis have a very high rate of amputation (O'Hare, 2003). Frequent examination of the feet by a podiatrist is important; with regular care focused on prevention of ulcer development, the risk of amputation can be minimized.

VII. CEREBROVASCULAR DISEASE. The incidence of stroke is higher in patients with diabetes undergoing dialysis compared with their nondiabetic counterparts. Although the use of aspirin has been shown to reduce the risk of stroke in nonuremic patients, the benefit of such therapy in patients with diabetes undergoing dialysis is unknown, and the use of aspirin theoretically increases the risk of intraocular hemorrhage. Coumarin anticoagulants increase bleeding risk in this population more than in nonuremic patients with diabetes and are associated with additional risks of vascular calcification and calciphylaxis.

VIII. EYE PROBLEMS IN PATIENTS WITH DIABETES ON DIALYSIS

A. Diabetic retinopathy. Retinopathy is present in almost all patients with type 1 diabetes and ESKD. In such patients, another cause of kidney disease should be sought if the retinal examination (including fluorescein angiography) is normal. The situation in patients with type 2 diabetes is not as clear. In one study, diabetic retinopathy was present in only 15 of 27 patients (56%) with biopsy-proven diabetic glomerulosclerosis (Parving, 1992). In another biopsy study, a close correlation was observed between the

presence of severe retinopathy and Kimmelstiel-Wilson nodules on biopsy, whereas those without retinopathy had mesangial sclerosis but not nodular sclerosis. Thus, the presence of retinopathy appears to increase the likelihood of more severe renal lesions (Schwartz, 1998). Diabetic retinopathy correlates with micro- or macroalbuminuria, declining GFR, neuropathy (cardiac autonomic and peripheral), macrovascular complications (cerebrovascular, cardiovascular, and peripheral), and cognitive impairment/dementia (Simó-Servat, 2019).

Hypertension, which is also present in the majority of patients undergoing dialysis, accelerates the progression of diabetic retinopathy and may by itself cause retinal and vitreous hemorrhage. Vascular events secondary to hypertensive retinopathy (branch retinal vein occlusion from obstruction at the site of arteriovenous crossings) can cause sudden decreases in vision. Control of hypertension may prevent this complication, as well as the more rare central retinal vein and artery occlusion.

Retinopathy ultimately progresses to a proliferative stage believed to be secondary to local hypoxia and characterized by intense proliferation of new blood vessels in the retina. These vessels, which are located in the surface layer of the retina, cause loss of vision through vitreous bleeding and by causing macular distortion or detachment. Discovery of proliferative retinopathy and/or diabetic macular edema is an indication for treatment. Vitreous hemorrhages from proliferative retinopathy obstruct the path of light and may lead to retinal detachment and blindness. Current treatment options for proliferative diabetic retinopathy and diabetic macular edema include antivascular endothelial growth factor (anti-VEGF) agents, laser photocoagulation, and less effectively, intravitreal glucocorticoids and vitrectomy (both are options for diabetes macular edema). Active collaboration with an ophthalmologist skilled in anti-VEGF injections and laser photocoagulation is necessary. Proactive eye surveillance and intervention have been effective in sustaining at least ambulatory vision in nearly all patients with diabetes undergoing dialysis.

B. Other eye problems. Patients with diabetes on dialysis are subject to other eye complications common to all patients on dialysis. **Conjunctivitis and keratitis** are treated with ophthalmic preparations of antibiotic, antifungal, or antiviral agents in the usual doses. The dose of antibiotics given systematically should be adjusted for dialysis. **Band keratopathy** (corneal-conjunctival calcification) may afflict patients undergoing dialysis with or without diabetes who have uncontrolled hyperphosphatemia. A "**red-eye syndrome**" due to irritation of the conjunctiva by calcium phosphate deposits may complicate band keratopathy. Superficial keratectomy or chelation of the calcium deposits with local application of ethylenediamine tetraacetic acid (EDTA) has been used to treat refractory cases. **Glaucoma and cataracts** in patients undergoing dialysis are treated in the same way as in the general population. **Optic neuropathy** is most commonly due to uremia and ischemia in ESKD.

IX. IMPOTENCE. Impotence is common in patients with diabetes undergoing dialysis. Autonomic neuropathy and peripheral vascular disease associated with diabetes are operative, as are the usual uremic causes.

X. FOOT CARE. Patients with diabetes are at high risk of amputation due to presence of diabetic neuropathy, small blood vessel disease, and other factors. The risk of foot

ulceration is increased in patients with stage 5 CKD. Implementation of a foot assessment program that includes monthly checks for patients deemed at high risk (Wilson, 2013) is an important part of quality care for this patient population.

XI. BONE DISEASE. Adynamic bone disease is common among patients with diabetes with ESKD (see Chapter 34).

XII. ANEMIA. The response to erythropoietin is satisfactory for anemic patients with diabetes treated with either HD or PD (see Chapter 32).

XIII. REFERRAL FOR TRANSPLANTATION. In patients with diabetes in whom no contraindication to transplantation exists, renal transplantation is the preferred method of managing ESKD because of improved survival with transplantation (~80% 3-year survival vs 50% 3-year survival in patients maintained on dialysis). Among predialysis CKD patients with diabetes who are eligible for transplantation, preemptive kidney transplantation is preferred to initiation of dialysis followed by transplantation. Living donor kidneys are preferred to deceased donor kidneys. Use of extended donor kidneys can increase the number of patients with diabetes undergoing dialysis undergoing successful transplantation. Screening coronary angiography may be necessary as part of the pretransplant workup; screening dobutamine stress echocardiography, if negative, may be sufficient in some patients (especially those not yet on dialysis, in whom there is a risk of contrast nephropathy).

XIV. CONCLUSION. The care of patients with diabetes and ESKD is a demanding task. In addition to members of the dialysis team, health care providers from other specialties (eg, endocrinology, vascular surgery, podiatry, ophthalmology, neurology, transplantation surgery) are needed. The existence of a diabetic team, with all the subspecialties available, working under the coordination of a nephrologist and a nurse-specialist in diabetes is highly desirable to provide the best care for this population.

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31 Hypertension and Volume Control

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Treatment of hypertension represents a major area of intervention for cardiovascular risk reduction in patients undergoing dialysis.

I. DEFINITION AND MEASUREMENT. Blood pressure (BP) is commonly measured before, during, and after a hemodialysis treatment, but such peridialytic measurements do not adequately reflect the BP burden. Indeed, measurements made immediately before dialysis overestimate the underlying average BP, and the reverse is true for postdialysis BP. Predialysis BP criteria had very good specificity (99%) and sensitivity (87%) for the diagnosis of treatment-resistant hypertension as defined by 44-h ambulatory blood pressure monitoring (ABPM) (Mallamaci, 2020), but there is no study testing whether this metric may be used to guide therapy. Pre- and postdialysis BP values, even if measured using a standardized protocol, are imprecise estimates of interdialytic BP (Agarwal, 2006) and normally should not be applied for diagnosing and managing hypertension. Thus, out-of-office BP monitoring is the preferable method for diagnosing and monitoring BP in patients undergoing hemodialysis. Increased systolic BP outside of the dialysis unit predicts mortality (Bansal, 2015). Both home and 24-hour ABPM can be applied, but ABPM is rarely used in a routine chronic hemodialysis setting unless some unusual problem with BP is suspected. Estimates based on home BP readings are more reproducible than pre- and postdialysis BP and associate with ABPM better than peridialytic measurements (Parati, 2021). Furthermore, home measurements reflect left ventricular hypertrophy (LVH) and cardiovascular prognosis better than pre- and postdialysis measurements (Agarwal, 2009). Two daily home measurements, one in the morning and the other before the night sleep, taken the day after a midweek dialysis session, averaged over 4 weeks, are considered adequate for the diagnosis of hypertension (Agarwal, 2009). The frequency of measurements should be higher when BP lability is noted. Midweek median intradialytic BP is a more sensitive indicator of the prevailing BP burden (ie, average ABPM) than predialysis or postdialysis BP and may be applied when home measurements are not feasible (Agarwal and Light, 2010). When ABPM is done, the period of monitoring should ideally cover the whole interdialytic interval (44 hours with a 3-per-week schedule, beginning after the midweek session). Although long sessions of ABPM are generally poorly tolerated, ABPM can give some information regarding the nocturnal BP profile, which is frequently altered in patients undergoing dialysis, but effective means of correcting an attenuation or absence of nocturnal BP dipping in this population have not been determined.

The definition of hypertension (Table 31.1) depends on the method of measurement (average home BP: >135/85 mm Hg; ABPM: >130/80 mm Hg; midweek median intradialysis BP: >140/90 mm Hg). Average home BP greater than 135/85 mm Hg is

considered a valid threshold for the definition of hypertension in patients on both hemodialysis and peritoneal dialysis. High visit-to-visit BP variability is common in end-stage kidney disease (ESKD) patients and is a strong predictor of mortality (Rossignol, 2012). Methods of reducing BP variability in this population have not been systematically evaluated.

TABLE 31.1 Definition of Hypertension Indications for Drug Therapy of Hypertension in Patients Undergoing Dialysis

Definition
Hypertension in patients undergoing dialysis should be preferentially defined on the basis of home or 24-h ABPM measurements during a midweek dialysis interval. Thresholds proposed by the European Society of Hypertension and the European Society of Cardiology can be adopted for these measurements (Mancia, 2013).
Home measurements: systolic BP >135 mm Hg and/or diastolic pressure >85 mm Hg 24-h **ABPM measurements (midweek dialysis interval):** systolic BP >130 mm Hg and/or diastolic pressure >80 mm Hg
If home or 24-h ABPM cannot be applied, hypertension can be diagnosed as **midweek median intradialysis** systolic pressure >140 and/or diastolic pressure >90 mm Hg when the patient is believed to be at "dry weight" (see text).
Drug therapy goals
Arterial pressure goals should be established individually, taking into account age, comorbid conditions, cardiac function, and neurologic status.
Treatment targets: home BP <135/85 mm Hg or 24-h ABPM <130/80 or median intradialysis BP <140/90 mm Hg.

ABPM, ambulatory blood pressure monitoring; BP, blood pressure.

II. PATHOPHYSIOLOGY

A. Extracellular fluid volume expansion and sodium retention remain the main cause of hypertension. A relationship between chronic volume expansion and mortality is well established (Wizemann, 2009; Zoccali, 2017). There is an association between extracellular fluid volume expansion and diastolic dysfunction in patients undergoing dialysis (Joseph, 2006), and it is not always clear to what extent volume overload is a cause rather than a marker for severe cardiac disease. Recent attention has been called to nonosmotic accumulation of sodium in the subcutaneous space and in other organs. Nonosmotic accumulation of sodium in the muscles has been found in human hypertension (Kopp, 2013) and in patients on chronic hemodialysis or peritoneal dialysis (Sahinoz, 2020), but neither muscle nor skin sodium content are related to systolic BP in analyses adjusted for gender, race, and diabetes. Higher plasma interleukin 6 (IL-6) and high-sensitivity C-reactive protein (hsCRP) levels correlated with increased muscle and skin sodium content in patients with ESKD, suggesting that elevated sodium stores may impact inflammatory mechanisms in these patients.

B. Inappropriately high vascular tone. Sodium accumulation in arterial smooth muscle cells may contribute to increased vascular stiffness. Sleep apnea, a condition characterized by high sympathetic activity, is exceedingly common in patients undergoing dialysis and is associated with vasoconstriction and nocturnal hypertension. Sympathetic overactivity triggered by afferent signals originating in diseased kidneys can cause secondary activation of the renin-angiotensin system, and this may play an important role in the high peripheral vascular resistance seen in ESKD. In fact, there are reports of BP and sympathetic activity both falling dramatically after bilateral

nephrectomy (Converse, 1992) in patients undergoing dialysis and radiofrequency ablation of renal sympathetic nerve fibers produces similar effects (Schlaich, 2013). Asymmetric dimethyl-arginine (ADMA), an endogenous inhibitor of nitric oxide synthase, is elevated in patients undergoing dialysis, and high levels are associated with elevated sympathetic nervous system activity (Mallamaci, 2004).

C. Hypertension and LVH. The usual reasons for treating hypertension are to reduce the risk of stroke and cardiovascular events. One popular surrogate outcome for cardiovascular events and mortality is the presence of LVH, and many studies looking at reduction of fluid overload and/or antihypertensive treatment of patients undergoing dialysis have focused on change in left ventricular mass. It is important to realize that substantial LVH can be present in patients undergoing dialysis even at normal levels of BP (Mominadam, 2008) and that when one is optimizing extracellular fluid status, one is doing it not only to control BP but also aiming at optimizing cardiac structure and function. A trial applying lung water measurements by ultrasound to guide hypertension treatment showed that the use of this technique reduced lung water, improved 48-h ABPM (Loutradis, 2019), and decreased cardiac chamber dimensions and left ventricular filling pressure (Loutradis, 2020).

III. TREATMENT

A. Prevention

1. **Continuation of diuretic treatment in patients with substantial residual renal function.** In some countries, it is common to discontinue diuretics in patients with CKD once they have been transferred to chronic hemodialysis. In one observational study of patients undergoing hemodialysis treated in the United States, continuation of loop diuretics at dialysis initiation was associated with a reduced incidence of intradialysis hypotension and a lower rate of hospitalizations (Sibbel, 2019). A meta-analysis of published studies found similar results (Tang, 2021). The presumed mechanism is a lower ultrafiltration rate, but increased residual kidney removal of uremic toxins that may impair vascular response to fluid removal may also be operative.
2. **Sodium and fluid restriction.** Most fluid intake is driven by salt ingestion. Patients should be encouraged to restrict sodium chloride ingestion to 5 g/d (2 g or 87 mmol sodium). Another source of sodium is diffusive gain from dialysis solution when the dialysate sodium is greater than the predialysis plasma level. Many units tend to use the same dialysate sodium level for all patients undergoing dialysis, regardless of their predialysis sodium, while patients' predialysis sodium levels may range from 130 to 145 mmol/L. Use of a dialysate sodium higher than that of plasma can improve hemodynamic tolerance to fluid subtraction but increases thirst and fluid intake postdialysis. This results in an increased interdialytic weight gain, which then requires a higher ultrafiltration rate during the next dialysis. The optimum level of dialysate sodium is an unresolved issue. Also unresolved is whether or not it is beneficial to "align" dialysate sodium with the predialysis serum level, especially in patients in whom predialysis sodium level is consistently at the lower range of normal. There are many studies, both observational and interventional, that find a reduction of interdialytic weight gain, and sometimes predialysis systolic BP, when dialysate sodium is reduced, usually from a default value of 138 to 142 mM to 135

mM or so. Some studies report a reduced incidence of intradialytic hypotension as well, although one small double-blind randomized trial did not (McCausland, 2022), and many of these studies find an increased incidence of side effects (cramps, postdialysis recovery times) when the lower dialysate sodium concentration was used. The effect of dialysate sodium on hard outcomes such as hospitalizations and mortality is not clear, and one recent large observational study (Pinter, 2024) found that dialysate sodium levels of 138 mM or lower were associated with a markedly higher mortality risk compared to when higher dialysate sodium concentrations were used, regardless of patient predialysis serum sodium level.

Some nephrologists favor the use of "sodium profiling," where, with the aid of an advanced dialysis machine, one can begin the dialysis session with a sodium level higher than the patient's plasma level, and then progressively reduce dialysate sodium during the treatment, so that dialysis ends with a dialysate sodium below the initial plasma level. Sodium profiling can offer some of the benefits of higher sodium dialysis in terms of hemodynamic stability while minimizing the interdialytic weight gain effect, but only if the time-averaged dialysate sodium level during the session does not exceed the initial plasma level.

3. **Longer and/or more frequent dialysis sessions.** Frequent dialysis schedules and long, nocturnal dialysis may substantially improve BP control in patients with hypertension undergoing dialysis and revert LVH. Apart from frequency, increasing the length of a dialysis session allows for a slower ultrafiltration rate and increases the time available to finish dialysis at the desired postdialysis weight. Six times per week in-center hemodialysis reduced long-term mortality over 3.6 years follow-up in the frequent hemodialysis trial (Chertow, 2016).

B. Correction of salt and fluid overload

1. **Clinical assessment of dry weight.** Ideally, a dialysis treatment should bring the patient back to a normal extracellular fluid volume. In clinical practice, the **dry weight** is defined as the level below which further fluid removal would produce hypotension, muscle cramps, nausea, and vomiting. However, the occurrence of such symptoms depends on how quickly fluid is removed, on the dialysis strategy used, on the predialysis volume status, and on concomitant drug treatment (many antihypertensive drugs impair the reflex cardiovascular adjustments to volume removal).
   a. **Time delay in BP fall after correction of fluid overload.** There may be a time delay between lowering extracellular fluid volume and correction of markedly elevated BP (Charra, 1998). For this reason, if BP does not reduce initially after lowering the dry weight, this does not exclude hypervolemia as a cause of the hypertension. The lag phenomenon fits well with the hypothesis that nonosmotic sodium accumulation may occur in patients undergoing dialysis. Although it may take a considerable amount of time for this sodium to be removed from various tissue spaces (this has not been well studied), it is more likely that delayed improvement in hypertension after correction of long-standing fluid excess is due to vascular remodeling.
   b. ***Need for frequent reassessment.*** Dry weight and nutritional status should be reevaluated frequently because loss of muscle mass due to malnutrition or to intercurrent illness can result in fluid overload. For example, when a patient

returns to the dialysis unit after a hospitalization, the previously determined level of "dry weight" will almost always need to be reset to a lower level, due to intercurrent loss of lean body mass.

2. **Technology**
   a. **Bioimpedance analysis (BIA).** The assessment of dry weight is based on subjective clinical assessment. Tracking optimal dry weight by the usual clinical criteria (presence of edema, jugular venous distension, lung rales) may be difficult. Furthermore, edema may not be detectable until the interstitial volume has risen by about one-third above normal (eg, about 5 L). Multifrequency bioimpedance spectroscopy has now emerged as a reliable method to measure body fluids. The Body Composition Monitor (BCM; Fresenius Medical Care) is one such device that has been well validated in patients undergoing dialysis (Moissl, 2006). The application of a BCM-based treatment policy aimed at minimizing fluid overload has been used to control hypertension in a dialysis setting (Moissl, 2013). In a randomized controlled trial, a BCM-guided fluid management approach led to clear-cut improvement in left ventricular mass index and vascular stiffness (Hur, 2013). However, in a meta-analysis (10 trials) testing the usefulness of bioimpedance for fluid management, the use of this technique did not improve survival (Beaubien-Souligny, 2019).
   b. **Other methods.** Continuous recording of hematocrit during dialysis (Crit-line Monitor) is considered a useful method, but a clinical trial testing the hypothesis that the systematic use of this device would improve clinical outcomes found higher, rather than lower, nonvascular and vascular access–related hospitalizations and mortality as compared with conventional monitoring (Reddan, 2005). Ultrasonography of the inferior vena cava diameter or the measurement of the diameter of the left atrium are both sensitive to volume changes but do not reflect interdialytic BP (Agarwal, 2011) and are therefore of limited value for assessing dry weight. Serum levels of brain natriuretic peptide (BNP) largely reflect left ventricular mass (Zoccali, 2001) and are unsuitable for volume monitoring (Agarwal, 2013). Pulmonary congestion can be detected and monitored by an easy-to-apply, reliable ultrasound technique that can be performed with virtually all ultrasound machines and probes (Mallamaci, 2010). Lung congestion is a strong predictor of death and cardiovascular events (Zoccali, 2013). In the "Lung Ultrasound Guided Treatment Strategy (LUST) in Patients with End Stage Kidney Disease at High Cardiovascular Risk" trial, the application of this technique did not modify the primary outcome of the trial (a composite of all-cause death, nonfatal myocardial infarction, and decompensated heart failure). However, in a post hoc analysis, the use of lung ultrasound significantly reduced the risk of hospitalization for recurrent pulmonary edema as well as the risk of hemodialysis hypotension in patients in the active arm of the trial as compared to the control arm (Zoccali, 2022).

C. Common clinical problems

1. **Excessive ultrafiltration.** Overzealous ultrafiltration may precipitate severe hypotension and disastrous cardiovascular consequences such as myocardial or cerebral infarction and mesenteric ischemia. Frequent intradialytic hypotensive episodes are associated with increased mortality, although it is not clear whether this

association is causal in nature (Shoji, 2004). Intradialytic hypotension is also associated with "myocardial stunning" (manifesting as cardiac wall motion abnormalities) and with subtle ischemic changes to brain white matter linked to mood and cognition (Selby and McIntyre, 2014). Intensification of ultrafiltration without markedly prolonging dialysis time improves hypertension control, but increases hospitalizations for cardiovascular complications, and also increases the risk of arteriovenous fistula clotting (Curatola, 2011). It is possible that the incidence of falls may be increased. Rapid ultrafiltration rates increase the risk of dialysis hypotension, and higher ultrafiltration rates are consistently associated with a higher risk of death (Mermelstein, 2023). Methods of minimizing the risk of intradialytic hypotension are discussed in Chapter 12. Another issue with reduction of extracellular fluid volume in both patients undergoing hemodialysis and peritoneal dialysis is an associated fall in residual urine volume. This urine volume is important in avoiding spikes in extracellular fluid volume, as well as in the associated removal of phosphate, higher weight middle molecules, and protein-bound uremic toxins. In patients with substantial residual urine output, it is not clear to what extent it is possible to achieve optimum levels of extracellular fluid volume while still maintaining residual kidney function. It may be that the loss of residual kidney function in such circumstances is an unavoidable price that must be paid.

2. **Intradialysis and end-dialysis hypertension** can occur in about 15% of patients undergoing dialysis and have been associated with a higher death risk (Inrig, 2009). This disturbance is multifactorial and may reflect subclinical volume overload. Sympathetic and renin-angiotensin overactivity have been linked to this condition. Patients with intradialytic hypertension display severely impaired endothelial repair capacity and diminished endothelial response to shear stress. Endothelial dysfunction is a plausible mechanism contributing to the high cardiovascular risk in these patients (Inrig, 2011). In a randomized trial, carvedilol, while producing modest improvements in endothelial function, improved intradialytic and interdialytic BP and reduced the frequency of intradialytic hypertension (Inrig, 2012). Because patients with intradialytic hypertension have markedly elevated BP load during the out-of-dialysis period (Van Buren, 2012), therapy should aim at controlling hypertension globally rather than focus just on the dialysis session period. Lowering the target dry weight works in some patients, but it is by no means clear that such patients are uniformly fluid overloaded.
3. **Recurrent hypertension.** If hypertension recurs in a patient after being well controlled by volume subtraction, the most likely explanation is that the patient has returned to a state of volume excess.

D. Antihypertensive drug use. In patients with baseline LVH, treatment by volume subtraction is more effective in reducing LVH than BP lowering by antihypertensive drug treatment (Ozkahya, 2006). Still, a substantial number of patients undergoing dialysis receive antihypertensive drug treatment, and observational data suggest that such treatment lowers mortality overall, with most documented benefits being reported for patients taking renin-angiotensin-aldosterone system (RAAS) inhibitors or β-blockers. The mean number of antihypertensive drugs prescribed for patients undergoing hemodialysis or peritoneal dialysis is 2.5 at the sixth month of dialysis treatment. Prescription patterns of these drugs vary by dialysis modality, and substantial

changes in prescription patterns of β-blockers, renin-angiotensin system antagonists, and calcium channel blockers occur from the sixth month onward. Furthermore, prescription classes vary by comorbidity, race/ethnicity, and age, but little by sex (St Peter, 2013).

1. **Angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin II receptor blockers (ARBs).** These drugs are generally well tolerated. The fact that plasma renin activity is overtly high in some patients undergoing dialysis and inadequately suppressed in volume-expanded patients provides a pathophysiologic rationale for use of these drugs. Because angiotensin II is strongly implicated in LVH even independently of hypertension, the use of this class of drugs would in theory be particularly useful in patients undergoing dialysis, as so many have LVH to begin with. However, randomized, placebo-controlled trials using ramipril in normotensive patients undergoing dialysis (Yu, 2006) and in patients with LVH and normal or high BP (Zannad, 2006) failed to show LVH regression. In a meta-analysis of 11 trials in patients undergoing peritoneal dialysis and hemodialysis, ACE-Is/ARBs therapy decreased the loss of residual renal function in patients on peritoneal dialysis. Globally, these drugs did not reduce cardiovascular events. However, separate analysis of the two classes of drugs showed that ARBs but not ACE-Is reduced cardiovascular events including heart failure, and this effect was independent of BP (Liu, 2017).
    a. ***Side effects and dosing adjustments.*** ACE-Is, by interfering with bradykinin breakdown, may be associated with an increased incidence of anaphylactoid reactions during dialysis. ACE-Is have been associated with hyperkalemia in patients with renal insufficiency, but can often be used in patients undergoing dialysis with minor adjustment to the potassium content of the diet, if needed. Other side effects are cough, skin rash, alteration of taste, and, rarely, agranulocytosis or angioedema. Lower angioedema and cough risk are factors in favor of ARBs. Worsening of anemia and erythropoietin resistance is another purported side effect of ACE-Is, an effect that depends on the accumulation of *N*-acetyl-seryl-aspartyl-lysyl-proline, a physiologic inhibitor of hematopoiesis, degradation of which depends on ACE. Because plasma half-life of many ACE-Is (or of their active metabolites) is prolonged in renal failure, reduction in dosage is often required. ARBs are extensively metabolized by the liver and do not require dose adjustment.
2. **Mineralocorticoid receptor antagonists.** A meta-analysis of 15 trials testing the hypotensive and cardioprotective effect of mineralocorticoid receptor antagonists showed a modest effect on systolic BP (−4.2 mm Hg) but important risk reductions for all-cause death (–58%) and cardiovascular events (–46%). However, these apparent benefits were counterbalanced by a significant rise in serum potassium (Liu, 2022). The Aldosterone Antagonist Chronic Hemodialysis Interventional Survival Trial (ALCHEMIST), and the Aldosterone Blockade for Health Improvement Evaluation in ESKD trial (ACHIEVE) should provide some answers on the effectiveness and safety of these drugs in patients undergoing dialysis. Preliminary results of the ALCHEMIST trial were negative in terms of the primary outcome, as presented to the American Society of Nephrology meeting in 2023 (Rossignol, 2023). At present, no formal recommendation about the use of mineralocorticoid receptor antagonists can be formulated.

3. **β-, α/β-, and α-Adrenergic blockers.** β-Blockers counteract the cardiovascular effects of high sympathetic activity and lower plasma renin activity and angiotensin II, which may all participate in causing high BP in patients undergoing dialysis. Many show a documented cardioprotective effect in the setting of myocardial ischemia or infarction. High plasma noradrenaline is associated with cardiovascular mortality in ESKD (Zoccali, 2002). Carvedilol, an α/β-blocker, reduces morbidity and mortality in patients with systolic dysfunction undergoing dialysis (Cice, 2003). A superior cardioprotective effect of β-blockade by atenolol over ACE inhibition by lisinopril was documented in the Hemodialysis Patients Treated with Atenolol or Lisinopril (HDPAL) trial (Agarwal, 2014). In this trial of 200 patients undergoing dialysis who were randomized to receive either lisinopril or atenolol, 44-hour ambulatory BP was similarly reduced over time in the atenolol and lisinopril groups (notwithstanding a greater decrease in postdialysis body weight and an increased use of other antihypertensive agents in lisinopril-treated patients). Importantly, the risk of major cardiovascular events was halved in the atenolol group as compared with the lisinopril group, to the point that the safety monitoring board for the study recommended early termination of the trial.
    a. **Side effects and dosing adjustments.** α-Blockers may cause postural hypotension. Prazosin has been associated with first-dose syncope, so the first dose must be administered at bedtime. β-Adrenergic blockers have a high incidence of side effects, such as drowsiness, lethargy, and depression. Nonselective β-blockers need to be used cautiously in patients with a tendency toward pulmonary edema or asthma and in patients already being treated with some calcium channel blockers. β-Blockers have an adverse effect on serum lipids; they may also have an adverse effect on cell potassium uptake, tending to increase the serum potassium level. They can mask the symptoms of hypoglycemia and augment insulin-induced hypoglycemia. All may cause bradycardia and interfere with reflex tachycardia following volume depletion.

       Water-soluble β-blockers, atenolol, nadolol, and bisoprolol, are removed substantially by hemodialysis and should be preferentially administered postdialysis.
4. **Calcium channel blockers.** These drugs are frequently used for the treatment of volume-resistant hypertension in patients undergoing dialysis. A large meta-analysis of BP lowering drugs in patients with hypertension and/or cardiovascular disease showed that calcium antagonists are more efficacious than other main classes of antihypertensive drugs, including β-blockers, ACE-Is, and ARBs in reducing the risk of stroke, and similarly effective in preventing coronary heart disease events (Law, 2009). In a large dialysis patient cohort treated with monotherapy, calcium channel blockers were the drug class associated with the lowest occurrence of intradialytic hypotension (Zoccali, 2024). In a randomized, double-blind trial in hypertensive patients undergoing dialysis, amlodipine produced a 9-mm Hg fall in systolic pressure and did not change diastolic pressure over a 19-month follow-up. Amlodipine treatment in this trial was associated with a 47% decrease in the combined secondary end point (mortality from any cause or cardiovascular event), while the risk reduction (~35%) for mortality (primary end point) failed to achieve statistical significance (Tepel, 2008).

a. ***Side effects and dosing adjustments.*** Verapamil can cause cardiac conduction problems, bradycardia, and constipation. Calcium channel blockers should be used very cautiously in combination with β-adrenergic blockers because congestive heart failure can be precipitated. Other side effects are ankle edema, headache, flushing, palpitations, and hypotension. Long-acting preparations should be used. Calcium channel blockers are excreted primarily by the liver, their pharmacokinetic profile is unaltered in chronic renal failure and by dialysis (Table 31.2), and their dosage does not require any adjustment.

TABLE 31.2 Antihypertensive Drugs in Patients Undergoing Dialysis: Dosages and Removal During Dialysis

Drug	Tablet Size (mg)	Initial Dose in Patients Undergoing Dialysis (mg)	Maintenance Dose in Patients Undergoing Dialysis (mg)	Removal During Hemodialysis
Calcium antagonists				
Amlodipine	5	5 q24h	5 q24h	No
Diltiazem extended release	120, 180, 240, 300, 360	120 q24h	120-300 q24h	No
Felodipine	5, 10	5 q24h	5-10 q24h	No
Isradipine	5	5 q24h	5-10 q24h	No
Nicardipine (slow release)	30	30 b.i.d.	30-60 b.i.d.	No
Nifedipine XL	30, 60	30 q24h	30-60 q24h	No
Verapamil	40, 80, 120	40 b.i.d.	40-120 b.i.d.	No
ACE inhibitors				
Captopril	25, 50	12.5 q24h	25-50 q24h	Yes[a]
Benazepril	5, 10, 20, 40	5 q24h	5-20 q24h	Yes[a]
Enalapril	2.5, 5, 10, 20	2.5 q24h or q48h	2.5-10 q24h or q48h	Yes[a]
Fosinopril	10, 20	10 q24h	10-20 q24h	Yes[a]
Lisinopril	5, 10, 20, 40	2.5 q24h or q48h	2.5-10 q24h or q48h	Yes[a]
Perindopril	4	2 q48h	2 q48h	Yes[a]
Quinapril	5, 10, 20, 40	2.5 q24h	10-20 q24h	No
Ramipril	1.25, 2.5, 5, 10	2.5-5 q24h	2.5-10 q24h	Yes[a]
β-Blockers				
Acebutolol	200, 400	200 q24h	200-300 q24h	Yes[a]
Atenolol	50, 100	25 q48h	25-50 q48h	Yes[a]
Bisoprolol	2.5	2.5 q24h	2.5 q24h	Yes[a]
Carvedilol	5	5 q24h	5 q24h	Yes[a]
Metoprolol	50, 100	50 b.i.d.	50-100 b.i.d.	Yes[a]
Nadolol	20, 40, 80,	40 q48h	40-120 q48h	Yes[a]

	120, 160			
Pindolol	5, 10	5 b.i.d.	5-30 b.i.d.	Yes[a]
Propranolol	10, 40, 80	40 b.i.d.	40-80 b.i.d.	Yes[a]
Adrenergic modulators				
Clonidine	0.1, 0.2, 0.3, TTS 0.2	0.1 b.i.d.	0.1-0.3 b.i.d., TTS weekly	No
Guanabenz	4, 8	4 b.i.d.	4-8 b.i.d.	No
Guanfacine	1, 2	1 q48h	1-2 q24h	No
Labetalol	100, 200, 300	200 b.i.d.	200-400 b.i.d.	No
Prazosin	1, 2, 5	1 b.i.d.	1-10 b.i.d.	No
Terazosin	1, 2, 5	1 b.i.d.	1-10 b.i.d.	No
Vasodilators				
Hydralazine	10, 25, 50, 100	25 b.i.d.	50 b.i.d.	No
Minoxidil	2.5, 10	2.5 b.i.d.	2.5-10 b.i.d.	Yes[a]
Angiotensin II receptor blockers				
Candesartan	4, 8, 16, 32	4 q24h	8-32 q24h	No
Eprosartan	400, 600	400 q24h	400-600 q24h	No
Irbesartan	75, 150, 300	75-150 q24h	150-300 q24h	No
Losartan	50	50 q24h	50-100 q24h	No
Telmisartan	40, 80	40 q24h	20-80 q24h	No
Valsartan	80, 160	80 q24h	80-160 q24h	No
Olmesartan	10-40	10 q24h	10-40 q24h	No

None of the drugs in the table undergo substantial removal during continuous ambulatory peritoneal dialysis.
q24h, daily; b.i.d., 2 times/d; q48h, every other day; ACE, angiotensin-converting enzyme; TTS, transdermal therapeutic system.

[a]The dose of drugs that are removed by hemodialysis should be scheduled so that it is administered after dialysis.

5. **Sympatholytic drugs (eg, methyldopa, clonidine, guanabenz).** As noted earlier, there appears to be increased tonic sympathetic activity in patients undergoing dialysis, so use of central sympatholytic drugs, which inhibit sympathetic outflow by stimulating α-adrenoreceptors in the brain stem, is theoretically attractive. One side benefit of clonidine is its usefulness in the treatment of diarrhea due to autonomic neuropathy. Moreover, methyldopa and clonidine are relatively inexpensive—often an important consideration. Moxonidine added to other antihypertensive drugs was well tolerated in one study of patients with advanced renal failure and was comparable to nitrendipine in terms of efficacy (Vonend, 2003). A low, nonhypotensive dose of this drug produces a sustained reduction in directly recorded sympathetic activity in patients undergoing dialysis (Hausberg, 2010).

a. **Side effects and dosing adjustments.** This class of drugs does have side effects. For clonidine, these include sedation, dry mouth, depression, and postural hypotension. The last may be a particular problem in patients with diabetes. Clonidine may cause rebound hypertension if it is abruptly withdrawn. Such side effects are substantially reduced with the transdermal formulation. Guanabenz and guanfacine are less likely to cause rebound hypertension but are more expensive. The large monoxidine congestive heart failure trial (MOXCON) was stopped because of excessive deaths in the moxonidine group (Cohn, 2003), which contrasts with the beneficial effect of β-blockers in the same condition. The use of this drug in patients with heart failure undergoing dialysis is therefore unwarranted. Methyldopa may cause hepatotoxicity or a positive direct or indirect Coombs test, interfering with cross-matching of blood. Methyldopa, clonidine, and guanfacine are excreted substantially by the kidneys, and dosage reductions may be required. Methyldopa is removed by hemodialysis to a substantial extent. Guanabenz is metabolized by the liver and requires no dosage adjustment in renal failure.

6. **Vasodilators (eg, hydralazine, minoxidil).** These are third-line drugs. They usually require the addition of a sympatholytic or β-blocking drug because they tend to cause reflex tachycardia. Side effects of both drugs relate primarily to this reflex tachycardia and resulting palpitations, dizziness, and worsening of angina pectoris. Hydralazine is effective and inexpensive, but can cause a lupus-like syndrome at dosages of more than 200 mg/d. Because of diminished renal excretion of its active metabolite(s), the maximum allowable dosage should be reduced in patients undergoing dialysis. Minoxidil has been associated with pericarditis and is generally avoided in women because of hypertrichosis. Minoxidil is usually reserved to treat resistant hypertension.
7. **Renal sympathetic nerve denervation.** Given the elevated level of sympathetic nerve activity found in patients with ESKD, as discussed previously, the concept of reducing BP, especially in patients resistant to the usual forms of treatment, by way of renal sympathetic nerve denervation, is of some interest (Mazza, 2023). At present, although some success has been reported in patients with stage 3 and 4 CKD, experience with such treatment in patients undergoing dialysis is limited.

IV. HYPERTENSIVE URGENCIES AND EMERGENCIES

A. Hypertensive urgency.

The term hypertensive urgency is reserved for patients who are at significant risk for a serious morbid event within a matter of days if left untreated.

1. **Treatment.** The ideal rate of BP reduction in hypertensive urgencies is a balance between the risks of inadequate versus too-rapid lowering. In chronic hypertension, the range of cerebral autoregulation is reset upward so that patients may be less able to compensate for a sudden fall in BP, which may precipitate cerebral infarction and blindness. For this reason, abrupt forms of therapy should be avoided. The short-acting formulation of nifedipine was used as a first-line drug for severe hypertension in the past, but is no longer recommended, as there are now a number of reports documenting myocardial, cerebral, and retinal ischemia after its use. The long-acting preparation of nifedipine or other long-acting calcium antagonist, or clonidine,

should be used instead as first-line therapy. If the patient is already on treatment with such drugs, a β-blocker, an ACE-I, or a combination thereof could be added. If oral therapy fails, parenteral drugs should be used (see below).

B. Hypertensive emergencies are defined as increases in arterial pressure that, if sustained *for a few hours*, would cause irreversible organ damage. Hypertensive encephalopathy, hypertensive left ventricular failure, hypertension associated with unstable angina/myocardial infarction, hypertension with aortic dissection, and cerebral hemorrhage/brain infarction are such emergencies. Hypertensive emergencies should be treated with parenteral drugs. Nitroprusside administered by continuous intravenous infusion (0.3-0.8 mcg/kg/min initially to a maximum of 8 mcg/kg/min) is particularly useful in heart failure and dissecting aneurysm but requires careful monitoring because its toxic metabolite (thiocyanate) is retained in renal failure. Cyanide levels should be monitored every 48 hours and should not exceed 10 mg/dL. The symptoms of thiocyanate toxicity are nausea, vomiting, myoclonic movements, and seizures. In general, the infusion should not be prolonged for more than 48 hours. Both nitroprusside and its metabolites are readily removed by dialysis. Intravenous labetalol may also be considered in patients without heart failure, asthma, or heart block (2 mg/min to a total of 2 mg/kg). Hydralazine 10 to 20 mg given slowly intravenously is a well-tried alternative, but this drug should be avoided in ischemic heart disease.

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32 Hematologic Abnormalities

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I. ANEMIA

A. Etiology.

The anemia of chronic kidney disease (CKD) is multifactorial in origin. The primary cause is insufficient production of the glycoprotein hormone erythropoietin (EPO). Although EPO can be produced in several of the body's tissues, in adults, EPO required for erythropoiesis generally is produced by fibroblast-like cells in proximity to the kidneys' tubules. The cells are located in the deep cortex, an area that is hypoxic under physiologic conditions and highly reactive to changes in ambient oxygen (Kaneko, 2022). As kidney excretory function is lost, there is a relative decline in the production of EPO that correlates with the declining glomerular filtration rate. The concentration of serum EPO may be normal or mildly diminished, but it is significantly reduced in relation to the low hemoglobin (Hb) concentration. In addition to relative EPO deficiency, inflammation may play an important role in the anemia of end-stage kidney disease (ESKD). It directly impedes erythropoiesis and stimulates the production of hepcidin, which impairs iron availability. Another central cause of the anemia of ESKD is iron deficiency, which develops in the predialysis period and worsens after initiating dialysis if not treated. The net effect is an anemia that is generally normocytic and normochromic. The severity of the resulting anemia varies, but if untreated, then Hb concentrations of 6 to 8 g/dL are typical in ESKD.

B. Consequences of anemia

1. **Symptoms.** The manifestations of anemia may be due both to the effects of decreased oxygen delivery to tissues and to the cardiovascular system's compensatory changes. The most prominent symptoms of anemia are fatigue and dyspnea. Symptoms develop slowly, and the patient may gradually restrict their activities in compensation. The patient's overall sense of well-being is diminished. Other symptoms may include difficulty concentrating, dizziness, sleep disorders, cold intolerance, and headaches. The heart responds to the diminished oxygen-carrying capacity of blood by attempting to maintain systemic oxygen delivery with increased cardiac output, which could lead to the development of left ventricular hypertrophy. Patients may notice worsening dyspnea and palpitations at this stage. Other problems include deranged hemostasis, impaired immune function, and diminished cognitive and sexual function. Exacerbations of angina, claudication, and transient ischemic attacks may be observed.
2. **Physical examination.** The primary physical examination finding of anemia is pallor, which may be best detected on the palms of the hands, the nail beds, and the oral mucosa. A systolic ejection murmur due to increased cardiac flow may be heard over the precordium.

C. Treatment

1. **Medications**
   a. **EPO analogues.** Because EPO deficiency is the primary cause of anemia in patients with CKD, agents that replace EPO have a lead role in treatment. At the

time of this writing, the drugs in common use in the United States are EPO analogues. Other agents in use elsewhere or in development may stimulate erythropoiesis by other mechanisms.

The first approved recombinantly produced EPO replacement was epoetin alfa, and other similar drugs followed. Since all were structural analogues of EPO, there was little need for a more encompassing terminology. But in the early 2000s, with newer agents contemplated and in development, a broader term, erythropoiesis-stimulating agents (ESAs) was introduced. This term is now widely accepted for EPO analogues. Newer agents like hypoxia-inducible factor–prolyl hydroxylase inhibitors (HIF-PHIs) (see text) also stimulate erythropoiesis, so technically are ESAs. But, in common use, it has emerged that drugs that directly stimulate the EPO receptor are deemed to be ESAs, while drugs with a more indirect effect are not. So, HIF-PHIs are not considered part of the ESA class.

Epoetin alfa, first approved in 1989, is a glycoprotein that is very similar to native human erythropoietin. It is manufactured by recombinant DNA technology and has a molecular weight of 30.4 kDa and a circulating half-life after intravenous (IV) administration of approximately 8 hours. **Darbepoetin alfa, approved by the US Food and Drug Administration (FDA) in 2001,** is a synthetic analogue of EPO with minor amino acid changes and increased carbohydrate content that increases the molecular weight by approximately 20% compared with native EPO. As a result of the altered structure, the drug's pharmacokinetics are changed, and the IV serum half-life is increased to approximately 24 hours. **Methoxy polyethylene glycol-epoetin beta, approved by the FDA in 2007,** has a molecular weight of approximately 60 kDa. The larger size and changed structure of this molecule lead to a substantially longer serum half-life than other ESAs, of approximately 130 hours. Biologic analogues of ESAs, so-called biosimilars, have been developed and are in use throughout the world.

b. HIF-PHIs. A newer class of drugs is the HIF-PHIs, the first of which was approved in China in 2018. These agents work via cells' oxygen sensing system. When cellular hypoxia occurs, the HIF system works to stimulate the production of a large number of gene products that function to protect the cell from hypoxic injury. HIF-PHI drugs are oral agents that operate via this system, stabilizing HIF-α as if hypoxia was occurring. Central among the resulting cascade of proteins produced include EPO, iron availability–promoting proteins, and other related gene products that act to stimulate erythropoiesis. In addition, thousands of other proteins unrelated to erythropoiesis, but that also protect against hypoxia, are generated. Several of the HIF-PHI drugs have been extensively studied, including roxadustat, vadadustat, daprodustat, molidustat, desidustat, and enarodustat. Studies have consistently found that these oral medications are efficacious in treating patients with anemia of both nondialysis and dialysis-dependent CKD. Additionally, it is likely that HIF-PHIs improve iron availability and may reduce IV iron dose requirements. At the time of this writing, there is some residual uncertainty as to the safety of HIF-PHIs. As a result only daprodustat and vadadustat have been approved in the U.S. for

patients on dialysis.

2. **Benefits of anemia treatment with ESA**
   a. **Effect on outcomes.** Cross-sectional and retrospective studies have found that anemia in patients undergoing hemodialysis (HD) is associated with increased mortality, particularly when the Hb concentration is less than 10 g/dL (100 g/L). Anemia is also associated with an increased rate of hospitalizations and left ventricular hypertrophy. It is important to recognize that, in contrast to these observational study findings, interventional studies with ESA treatment have failed to show improvement in outcomes. Since the key studies used high Hb treatment targets (13-15 g/dL), it remains possible that ESA treatment could improve outcomes with treatment to more conventional Hb targets.
   b. **Reduction in blood transfusions.** Prior to ESA therapy, up to 20% of patients on dialysis required frequent transfusions, with attendant risk of transfusion reactions, viral infection, iron overload, and immune sensitization. The rate of blood transfusion has been greatly reduced by the use of ESA therapy among patients on dialysis. The magnitude of this effect may be underappreciated in the current era, where the large majority of patients are routinely treated with ESAs. A particularly helpful view of the true effect can be appreciated from a pivotal 1989 study. Among 333 patients undergoing HD, the number of transfusions after initiating epoetin was reduced from 1,030 in the 6 months prior to ESA treatment to none within 2 months of therapy (Eschbach, 1989).
   c. **Improved quality of life (QOL) and overall sense of well-being.** ESA treatment relieves symptoms of anemia, and various assessment tools have documented the resulting improved QOL and functional status. It has been difficult to determine the magnitude of improvement and its relation to specific Hb changes. In addition, early trials of ESA were uncontrolled, and many subsequent studies used open-label designs, limiting the quality of evidence. Reconsideration of study results led the FDA to remove QOL language from ESA drug labels in 2008. Nonetheless, it is our observation that ESA treatment generally results in symptom improvement, which can be dramatic in patients with severe anemia. Patients feel less fatigued, dyspnea improves, and exercise capacity and life activity increase. Nonetheless, as with most medications, treatment response may be variable, and accordingly, the Kidney Disease: Improving Global Outcomes (KDIGO) anemia guidelines emphasize individualization of treatment.
3. **Risks of ESA therapy.** Initial studies of ESA use identified adverse reactions including myalgias, thrombosis, increased blood pressure, and rarely, seizures, if Hb rose too rapidly. At first, ESA treatment was used simply to correct severe anemia by raising the Hb only moderately, to targets of 10 to 12 g/dL. Subsequently, well-powered randomized controlled trials explored the utility of ESA treatment aiming for full anemia correction (Hb targets: 13-15 g/dL or 130-150 g/L). In these studies, the comparison groups (controls) were either ESA treatment to a lower Hb target or, in one study, the control group received placebo. Four such trials are particularly noteworthy: the Normal Hematocrit Trial (Besarab, 1998), CREATE (Drüeke, 2006), CHOIR (Singh, 2006), and TREAT (Pfeffer, 2009). Only one of these four

studies (Besarab, 1998) was conducted in patients undergoing dialysis; the other three enrolled only patients with nondialysis CKD. The study results were striking. ESA treatment to higher (normal) Hb targets resulted in increased thrombotic complications and a tendency to increased risk for unfavorable cardiovascular outcomes including an increased risk of mortality. It is important to repeat that the increased risks occurred in studies targeting Hb concentrations higher than had ever been used routinely in clinical practice. What remains unknown is whether any of the observed risks would extend to more intermediate (eg, lower) Hb targets including those used in prevailing clinical practice.

The mechanism of cardiovascular risk for ESA treatment with Hb targets greater than 13 g/dL is unknown. Post hoc analyses of certain high Hb target studies did not show a relationship between higher achieved Hb concentration and adverse outcomes. Rather than Hb concentration, risk was more closely associated with higher doses of ESAs. More generally, ESA hyporesponse is associated with a diminished prognosis for survival. Taken together, the results of these analyses suggest that adverse cardiovascular outcomes observed in the studies described above may be due to the interplay of several factors occurring when treating with ESA to high Hb targets. Until the pathobiology is more clearly elucidated, it can only be concluded that clinicians should avoid higher Hb targets (see below) and should similarly avoid high ESA doses.

4. **Indications for ESA, HIF-PHI therapy, and target Hb.** The FDA prescribing information (label) for ESA treatment lists an indication for the treatment of anemia of CKD that includes patients on dialysis. ESA therapy should generally be initiated in patients with CKD when the Hb falls below 10 g/dL (100 g/L). After initiation, the optimal maintenance Hb target or range is not known (see above). The FDA label states that for patients on dialysis, ESA dosing should be reduced or interrupted when the Hb concentration rises above 11 g/dL. The KDIGO anemia guidelines (2012) state that Hb should not generally be maintained above 11.5 g/dL (115 g/L). In consideration of the FDA label and KDIGO guidelines, and since Hb tends to rise and fall over time, we suggest an Hb target range for most patients on dialysis of 9.5 to 11.5 g/dL (95-115 g/L). At the time of this writing, two HIF-PHI agents, daprodustat and vadadustat, have been approved by the FDA for the treatment of anemia of CKD in patients receiving chronic dialysis.
    a. **Effect of volume status on target Hb.** Hb is usually measured prior to the HD session when the patient's circulating volume tends to be expanded due to fluid ingestion during the prior interdialytic period. As a result, the measured Hb is decreased due to dilution. This is particularly true for patients with larger fluid weight gains in the interdialytic period. The effect of volume on Hb is generally modest enough that it doesn't need to factor into anemia management decisions. However, for patients with excessive interdialytic weight gains, a somewhat lower Hb target may be selected to avoid potential safety issues due to intradialytic hemoconcentration and other factors. Similarly, if one is trying to parse Hb targets from nondialysis patients with CKD to patients receiving HD, an Hb target of 11 g/dL (110 g/L) in CKD may correspond to a somewhat lower predialysis target value in patients undergoing dialysis due to the dilution effect.
5. **Route of administration.** HIF-PHIs are administered orally, so there is no route

of administration decision. This is not the case for ESAs, as they are parenteral agents. For patients treated with peritoneal dialysis (PD), the subcutaneous route of these drugs is well tolerated and effective. In HD, administration intravenously through the dialysis tubing is convenient and avoids an extra needle stick. Studies have been conducted in patients on HD comparing the efficiency of IV compared to subcutaneous ESA dose administration. The results have generally indicated that the required ESA dose is reduced by approximately 25% to 30% when administered subcutaneously (Kaufman, 1998).

The mechanism of this reduced dose requirement is probably related to the more rapid rate at which epoetin enters the circulation and becomes available to EPO receptors when injected intravenously. The rapid surge in serum concentration probably results in some drug never binding to EPO receptors prior to clearance from the circulation. In contrast, when administered subcutaneously, the serum half-life of epoetin is extended, allowing for more efficient receptor binding and a greater erythropoietic effect. Despite the efficiency of subcutaneous treatment, since 2019, more than 99% of US patients on HD receive the drug intravenously, primarily to save the patient from the pain of injection.

6. Dosing

a. Initial dose. Treatment with ESA should ideally be initiated, if required, in the pre-ESKD period. The FDA label for epoetin alfa recommends a starting dose of 50 to 100 units/kg 3 times weekly, darbepoetin alfa 0.45 mcg/kg weekly, or 0.75 mcg/kg every 2 weeks, and methoxy polyethylene glycol-epoetin beta 0.6 mcg/kg body weight once every 2 weeks. Among HIF-PHIs, the FDA label for daprodustat limits initiation to after 4 months of dialysis. For vadadustat, the FDA label limits initiation to after 3 months of dialysis. The initial daily oral dose depends on the previous ESA dose. The selection of a specific dose can be modified based on how symptomatic the patient is, Hb concentration, and other clinical circumstances. An excessively rapid rise in the Hb level should be avoided, as this may lead to worsening hypertension and other safety issues.

b. Initial response and plateau effect. During the initiation phase of therapy, Hb should be checked every 1 to 2 weeks, and the ESA dose adjusted as needed. It is very common during the initiation of treatment for a “plateauing” of effect to occur; either the Hb stops increasing or escalating doses of ESA are required to reach therapeutic targets. This period of blunted response is often due to the development of iron deficiency, as iron stores are used for erythropoiesis. Once the target level of Hb has been reached, Hb should be checked every 2 to 4 weeks. During this maintenance phase of therapy, the dose of ESA should be adjusted on the basis of subsequent changes in Hb and clinical circumstances (Figure 32.1).

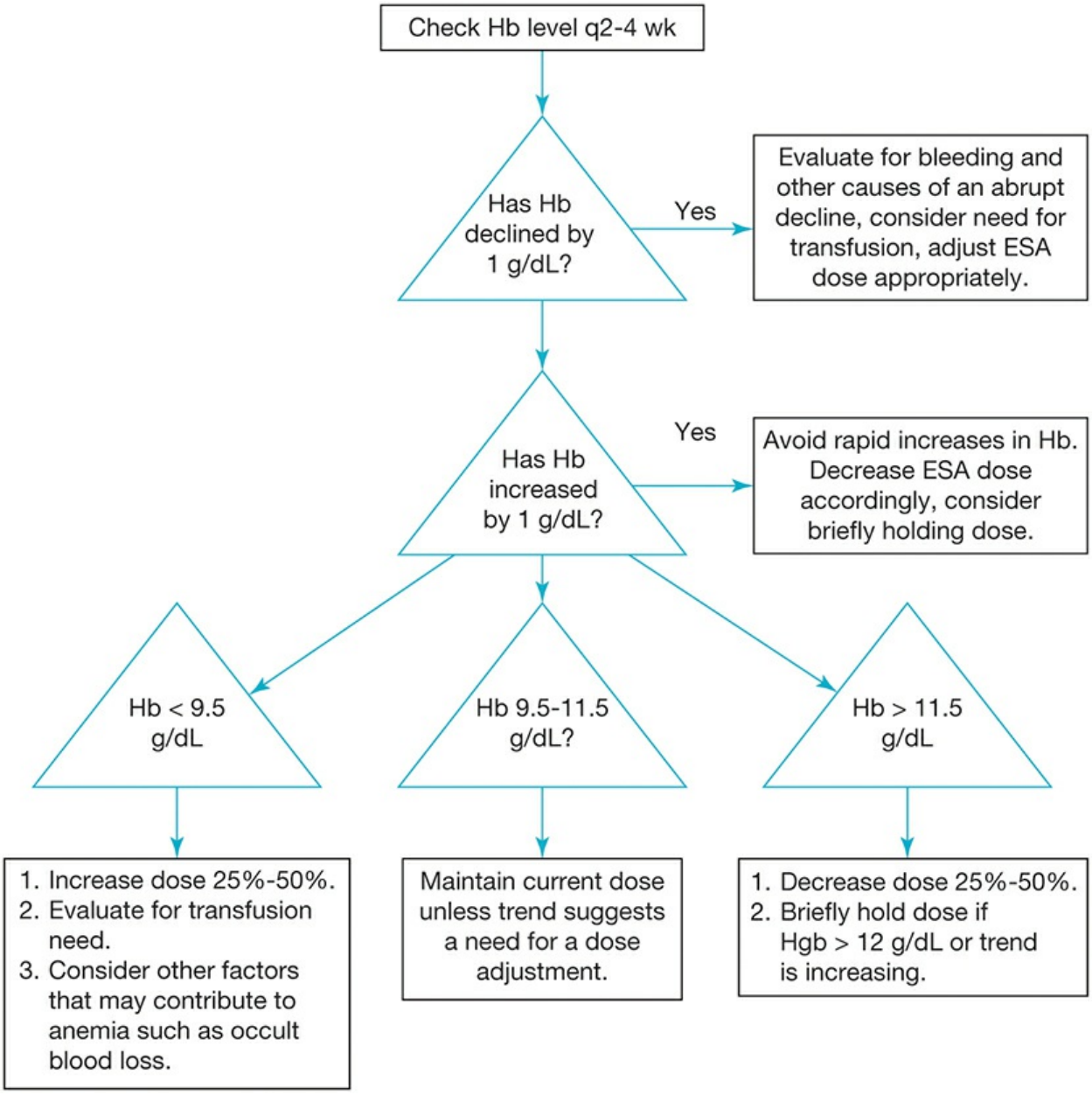


FIGURE 32.1: Flow chart for adjusting erythropoiesis-stimulating agents (ESA) dose based on hemoglobin (Hb) results.

D. Side effects of ESA (HIF-PHI) therapy. See Section 3 above for a discussion of cardiovascular risks of ESA therapy. Studies comparing ESAs to HIF-PHIs in dialysis found similar safety profiles. The side effects listed below can be considered to apply to both classes of drugs.

1. **Worsening of hypertension.** This is a common problem during treatment of anemia with ESA therapy. In some patients, there will be a need to increase antihypertensive medication doses. However, it is rare for ESA to be withdrawn because of uncontrollable hypertension. The relationship between the erythropoietic system and the treatment of blood pressure has been long known. In a study of 8,000 individuals with and without kidney disease, serum EPO concentration was found to

be associated with prevalent hypertension, systolic blood pressure, and pulse pressure (Sun, 2021). The cause of the hypertensive effect is incompletely understood. Factors that may contribute to ESA treatment and increased blood pressure include the partial reversal of hypoxic vasodilation as the Hb rises, reduced nitric oxide, increased cytosolic calcium levels, increased plasma endothelin levels, activation of the renin-angiotensin-aldosterone system, and others. Clinical risk factors include preexisting hypertension, a rapid increase in Hb, higher Hb targets, and severe anemia prior to treatment.

Generally, a slower rate of rise of Hb during ESA initiation seems to cause less of a hypertensive effect. Various antihypertensive medications, including long-acting calcium channel blockers, are effective for treating hypertension associated with ESA.

2. **Seizures.** These may occur in a small number of patients during periods of an excessively rapid increase in Hb, in association with severe hypertension and encephalopathy. This syndrome was reported in the earliest studies of epoetin treatment. A subsequent meta-analysis did not find an increased risk of seizures with ESA treatment (Strippoli, 2004). The risk for seizures is probably minimal using current ESA dosing protocols.
3. **Vascular access clotting.** Increased blood viscosity or other factors that occur with ESA treatment and rising Hb can increase the risk of vascular access (especially arteriovenous graft) thrombosis. This was noted in the first studies of epoetin alfa in the 1980s and has been a consistent finding in subsequent studies, particularly trials of treatment to higher Hb targets. As discussed previously, some patients may experience substantial hemoconcentration during or after the HD treatment, and effects on blood viscosity and risk for vascular access thrombosis may be a particular concern among these patients. More recently, studies of HIF-PHI drugs have found similar risks of vascular access clotting when compared to ESAs. The treatment approach most likely to prevent thrombotic complications is avoiding higher Hb targets and raising Hb fairly gradually during initial treatment (0.5 g/dL/mo).
4. **Stroke.** The risk of stroke was increased in some of the randomized trials of ESAs where a high Hb concentration was targeted. In the TREAT study (patients with diabetes and nondialysis CKD), with 29 months of median follow-up, stroke occurred in 5% of patients treated with darbepoetin (Hb target 13 g/dL) compared to 2.6% of patients in the placebo group. The investigators were unable to find any patient characteristic that identified patients at increased risk for stroke (Skali, 2011). In contrast to the high Hb target in the TREAT study, it isn't known whether the risk for stroke is increased with ESA treatment to more conventional Hb targets. Accordingly, the Hb target should be kept well below the concentration of 13 g/dL used in TREAT.

E. ESA treatment and cancer. In studies of ESA treatment for anemia in patients with cancer, there has been some evidence to suggest that ESA treatment could reduce overall and progression-free survival. In addition, among these hypercoagulable patients, the risk for venous thromboembolism during ESA treatment is clearly increased. This has led to significant changes in the approach to ESA treatment in patients with cancer. Because some patients with ESKD may have either an active or

past malignancy, the subject is relevant and affects dialysis anemia treatment decisions (Hazzan, 2014).

The data on ESAs and cancer, however, are not entirely consistent. For example, several published meta-analyses of published trials have not found ESA treatment to adversely impact complete responses, disease progression, or progression-free survival. It should be noted that in studies demonstrating potential harm, ESA treatment was used to target relatively high Hb levels (up to 16 g/dL in men). Although the meta-analyses provide some reassurance, the residual uncertainty should drive a conservative approach to treatment until the question is fully resolved.

We would suggest that for patients with ESKD with a history of past malignancy, ESA therapy can be cautiously employed with Hb targets as noted above for general treatment of patients with ESKD. In patients with active malignancy, decisions on anemia treatment should be made in collaboration with the treating oncologist and with the patient involved in the discussions.

F. Decreased response to ESA therapy

1. **General concepts.** Most patients will respond to ESA treatment with achievement of Hb values consistently greater than 10 g/dL (100 g/L). Among patients whose Hb level falls to less than 10 g/dL despite increasing doses of ESA, a state of relative ESA resistance (an alternative term is hyporesponse) is said to exist. Responsiveness to ESA should be assessed on an ongoing basis because patients' degree of responsiveness changes over time. Patients resistant to ESA are notable not just because ESA treatment is more difficult, but additionally because ESA hyporesponse is associated with adverse outcomes. While this may simply be a reflection of the patient's clinical risk characteristics, it is also possible that high ESA doses, as required by these patients, may themselves be toxic and contribute to poor outcomes. For these reasons, the 2012 KDIGO anemia guidelines recommend not generally exceeding 4 times the usual baseline weight-adjusted dose of ESA when managing resistant patients (KDIGO, 2012). When ESA resistance occurs, the cause should be determined, if possible. There are several common causes.
2. **Iron deficiency.** The most important initial cause of a suboptimal response to ESA therapy is iron deficiency. Iron deficiency can be present at the outset of therapy, but also frequently develops during ESA therapy, either due to rapid utilization of iron to support erythropoiesis or as the result of blood loss (Table 32.1).

TABLE 32.1 Causes of Iron Deficiency in Patients Undergoing Hemodialysis

- Blood loss
  1. Blood retention by the dialysis lines and filter
  2. Blood sampling for laboratory testing
  3. Accidents related to the vascular access
  4. Surgical blood loss
  5. Occult gastrointestinal bleeding
- Decreased dietary iron absorption
  1. Phosphate binders inhibit iron absorption.
  2. Histamine-2 blockers, proton pump blockers, and functional achlorhydria impair iron absorption.
  3. Uremic gut does not absorb iron optimally.

- Increased iron demand
  1. Due to the increased rate of erythropoiesis induced by erythropoiesis-stimulating agents
  2. Impaired release of iron from storage tissues (reticuloendothelial blockade)

a. Causes of iron deficiency in ESKD

1. **Blood loss.** Patients on HD develop iron deficiency primarily because of chronic blood loss. Between retention of blood in the dialysis lines and filter, surgical blood loss, accidental bleeding from the access, blood sampling for laboratory testing, and occult gastrointestinal (GI) bleeding, iron losses may be substantial. Because of the overall burden of blood loss, it is very difficult to maintain iron stores in patients on HD using oral iron supplements only. Losses in patients undergoing PD are less, and these patients can often be maintained on oral or IV iron therapy.
2. **Functional iron deficiency.** In addition to a depleted iron supply, the demand for iron increases during ESA treatment, leading to a further strain on depleted iron stores. After the IV injection of ESA, there is an increase in the rate of erythropoiesis that leads to a greater immediate need for iron. Moreover, inflammation leads to hepcidin production, resulting in a rapid reduction in iron availability. Together, the effect is that even with adequate iron stores, there may be insufficient iron available for optimal erythropoiesis. This phenomenon has been termed “functional iron deficiency” or iron-restricted erythropoiesis.

3. **Poor intestinal absorption of iron.** Iron deficiency among patients on dialysis may be exacerbated by poor absorption of dietary or medicinal iron. There may be several factors that contribute to this. Most important, as discussed above, are inflammation and hepcidin, which directly block intestinal iron absorption.

a. Diagnosis of iron deficiency

1. **Serum ferritin.** Ferritin is a protein used to store iron inside cells in a nontoxic form. Free iron is noxious to cells because it generates free radicals. Although most ferritin is intracellular, some appears in the circulation, serving as an indicator of iron stores. Because serum ferritin is cleared by the liver, in hepatic insufficiency, serum levels may be markedly increased. It is important to be aware that while serum ferritin is a measure of storage iron, it is also greatly affected by inflammation. In the presence of inflammation (as noted above), hepcidin is produced, which leads to iron being sequestered in storage tissues. Since serum ferritin reflects storage iron, the concentration will be increased during inflammation. Serum ferritin levels can also be high in certain cancers and with malnutrition. If the serum ferritin level is less than 200 mcg/L in patients on dialysis, the likelihood of iron deficiency is very high. However, absolute iron deficiency can be present even with normal or elevated serum ferritin levels in the presence of inflammation.
2. **Transferrin saturation (TSAT).** Transferrin is a glycoprotein that normally transports iron in the blood. In diagnosing anemia, transferrin levels are not measured directly. Instead, one can measure total iron binding capacity (TIBC) after loading a serum sample with iron. This test measures how much iron the blood can carry in non-Hgb form and is an indirect

reflection of the transferrin level. Normal values for TIBC are 240 to 450 mcg/dL (43-81 mcmol/L). The percent TSAT is calculated by dividing the serum iron by the TIBC, and the value for TSAT normally is about 30% with a range of 20% to 50%. As compared to serum ferritin which is more a measure of storage iron, TSAT tends to be a reflection of circulating iron. Among patients on dialysis, a level less than 20% is a strong indication of iron deficiency.

3. **Use of serum ferritin and TSAT in ESKD iron management.** The serum ferritin concentration and TSAT percentage have been the two most widely used tests for assessing iron status in patients undergoing dialysis. Unfortunately, neither test is very accurate for the assessment of iron availability in this patient population. Accordingly, the National Kidney Foundation's (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) anemia guidelines state that iron tests should be interpreted in the context of patients' clinical status, Hb level, and ESA responsiveness. The 2012 KDIGO anemia in CKD guidelines suggest evaluating iron status (TSAT and serum ferritin) at least every 3 months during ESA therapy. The guidelines recommend monitoring levels more frequently (1) when initiating or increasing ESA dose, (2) when there is blood loss, (3) when monitoring response after a course of IV iron, and (4) in other circumstances where iron stores may become depleted.

   In our opinion, intensification of iron therapy for patients on HD should be considered at a serum ferritin of less than 500 ng/mL or TSAT of less than 20%. We would recommend maintaining TSAT greater than 20% and serum ferritin greater than 200 ng/mL in patients undergoing PD. Iron testing should usually be delayed for 1 week after treatment with IV iron. **Functional iron deficiency** can manifest as low TSAT with normal or elevated ferritin levels. With inflammation and **reticuloendothelial blockade**, ferritin levels are typically increased, but TSAT may be normal or reduced.

4. **Reticulocyte hemoglobin content (CHr).** This test is used to assess iron status and is a more direct measure of iron availability at the level of red blood cell production (Brugnara, 2003). Several studies document a good level of diagnostic accuracy and cost effectiveness, and the test shows less variability than other tests of iron status (Fishbane, 2001). More recently, the test has been available under the name reticulocyte hemoglobin equivalent. UK National Institute for Health and Care Excellence (NICE) guidelines discuss both CHr and a related test, the percentage of hypochromic red blood cells (HRC). For the latter test, they note, "in order for the percent HRC to be accurately measured, blood samples must be processed within six hours to prevent red cell swelling. Most outpatient dialysis facilities in the United States do not use HRC for this reason." NICE guidelines recommend the use of CHr if testing within 6 hours is not possible (Ratcliffe, 2016).

b. Iron treatment

1. **General principles.** Iron therapy is an integral component of anemia treatment in ESKD. Iron may be administered on an episodic basis as needed

when iron deficiency develops or by the repeated administration of small doses to maintain iron balance and prevent the development of iron deficiency.

2. **Oral iron.** Oral iron preparations are safe and relatively inexpensive. However, they are associated with questionable efficacy and troublesome side effects, such as constipation, dyspepsia, bloating, and diarrhea. Three randomized trials have compared oral iron with either placebo or no iron treatment in patients undergoing HD; none of the three was able to demonstrate any efficacy for oral iron. Therefore, traditional oral iron agents should not be used for most patients on HD.

   Since the last edition of this handbook, a new oral agent, ferric citrate, has emerged as a reasonable treatment option. Ironically, its primary indication in dialysis is as a phosphate binder (in nondialysis CKD, it is indicated for treatment of iron deficiency anemia). A side benefit is that while binding phosphate, a significant amount of iron is absorbed. Umanath et al studied 441 patients on HD randomized to either ferric citrate or other phosphate binders. Patients in the ferric citrate group had significant increases in serum ferritin and TSAT levels, reduced IV iron requirements, and a significant reduction in ESA dose. The drug was well tolerated; there were fewer GI side effects with ferric citrate than in the comparator group, patients taking sevelamer carbonate, calcium acetate, or both (Umanath et al, 2015). Taken together, the results of this and other studies point to ferric citrate as an oral iron supplement with excellent utility. If used per its FDA indication as a phosphate binder, then iron supplementation is a secondary benefit. See below for information on dosing.

   a. **Dosage and administration.** Oral iron is particularly convenient for patients undergoing PD to avoid the need for IV iron. It has traditionally been given as ferrous sulfate, fumarate, or gluconate, in a dosage of 200 mg of elemental iron per day. Ferric citrate, per its FDA-labeled indication as a phosphate binder, has a starting dose of two tablets orally 3 times per day with meals. It will lower the phosphate concentration and deliver a considerable amount of iron. We find this dose to be higher than usually needed for iron supplementation alone. In this setting, we recommend a dose of one tablet thrice daily between meals. The primary sites of iron absorption are the duodenum and proximal jejunum, and GI symptoms are proportional to the amount of elemental iron presented to the duodenum; reduction of symptomatology may require changing the oral preparation, using pediatric dosages at more frequent intervals, or even taking the iron dosage with food. A common problem with traditional oral iron agents is constipation, which can be partially managed, if necessary, with stool softeners or laxatives.

3. **Intravenous iron.** IV iron has superior efficacy when compared with oral iron therapy. In patients on HD, with greater obligate blood loss, the target Hb level is difficult to achieve without IV iron treatment. As a result, most patients on HD will require IV iron on a regular basis. Recently, 60% of patients received at least one dose per month. In contrast, IV iron therapy

costs more, and its safety profile is less clear than that of oral iron. There are two commonly used IV iron dosing strategies. One is to treat established iron deficiency with a repletive 1,000-mg dose administered over 10 consecutive HD treatments. Alternatively, since iron deficiency occurs so frequently in patients on HD, a weekly maintenance dose of 25 to 100 mg may be used. One observational study found the repletion method to have greater efficacy compared with maintenance dosing (Kshirsagar, 2013a), while not increasing the risk for cardiovascular events (Kshirsagar, 2013b). However, a repletion strategy may have a greater infection risk compared with bolus therapy (Brookhart, 2013). When IV iron is required for patients undergoing PD, infusions of 200 mg of iron sucrose may be administered over 1 to 2 hours, or other forms of IV iron that can be administered at higher doses can be used (see below).

a. **Intravenous iron safety: general considerations.** The injection of large doses of iron directly into the circulation, with its potential oxidizing properties, fuels lingering concerns regarding risk, including immediate infusion reactions, infection susceptibility, and promotion of cardiovascular adverse events. Decades of observational studies and underpowered clinical trials did little to clarify the risk profile. A meta-analysis including 240,000 patients published in 2018 (Hougen, 2018) and a large randomized controlled trial, the PIVOTAL Study (Macdougall, 2019), published in 2019, provided helpful, but only partial reassurance, on these and other safety issues.
b. **Intravenous iron safety: anaphylaxis.** The best-understood complication of IV iron treatment is the rare occurrence of anaphylactoid-type reactions. These are characterized by the abrupt occurrence of hypotension, dyspnea, flushing, and back pain. With iron dextran, the rate has been estimated as 0.7% of patients treated. Although studies have suggested varying rates with different forms of IV iron, it is unlikely that any differences are clinically meaningful. If a reaction occurs, it should be managed immediately with appropriate interventions.
c. **Intravenous iron safety: infection.** Iron is a vital growth factor for microorganisms, and injecting iron directly into the bloodstream has the potential to make iron more readily available to pathogens. In vitro studies have suggested that iron treatment may interfere with the phagocytic function of white blood cells. Several population-based observational studies found higher serum ferritin levels in patients on HD, or IV iron treatment itself, to be associated with an increased risk of infection. In contrast, a large, prospective observational, multicenter study (Hoen, 2002) found no relation between serum ferritin or treatment with IV iron and risk of bacteremia. The PIVOTAL study (Macdougall, 2019) randomized 2,141 patients on HD to a more intensive iron treatment strategy (400 mg monthly) compared to a more conservative approach (treatment only when serum ferritin fell below 200 ng/mL). As to be expected, there was a significantly greater exposure to IV iron in the intensive treatment group, creating a unique opportunity to better

understand the infection risk. Notably, no difference was found in the number of infection episodes between the two groups. This result was reassuring but does not completely exclude an effect of IV iron on infection risk since both groups received fairly large amounts of iron. As it stands, the most prudent approach is to avoid IV iron treatment during acute infectious episodes. Treatment with iron is not urgent, and it is safer to wait until patients recover from their infection.

d. **Intravenous iron safety: oxidation and cardiovascular risk.** Iron is a highly oxidative substance, and treatment with IV iron has the potential to overburden the body's innate antioxidant systems. Oxidative damage to tissues and molecules has been demonstrated experimentally, although the clinical significance of such findings is not clear (Fishbane, 2014). A potential harmful effect of vascular oxidative damage would be an acceleration of atherosclerosis.

   Observational research has been mixed but hasn't clearly pointed to an increase in cardiovascular adverse events with IV iron treatment. The above-mentioned PIVOTAL trial focused on cardiovascular outcomes. In that study, there was no evidence of harm with more intensive iron treatment. In fact, in the lower dose iron group, there was a trend to increased all-cause mortality and an increase in myocardial infarction and hospitalizations for heart failure. These findings could indicate that higher-dose IV iron actually conveys cardiovascular protection (either directly or indirectly through lower ESA doses). Alternatively, it is equally plausible that the increase in cardiovascular events in the low-iron group indicates the danger of iron deficiency among patients on HD.

4. **Intravenous iron drugs**
   a. **Iron dextran.** The longest-used IV iron treatment, iron dextran, is effective and generally well tolerated. It is comprised of iron complexed to glucose polymers. There may be an increase in immediate hypersensitivity reactions with this agent compared to other iron drugs, but this has not been a consistent finding. It can be administered at 100 mg doses used sequentially or in larger doses as needed.
   b. **Iron sucrose.** Intravenous iron sucrose has been in use throughout the world for decades. After approval in the United States in 2000, it quickly became the most widely used iron drug in US HD centers. The drug is effective and generally well tolerated. In one study, no serious adverse reactions occurred in 665 patients undergoing HD receiving 8,583 doses of the drug (Aronoff, 2004). The drug may be administered as iron replacement therapy, 100 mg for 10 consecutive doses, or as a weekly dose of 25 to 100 mg. The one disadvantage of iron sucrose is that it causes hypotension when administered at higher doses. As a result, patients undergoing PD may need to return to the clinic for repeated injections.
   c. **Other IV iron drugs: sodium ferric gluconate.** IV sodium ferric gluconate is a nondextran form of iron used in the United States since 1999 and in Europe for several decades. It has similar characteristics to

iron sucrose. In a prospective observational study, with single-dose exposure, the rate of severe reactions was 0.04%, and no severe reactions were observed with repeated administration of 13,151 doses to 1,321 patients (Michael, 2002, 2004). In HD, it is usually administered in doses of 62.5 or 125 mg. Like iron sucrose, it is not well tolerated when administered in higher single doses. **Ferumoxytol** has a favorable characteristic that 510 mg can be administered in one treatment over 15 or more minutes. This may make it more convenient for patients on PD. The drug includes a distinct safety warning related to the risk for anaphylactic reactions. **Ferric carboxymaltose** was approved in the United States in 2013. It can be administered at higher doses of 750 to 1,000 mg at a time, but does not have a current FDA indication for patients on dialysis. **Ferric derisomaltose** was approved in the United States in January 2020. It can be given as a 1,000-mg infusion. Its indication is for "patients who have non-HD dependent chronic kidney disease." Thus, it can be used within the labeled indication for patients on PD.

d. **Iron added to the dialysate.** Ferric pyrophosphate citrate (Triferic) is an iron compound designed to be added to the dialysis solution, with the goal of supplementing a small amount of iron to the patient during each dialysis treatment. The agent is not as effective as IV iron drugs, but seems to avoid immediate hypersensitivity reactions. At the time of this writing, it has not been widely utilized in US HD centers.

5. **Other causes of decreased response to ESA therapy**

a. **Bleeding.** An important cause of an apparent hyporesponsiveness to ESA is bleeding. Usually, the bleeding is occult, as in GI blood loss. Sometimes the bleeding may be obvious, as in patients undergoing surgery, menstruating women, or those with accidents involving vascular access. Because anemia treatment is usually driven by protocols and managed by nurses, nephrologists may be somewhat detached from the process of ESA dosing. As a consequence, doses may be repeatedly and sequentially increased without the nephrologist's direct involvement. As a result, blood loss may cause a decrease in Hb with a delay in detection. Accordingly, nephrologists should review Hb levels and ESA doses every month and be alert for evidence of ESA resistance.

b. **Shortened erythrocyte lifespan.** Red blood cell (RBC) lifespan is shorter on average in patients with ESKD compared to normal subjects (Vos, 2011). This impacts on ESA treatment in that there is a correlation between the degree of shortening of RBC lifespan and ESA resistance (Dou, 2012). The cause of reduced red cell survival is not completely known but probably related to the uremic milieu and in HD, perhaps by shearing of cells by dialysis needles.

c. **Inflammation and infection.** Inflammatory states lead to diminished response to ESA therapy. More than 30% of patients on dialysis have evidence of active inflammation (Gluba-Brzózka, 2020), although the cause of inflammation may not be readily apparent. In the iron section

above, the important role of inflammation in causing hepcidin production was reviewed. Hepcidin causes a reduction in intestinal iron absorption and blocks the release of iron from the body's storage pools (D'Angelo, 2013). The net effect is reduced iron availability for erythropoiesis. In addition, inflammation has direct effects (not through hepcidin) to diminish erythropoiesis. With the current widespread treatment with IV iron in patients on HD, iron deficiency may be a lesser cause of ESA resistance than in the past, and inflammation may now be the most important cause of resistance. There is no perfect marker to test for occult inflammation, but C-reactive protein (CRP) is a helpful test and should be considered in all patients with ESA hyporesponsiveness (Kalantar-Zadeh, 2003). When CRP is elevated, a complete history and exam may help determine the source of inflammation. There are various reasons that inflammation may be present in patients on dialysis, yet in many patients there is not a clear etiology. Examples of causes include a retained, nonfunctioning kidney allograft, which can increase CRP levels and be a source of EPO resistance (López-Gómez, 2004). Old, nonfunctioning but infected arteriovenous grafts can cause ongoing inflammation; treatment of the infection may reverse ESA resistance (Nassar, 2002).

There is currently no direct treatment to counteract the effect of inflammation on anemia. A recent study tested a monoclonal antibody against the cytokine IL-6 (a key mediator of inflammation in HD). The result was reduced CRP concentrations with increased Hb and improved ESA responsiveness (Pergola, 2021). Other drugs are in development targeting inflammation and its effects.

d. **Hyperparathyroidism.** Hyperparathyroidism is a recognized cause of ESA resistance. Observational studies have generally found that higher serum levels of intact parathyroid hormone (iPTH) are associated with diminished ESA response. In addition, after parathyroidectomy, responsiveness improves (Koncicki and Fishbane, 2017). Similarly, medical treatment of hyperparathyroidism can improve ESA response (Tanaka, 2016). It does not appear that parathyroid hormone itself inhibits erythropoiesis. The pathogenesis is incompletely understood, but bone marrow fibrosis may play an important role. In patients with ESA resistance who are found to have significantly elevated iPTH levels, an intensification of the treatment of hyperparathyroidism is indicated. An interesting development has been the recognition that fibroblast growth factor 23 (FGF-23), another marker of bone and mineral disease, is also associated with anemia of CKD (Mehta, 2017). The clinical implications are yet to be determined.

e. **7-Vitamin B_{12} deficiency.** Vitamin B_{12} and folic acid levels should be checked when unexplained ESA resistance is present. Deficiencies in either can cause megaloblastic anemia. Many patients undergoing dialysis are treated with proton pump inhibitors, known to be associated with subnormal B_{12} levels, and intensive, high-flux HD and

hemodiafiltration treatments have been shown to lower vitamin B_{12} levels.

f. **Inadequate dialysis.** Severe underdialysis results in difficult-to-treat anemia. In contrast, in the urea reduction ratio (URR) range of 60% to 75%, there appears to be only a weak association between increased hematocrit and higher levels of URR (Ifudu, 2000). Beyond that, randomized studies of more frequent dialysis (ie, the Frequent Hemodialysis Network Trials), either in-center or nocturnal, have shown no consistent benefit in terms of increasing ESA responsiveness.

g. **Aluminum intoxication.** Although problems with aluminum have become less common among patients undergoing dialysis, occasional problems may still occur, especially in patients who have been on dialysis for many years. The effect on erythropoiesis is a microcytic anemia associated with impaired iron utilization. Interestingly, intestinal aluminum absorption is significantly increased in patients with iron deficiency. A serum aluminum level provides a rough guide to aluminum status; if the results are suggestive, either a deferoxamine stimulation test or a bone biopsy may be warranted.

h. **Angiotensin converting enzyme (ACE) inhibitors.** ACE inhibitors may reduce EPO production in patients with CKD or following kidney transplant. Among patients on dialysis, a reduction in ESA responsiveness has not been uniformly demonstrated in association with these agents.

i. **Pure red cell aplasia.** An outbreak of immune-mediated pure red cell aplasia was reported, primarily in Europe, in association with ESA treatment. In the first 10 years of worldwide ESA availability, only three cases were noted among more than a million treated patients. Subsequently, the rate increased dramatically, with at least 184 cases reported between 1998 and 2003. In ESA-associated pure red cell aplasia, Hb declines rapidly as does the reticulocyte count. Patients become transfusion dependent, and the bone marrow demonstrates the absence of erythroid precursors. The cause is the development of anti-EPO antibodies that neutralize both therapeutic and endogenous EPO. The majority of cases occurred in Europe, with epoetin alfa sold under the brand name Eprex. After a peak in cases in 2002, the number declined substantially, but sporadic cases continued to develop. Certain biosimilar forms of ESAs have been associated with a greater risk for anti-EPO antibodies, so vigilance is required as the use of biosimilar ESAs increases. This is particularly true in areas with less rigorous development pathways (Wish, 2016).

j. **Other hematologic diseases.** Patients on dialysis are at risk for developing the same hematologic diseases as nonuremic subjects. Because of the emphasis on EPO deficiency, other hematologic diseases may go unrecognized. Among other potential causes of ESA resistance not already discussed above are hematologic malignancy, myelodysplastic syndromes, and hemolysis. When an exhaustive

evaluation for causes of ESA resistance is unrevealing, hematology consultation and a bone marrow biopsy may be considered in the process to rule out unexpected hematologic disease.

6. **RBC transfusions.** Transfusion of packed red cells should be used in patients with severe anemia who are experiencing symptoms or with a rapid decline in the Hb concentration. Transfusion always carries a risk for allosensitization, which may diminish the opportunity for transplantation and increase the risk for subsequent rejection.
7. **Carnitine.** It has been suggested that carnitine may enhance responsiveness to ESA. A multicenter, randomized, double-blind, placebo-controlled trial found that administration of carnitine failed to improve response to ESA therapy (Mercadal, 2012). The 2012 KDIGO anemia in CKD guidelines do not recommend the use of carnitine as an adjuvant to ESA treatment. However, a recent observational study suggested improved ESA response with carnitine supplementation in patients undergoing PD (Kaneko, 2021).
8. **Ascorbic acid.** Although the literature is mixed, several studies have found that IV ascorbic acid may improve epoetin responsiveness for patients on HD. A typical regimen is intravenous vitamin C given 3 times weekly with the HD treatment. Deved (2009) conducted a meta-analysis. Although concerned about small sample sizes and deficits in study quality, the authors found ascorbic acid to generally result in increased Hb and decreased ESA dose. Since vitamin C may lead to increases in oxalate production, appropriate caution must be used in patient selection and duration of therapy.
9. **Vitamin D.** Vitamin D deficiency is a common problem among patients with kidney disease. The vitamin is important for mineral and bone health, and may be involved in early erythropoiesis by stimulating an increase in erythropoietin and erythrocyte precursor development. Small studies found that vitamin D supplementation could enhance the response to ESA treatment. A subsequent meta-analysis confirmed that either in its vitamin or activated form that vitamin D supplementation could enhance erythropoietic effect (Ahmad, 2023).

II. HEMOLYSIS

A. General comments. Destruction of RBCs, either intravascularly or extravascularly, may occasionally contribute to anemia in patients undergoing dialysis. Generally speaking, red cell survival appears to be shortened with chronic kidney failure (~30% compared with healthy subjects; Ly, 2004). This is likely due not to an inherent abnormality of the red cell but to the effect of the uremic environment.

B. Diagnosis. Chronic hemolysis should be suspected when a patient develops ESA resistance in the presence of increased serum lactic dehydrogenase (LDH), unconjugated bilirubin, or a decrease in serum haptoglobin. The differential diagnosis of chronic hemolysis is broad and includes all causes of hemolysis seen in nonuremic patients (Table 32.2) and several causes specific to patients treated with HD. Occasionally, hemolysis can be acute and severe, associated with hypotension, or sometimes hypertension, and with abdominal, chest, and/or back pain, shortness of breath, nausea, vomiting, or diarrhea, and encephalopathy developing during the dialysis

procedure (Duffy, 2000).

TABLE 32.2 Causes of Hemolysis in Patients Undergoing Dialysis

Related to the hemodialysis procedure
Dialysis solution
Contaminants
Chloramine
Copper, zinc
Nitrates, nitrites
Overheated
Hypo-osmolar
Reuse of sterilants (formaldehyde)
Kinked or defective tubing—trauma to RBCs
Needle trauma to RBCs
Insufficient dialysis
Hypersplenism
Associated diseases
Sickle cell anemia
Other hemoglobinopathies
Connective tissue diseases with vasculitis
Drug induced
Hypophosphatemia

RBC, red blood cell.

C. Etiology. The most common acute correctible cause of hemolysis is due to a problem with the HD system. Faulty or kinked bloodline tubing can do this via mechanical damage to RBCs. Chloramine in the dialysis solution; use of a hypotonic or overheated dialysis solution; copper, zinc, or nitrate in the water supply; or formaldehyde not rinsed out of the dialyzer after reprocessing are among the causes. Machine/dialysis solution–based issues are discussed in Chapters 4, 10, and 12.

D. Treatment. If acute, severe hemolysis is suspected, the dialysis treatment should be terminated immediately. Circulatory support should be provided as needed, and an electrocardiogram must be obtained to determine whether hyperkalemic changes are present (which may be delayed) and to assess for acute cardiac ischemia. A blood sample should be obtained for the determination of Hb, hematocrit, and serum chemistries, especially serum potassium.

III. DISORDERS OF HEMOSTASIS

A. Introduction. The formation of a blood clot in response to vascular injury is a complex and highly conserved process in mammalian species. Disorders of platelet quantity or function can lead to bleeding in superficial sites, such as the skin and mucous membranes. Disorders of the coagulation system usually lead to bleeding into deeper structures, such as muscles and joints. Prior to the introduction of dialysis, bleeding tendencies were long recognized among patients with uremia. Dialysis partially reverses

the abnormal hemostasis, but ecchymoses, excessive access bleeding, and occasional severe bleeding episodes still occur.

B. Pathophysiology. Many factors contribute to the deranged state of uremic hemostasis, with disorders in platelet function (thrombasthenia) being the most important. Platelet counts may be slightly reduced, but commonly are normal in well-dialyzed patients, and severe thrombocytopenia indicates a primary hematologic disorder. A systematic review published in 2021 found that the most common defects of platelet function were increased bleeding time and reduced platelet adhesion (Baaten, 2021). In addition, platelet aggregation is abnormal, probably because of reduced platelet granule adenosine phosphate and serotonin levels and defective thromboxane A_2 production. An adhesion receptor, the glycoprotein (GP) IIb-IIIa complex, plays an important role in controlling the formation of platelet thrombi. In patients with uremia, the activation of the GP IIb-IIIa receptor is impaired, but activation is partially restored by dialysis. There has been a suggestion that abnormalities of von Willebrand factor (important for maintaining platelet adhesion in rapid blood flow) may contribute to disordered uremic hemostasis, but study results have been inconsistent. Anemia itself probably contributes to uremic bleeding. Red cells circulate in the middle of the circulatory stream, driving platelets out to the periphery of the bloodstream where they are in better contact with the vascular endothelial surface. Accordingly, with anemia, platelets may have diminished contact. An abnormally prolonged bleeding time is significantly improved when the hematocrit is increased to greater than 30%. The HD procedure itself may impact platelet number and function. Polysulfone dialyzers sterilized by electron beam have been reported to cause a reduction in platelet count, but this effect may vary with how the membrane is produced and is not a consistent finding. Antiplatelet drugs may further impair platelet function in ESKD. Patients on HD have a greater risk of bleeding complications while on these drugs than the general population (Hiremath, 2009).

C. Assessment. Disordered hemostasis should be evaluated in terms of clinical manifestations. Patients with ecchymoses, excessive access bleeding, or any clinically significant bleeding episodes (including hemorrhagic pericarditis) should have their platelet count, prothrombin time, and partial thromboplastin time tested. Bleeding time testing, previously recommended, has been found to be an imprecise predictor of bleeding risk. Studies have shown that as GFR falls, bleeding risk increases. Risk for clinically significant bleeding is greatest for patients with ESKD.

D. Treatment. The management of patients undergoing dialysis experiencing bleeding requires (a) an estimate of the severity of blood loss, (b) hemodynamic stabilization, (c) transfusion with blood products as needed, (d) identification of the bleeding source, and (e) treatment of platelet dysfunction and other factors contributing to the bleeding diathesis. Intensive dialysis of patients who were previously severely underdialyzed results in an improvement in bleeding tendency. Desmopressin (a synthetic analogue of antidiuretic hormone) leads to increased release of von Willebrand factor multimers. A dose of 0.3 mcg/kg body weight may be administered diluted in 50 mL of saline intravenously over 30 minutes. In one study, this regimen led to a reduction in bleeding time in 1 hour, which lasted for 8 hours. Tachyphylaxis develops fairly quickly, so repeated dosing may be less efficacious. The drug has little vasoconstrictive effect and should not cause hyponatremia in patients with limited urine output. Presumably, the

beneficial effect of desmopressin on laboratory testing of platelet function aligns with the actual reduction in clinical bleeding risk. Unfortunately, there is not much in the way of conclusive evidence in this regard.

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33 Infections

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I. DERANGEMENT OF IMMUNE FUNCTION IN UREMIA

A. Etiology. In patients on dialysis, there is impairment of several aspects of lymphocyte and granulocyte function. Unidentified uremic toxins are thought to be responsible; malnutrition or vitamin D deficiency can sometimes be contributory factors.

B. Clinical implications

1. **Increased susceptibility to infection**
   - a. **Frequency of bacterial infections.** Bacterial infections occur more often in patients on dialysis than in their nonuremic counterparts; the increase is related not only to immune system dysfunction associated with uremia, but also to frequent violation of normal skin and mucosal barriers.
   - b. **Severity of bacterial infections.** Owing to the presence of vascular access, infections in patients on hemodialysis (HD) are often associated with bacteremia, and there is a substantial risk of serious complications such as endocarditis, osteomyelitis, and epidural abscess. Use of an HD catheter is associated with a 3-fold increase in hospitalization and death from septic complications as compared with the use of a native or graft fistula (Allon, 2004). In patients on peritoneal dialysis, peritonitis is rarely associated with systemic infection.

II. DERANGEMENT OF TEMPERATURE CONTROL IN UREMIA

A. Baseline hypothermia in patients with uremia. In about 50% of patients on HD, the predialysis body temperature is subnormal. The reason for this is unknown.

B. Reduced pyrexic response associated with infections. Uremia per se does not appear to affect the temperature response to pyrogens. However, because of baseline hypothermia, and possibly because of frequently coexisting malnutrition, severe infections in some patients on dialysis may be associated with an attenuated or absent fever response.

III. BACTERIAL INFECTIONS IN PATIENTS ON DIALYSIS

A. Related to the access site

1. **Patients on HD.** Prevention, diagnosis, and treatment of vascular access infections are described in Chapters 8 (fistulas and grafts) and 9 (venous catheters). Several additional clinical points are emphasized here.
   - a. **Bacteremia versus pyrogen reaction.** The patient on dialysis with bacteremia generally presents with chills and fever and may appear quite toxic. On occasion, however, symptoms and signs of infection are remarkably few or absent. Although redness, tenderness, or exudate at the access site may help to incriminate it as the source of the infection, in many cases an infected access site

can appear normal. With bacteremia, hypotension can occur during or immediately after dialysis; bacteremia/sepsis may not be initially suspected in the setting of hypotension when the patient is afebrile. Delayed treatment of sepsis in patients on dialysis is an important cause of morbidity and mortality. Patients with HD catheters who develop fever should be suspected to have catheter-related bacteremia and treated with broad-spectrum antibiotics pending the results of blood cultures.

1. **Pyrogen reaction.** Low-grade fever during HD may be related to pyrogens present in the dialysis solution rather than to actual infection. The time course of fever may be somewhat helpful in making the distinction between pyrogen reaction and infection: Patients with pyrogen-related fever are afebrile prior to dialysis but become febrile during dialysis; fever resolves spontaneously after cessation of dialysis. Patients with access site–related bacteremia are often febrile prior to institution of dialysis and, in the absence of treatment, fever persists during and after dialysis. There is one exception to this rule: Fever and chills that occur shortly after catheter manipulation (eg, commencement or cessation of dialysis) suggest catheter-associated bacteremia. Dialyzer reuse is associated with an increased incidence of pyrogenic reactions. Blood cultures should always be obtained in any febrile patient on HD, even when a pyrogen reaction is the suspected cause of the fever and, in most cases, antibiotics should be administered until infection is excluded.
2. **Contamination of HD machines or solutions.** Occasionally, bacteremia/sepsis may result from contamination of HD machines. These are generally caused by gram-negative bacilli and occasionally fungal infections. Outbreaks of such infections have been caused by inadequate disinfection of water treatment or distribution systems or reprocessed dialyzers (Rao, 2009). Contamination of the waste drain ports and wall boxes of the HD machine has also been described (Novosad, 2019).

b. Prophylactic antimicrobial administration

1. **Systemic prophylaxis prior to an invasive procedure likely to result in bacteremia.** Although there is no definite evidence in the literature, it is likely a good policy to administer antimicrobial prophylaxis to patients on HD prior to invasive procedures associated with a substantial risk of bacteremia because of the presence of either the dialysis catheter or the abnormal arteriovenous communication. These include dental procedures (especially extractions); gastrointestinal (GI) procedures such as esophageal stricture dilation, sclerotherapy for esophageal varices, and endoscopic retrograde cholangiography with biliary obstruction (not necessary for routine endoscopy with or without biopsy); and genitourinary procedures including cystoscopy, urethral dilation, and transurethral prostate resection. The recommended antimicrobial is amoxicillin 2.0 g given 1 hour before the procedure (or ampicillin 2.0 g intramuscularly [IM] or intravenously [IV] given 30 minutes before the procedure). In patients who are allergic to penicillin, either clindamycin 600 mg by mouth (PO) or IV (dental or esophageal procedures) or vancomycin 1.0 g IV (eg, for other GI or

genitourinary procedures) can be substituted.

2. **Long-term, continuous topical prophylaxis.** The skin and nasal carriage rate of *Staphylococcus aureus* in patients on HD is about 50%. Intranasal mupirocin ointment may be effective in eradicating the carrier state and, in uncontrolled studies, has decreased the incidence of staphylococcal infection, though not necessarily permanently. Decision analysis suggests that weekly use of this agent in all patients without screening will decrease infection rates and is cost-effective (Bloom, 1996). However, a major concern is the development of mupirocin resistance with chronic use. In general, there is insufficient evidence to support routine *S. aureus*, including methicillin-resistant *Staphylococcus aureus* (MRSA), decolonization.

On the other hand, a reduction in catheter-related bacteremia has been demonstrated by the use of prophylactic topical antimicrobial ointments at the catheter exit site, the use of prophylactic catheter locking solutions, fastidious catheter care, and the use of vascular access managers and quality initiative programs (Golestaneh and Mokrzycki, 2018; Lok and Mokrzycki, 2011; Niyyar, 2019; Salim, 2021). Their use is particularly beneficial in patients who have nasal carriage of *S. aureus*. Dry gauze dressings rather than transparent film dressings are recommended because transparent film dressings pose a greater threat of exit site colonization (Conly, 1989). A surgical mask worn by the patient and nurse any time the catheter is accessed reduces the spread of infectious droplets and reduces contamination of the catheter site. Currently, the Centers for Disease Control and Prevention (CDC) recommendation for adults 18 or older is to use ointments compatible with the particular catheter or US Food and Drug Administration (FDA)-cleared chlorhexidine-impregnated sponge dressings that are for short-term non-tunneled catheters. At each HD session, a triple antibiotic ointment or a povidone iodine ointment should be used. For both HD and, especially for, peritoneal dialysis, when applying topical ointments at the catheter exit site, it is important to check for their chemical compatibility with the material used to make the HD or peritoneal dialysis catheter. For example, the polyethylene glycol base in mupirocin can damage polyurethane catheters and gentamicin cream may damage silicone catheters (Gardezi, 2016; Khandelwal, 2003).

3. **Catheter caps.** A number of specialized caps, some containing disinfectant, have been developed for HD catheters, with the goal of reducing the entry of infective organisms via the connecting end of the catheter. The clinical utility of one such cap, the ClearGuard from ICU Medical in San Clemente, CA, to reduce the infection rate, was supported by a large, cluster-randomized trial (Brunelli, 2018).
4. **Antibiotic locks.** Biofilm formation can occur in the presence of heparin and adding high concentrations of antibiotics concurrently when not utilizing the catheter has been associated with decreases in infections. Trisodium citrate has been used to prevent coagulation and does have some antimicrobial activity. There is evidence that it is associated with lower rates of catheter-associated bloodstream infections than the use of heparin (Weijmer, 2002).

c. **Vancomycin-resistant gram-positive infections.** Concern about an increasing prevalence of vancomycin-resistant enterococci (VRE) in hospitalized patients has resulted in recommendations that vancomycin use be restricted in patients on dialysis. Because of the relatively high incidence of staphylococcal organisms resistant to antistaphylococcal penicillins and cephalosporins, it is currently reasonable to utilize vancomycin as initial therapy of suspected life-threatening *S. aureus* infections (eg, catheter-related bacteremia). Vancomycin may be discontinued depending on the organism that grows and its corresponding susceptibility results and replaced by a cephalosporin. Certain cephalosporins (eg, cefazolin) have a very prolonged half-life in patients with end-stage kidney disease (ESKD) and can be dosed conveniently postdialysis.

2. **Patients on peritoneal dialysis**

a. **Antimicrobial prophylaxis.** In the absence of other indications for prophylaxis, it is not routinely necessary to administer antibiotics prior to invasive procedures unless a vascular access is present. For more information about the prevention of peritonitis and peritoneal catheter infection, see Chapter 25 and also Chow (2023).

B. Unrelated to the access site

1. **Urinary tract infection (UTI).** In patients on dialysis, the incidence of UTI is high, especially in patients with polycystic kidney disease.

a. **Clinical presentation.** In patients with oliguria, the symptoms of cystitis are similar to those in nonoliguric individuals, although gross hematuria is common and occurs in up to one-third of the patients. Patients with anuria may present with suprapubic discomfort or foul-smelling urethral discharge and may progress to pyocystis (see later).

b. **Diagnosis.** Voided urine samples from patients with oliguria, even from those voiding only a few milliliters per day, are usually sufficient for diagnosis. Urethral catheterization and bladder lavage may cause infection and should be reserved for the patient with symptomatic anuria. The presence of pyuria is not a useful finding to rule in or rule out infection. Absence of visible bacteria does not rule out UTI. A urine culture is essential to make the diagnosis. In one study of 100 asymptomatic patients on dialysis with residual renal urine output, half of whom were women, UTI was defined as the presence of both pyuria and bacteriuria. Pyuria was considered present when there were more than five white blood cells per high-power field of a centrifuged clean-catch urine specimen, and bacteriuria was defined as a colony count greater than 10^4 in men or 10^5 in women. The prevalence of "UTI" defined in this manner was 26% (20% of the male patients and 38% of the female patients). Although the causative organisms were identified, no treatment data were presented (Yamashita, 2022). It would be interesting to study whether asymptomatic UTIs are an unrecognized cause of increased inflammatory markers in this population.

c. **Treatment.** Optimally, antimicrobial therapy should be based on sensitivity testing of the organism involved. If empiric therapy is warranted, prior culture results and patient-specific risk factors for multidrug-resistant organisms (MDROs) should be considered. Unless MDROs are suspected, penicillin, ampicillin, cephalexin, fluoroquinolone, or trimethoprim should be used because

they are safe and may attain adequate urine levels in patients with ESKD. The recommendation has been made to test male patients (nondialysis patients with human immunodeficiency virus [HIV]) from susceptible populations (Asian and Mediterranean) for glucose-6-phosphatase deficiency before prescribing trimethoprim-sulfamethoxazole (Serpa, 2010) to minimize the risk of hemolytic anemia. In female patients on dialysis, trimethoprim-sulfamethoxazole is generally chosen over ampicillin for the treatment of recurrent UTIs; trimethoprim-sulfamethoxazole is less likely to be associated with the emergence of resistant organisms in the fecal flora, the source of most urinary pathogens in women.

The most appropriate treatment schedule for patients on dialysis with cystitis has not been well studied. Therapy should be continued for a total of 5 to 7 days. Ten days of antimicrobial therapy is warranted in patients with adult polycystic kidney disease because of their increased susceptibility to pyogenic complications of UTIs.

It is difficult to achieve adequate urinary drug levels of doxycycline, sulfisoxazole, and the aminoglycosides in patients on dialysis; hence, these agents are not recommended for the treatment of cystitis. However, when the responsible urinary pathogen is resistant to trimethoprim-sulfamethoxazole, cephalexin, fluoroquinolones, and the penicillins, one of these alternative drugs can be employed if its use is supported by the results of bacterial sensitivity. The use of nalidixic acid, nitrofurantoin, tetracycline, or methenamine mandelate is generally contraindicated in patients with anuria due to the prolonged half-lives of these agents and the accumulation of toxic metabolites. One study describing treatment results of UTIs in patients on dialysis (many of whom were anuric) found a resolution rate of over 90%, regardless of whether or not the antimicrobial used was known to be excreted in the urine (El Nekidy, 2022).

If a source of bacteria, such as a staghorn calculus, is identified, it must be removed to cure the UTI permanently. Bacterial persistence or recurrence suggests infection from a source within the urinary tract, particularly if infections with the same bacteria return soon after treatment is completed. Causes include infected cysts, infection stones (eg, staghorn calculus), and bacterial prostatitis. Reinfection caused by the same or different species of bacteria entering the urinary tract at varied intervals is not usually due to an identifiable anatomic lesion but rather to reintroduction of bacteria from a source outside the urinary tract, most frequently the rectal flora. Vesicoenteric and vaginal fistulas are rare causes of reinfection.

Patients with recurrent infections should be evaluated for residual urine and urethral stenosis, urethral stricture, or bladder outlet obstruction. A renal ultrasonographic study and plain film tomograms of the kidney should be obtained in patients on dialysis with possible bacterial persistence. Computed tomography (CT) with and without contrast infusion may be used if ultrasonographic findings are indeterminate. Cystoscopy is recommended if hematuria occurs or to help rule out enterovesical fistula in patients with pneumaturia. Ureteral catheter localization studies should also be performed if bacterial persistence is suspected. Patients found to have a congenital or acquired

anatomic abnormality responsible for their infections should have the defect repaired surgically, if possible. The safety of long-term antimicrobial prophylaxis in patients on dialysis with frequent urinary bladder reinfections is not known. Low-dose trimethoprim-sulfamethoxazole and cephalexin would probably be the safest drugs to use.

d. Upper UTIs and pyogenic complications. Upper tract infections in patients on dialysis occur most commonly as a result of retrograde ascent of urinary pathogens in the urinary tract. Rarely, acute pyelonephritis occurs in patients on dialysis from a hematogenous route. Patients with cystic kidneys and especially those with adult polycystic disease are particularly susceptible to upper tract infection and its complications. Infected cysts, pyonephrosis, and renal and perirenal abscesses may develop.

A patient with an infected cyst or renal or perirenal abscess usually presents with dysuria, recurrent UTIs, fever, night sweats, abdominal or flank pain, or sepsis. Occasionally, the patient may be asymptomatic. A tender, tense mass may be palpable in the flank or abdomen. With systemic symptoms, these patients may develop dehydration due to poor fluid and food intake, sweating, and fever.

Leukocytosis is commonly present. Urine culture will identify the responsible organism if the parenchymal infection communicates with the collecting system. However, culture results can be negative when an infected cyst does not communicate with the urinary tract, or when there is pyonephrosis due to a cyst or stone that completely obstructs the ureter. Ultrasonography or CT may identify infected cysts and provide a point of reference for determining response to antimicrobial therapy. The use of indium-111 (^{111}In) leukocyte imaging and gallium-67 (^{67}Ga) citrate single photon emission computed tomography (SPECT) transaxial imaging in localizing infected cysts has been described and may be considered when findings from ultrasonography or CT are inconclusive.

In patients with cystic kidneys, antimicrobial therapy of upper tract infection should be continued for at least 3 weeks. Many antimicrobials penetrate renal cysts poorly, and the degree of antimicrobial penetration depends on whether the cysts are derived from the proximal tubule or the distal nephron. Lipid-soluble trimethoprim, ciprofloxacin, metronidazole, clindamycin, erythromycin, and doxycycline have been shown to achieve good bactericidal levels in the fluids of both types of cysts and should be good treatment selections, depending on the suspected organism. Ciprofloxacin has been shown to sterilize infected cysts in some patients. Non–lipid-soluble antimicrobials, such as the aminoglycosides, the third-generation cephalosporins, and the penicillins have generally failed to cure infections in polycystic kidneys, presumably because of their poor penetration into cysts derived from the distal nephron.

Patients with adult polycystic kidneys with bacterial persistence localizing to one side (as documented by ureteral catheter localization studies) should have the source of infection removed surgically. Pyonephrosis and renal and perirenal abscesses cannot be cured by antimicrobial therapy alone and require prompt and definitive surgical intervention. Percutaneous drainage of an infected cyst

under radiographic imaging may be appropriate in medically unstable patients, but surgical intervention currently remains the procedure of choice for most localized abscesses. Laparoscopic unroofing of a clearly identifiable infected cyst may be considered. Nephrectomy is indicated only when an infected cyst is unresponsive to antimicrobial therapy or cyst drainage. Delay in nephrectomy is associated with increased morbidity and mortality.

e. **Pyocystis.** In patients with a neurogenic bladder (eg, patients with diabetes), pyocystis (pus in the defunctionalized bladder) may be an unsuspected source of infection. Pyocystis should always be suspected in a patient on dialysis with anuria with fever of unknown origin. Symptoms can include suprapubic or abdominal pain, foul-smelling urethral discharge, or sepsis. Suprapubic tenderness and a distended bladder may be found on examination. A complete peripheral blood count often shows relative leukocytosis. Blood cultures may or may not be positive. Bladder catheterization reveals pus, the culture of which may grow mixed flora. Treatment consists of adequate drainage via an indwelling urethral catheter, followed by intermittent catheterization and bladder irrigations with antimicrobial solutions until the infection clears. Parenteral antimicrobials, chosen according to culture and susceptibility results, should be administered if systemic manifestations are present. Cystourethroscopy and possibly cystometrography should be performed to rule out a bladder outlet obstruction, a large bladder diverticulum, or a neurogenic bladder. Rarely, surgical drainage procedures or even simple cystectomy may be needed in refractory cases.

2. **Pneumonia.** Pneumonia is an important cause of mortality in this population; the possibility of gram-negative infection should be considered in patients dialyzed in a hospital setting. Patients on dialysis may have unusual pulmonary infiltrates due to pulmonary calcification (now uncommon), which can resemble those due to pneumonia. Fluid overload sometimes can be mistaken for pneumonia and should be suspected especially when there are bilateral pulmonary infiltrates; such infiltrates can frequently improve after an increase in ultrafiltration. Pleural effusions are commonly exudative in character owing to uremia-associated inflammation, even in the absence of infection.
3. **Intra-abdominal infections.** Diverticulosis and diverticulitis occur commonly in patients on dialysis, and especially in those with polycystic kidney disease. Strangulated hernia is also frequently encountered. In patients on peritoneal dialysis, the differentiation between dialysis-associated peritonitis and peritonitis due to a disease process involving the abdominal viscera can be difficult to discern (see Chapter 25). Acalculous cholecystitis has been reported (Karahan and Şahin, 2024). Intestinal infarction can occur as a complication of hypotension occurring during a dialysis session or between dialyses; bowel infarction should always be suspected in a patient on dialysis with unexplained, refractory septic shock.
4. **Tuberculosis.** The incidence of tuberculosis has been estimated to be as much as 10-fold higher among patients on HD than among the general population. Tuberculosis in patients on HD is frequently extrapulmonary; disseminated disease may occur in the absence of chest x-ray abnormalities. Difficulty in making the diagnosis is increased because delayed skin hypersensitivity to tuberculin reagent is

often absent or diminished due to cutaneous anergy. Immunologic tests using interferon-γ release assays have shown promise in patients with ESKD (Grant, 2012; Segall and Covic, 2010). A number of subtle, atypical presentations of tuberculosis can be encountered; for instance, patients may present with ascites and intermittent fever only, or with hepatomegaly, weight loss, and anorexia. The diagnosis of tuberculosis in extrapulmonary cases is usually made by demonstrating typical caseating granulomas on pleural or hepatic biopsy or by recovery of tubercle bacilli from the culture of biopsy material. When the index of suspicion for tuberculosis is high, presumptive therapy with antitubercular agents is sometimes warranted. Mortality in patients on dialysis with tuberculosis has been reported to be as high as 40%. Biopsies may be difficult to obtain and next-generation sequencing with cell-free DNA can be helpful diagnostics for various pathogens including mycobacteria.

5. **Listeriosis.** Listeriosis, an unusual infection in the non-immunocompromised host, has been reported to occur in patients on HD suffering from iron overload.
6. **Salmonella septicemia.** In patients on dialysis, severe *Salmonella* septicemia has been noted to occur; in patients without uremia, *Salmonella* enteritis rarely progresses to sepsis.
7. ***Yersinia* septicemia.** This infection has been reported in patients on dialysis with iron overload receiving deferoxamine chelation therapy.
8. **Mucormycosis.** This sometimes fatal infection is seen with unusual frequency in patients being treated with deferoxamine.
9. **Helicobacter *pylori*.** Although patients with ESKD frequently have upper GI complications, the prevalence of this infection appears to be the same in patients with ESKD as in patients with normal renal function. Therapy is similar to that for patients without uremia.

IV. VIRAL INFECTIONS

A. Hepatitis A.

The incidence of hepatitis A in patients on dialysis is no greater than in the general population, given that transmission is usually by the fecal-oral route. The disease pursues the usual clinical course in patients on dialysis. Chronic hepatitis after hepatitis A infection is believed to occur rarely, if at all.

B. Hepatitis B

1. Epidemiology

a. Patients on HD. The incidence of infection with hepatitis B virus (HBV) has decreased in the United States (Finelli, 2005), likely due to screening of the blood supply for evidence of this infection, vaccinations, and to low transfusion requirements due to the availability of erythropoietin. However, outbreaks of hepatitis B in several HD units have occurred. Patients with ESKD are at an increased risk of maintaining a carrier state of hepatitis B due to their immunosuppressed state.

b. Patients on peritoneal dialysis. This group is at a lower risk of acquiring hepatitis B infection. Nevertheless, hepatitis B can be transmitted through exposure to peritoneal effluent.

2. Clinical presentation. Hepatitis B infection is largely asymptomatic in patients on dialysis. Commonly, malaise is the only complaint. The occurrence of visible jaundice is rare. The only manifestation of infection may be an unexplained, mild

(2- to 3-fold) elevation in the serum aspartate (AST) or alanine aminotransferase (ALT) level, or even an increase from a lower to a higher level within the normal range. The serum bilirubin and alkaline phosphatase concentrations may remain normal or be elevated only slightly.

3. **Chronic hepatitis B infection.** Hepatitis B infection in patients on dialysis often runs a protracted course and in 50% of cases progresses to a chronic, HBsAg-positive state. Development of clinically important persistent (or active) hepatitis is not nearly as common as it is in patients not receiving dialysis. Patients with high serum ferritin levels appear to be at increased risk for developing persistent hepatitis. Treatment is indicated in patients who are hepatitis B surface antigen (HBsAg) positive with evidence of viral replication and abnormal transaminase levels, preferably in conjunction with liver histology. A level of 4 to 5 $\log_{10}$ copies per milliliter for HBV DNA is usually taken as the threshold to start treatment. It is important to recognize that hepatitis B e-antigen (HBeAg) can be negative despite active disease. Interferon is rarely used now in view of its side effects; nucleotide or nucleoside analogs are better choices. Entecavir or tenofovir is the recommended first-line therapy in patients on dialysis. Second-line therapy would be adefovir or telbivudine. Lamivudine, adefovir, tenofovir, telbivudine, or entecavir can each be used. The doses of many antiviral medications must be adjusted appropriately according to renal function.
4. **Routine screening.** Patients on HD should be screened for HBV surface antigen (HBsAg), surface antibody (anti-HBs), and core antibody (anti-HBc) on admission to the dialysis unit (or hospital). HBsAg should be tested and monitored on a regular basis for all HBV-susceptible patients, including nonresponders to the vaccine, and anti-HBs with antibody titer measured annually. Testing for HBV DNA should be done if HBsAg is positive, and may be indicated in patients who are positive for anti-HBc but negative for HBsAg and anti-HBs as such patients can occasionally be infectious.
5. **Prevention**
   a. **Restricting the possibility of exposure to the virus.** Epidemiologic principles can be utilized to decrease the risk of hepatitis B infection, both among patients and among dialysis staff. Table 33.1 lists some helpful precautions. Some centers recommend that patients with hepatitis B antigenemia be treated with either home HD or home peritoneal dialysis in order to decrease the chance of transmission to other patients and staff.

TABLE 33.1 Infection Control Practices in the Hemodialysis Unit

1. General precautions for staff and patients
   a. Surveillance for hepatitis B surface antigen (HBsAg) and antibody (HBsAb) (see text)
   b. Isolation of patients who are HBsAg positive (not necessary for patients with human immunodeficiency virus [HIV] or hepatitis C virus [HCV] infections)
   c. Cleansing of dialysis machines and blood/body fluid contaminated areas with 1% sodium hypochlorite (bleach) solution
   d. Dialyzer reuse prohibited for patients who are HBV positive (acceptable for patients with anti-HCV and probably HIV)
   e. Universal precautions (see below)

f. Protocol for exposure to blood/body fluids (see below)

2. Universal precautions

a. Staff must wear fluid-impermeable garments.
b. Gloves are to be used whenever there is potential for exposure to blood or body fluids.
c. Gloves must be changed and hands washed between patients.
d. Protective eyewear and face shields are worn when there is potential for splashing of blood (eg, initiation and discontinuation of dialysis, changing the blood circuit).
e. No recapping of contaminated needles; prompt disposal in appropriate container

3. Exposure to blood

a. Testing for HBsAg and HBsAb at time of incident and 6 wk later
b. Testing for HIV (employee consent required) at time of incident and 6 wk and 6 mo later
c. If HBsAg status of source patient is positive or unknown, administer hepatitis B immune globulin.
d. Test source patient for HIV (inform patient; consent may not be required).

b. Vaccination. See Section V.

c. Hepatitis B immune globulin. This should be given after any exposure to the body fluids of a person known to be infected with HBV.

C. Hepatitis C. The prevalence of antibodies to hepatitis C virus (anti-HCV) in patients on dialysis is higher than in healthy populations. About 5% of patients on dialysis in the United States have anti-HCV based on 2005-2016 data (Deshpande, 2019). In China, the prevalence was substantially higher but has diminished markedly during the course of the first two decades of this century to 7.4% for 2019-2021 (Gan, 2022). The continued incidence and prevalence of HCV infection among patients on dialysis can be attributed to several risk factors, including number of blood transfusions, duration of dialysis, mode of dialysis (lower risk in patients on peritoneal dialysis), and a history of previous organ transplantation or IV drug misuse. At the present time, there is no evidence that the sharing of dialysis machines, type of dialysis membrane used, or dialyzer reprocessing are risk factors. Therefore, the CDC does not recommend dedicated machines, isolation of patients, or prohibition of reuse in patients on HD with anti-HCV. However, observations suggest both a higher incidence of hepatitis C in new patients in units with a higher prevalence of HCV infection and a decreased incidence of HCV in units that implement infection control measures; therefore, in dialysis units with a high prevalence of infection, isolation of patients who are HCV positive, use of dedicated machines, and restriction of dialyzer reuse for patients infected with HCV may be warranted (Agarwal, 2011). The CDC recommends that all patients on HD should be tested for anti-HCV antibodies on admission, and anti-HCV-negative patients should be tested for anti-HCV antibodies semiannually thereafter.

The prevalence of anti-HCV among dialysis staff is similar to that of the general population. Immune globulin and α-interferon for postexposure prophylaxis against hepatitis C in health care workers are not recommended.

The natural history of hepatitis C in patients on dialysis is difficult to ascertain since there have been no large studies in which liver biopsy was performed. The association between liver enzymes (eg, ALT) and histologic severity is poor. Multivariate analyses have shown an increased risk of death in patients with hepatitis C infection, with excess mortality predominantly due to cirrhosis and liver cancer.

With the advent of direct-acting antiviral (DAA) agents that provide sustained virologic response and fewer side effects, the use of interferon and ribavirin has been, for the most part, supplanted (Gentile, 2014). Ribavirin is normally renally excreted and

causes dose-related hemolysis; therefore, it must be used with extreme caution and at a reduced dose in patients on dialysis if it is administered.

The recent high cure rates achieved with new interferon-free drug regimens using combinations of DAA agents have markedly enhanced the chances for cure of hepatitis C infection in patients on dialysis. With asymptomatic HCV infection, antiviral treatment should be undertaken on a case-by-case basis taking into account a reasonable likelihood of prolonged survival, especially in patients in whom transplantation is planned. Most patients should be treated with either glecaprevir-pibrentasvir or a sofosbuvir-containing combination.

The selection of the antiviral regimen for patients on dialysis is largely the same as that among patients without renal disease and depends on genotype, extent of underlying liver disease, and treatment history. In general, glecaprevir-pibrentasvir and sofosbuvir-velpatasvir are the preferred pangenotypic options. Ledipasvir-sofosbuvir is another preferred option for genotype 1, 4, 5, and 6 infections. No dose adjustments are needed for DAA agents in patients undergoing dialysis with severe renal impairment or those on dialysis. Addition of ribavirin is rarely warranted, but if used, the dose should be reduced for renal function with close monitoring for worsening anemia. It is useful to consult a specialist in treating liver disease to assist with management.

D. Cytomegalovirus (CMV) and mononucleosis. These viral infections can mimic hepatitis due to B or C virus but occur uncommonly in patients on dialysis.

E. Influenza. Patients on dialysis are at increased risk for developing complications during influenza infection and should be vaccinated. Use of antiviral agents for influenza prevention and treatment is discussed later. Meticulous hand hygiene helps decrease transmission. During periods of increased acute respiratory infections in the community, coughing patients and anyone suspected of having influenza should wear a mask at all times unless they are isolated in a private room.

F. Human immunodeficiency virus

1. **Clinical manifestations.** Patients on dialysis who are HIV positive may be asymptomatic or may present with the full-blown acquired immunodeficiency syndrome (AIDS). HIV-related renal disease may be an important cause of renal failure in some patients. Since the availability of highly active antiretroviral therapy (HAART), the prognosis of patients with HIV infection has markedly improved, and many patients who are HIV positive without other clinical manifestations can live for many years on dialysis.
2. **Routine screening.** The recommendation from the CDC is for routine screening for HIV in patients in health care settings unless they decline to give permission.
3. **Dialysis in patients who are HIV positive.** The CDC recommendation is that the choice between HD and peritoneal dialysis should not be affected by the finding of HIV positivity. However, home dialysis will obviously lessen any possible risk of transmission to other patients and to dialysis staff. The peritoneal effluent of patients who are HIV positive should be considered infectious and handled appropriately. If HD is elected, the CDC guidelines maintain that only the usual body fluid precautions attendant to routine dialysis need to be followed. The CDC does not recommend that a special dialysis machine be set aside for patients who are HIV positive, and dialyzer reuse in patients who are HIV positive is not forbidden.

   Rarely, health care workers have developed HIV infection after skin or mucous

membrane contact with HIV-infected blood, underscoring the importance of universal precautions while performing dialysis (see Table 33.1).

G. COVID-19

COVID-19 infection substantially increases mortality risk and severe disease in patients with ESKD, with studies showing that the virus can damage kidneys to the point of requiring renal replacement therapy (Bell, 2023). There is the additional problem of easy patient-to-patient and patient-to-staff transmission in a setting where patients with potential infection need to be treated on a repeated basis in a unit where other patients and staff are present.

Apart from vaccination, discussed later, other COVID preventive measures used by various units have been reviewed by Noordzij (2022). The degree of preventive measures used has changed for many as COVID has mutated over time into a generally less severe infection. Dialysis centers should enforce face coverings and frequent hand washing and comply with up-to-date infection prevention practices based on CDC guidelines. Health care providers should be aware of any signs and symptoms patients may have. Many units have all patients in an HD unit wear masks throughout their treatment, although some apply this only to patients who exhibit symptoms of a respiratory infection. All patients with respiratory symptoms should be tested for COVID-19 with a polymerase chain reaction (PCR) swab. Many dialysis units continue to isolate patients with COVID infection in a separate room of the dialysis facility during HD treatments.

Another issue that has arisen in patients who are immunocompromised, such as those with renal transplants, is that this virus, which is known to develop mutations, can persist in individuals who are immunocompromised, potentially leading to the emergence of new variants. Fortunately, there are therapies for outpatient treatment of mild to moderate disease, such as nirmatrelvir + ritonavir; however, significant and serious potential drug interactions exist, particularly with immunosuppressive medications, and the drug leaves a very bad taste that lingers. That being said, it has been shown to decrease hospitalization from COVID in older patients (Arbel, 2023). Remdesivir is an IV drug that inhibits RNA polymerase of the virus and can be administered for the first 3 days of early diagnosed infection to decrease the risk of hospitalization and risk of respiratory failure (Panagopoulos, 2022). A longer course can be used for treatment of hospitalized patients with COVID. Although the dual monoclonal antibody combination tixagevimab and cilgavimab is no longer available, this duo was effective as pre-exposure prophylaxis in individuals unable to mount antibody response effectively (Levin, 2022). Unfortunately, it did not have activity against subsequent circulating strains; but it does prove that the development of monoclonal antibody therapy may be another preventive strategy that could serve as a potential prophylaxis for other respiratory viruses, such as influenza.

V. VACCINATION.

In patients on dialysis, the antibody response to a number of commonly used vaccines is suboptimal. Nevertheless, vaccination against pneumococcus, influenza, and hepatitis is believed to be indicated for almost all patients on dialysis. Table 33.2 lists the recommended frequency of administration of commonly used vaccines. For all vaccines other than hepatitis B, the dosages are identical to those used in the general population. Vaccines recommended for individuals with ESKD include yearly recombinant influenza

vaccine, one dose of tetanus-diphtheria-acellular pertussis at least once as an adult and then a tetanus booster every 10 years, two doses of the Shingrix recombinant zoster vaccine (RSV), the 9-valent human papillomavirus (HPV) vaccine (through age 26 at least but consider in up to age 45), one dose of 15-valent pneumococcal conjugate vaccine (PCV15), and then the 23-valent pneumococcal polysaccharide vaccine (PPSV23) or alternatively, one dose of the 20-valent pneumococcal conjugate vaccine (PCV20). COVID-19 vaccination and yearly boosters are currently recommended by the US CDC and many other countries. COVID vaccination substantially improved survival in patients on dialysis during the early phase of the epidemic (Blankenship, 2023). However, the prevalent COVID-19 variants as well as the vaccines are changing over time. More information is needed regarding the long-term safety of receiving multiple booster doses of the current messenger RNA (mRNA) or adenovirus COVID-19 vaccines, which were initially approved on an emergency use basis, bypassing the normal vaccine safety evaluation process. Vaccination recommendations do change over time, and updated information can be found on the CDC website for vaccination schedules (cdc.gov/vaccines). Vaccination has been shown to decrease mortality and morbidity (Bell, 2022); however, due to the potential for decreased vaccine response in individuals who are immunocompromised, including patients with renal disease, encouraging household contacts to get vaccinated and keeping patients and their contacts up to date on boosters may be beneficial (Perkins, 2022). Another concern regarding vaccination in renal transplant recipients is the possibility of mycophenolate impairing antibody response to vaccine. Study results have been equivocal (Kho, 2023). Cell-mediated immunity, however, is particularly important in individuals unable to mount a significant antibody response to vaccine or infection and is often impaired in transplant recipients taking antimetabolites like mycophenolate (Petr, 2024).

TABLE 33.2 Immunizations Recommended for Patients on Dialysis

Vaccine	Frequency of Administration
Influenza A and B	Annually
Tetanus, diphtheria	Booster every 10 y
Pneumococcus	Revaccination dependent on antibody response
Hepatitis B	For initial vaccination schedule, give a total of four double doses with each injection split between the left and right deltoid muscles.
	Requirement for revaccination not yet known, but recommended if there is a fall in antibody titer (see text)

A. Vaccination against hepatitis B. All patients on dialysis except those who are HBsAg or HBsAb (antibody) positive should receive the hepatitis B vaccine. To increase the chances of successful vaccination, the dosage of hepatitis B vaccine in patients on dialysis should be twice the normal amount. Giving an additional dose, especially if there is a fall in antibody titer below 10 mIU/mL, can be done. The injection series depends upon the brand of hepatitis B vaccine. The more recent Heplisav (HepB-CpG) requires two shots about a month apart. Injection into the gluteal muscle is not recommended because gluteal injection has been associated with failure to develop antibody or with loss of antibody 6 months to 1 year following immunization

(in patients without uremia as well as in those with uremia).

Overall, the percentage of successful vaccination against hepatitis B in patients on dialysis is less than in the general population, and rates as low as 50% to 60% have been reported. Some patients may not have responded because of gluteal vaccine administration or because of failure to complete the vaccination regimen. The usefulness of adjuvant vaccines and vaccines given intradermally continues to be studied (Fabrizi, 2011).

VI. ANTIMICROBIAL USAGE IN PATIENTS ON DIALYSIS. Table 33.3 lists dosing guidelines for the most commonly used antimicrobial, antifungal, and antiviral agents in patients treated with intermittent HD and peritoneal dialysis. Due to the increased efficiency of drug removal with continuous renal replacement therapy (CKRT), optimal dosing strategies for antimicrobials in patients being treated by CKRT differ from traditional dialysis dosing. Additional dosing recommendations for drugs used in patients treated by CKRT are provided in Chapter 14.

TABLE 33.3 Systemic Antibiotic, Antiviral, and Antifungal Drug Dosages for an Adult Patient on Dialysis

Drug	Usual Nonuremic Dose[a]	Half-life (h)		Usual Dosage for Patient on Dialysis	Post-HD Supplement	Dosage for CAPD[b]
		Patient Without Uremia	Patient on Dialysis			
Antibiotics						
Penicillins						
Amoxicillin PO	250-1,000 mg q8h	1.2	5-20	250-500 mg q12-24h	DAD	250-500 mg q12h
Amoxicillin/clavulanate PO	500-875/125 mg q8-12h	1.4 (amox) 1 (clav)	5-20 (amox) 4 (clav)	250-500 mg q12-24h	DAD	250-500 q12h
Ampicillin IV	1-2 g q4-6h	1-1.8	7-20	1-2 g q12-24h	DAD	500 mg-1 g q12h
Ampicillin/sulbactam IV	1.5-3 g q6h; 9 g q8h extended infusion	1.4 (amp) 1.7 (sulb)	7-20 (amp) 10 (sulb)	1.5-3 g q24h	DAD	3 g q24h
Dicloxacillin PO	250-500 mg q6h	0.7	0.7	No dose adjustment	None	No dose adjustment
Nafcillin IV	1-2 g q4h	0.5-1	0.5-1	No dose adjustment	None	No dose adjustment
Oxacillin IV	2 g q4h	0.5-0.7	0.5-0.7	500 mg-1 g q4-6h	None	500 mg-1 g q4-6h
Penicillin G IV/IM	0.5-4 mU q4h	0.5	6-20	0.5-4 mU q12h	DAD	0.5-4 mU q12h
Penicillin V PO	250-500 mg q6-8h	0.5	4.1	No dose adjustment	DAD	No dose adjustment
Piperacillin IV	3-4 g q4-6h	1	3-5	2 g q8h	Additional 1 g after dialysis	3-4 g q8h
Piperacillin/tazobactam IV	3.375-4.5 g q6-8h	1 (pip) 1 (tazo)	3-5 (pip) 2.8 (tazo)	2.25 g q8-12h or 3.375-4.5 g q12h (extended infusion)	Additional 0.75 g dose after dialysis for non-extended infusion	2.25 g q8h or 4.5 g q12h

Ticarcillin/clavulanate IV	3 g q4-6h	1.1	13	2 g (ticarcillin) q12h or 2 g q8h without supplemental dose	3 g	3 g q12h
Cephalosporins						
Cefaclor PO	250-500 mg q8h	0.8	3	500 mg q12h	DAD	500 mg q12h
Cefadroxil PO	500 mg-1 g q12h	1.5	20	1 g LD then 500 mg-1 g on HD days	DAD	500 mg q24
Cefazolin IV/IM	1-2 g q8h	2	40-70	500 mg-1 g q24 or 2 g/2g/3g on HD days	DAD	500 mg q12h
Cefdinir PO	600 mg q24h or 300 mg q12h	1.7	16	300 mg q48h	DAD	300 mg q48h
Cefepime IV	1-2 g q8-12h	2	18	1 g q24h or 2 g tiw	DAD	2 g q48h
Cefotaxime IV	1-2 g q4-12h	1.5	15-35	2 g q24h	1 g	500 mg-1 g q24h
Cefotetan IV/IM	1-2 g q12h	3-4.6	12-30	1-2 g q24h	1 g	1 g q24h
Cefoxitin IV/IM	1-2 g q6-8h	0.8	13-23	2 g q24-48h	1 g	1 g q24h
Cefpodoxime PO	100-400 mg q12h	2.3	10	200 mg q24h	DAD	200 mg q24h
Cefprozil PO	500 mg q24h or 250-500 mg q12h	1.5	5-6	250mg q12h	DAD	250 mg q24h
Ceftaroline IV	600 mg q8-12h	1.6-2.7	No data	200 mg q8-12h	DAD	200 mg q8-12h
Ceftazidime IV/IM	1-2 g q8-12h	1-2	13-25	500 mg-1 g q24h or 1-2 g tiw[c]	DAD	1 g q24h
Ceftazidime/avibactam IV	2.5 g q8h	2.8 (ceftaz) 2.7 (avi)	13-25 (ceftaz)	0.94 g q24-48h	DAD	0.94 g q24-48h
Ceftibuten PO	400 mg q24h	2.5	13-22	100 mg q24h	DAD	100 mg q24h
Ceftriaxone IV	1-2 g q12-24h	5-9	12-16	No dose adjustment	None	No dose adjustment
Cefuroxime PO	250-500 mg q12h	1-2	17	250-500 mg q48h	250-500 mg	250-500 mg q24h
Cefuroxime IV	750 mg-1.5 g q6-8h	1-2	17	750 mg-1.5 g q24h	DAD	750 mg-1.5 g q24h
Cephalexin PO	250 mg-1 g q6h	0.5-1.2	5-30	250-500 mg q12-24h	DAD	250-500 mg q12-24h
Carbapenems/monobactams						
Aztreonam IV	500 mg-2 g q6-12h	1.5-2	6-8.4	2 g q24h	DAD	2 g q24h
Doripenem IV	500 mg q8h	1	18	250 mg q24h, for PSA 500 mg q12h (on day 1) then 500 mg q24h	None	No specific recommendation
Ertapenem IV/IM	1 g q24h	4	>4	500 mg q24h	150 mg if daily dose given ≤6h before HD	500 mg q24h
Imipenem/cilastatin IV/IM	500 mg-1 g q6-8h	1	4	HD: 250-500mg q12hr	DAD	CAPD: 250-500mg q12hrs
Meropenem IV	500 mg-2 g q8h	1-1.5	10	500 mg q24h	DAD	500 mg q24h
Fluoroquinolones						
Ciprofloxacin PO	IR: 250-750 mg q12h; ER: 500-1,000 mg q24h[d]	3-4 (IR) 5-7 (ER)	6-9	IR: 250-500 mg q24h; ER 500 mg q24h	DAD	IR: 250-500 mg q24h; ER: 500 mg q 24h
Ciprofloxacin IV	200-400 mg q8-12h	4	6-9	200-400 mg q24h	DAD	200-400 mg q24h
Gemifloxacin PO	320 mg q24h	7	>7	160 mg q24h	DAD	160 mg q24h

Levofloxacin IV/PO	250-750 mg q24h	6-8	76	750 mg once then 500 mg q48h	DAD	750 mg once then 500 mg q48h
Moxifloxacin IV/PO	400 mg q24h	8-15 (IV) 11-16 (PO)	9-16	No dose adjustment	None	No dose adjustment
Ofloxacin IV/PO	200-400 mg q12h	7	28-37	200 mg q24h	DAD	200 mg q24h
Aminoglycosides						
Amikacin IV	5-7.5 mg/kg q8-12h (conventional dosing); 15-20 mg/kg q24h (high-dose, extended interval)	2-3	30-70	5-12.5 mg/kg/dose on dialysis days[e]; see text	DAD; see text	5-12.5 mg/kg/dose q48-72h; see text
Gentamicin IV	3-5 mg/kg q8-12h (conventional dosing); 5-7 mg/kg q24h (high-dose, extended interval)	1.5-3	17-65	1-3 mg/kg/dose t.i.w[f]; see text	DAD; see text	1-3 mg/kg/dose q48-72 based on serum concentrations; see text
Neomycin PO	500 mg-2 g q6-8h	2-3	Avoid in renal failure			
Streptomycin IM	10-15 mg/kg q12-24h; 25-30 mg/kg 2—3× wk	2-4.7	30-70	7.5-15 mg/kg tiw on dialysis days	DAD	See text
Tobramycin IV	3-5 mg/kg q8h (conventional dosing); 5-7 mg/kg q24h (high-dose extended interval)	2-3	5-70	2-3 mg/kg LD then 1-2 mg/kg q48-72h (high-dose extended interval)[f]	DAD; see text	See text
Macrolides and ketolide						
Azithromycin IV/PO	250-500 mg q24h; 1-2 g ×1 dose	68-72	68-72	No dose adjustment	None	No dose adjustment
Clarithromycin PO	250-500 mg q12h	5-7	22	500 mg q24h	DAD	500 mg q24h
Erythromycin PO	250-800 mg q6-12h	2-4	5-6	No dose adjustment	None	No dose adjustment
Erythromycin IV	15-20 mg/kg/d divided q6h	2-4	5-6	No dose Adjustment	None	No dose adjustment
Telithromycin PO	800 mg PO q24h	10	15	600 mg q24h	DAD	No specific recommendation
Glycopeptides						
Telavancin IV	10 mg/kg q24h	6.6-9.6	17.9	No specific recommendation	None	No specific recommendation
Vancomycin IV	15-20 mg/kg q8-12h	6	200-250	7.5-10 mg/kg tiw on dialysis days	See text	See text
Tetracyclines						
Demeclocycline PO	150 mg q6h or 300 mg q12h	10-14	Use with caution in renal failure			
Doxycycline IV/PO	100-200 mg q12-24h	18-22	18-22	No dose adjustment	None	No dose adjustment
Minocycline IV/PO	200 mg LD, 100 mg q12h	16	16	No dose adjustment	None	No dose adjustment
Tetracycline PO	250-500 mg q6-12h	6-12	57-108	25-500 mg q24h	None	250-500 mg q24h
Nitroimidazoles						
Metronidazole IV/PO	500 mg q6-12h	6-14	7-21	500 mg q8-12h	DAD	No dose adjustment
Tinidazole PO	2g q24h	13	14.9-21.9	2 g q24h	Extra 1 g dose after dialysis	No specific recommendation

Diaminopyrimidines						
Pyrimethamine PO	25-75 mg q24h	96	96	No specific recommendation	None	No specific recommendation
Trimethoprim (T)/sulfa-methoxazole (S) IV/PO	Based on indication; see text	8-15 (T) 10 (S)	20-49 (T) 20-50 (S)	See text	See text	See text
Antituberculars						
Ethambutol PO	15-25 mg/kg q24h	4	7-15	15 mg/kg q48h	DAD	15 mg/kg q48h
Isoniazid IV/PO	300 mg q24h or 15 mg/kg/dose 1-3 wk	0.7-4[g]	8-17	No dose adjustment	DAD	No dose adjustment
Pyrazinamide PO	20-25 mg/kg q24h	10-16	26	25 mg/kg q48h	DAD	25 mg/kg q24h
Rifabutin PO	300 mg q24h	32-67	32-67	150 mg q24h	None	No specific recommendation
Rifampin IV/PO	600 mg q24h	1.5-5	11	300-600 mg q24h	None	300-600 mg q24h
Miscellaneous antibiotics						
Colistin	2.5-5 mg/kg CBA q6-12h	6.3-12	≥48	300 mg CBA LD, 180 mg CBA on HD days and 130 mg CBA on nondialysis days	DAD	300 mg CBA LD then 150-200 mg CBA q24h
Clindamycin PO	150-450 mg q6-8h	2-3, 3.4-5.1 (older patient)	4	No dose adjustment	None	No dose adjustment
Clindamycin IV	600-900 mg q8h	2-3, 3.4-5.1 (older patient)	4	No dose adjustment	None	No dose adjustment
Dapsone PO	50-100 mg q12-24h	10-50	No data	Pneumocystis pneumonia prophylaxis 50 mg q12h	DAD	No specific recommendation
Daptomycin IV	4-12 mg/kg q24h	8-9	30	Administer usual dose q48h	DAD	6 mg/kg q48h
Linezolid IV/PO	600 mg q12h	5	6-8	No dose adjustment	DAD	No dose adjustment
Methenamine PO	1 g q12h (hippurate) 1 g q6h (mandelate)	4	Not recommended in patients with creatinine clearance <50 mL/min			
Nitrofurantoin PO	50-100 mg q6h-12h	1	Not recommended in patients with creatinine clearance <30 mL/min			
Quinupristin (Q)/Dalfopristin (D) IV	7.5 mg/kg q12h	0.85 (Q); 0.7 (D)	0.85 (Q); 0.7 (D)	No Dose Adjustment	None	No dose adjustment
Spectinomycin IM	2-4 g once	1.5-2	4.7-29.3	No dose adjustment	None	No dose adjustment
Antivirals						
Acyclovir PO	400-800 mg q8h—5×/d	2.5-3.5	20	800 mg q12h	Supplemental dose after dialysis	800 mg q12h
Acyclovir IV	5-12.5 mg/kg q8h	2.5-3.5	20	2.5-6.25 mg/kg q24h	DAD	2.5-6.25 mg/kg q24h
Amantadine PO	Age <65 y: 100 mg q12 Age ≥65 y: 100 mg q24h	16	192	200 mg q wk[h]	None	No specific recommendation

Boceprevir	300 mg TID	3.4	3.4	No dose adjustment	None	No dose adjustment
Cidofovir IV	5 mg/kg weekly to every other week	2.6	Contraindicated with creatinine clearance ≤55 mL/min or serum creatinine >1.5 mg/dL			
Famciclovir PO	125-500 mg q8-12h	2-3	10-22	250 mg q24h	DAD	No specific recommendation
Foscarnet IV	90 mg/kg q12h or 60 mg/kg q8h × 3 wk, then 90-120 mg/kg q24h	3 (terminal ~88 h due to bone deposition)	25.3	45-60 mg/kg tiw	DAD	60 mg/kg/dose q48-72h
Ganciclovir IV	5 mg/kg/d q12-24h	3.5	30	0.625-1.25 mg/kg/dose tiw	DAD	0.625-1.25 mg/kg/dose tiw
Oseltamivir PO	75 mg q12-24h	6-10	>20	30 mg ×1, then 30 mg after every HD or alternating HD cycles if for prophylaxis	DAD	30 mg ×1 (treatment); 30 mg ×1 then, 30 mg q7d (prophylaxis)
Ribavirin PO	600-1,200 mg q24g in one to two divided doses	24 (capsule), 120-170 (tablet)	No data	200 mg q24h	None	200 mg q24h
Rimantadine PO	Age <65 y: 100 mg q12h Age ≥65: 100 mg q24h	25.4; 32 (older patient)	40	100 mg q24h	None	100 mg q24h
Valacyclovir PO	500 mg-2 g q 8-24h	3	14	500 mg q24h	DAD	500 mg q24h
Valganciclovir PO	900 mg q1224h	4	Not recommended for patients on dialysis			
Zanamivir PO	10 mg q12-24h	2.5-5.1	4-8.1	No dose adjustment	None	No dose adjustment
Antiretrovirals						
Abacavir PO	300 mg q12h or 600 mg q24h	1-1.5	No data	300 mg q12h	None	No specific recommendation
Adefovir PO	10 mg q24h	7.5	15	10 mg q7d	DAD	No specific recommendation
Atazanavir PO	300-400 mg q24h	7	No data	300 q24h; not recommended in ART experienced patient	None	No specific recommendation
Darunavir	600 mg q12h or 800 mg q24h	15	No data	No dose adjustment	None	No specific recommendation
Delavirdine PO	400 mg q8h	5.8	5.8	No specific recommendation	None	No specific recommendation
Didanosine PO	25-60 kg: 250 mg q24h >60 kg: 400 mg q24h	1.6	4.5	<60 kg: capsule not recommended; solution 75 mg q24h ≥60 kg: 100-125 mg q24h	None	<60 kg: capsule not recommended; solution 75 mg q24h ≥60 kg: 100-125 mg q24h
Entecavir PO	0.5-1 mg q24h	128-149	No data	0.05-0.1 mg q24h	DAD	0.05-0.1 mg q24h
Efavirenz PO	600 mg q24h	40-55	No data	No dose adjustment	None	No dose adjustment

Elvitegravir (EVG)/ cobicistat(C)/ emtricitabine (FTC)/ tenofovir (TDF) PO	1 tab q24h	12.9 (EVG) 3-4 (C) 10 (FTC) 17 (TDF)	Not recommended in patients on dialysis			
Enfuvirtide SC	90 mg q12h	3.8	No data	No dose adjustment	None	No specific recommendation
Emtricitabine PO	Capsule 200 mg q24h; solution 240 mg q24h	10	>10	Capsule 200 mg q96h; solution 60 mg q24h	DAD	No specific recommendation; consider using HD recommendations
Fosamprenavir PO	1,400 mg q24h or 700 mg q12h	7.7	No data	1,400 mg q24h	None	No specific recommendation
Indinavir PO	800 mg q8-12h	1.2-2	No data	No specific recommendation	None	No specific recommendation
Lamivudine PO	150 mg q12h or 300 mg q24h (HIV); 100 mg q24h (hepatitis)	5-7	15-35	25-50 mg q24h	DAD	25-50 mg q24h
Lopinavir(L)/ ritonavir(R) PO (1 tablet = 200 mg lopinavir and 50 mg ritonavir)	Two tablets q12h	6.9 (L); 3-5 (R)	No data	2 tablets q12h	None	No specific recommendation
Maraviroc PO	300 mg q12h (150-600 mg q12h depending on presence of CYP3A inhibitors or inducers)	14-18	No data	No dose adjustment if not coadministered with cyp3A inhibitors/ inducers)	DAD	No dose adjustment if not coadministered with cyp3A inhibitors/ inducers)
Nelfinavir PO	1,250 mg q12h	3.5-5	No data	No specific recommendation	None	No specific recommendation
Nevirapine PO	200 mg q12-24h	25-30	No data	200 mg q12h	200 mg	No specific recommendation
Raltegravir PO	400-800 mg q12h	9	No data	No dose adjustment	DAD	No specific recommendation
Rilpivirine PO	25 mg q24h	45-50	No data	No dose adjustment	None	No specific recommendation
Ritonavir PO	100-400 mg q12-24h	3-5	No data	No dose adjustment	None	No specific recommendation
Saquinavir	1,000 mg q12h or 2,000 mg q24h	1-2	No data	No dose adjustment	None	No specific recommendation
Stavudine PO	<60 kg: 30 mg q12h ≥60 kg :40 mg q12h	1.2-1.6	5.5-8	<60 kg: 15 mg q24h; ≥60 kg: 20 mg q24h	DAD	No specific recommendation
Telaprevir PO	1,125 mg q12h	4-11	No data	No dose adjustment	None	No dose adjustment
Telbivudine PO	600 mg q24h	40-49	No data	600 mg q96h	DAD	No specific recommendation
Tenofovir disoproxil PO	300 mg q24h	17	No data	300 mg q7d	DAD	Avoid use if possible; may consider HD dosing if no alternative
Tenofovir alafenamide PO	25 mg q24h	0.51	No data	No dose adjustment	DAD	No specific recommendation

Tipranavir PO	500 mg q12h	5.5-6	No data	No dose adjustment	DAD	No specific recommendation
Zidovudine PO	300 mg q12h	0.5-3	1.3-3	100 mg q6-8h	DAD	100 mg q6-8h
Antifungals						
Amphotericin B cholesteryl sulfate complex (Amphotec)	3-4 mg/kg/d	28	28	No dose adjustment	None	No dose adjustment
Amphotericin B deoxycholate (Fungizone IV)	0.3-1.5 mg/kg q24h	15-48	15-48	No dose adjustment	None	No dose adjustment
Amphotericin B lipid complex (Abelcet IV)	5 mg/kg q24h	173 (after multiple doses)	173	No dose adjustment	None	No dose adjustment
Amphotericin B liposome (Am-Bisome IV)	3-5 mg/kg q24h	7-10 (after a single dosing interval) 100-153 (multiple doses)	7-10	No dose adjustment	None	No dose adjustment
Anidulafungin IV	100-200 mg day 1, then 50-100 mg q24h (higher doses necessary in pt >140 kg)	26.5	26.5	No dose adjustment	None	No dose adjustment
Caspofungin IV	70 mg LD, 50 mg q24h	9-11	9-11	No dose adjustment	None	No dose adjustment
Fluconazole IV/PO	100-800 mg q24h	20-50	100	50-400 mg q24h	DAD	50-200 mg q24h
Flucytosine PO	50-100 mg/kg/d in divided doses q6h	3-5	75-200	25-50 mg/kg q48-72h	DAD	25mg/kg q48h
Griseofulvin PO (microsize)	500-1,000 mg q24h	9-24	No data	No dose adjustment	None	No specific recommendation
Griseofulvin PO (ultramicrosize)	375-750 mg q24h	9-24	No data	No dose adjustment	None	No specific recommendation
Itraconazole PO capsule	200-600 mg in divided doses daily	16-28 (single dose) 35-40 (multiple doses)	35-40	No dose adjustment	None	No dose adjustment
Itraconazole PO solution	100-200 mg q24h	16-28 (single dose) 35-40 (multiple doses)	35-40	No dose adjustment	None	No dose adjustment
Ketoconazole PO	200-400 mg q24h	8	8	No dose adjustment	None	No dose adjustment
Micafungin IV	50-150 mg q24h	15-17	15-17	No dose adjustment	None	No dose adjustment
Posaconazole PO delayed-release tablet	300 mg q12-24h	22-35	22-35	No dose adjustment	None	No dose adjustment
Posaconazole PO oral suspension	100-400 q12h or q24h or 200 mg q8h (varies based on indication)	20-66	20-66	No dose adjustment	None	No dose adjustment
Posaconazole IV	300 mg q 12-24h (400 mg q12h for pt >140 kg)	27	Not recommended in patients with creatinine clearance <50 mL/min			
Terbinafine PO	250 mg q24h	36	Not recommended in patients with creatinine clearance ≤50 mL/min			
Voriconazole PO	≥40 kg: 400 mg q12h LD, 200 mg q12h <40 kg: 200 mg q12h LD, 100 mg q12h	Variable and dose dependent	Variable and dose dependent	≥40 kg: 200 mg q12h <40 kg: 100 mg q12h	None	No dose adjustment
Voriconazole IV	6 mg/kg q12h LD, 4 mg/kg q12h	Not recommended in patients with creatinine clearance ≤50 mL/min				

ART, antiretroviral therapy; bid, two times per day; DAD, no post-HD supplement required, but on hemodialysis days schedule the usual dose for patient on dialysis after the dialysis session; CAPD, continuous ambulatory peritoneal dialysis; HD, hemodialysis; IM, intramuscular; IV, intravenous; LD, loading dose; PD, peritoneal dialysis (primarily CAPD); PO, oral; q24h, daily; qhs, at bedtime; SC, subcutaneous; tid, three times per day; tiw, three times per week.

[a]Usual doses recommended for treatment of moderate-to-severe infections.

[b]Same as usual dosage for patients on dialysis.

[c]Prolonged half-life allows dosing thrice weekly post-HD.

[d](ER) extended release, (IR) immediate release.

[e]Redose when pre-hemodialysis amikacin concentration is less than 10 mg/L or when post-hemodialysis amikacin concentration is less than 6 to 8 mg/L.

[f]Consider redosing for pre-HD or post-HD concentrations as indicated.

[g]May vary in fast versus slow acetylators.

[h]Long-term administration best avoided unless blood levels are followed.

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A. Penicillins. Most penicillins are normally excreted by the kidney to a substantial extent (40%-80%) and are removed to a moderate degree by both HD and peritoneal dialysis. Therefore, both dosage reduction and post-HD supplementation are generally recommended. From a practical standpoint, postdialysis supplementation is probably unnecessary; however, dosing should be timed so that a dose is given immediately after dialysis. Two exceptions to this general rule are nafcillin and oxacillin; because these drugs are substantially excreted by both the liver and the kidney, dosage reduction is not

necessary unless liver function is also impaired. Because of the high therapeutic index of penicillins, monitoring of serum levels is generally not necessary.

Penicillins contain a β-lactam ring, and many bacteria that are resistant to penicillins and other β-lactam containing antibiotics, such as the cephalosporins and carbapenems, effect this resistance through degradation of this portion of the antimicrobial drug using β-lactamase enzymes. Amoxicillin-clavulanate, piperacillin-tazobactam, and ampicillin-sulbactam are examples of penicillins combined with β-lactamase inhibitors. β-Lactamase inhibitors slow the breakdown of β-lactams by bacteria exhibiting resistance to penicillins. The β-lactamase inhibitors in these combination drugs may exhibit longer half-lives in ESKD than the penicillin components. Clavulanate is a β-lactamase inhibitor that is frequently combined with amoxicillin. The half-life of clavulanate increases from 0.75 to about 5.0 hours with renal failure, but clavulanate is dialyzable. The dosing recommendations for the parent antimicrobial in Table 33.3 usually apply to the antimicrobial-clavulanate combination as well.

In renal failure, the β-lactamase inhibitor tazobactam accumulates proportionally to piperacillin, and dosing is based on the optimal piperacillin dose. Piperacillin-tazobactam should be dosed more frequently (2.25-4.5 g every 8-12 hours) for nosocomial pneumonia in patients on HD. Ideally dose should be adjusted based on clinical status as well as the type of infecting organism and the minimum inhibitory concentration (MIC) of the antimicrobial against the bacteria being targeted. Piperacillin-tazobactam is cleared by all forms of CKRT. In continuous hemofiltration (C-H), the recommended dose is 2.25 to 3.375 g every 6 to 8 hours, and in C-HD (continuous hemodialysis), the dose is slightly higher: 3.375 to 4.5 g every 6 to 8 hours. Treatment of resistant pathogens, such as *Pseudomonas*, requires higher doses, and an alternate dosing of 4.5 g every 6 hours (or every 8 hours when extended infusion is utilized) has been recommended (Cutro, 2014). In CKRT, there is some concern about tazobactam accumulation, given its lower clearance relative to piperacillin, and using piperacillin alone or alternating with piperacillin-tazobactam, particularly in patients being treated with continuous hemodiafiltration (C-HDF), may minimize this concern. Ampicillin-sulbactam has similar pharmacokinetics to piperacillin-tazobactam, and dose adjustments are similar.

B. Cephalosporins. Ceftriaxone is the only cephalosporin that is both highly protein bound and hepatically metabolized; thus, no dose adjustment is required in patients on dialysis. The remaining cephalosporins are excreted by the kidney to a large extent (eg, 30%-96%), and most are removed to some extent by dialysis; therefore, dosage reduction is almost always necessary for patients on dialysis. Some of the long-acting cephalosporins (eg, cefazolin, ceftazidime) can be administered thrice weekly after each HD session in patients being dialyzed (3 times a week). In patients on intermittent HD, cefotetan should be administered at 25% of the usual dose every 24 hours on days between dialysis and 50% of the usual dose on the day of dialysis. Cefepime does require renal dosage adjustments in those with renal insufficiency as well as *patients being treated with* HD in order to minimize the potential for neurotoxicity. Neurotoxicity often occurs in patients with renal dysfunction and of older age (Maan, 2022). Ceftaroline is the newest fifth-generation cephalosporin and is the only cephalosporin with some activity against MRSA. It is approved for treatment of skin

and soft tissue infections as well as community-acquired pneumonia. Like others in its class, it is renally cleared and requires a significant dose reduction in ESKD.

Not all cephalosporins have been studied in CKRT; however, extrapolations on dosing can be made based on antibiotics of similar pharmacokinetic and molecular properties.

1. Ceftazidime-avibactam: Both ceftazidime and the β-lactamase inhibitor avibactam undergo significant removal with dialysis.
2. Ceftolozane-tazobactam: Ceftolozane, a novel cephalosporin antibiotic targeted toward *Pseudomonas aeruginosa*, undergoes substantial removal with dialysis.
3. Cefiderocol: Cefiderocol, the newest member of the cephalosporin class, significantly undergoes removal by renal replacement therapy and also requires dosage adjustments in patients with renal dysfunction. Interestingly, there are dosage recommendations outlined in the cefiderocol package insert recommending various doses according to differing CKRT effluent flow rates (Fetroja package insert, Shionogi Inc.).

C. Carbapenem/monobactams. Imipenem is available with cilastatin at a 1:1 dosage ratio between the two compounds. Cilastatin is an inhibitor of the renal dipeptidase enzyme that rapidly breaks down imipenem. Cilastatin accumulates more than imipenem in patients with renal failure. The half-life for cilastatin is prolonged from 1 hour to about 15 hours in renal failure, but cilastatin is dialyzable. In CKRT, imipenem/cilastatin doses of 250 mg every 6 hours or 500 mg every 8 hours are recommended, while higher doses of 500 mg every 6 hours may be required for more resistant infections (Trotman, 2005).

Ertapenem and meropenem are resistant to renal degradation and are not given with an adjunctive dipeptidase inhibitor. Ertapenem has a broad spectrum of activity, covering the gram-positives, gram-negatives, and anaerobes. Unlike the other carbapenems, ertapenem lacks coverage against *Pseudomonas* and *Acinetobacter* sp. Ertapenem has the advantage of once-daily dosing. The dose should be reduced by 50% in patients with renal dysfunction (creatinine clearance [CrCl] <30 mL/min). Meropenem has similar coverage to imipenem/cilastatin, and doses of 500 to 1,000 mg every 8 hours are recommended in CKRT.

Meropenem-vaborbactam, a novel carbapenem/β-lactamase inhibitor combination antimicrobial, requires similar renal dosage adjustments to meropenem in renal dysfunction as well as HD. Interestingly, within the package insert, dosage adjustments are calculated based on the Modification of Diet in Renal Disease (MDRD) equation rather than the more standard Cockcroft-Gault equation (Vabomere package insert). Similarly, there is also another novel carbapenem/β-lactamase combination antimicrobial: imipenem-cilastatin-relebactam. This antimicrobial also requires renal dosage adjustments similar to its parent drug, imipenem-cilastatin (Recarbrio package insert).

Aztreonam is the sole monobactam antibiotic in its class with gram-negative coverage only (including coverage of *Pseudomonas*). Owing to the cost of aztreonam, this antibiotic is typically reserved for patients who have a history of allergy to both penicillins and cephalosporins or patients who have an immediate-type allergy (ie, anaphylaxis) to the penicillins. For patients receiving dialysis, a loading dose of 500 mg, 1 g, or 2 g, followed by 25% of the initial dose at the usual interval (every 6-8 hours),

should be given. For serious/life-threatening infections, administer 12.5% of the initial dose after each dialysis session (given in addition to the maintenance doses). Alternatively, aztreonam can be dosed at 500 mg every 12 hours or 1 to 2 g once daily in patients on HD (Gross, 2018; Heintz, 2009).

D. Fluoroquinolones. Moxifloxacin has better coverage against gram-positive pathogens (particularly *Streptococcus pneumonia*e) versus the older fluoroquinolones. The majority of the fluoroquinolones can be administered both PO and IV. Moxifloxacin is the only antibiotic in this class that does not require dosage adjustment with intermittent HD or CKRT. Levofloxacin is removed by *continuous hemodialysis (C-HD)* and C-HDF but not intermittent HD. Higher doses of ciprofloxacin may be required with CKRT. Ciprofloxacin also comes as an extended-release oral formulation that is dosed once daily, is not interchangeable with immediate-release formulations, and is approved only to treat UTI. PO and IV formulations of gatifloxacin were discontinued in 2006 owing to the risk of profound hypoglycemia. Delafloxacin, the newest member of the fluoroquinolone class, also uniquely has activity against MRSA. This antimicrobial requires renal dosage adjustments for CrCl less than 30 mL/min for the IV product, but not for the PO formulations. Both IV and PO products are not recommended *when* CrCl *is* less than 15 mL/min *or for patients with* ESKD, due to lack of data in these populations (Baxdela package insert).

E. Polymyxins. Colistimethate (Colistin), or polymyxin E, was largely supplanted by aminoglycosides 30 years ago owing to its high risk of dose-dependent nephrotoxicity and neurotoxicity. Recent reports indicate that the incidence of acute kidney injury with colistin can be as high as 60% (Kubin, 2012). However, the polymyxins are one of the few antimicrobial classes that can still have activity against multidrug-resistant gram-negative organisms such as *Pseudomonas* and *Acinetobacter*. Colistin is a large, highly tissue-bound molecule, and the amount of dialytic removal is small. Doses should be based on ideal body weight in patients who are obese, and recommended doses are expressed in terms of colistin base. Colistin must be frequently dose adjusted for renal dysfunction as well as for HD and CKRT, since it is primarily excreted by the kidney. Colistin also comes in nebulized inhalation form that can be used for bronchiectasis and pulmonary colonization/infection in patients with cystic fibrosis. The other member of the polymyxin class, polymyxin B, undergoes minimal renal excretion and therefore does not require renal dosage adjustments for renal dysfunction or dialysis. Polymyxin B, although known to be nephrotoxic, may exhibit less nephrotoxicity and has improved pharmacokinetic properties when compared to colistin (Tsuji, 2019).

F. Aminoglycosides. Renal excretion of aminoglycosides is normally greater than 90%, and a substantial increase in dosing interval is necessary in patients with renal dysfunction. Drug removal by dialysis is around 50%, requiring a postdialysis supplement or addition of aminoglycoside to peritoneal dialysis solutions. The therapeutic index of these agents is low, with the major risk (in patients on dialysis) being otovestibulotoxicity. Loss of clinically important residual renal function may also occur. High-dose extended interval dosing is not recommended in patients with ESKD. Dosing for all aminoglycosides is based on ideal body weight and adjusted body weight for patients who are obese.

1. **Gentamicin and tobramycin**
    a. **Patients on HD.** In patients receiving HD 3 times a week, a loading dose of 2

to 3 mg/kg is recommended followed by maintenance doses according to indication as follows: For mild UTI or synergy (making use of a synergistic effect of aminoglycoside with other concomitantly administered antibiotics), 1 mg/kg every 48 to 72 hours is recommended and redosing for pre-HD or post-HD concentrations of less than 1 mg/L should be considered. For moderate-to-severe UTI, 1 to 1.5 mg/kg every 48 to 72 hours is recommended, and redosing for pre-HD concentrations of less than 1.5 to 2 mg/L or post-HD concentrations of less than 1 mg/L should be considered. For systemic gram-negative rod infection, 1.5 to 2 mg/kg every 48 to 72 hours and redosing for pre-HD concentrations of less than 3 to 5 mg/L or post-HD concentrations of less than 2 mg/L is recommended. Although removal of gentamicin and tobramycin is primarily renal, extrarenal excretion of up to 20 to 30 mg/d has been reported in patients on dialysis. Furthermore, many patients on dialysis have some residual renal function, accounting for some renal drug removal. The postdialysis dose will replace the drug lost during HD and the drug removed due to nonrenal and residual renal excretion; thus, the amount of postdialysis dose may vary considerably and should be adjusted on the basis of the plasma drug levels achieved (see later).

b. Patients on peritoneal dialysis. The easiest strategy for treating nonperitoneal infections in patients on continuous ambulatory peritoneal dialysis (CAPD) and those on automated peritoneal dialysis (APD)is to give the usual loading dose IV and then to add 4 to 6 mg/L to the peritoneal dialysis solution. Although the strategy is simple, its efficacy and safety have not been evaluated, and there is a concern for otovestibular toxicity if treatment is prolonged. An alternative strategy for patients receiving CAPD or APD would be to give the usual loading dose followed by parenteral (IV or IM) or intraperitoneal (IP) administration of additional small doses based on serum drug levels.

c. CKRT. CKRT effectively removes aminoglycosides. The half-life of aminoglycosides in patients on CKRT is around 18 to 60 hours. In CKRT, a loading dose of 2 to 3 mg/kg should be followed by 1 mg/kg every 24 to 36 hours (redose when concentration <1 mg/L) for mild UTI or synergy, 1 to 1.5 mg/kg every 24 to 36 hours (redose when concentration <1.5-2 mg/L) for moderate-to-severe UTI, or 1.5 to 2.5 mg/kg every 24 to 48 hours (redose when concentration <3-5 mg/L) for systemic gram-negative infection. As with any aminoglycoside dosing, serum drug levels should be obtained to ensure therapeutic levels and avoidance of toxicity.

G. Amikacin. The strategy for amikacin is similar to that for dosing gentamicin or tobramycin; however, the loading dose should be 5.0 to 7.5 mg/kg. Redosing is recommended when pre-HD concentration is less than 10 mg/L or when post-HD concentration is less than 6 to 8 mg/L (Heintz, 2009). In patients on peritoneal dialysis, the recommended amount of amikacin to add to the peritoneal dialysis solution was formerly 18 to 25 mg/L. Now there has been a trend to use lower doses of amikacin (eg, for peritonitis as discussed in Chapter 25). The recommended CKRT dose for amikacin is a 10 mg/kg load with a maintenance dose of 7.5 mg/kg every 24 to 48 hours, with further adjustment based on serum drug levels. For severe gram-negative rod infections, the target peak concentration is 15 to 30 mg/L, and redosing is recommended when the

concentration is less than 10 mg/L (Heintz, 2009).

H. Streptomycin. One-half of the normal (nonuremic) dosage should be administered after HD. In patients on CAPD, 20 mg/L should be added to the dialysis solution. In CKRT, administer doses every 24 to 72 hours and monitor levels.

I. Monitoring of serum aminoglycoside levels. Serum drug levels should be monitored in all patients on dialysis receiving aminoglycosides, except perhaps those being treated with IP aminoglycosides for peritonitis. Monitoring of serum aminoglycoside levels is especially important in cases of serious infection where maximal efficacy is of paramount importance and during prolonged use where otovestibular toxicity is common.

1. **Peak aminoglycoside levels.** The volume of distribution for aminoglycosides in patients on dialysis is similar to that for patients without uremia; therefore, peak serum levels should be similar to those in patients without uremia given a similar dosage with a similar trough (predose) serum concentration. Ideally, peak levels should be drawn 30 minutes after the end of dose infusion.
2. **Trough aminoglycoside levels.** In patients without uremia, the dosing interval of the aminoglycosides is adjusted based on the trough (predose) level, as trough levels greater than 2 mg/L (gentamicin, tobramycin) or 10 mg/L (amikacin) are associated with toxicity. In patients on dialysis, the altered pharmacokinetics of aminoglycosides may lead to difficulties in dosing. For example, when gentamicin is given post-HD, the magnitude of a subsequent predialysis level will depend on the frequency of dialysis, as well as on the amount administered and the gentamicin half-life. With daily or even every-other-day dialysis, therapeutic peak levels of approximately 4.0 to 6.0 mg/L may be associated with predialysis levels of greater than 2.0 mg/L. Thus, predialysis levels of greater than 2.0 mg/L may need to be accepted if therapeutic peak levels are desired. Whether predialysis levels of greater than 2.0 mg/L in a dialysis setting predispose patients to otovestibulotoxicity is unknown. This may be an important consideration with prolonged (>7-10 days) therapy.

   Prolonged aminoglycoside therapy in patients on peritoneal dialysis using IP maintenance dosages will result in random serum aminoglycoside levels of greater than 2 mg/L (for gentamicin or tobramycin) or greater than 8 mg/L for amikacin. For example, the addition of 6 mg/L of gentamicin into the dialysate may result in a steady-state serum level of 3 to 6 mg/L, which may result in otovestibulotoxicity. Recommendations include administering IP aminoglycosides once daily only or decreasing the concentration of IP aminoglycoside when prolonged therapy is indicated.
3. **When the MIC is known.** When the organism is known and the aminoglycoside MIC has been determined, the strategy should be to achieve a peak serum drug level at least 4 times greater than the MIC value. Of course, one cannot exceed maximum safe peak drug levels; however, in some instances, the MIC may be quite low, allowing a reduction in aminoglycoside dosage and serum drug levels without compromising treatment efficacy.

J. Macrolides. Erythromycin undergoes 5% to 20% renal excretion in patients without uremia and requires no dosage adjustment in the presence of renal insufficiency. The use of erythromycin has been largely supplanted by azithromycin and clarithromycin,

which have a more favorable side-effect profile and fewer drug-drug interactions. Clarithromycin doses should be reduced by 50% in those patients with CrCl less than 30 mL/min and given after dialysis. Additional dose adjustments are necessary if coadministered with the protease inhibitors atazanavir and ritonavir, which may increase the serum concentration of clarithromycin. As with erythromycin, azithromycin does not require dosage adjustment for intermittent HD, peritoneal dialysis, or CKRT (Heintz, 2009).

K. Glycopeptides. Vancomycin is useful for the treatment of severe gram-positive infections in patients on dialysis. As vancomycin is excreted by the kidneys, dosing intervals can be substantially increased in patients with renal failure. In the past, doses could be administered every 7 to 10 days in patients with no renal excretory function since drug removal is negligible when low-flux dialyzers are employed. However, now that high-flux membranes are used routinely, substantial extracorporeal removal of vancomycin during dialysis can be expected, and postdialysis supplements are needed.

Measurement of serum drug levels is necessary to ensure adequate bactericidal levels and to avoid ototoxicity and nephrotoxicity. More recent evidence suggests that the prior vancomycin trough targets of 15 to 20 mg/L are associated with increased odds of nephrotoxicity, compared to lower trough levels of less than 15 mg/L (van Hal, 2013). In addition to this, area under the concentration-time curve (AUC) based dosing is now preferred over trough-based dosing for serious infections due to MRSA (Rybak, 2020). This is due to evidence that suggests reduced nephrotoxicity with AUC-based dosing when compared to trough-based dosing, with similar efficacy seen with AUC/MIC ratios of 400 to 600 mg·h/L (Neely, 2018; Rybak, 2020).

Regarding loading doses, hospitalized patients with life-threatening infections should be considered to receive a 20 to 35 mg/kg (max 3 g) loading dose. In patients on HD, data regarding specific AUC/MIC goals are unfortunately lacking. However, it is likely that predialysis concentrations of 15 to 20 mg/L should be analogous to an AUC/MIC target of 400 to 600 mg·h/L. When utilizing standard intradialytic thrice weekly vancomycin dosing, loading doses of 30 to 35 mg/kg and maintenance doses of 7.5 to 15 mg/kg should be utilized, depending on dialyzer permeability (Rybak, 2020). In patients receiving CKRT, loading doses of 20 to 25 mg/kg and maintenance doses of 7.5 to 10 mg/kg every 12 hours should be considered for those receiving effluent rates of 20 to 25 mL/kg/h. Data specifically in patients with CKRT are lacking; however, an AUC of 400 to 600 mg·h/L should still be targeted (Rybak, 2020).

In 2009, telavancin, an IV glycopeptide with activity against MRSA, became available for the treatment of complicated skin infections. It exhibits concentration-dependent killing and is nearly 90% protein bound. In 2013, it received expanded indications for hospital-acquired and ventilator-associated pneumonia caused by susceptible *S. aureus.* Use should be limited to situations when alternative treatments are not suitable, owing to increased mortality in patients with renal insufficiency treated for pneumonia with telavancin compared with vancomycin (Rubinstein, 2011). Black box warnings for telavancin also include the risk of new-onset nephrotoxicity and potential teratogenicity. Patients with baseline comorbidities or receiving concomitant medications known to affect kidney function are particularly vulnerable to nephrotoxicity. Renal adjustment is necessary for patients with CrCl less than 50 mL/min; however, no adjustments are provided by the manufacturer for patients with

CrCl less than 10 mL/min or on HD owing to limited studies.

L. Linezolid. Linezolid is predominantly metabolized by the liver into two inactive metabolites. Although nearly one-third of the dose is excreted unchanged by the kidneys, renal dose adjustment is not required. The two primary metabolites may accumulate in patients with renal impairment, but the clinical significance is unknown. Monitoring for hematopoietic (eg, anemia, leukopenia, thrombocytopenia) and neuropathic (eg, peripheral neuropathy) adverse events when administering for extended periods is recommended. If linezolid is not given immediately after a dialysis session, then a supplemental dose, especially early in the treatment course, may be considered. However, no supplemental dose or dosage adjustment for patients on intermittent HD, peritoneal dialysis, or CKRT has been suggested (Heintz, 2009; Trotman, 2005).

The newest member of the oxazolidinone class, tedizolid, similarly does not require renal dosage adjustments in patients with renal impairment or those on intermittent HD (Sivextro package insert).

M. Daptomycin. Daptomycin is a large molecule that does not appear to be readily removed by dialysis or CKRT. Higher doses of 8 to 12 mg/kg every 24 hours are recommended for severe *Staphylococcal* and *Enterococcal* infections (Casapao, 2013; Kullar, 2013). In patients who are obese, doses should be based on adjusted body weight. Dose adjustments in HD and CKRT are used to coincide with the dose recommended for patients with CrCl less than 30 mL/min (Trotman, 2005); however, for CKRT, this dosing strategy appears to result in a low C_{max}. Thus, patients on CKRT may require 8 to 12 mg/kg every 24 hours (Heintz, 2009; Xu, 2017). In patients being treated with intermittent HD or peritoneal dialysis, daptomycin can be dosed at standard doses depending on the infection type. For patients on HD who receive treatment 3 times a week, doses are given after each dialysis session (Salama, 2010). There are some pharmacokinetic data suggesting that doses may need to be increased by approximately 50% prior to the weekend (72-hour) interdialytic period; however, this has been primarily studied using lower overall daptomycin doses (Butterfield, 2013). Baseline and weekly creatine phosphokinase monitoring should be performed while patients receive daptomycin in view of the risk of myopathy and rhabdomyolysis.

N. Tetracyclines. Use of tetracyclines is generally avoided in patients with renal insufficiency because of the antianabolic effect of these drugs; the use of tetracyclines can lead to an increase in the serum urea nitrogen level and to worsening acidosis. When a tetracycline is necessary, doxycycline may be used. Although doxycycline also has antianabolic effects, the percentage of renal excretion for doxycycline (normally 40%) is lower than that for tetracycline (60%). Doxycycline is poorly removed by dialysis, and no supplemental dose or dosage adjustment is necessary for patients on intermittent HD, peritoneal dialysis, or CKRT. Minocycline is minimally excreted by the kidney and can be given in the usual dosages, but should not exceed 200 mg/d.

O. Glycylcyclines. Tigecycline is the first FDA-approved drug from a new class of antibiotics called the glycylcyclines. It is indicated for complicated skin and skin structure infections, complicated intra-abdominal infections, and community-acquired bacterial pneumonia. Owing to a 2010 analysis showing an increased risk of death with tigecycline for approved uses as well as unapproved uses, it should be reserved for situations when alternative treatments are not suitable. Tigecycline is structurally similar to the tetracyclines and is derived from minocycline. It has gram-positive and gram-

negative activity as well as activity against MRSA. Tigecycline is cleared by the liver and requires no renal dose adjustments in HD, peritoneal dialysis, or CKRT.

Eravacycline and omadacycline are two of the newest members of the glycylcycline class. Owing to their minimal urinary excretion, renal and dialysis dosage adjustments are not required for either of these new antimicrobials. (Nuzyra package insert, Paratek Pharmaceuticals Inc.; Xerava package insert, Tetraphase Pharmaceuticals Inc.)

P. Diaminopyrimidines. Trimethoprim may raise serum creatinine values in patients with renal impairment because of interference with tubular secretion of creatinine; this is not accompanied by a reduction in the true glomerular filtration rate (as measured by the clearance of inulin). Trimethoprim is normally 80% to 90% excreted by the kidney. Renal excretion of sulfamethoxazole is normally 20% to 30%. Trimethoprim and sulfamethoxazole are removed well by HD but poorly by peritoneal dialysis. For the treatment of UTIs, one single-strength tablet containing 80 mg of trimethoprim and 400 mg of sulfamethoxazole should be given twice daily. When giving high-dose IV trimethoprim/sulfamethoxazole (eg, for treatment of *Pneumocystis jirovecii* pneumonia) in patients on dialysis, 50% of the usual dose (the latter being 15-20 mg/kg/d based on the trimethoprim component) is given as divided doses every 6 to 12 hours; the incidence of leukopenia may be increased when treating patients on dialysis, and careful monitoring is essential. In CKRT, doses of 2.5 to 7.5 mg/kg of trimethoprim every 12 hours are recommended and are highly dependent on indication. Critically ill patients with *P. jirovecii* pneumonia receiving C-HDF may require up to 10 mg/kg every 12 hours (Heintz, 2009).

Q. Antituberculars. Rifampin is used in the treatment of *S. aureus* skin exit site infections and peritonitis. Rifampin dosage does not need to be adjusted in patients on dialysis as the half-life does not differ if dosing is less than 600 mg daily. The percentage of renal excretion of isoniazid will vary depending on whether the patient acetylates the drug slowly (renal excretion = 30%) or rapidly (renal excretion = 7%); however, this rate does not seem to alter clinical results. Isoniazid is removed well by dialysis (50%-100%) and should be given postdialysis. Usually, doses are not adjusted in patients on dialysis because decreased renal excretion is balanced by removal during dialysis. However, some authors recommend a small dosage reduction (eg, 200 mg/d rather than 300 mg/d), because the accumulation of isoniazid may occur in patients who are “slow acetylators” receiving 300 mg/d.

Ethambutol is largely excreted by the kidney in patients without uremia. In patients undergoing dialysis, an increase in the dosing interval is required (see Table 33.3). Patients on dialysis should receive the same pyrazinamide dose as patients with a CrCl of less than 30 mL/min.

R. Antivirals. The neuraminidase inhibitors zanamivir and oseltamivir are used for prophylaxis and treatment against influenza A and B, whereas the adamantines, amantadine and rimantadine, are no longer recommended for use in the United States for this purpose owing to high resistance rates (Fiore, 2011). Amantadine can also treat parkinsonism and drug-induced extrapyramidal symptoms. Amantadine should be used with great caution in patients on HD as excretion of amantadine is almost exclusively renal. Because of its large volume of distribution, amantadine is removed very slowly by either HD or peritoneal dialysis. Rimantadine is primarily metabolized by the liver, with less than 25% typically excreted unchanged by the kidney, and is not removed by

HD.

Oseltamivir requires dose adjustment for CrCl less than 60 mL/min and requires weight-based dosing in children with renal impairment. However, it does not appear to cause serious dose-related adverse events (Aoki, 2012). Zanamivir is administered via inhalation; owing to the low likelihood of its systemic absorption, renal dose adjustment is not necessary.

Acyclovir, famciclovir, and valacyclovir all treat herpes simplex and varicella-zoster infections and require dosage reduction in the presence of renal dysfunction. Failure to appropriately reduce the dose of acyclovir can lead to severe central nervous system toxicity, particularly in patients on CAPD (Stathoulopoulou, 1996). In patients with residual renal function, IV acyclovir can lead to the formation of insoluble crystals in the renal tubules, which can lead to acute kidney injury (Perazella, 2003). Risk is decreased with administration of IV acyclovir over 1 to 2 hours, along with adequate hydration as tolerated (Laskin, 1983). Valacyclovir is the prodrug to acyclovir and offers about 55% more bioavailability (Perry and Faulds, 1996). PO famciclovir is a prodrug to penciclovir, and the latter is available only as a topical formulation. Famciclovir provides good bioavailability, which requires adjustment for renal dysfunction, and it has a similar toxicity profile to acyclovir.

Several antiviral agents are currently employed for the treatment of CMV infections and CMV prevention in transplanted patients (cidofovir, foscarnet, ganciclovir, valganciclovir). Cidofovir has an active metabolite with a half-life of 65 hours, thus allowing for weekly dosing. It is contraindicated in patients with a CrCl of 55 mL/min or less (Lea and Bryson, 1996). Its most significant side effect is dose-dependent nephrotoxicity that presents like a Fanconi-type syndrome. The risk can be reduced by giving 1 L of normal saline over 1 to 2 hours directly before cidofovir administration and giving probenecid 2 g PO 3 hours beforehand and 1 g 2 and 8 hours following cidofovir.

Foscarnet is primarily used in patients with CMV infection that have resistance to ganciclovir. It is only available IV owing to poor bioavailability of the PO formulation. Foscarnet is associated with a greater than 10% incidence of renal insufficiency, likely attributed to direct toxicity to renal tubular cells (Trifillis, 1993). High-flux dialysis for 2.5 hours has demonstrated 38% removal of foscarnet. Induction therapy with foscarnet of 60 to 90 mg/kg post-dialysis followed by maintenance doses of 45 to 60 mg/kg, aiming at peak plasma concentrations of 400 to 800 mcmol/L has been suggested. In CKRT, dosing should be the same as for patients with CrCl of 10 to 50 mL/min. Valganciclovir is a prodrug of ganciclovir with higher PO bioavailability than PO ganciclovir. Owing to ganciclovir's poor bioavailability, the PO formulation is no longer used. The manufacturer recommends that valganciclovir be avoided in patients receiving HD and to consider ganciclovir, instead. There are dosing recommendations in the Canadian package insert for valganciclovir, recommending the use of PO solution at a dose of 200 mg after each HD session and 100 mg after each HD session, respectively. This recommendation is primarily based on pharmacokinetic data rather than clinical data, however (Lucas, 2014). Patients should be closely observed for bone marrow toxicity while on any of these four antivirals.

S. Antiretrovirals. The nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) were the first class of antiretrovirals available for clinical use. Zidovudine

(azidothymidine or AZT) was the first NRTI to be approved for the treatment of HIV/AIDS. It is predominantly hepatically metabolized to the inactive glucuronide metabolite GZDV with only about 20% excreted unchanged by the kidneys. In renal failure, alteration in elimination and GZDV accumulation necessitate dosage reduction (generally a 50% reduction) in order to avoid toxicity. Severe granulocytopenia in patients with ESKD with 100 mg tid dosing has been observed. There is no significant removal of the drug or its metabolite by either HD or peritoneal dialysis. Other NRTIs (eg, didanosine, emtricitabine, lamivudine, tenofovir, stavudine) also require dosage adjustments in renal failure (see Table 33.3). Abacavir is the only NRTI that does not require dosage adjustment. Tenofovir has been reported to cause nephrotoxicity, which could be important in patients with residual renal function.

With the exception of lopinavir/ritonavir and atazanavir, none of the protease inhibitors—darunavir, fosamprenavir, indinavir, nelfinavir, ritonavir, saquinavir, and tipranavir—require dosage adjustment in patients with renal failure not on HD. Pharmacokinetic evaluations of most protease inhibitors in patients on HD have not been conducted. Studies have been performed with atazanavir, lopinavir, and ritonavir that exhibit significantly lower concentrations in patients on HD despite being hepatically cleared. Boosted therapy of atazanavir 300 mg with ritonavir 100 mg once daily is recommended in patients on dialysis considered antiretroviral-naïve. However, atazanavir should be avoided altogether in antiretroviral-experienced patients on dialysis because of evidence of moderate increases in atazanavir clearance and decreased exposure levels in patients managed with HD. Lopinavir/ritonavir should not be given less than twice daily with HD. Caution should be exercised with patients whose HIV has protease inhibitor resistance mutations, as lopinavir and ritonavir levels may not be adequate for viral suppression in patients on dialysis. Numerous drug-drug interactions with protease inhibitors exist because of their metabolism through the hepatic cytochrome P450 isoenzyme system, and monitoring for these interactions is warranted.

The nonnucleoside reverse transcriptase inhibitors (NNRTIs) nevirapine, delavirdine, efavirenz, rilpivirine, and etravirine are a heterogenous group with respect to limited renal clearance (see Table 33.3). Dose adjustments for patients with chronic kidney disease not on dialysis are not provided by the manufacturer for nevirapine, delavirdine, and efavirenz, owing to limited studies. A supplemental dose of 200 mg is recommended for nevirapine following each dialysis session. Rilpivirine exhibits extensive protein binding, which makes significant removal by HD or peritoneal dialysis unlikely.

Enfuvirtide belongs to a different class of antiretrovirals (ie, fusion inhibitors). This drug is reserved only for patients who require salvage therapy and are resistant to all classes of antiretrovirals. The use of this antiretroviral is limited by the need for subcutaneous injections and the substantial cost. Dosage adjustment for chronic kidney disease with enfuvirtide does not appear necessary.

Maraviroc is a chemokine coreceptor antagonist that does not require dose adjustment in mild-to-moderate chronic kidney disease. However, patients concomitantly receiving potent cytochrome P450-3A inhibitors or inducers and with CrCl less than 30 mL/min should not receive maraviroc. HD has minimal effect on clearance; however, if postural hypotension occurs in patients with ESKD, the maraviroc dose should be reduced to 150 mg twice daily.

Raltegravir, elvitegravir/cobicistat, dolutegravir, bictegravir, and cabotegravir all work by inhibiting integrase, the viral enzyme used to incorporate viral DNA into the host cell. While raltegravir does not require dose adjustment for mild, moderate, or severe chronic kidney disease, elvitegravir/cobicistat used in combination with emtricitabine/tenofovir should not be initiated in patients with CrCl less than 70 mL/min and should be discontinued in patients with CrCl less than 50 mL/min.

To reduce the increasing pill burden of antiretroviral regimens, numerous fixed-dose combinations are currently available. The general rule in HD is to substitute with the component drugs and adjust the dose of each drug separately.

T. Antifungals.

1. **Amphotericin B.** The use of amphotericin B deoxycholate (conventional amphotericin B), the standard for treatment of fungal infections for decades, is limited because of its high risk of nephrotoxicity. Three lipid-based amphotericin B formulations are FDA approved—amphotericin B cholesteryl sulfate (Amphotec), amphotericin B lipid complex (Abelcet), and amphotericin B liposome (AmBisome)—and all possess less nephrotoxicity compared with amphotericin B deoxycholate. Nephrotoxicity may still be a consideration with prolonged use of amphotericin B in patients with residual renal function. All formulations of amphotericin are not dialyzed well, and, consequently, doses do not need to be adjusted for any dialysis modality.
2. **Azole antifungals.** The systemic azole antifungals can be sorted into two groups: the triazoles, which include fluconazole, itraconazole, voriconazole, posaconazole and isavuconazole, and the imidazole group, which includes ketoconazole. Imidazoles have largely been supplanted by triazoles on account of improved efficacy and safety profiles, and the FDA has advised against using ketoconazole as first-line therapy for fungal infections. A patient's medication profile should be reviewed carefully before prescribing these agents in light of the multiple drug-drug interactions, particularly through the cytochrome P450 enzyme system.
    a. **Fluconazole.** Fluconazole has excellent bioavailability and efficacy against yeast, though it has no activity against molds. The only azole antifungal that requires dosage adjustment in renal dysfunction is fluconazole; some will decrease the dose by one-half in patients with renal dysfunction, while others will extend the interval to every 48 hours while keeping the dose the same. The latter may be more appropriate owing to fluconazole's dose dependence (eg, the higher the dose, the higher the serum concentration will be above the MIC of the organism). Fluconazole levels are not usually monitored given its predictable bioavailability (Andes, 2009).
    b. **Itraconazole.** There are two main formulations of itraconazole: a capsule and a PO solution. Itraconazole bioavailability is erratic, and that of the PO solution is much improved compared to the capsule. There is a newer capsule formulation of itraconazole as well—SUBA-itraconazole, which has improved bioavailability compared to conventional capsules (Thomson, 2020). Itraconazole does not require dose adjustments for any form of dialysis and is not known to be nephrotoxic.
    c. **Voriconazole.** Voriconazole is available in tablet, capsule, and IV formulations. Voriconazole can also exhibit decreased bioavailability when

taken with high-fat meals, and bioavailability is subject to variability on account of genetic factors. Voriconazole is the gold standard for the treatment of invasive aspergillosis. PO voriconazole pharmacokinetics are not affected by renal dysfunction, and therefore there is no dose adjustment required for renal impairment or dialysis. For patients with a CrCl of less than 50 mL/min, PO voriconazole is preferred over IV due to the risk of accumulation of the solubilizing agent, sulfobutylether-β-cyclodextrin (SBECD). If IV voriconazole must be used in patients with renal dysfunction, serum creatinine should be monitored. There is currently evidence that although SBECD is known to accumulate in patients with reduced renal function, there has not been nephrotoxicity observed as a result of this accumulation (Luke, 2010; Oude Lashof, 2012).

d. Posaconazole. Posaconazole affords a very broad spectrum of antifungal activity and interacts less with other drugs; however, the PO suspension has erratic bioavailability owing to its dependence on a high-fat meal. It is also available as delayed-release tablets, which is the preferred formulation. An IV version is also available; this contains SBECD, similar to voriconazole, and so the concerns discussed earlier related to SBECD and voriconazole apply to IV posaconazole, also.

e. *Isavuconazole*. Isavuconazole is the newest available triazole antifungal. It is available in both PO capsules as well as IV formulations. Uniquely, isavuconazole does not contain SBECD as a solubilizing agent; therefore, accumulation of this agent is not a concern in patients with impaired renal function. Isavuconazole pharmacokinetics are not affected by renal impairment or dialysis, similar to the other triazole antifungals.

3. Echinocandins. There are three members of the echinocandin class of antifungals; caspofungin, micafungin, and anidulafungin. This class of antifungals works on the fungal cell wall in contrast to amphotericin formulations and the azole antifungals, which act on fungal cytoplasmic membranes. Benefits of this drug class include effective treatment of fluconazole-resistant *Candida glabrata* and *krusei*, in addition to having fewer side effects relative to other antifungals. The spectrum of activity of all echinocandins is comparable, and all have FDA indications for esophageal candidiasis and invasive candidiasis. Moreover, all agents are administered in IV form and dosage does not need to be adjusted for renal dysfunction. Unlike the azoles, echinocandins do not interact significantly with the cytochrome P450 enzyme class, resulting in significantly fewer drug interactions. One concern regarding the echinocandin class in patients on dialysis is that all members of the class must be given daily and are only available IV. Therefore, a separate central vascular access must be placed for those patients who require long-term, outpatient use of echinocandins, which is often not feasible in patients with ESKD.

U. Postdialysis supplements. Recommended post-HD supplements are listed in Table 33.3. These should be given in addition to the maintenance dosages listed. The post-HD supplements recommended here are geared for a conventional, 4-hour HD treatment only. With very short dialysis treatments, the amount of drug removed by HD may not be substantial enough to necessitate a post-HD supplement, but the timing of dosing so that a dose is given after dialysis is recommended. In general, patients on peritoneal

dialysis can be treated with usual doses for patient on HD. Drug dosing during CKRT has been reviewed elsewhere (Heintz, 2009; Kanji, 2023; McKnite, 2024).

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34 Mineral and Bone Disease

Morgan B. Schoer and Daniel W. Coyne

The bone mineral axis is comprised of calcium, phosphorus, and a number of hormones, including parathyroid hormone (PTH), fibroblast growth factor-23 (FGF23), and 1,25-dihydroxyvitamin D (calcitriol or 1,25D). During progressive loss of kidney function, these hormone levels change to maintain normal serum calcium and phosphate. However, by late chronic kidney disease (CKD) stage 4, relative hypocalcemia and hyperphosphatemia are common. Dysregulation of the mineral bone axis primarily results in hyperparathyroidism and consequent bone disease with increased fracture risk. These changes are also associated with an increased risk of cardiovascular disease, vascular calcification, and death. Control of this axis with dietary modifications, optimizing dialysis phosphate clearance and calcium balance, and use of medications reduce these comorbidities and all-cause mortality (Zhang, 2023). To understand the management of chronic kidney disease–mineral bone disease (CKD-MBD), a basic understanding of its pathophysiology is necessary.

I. PATHOPHYSIOLOGY.

The goal of the bone mineral axis is a finely regulated maintenance of the ionized calcium set point, normophosphatemia, and mineralized bone with balanced formation and resorption. PTH is the main regulator of ionized calcium, while the actions of FGF23 maintain normal serum phosphate. 1,25D enhances intestinal absorption of calcium and phosphate and suppresses PTH secretion and gland hyperplasia.

In the nondiseased state, the kidneys work together with the gastrointestinal (GI) tract, parathyroid glands, and bones to help maintain normal calcium and phosphate homeostasis. When serum calcium is low, PTH secretion from the parathyroid gland increases, leading to (1) increased osteoclastic activity, with the resultant release of calcium and phosphate from bone into the circulation; (2) increased 1-α hydroxylation of 25(OH)D to create 1,25D, which enhances calcium and phosphate intestinal absorption; and (3) increased proximal tubular reabsorption of calcium with decreased reabsorption of phosphate. As the calcium rises and returns to the normal range, the calcium-sensing receptor (CaSR) of the parathyroid gland is activated, which reduces further PTH release.

As the glomerular filtration rate falls in CKD, changes in FGF23, PTH, and 1,25D levels occur to maintain mineral homeostasis. Increased FGF23, stimulated by mild phosphate elevations, occurs as early as CKD stage 2 and has two major actions. FGF23 enhances phosphaturia by downregulating sodium-phosphate cotransporters in the brush border of the renal proximal tubules. FGF23 also downregulates the proximal tubule 1-α hydroxylase enzyme, resulting in decreased calcitriol production.

Calcitriol normally has three major actions: (1) increasing gut calcium and phosphate absorption, (2) increasing calcium reabsorption in the kidney, and (3) suppressing PTH production by the parathyroid gland. By stage 3 CKD, due to the downregulated activity of 1-α hydroxylase enzyme by FGF23 (as discussed above) and decreased renal mass, mean calcitriol levels fall. This relative 1,25D deficiency acts in parallel with FGF23 to lower serum phosphate, by decreasing gut phosphate absorption.

Calcitriol is synthesized in three steps. Ultraviolet light on the skin converts 7-hydroxycholesterol into cholecalciferol (vitamin D_3). Cholecalciferol is an inactive steroid prohormone and is constitutively hydroxylated in the 25-position by the liver to produce 25(OH)D. 25(OH)D can then be fully activated by a third step: hydroxylation of the steroid ring at the 1-position. This hydroxylation step can occur in a variety of tissues locally, but most calcitriol is synthesized in the proximal tubules by the enzyme 1-α hydroxylase. This enzyme is downregulated by FGF23, high serum calcium, and calcitriol; it is upregulated by PTH, low serum calcium, and hypophosphatemia.

PTH is an 84-amino-acid peptide hormone synthesized by the parathyroid glands. Hypocalcemia, detected by the CaSR, is the main stimulus for PTH secretion. High phosphate levels also stimulate PTH secretion. PTH maintains normal ionized calcium level by (1) stimulating the activity of the 1-α hydroxylase in the kidney to create calcitriol, which in turn enhances gut absorption of calcium, (2) increasing bone turnover, thus releasing more calcium from bone, and (3) decreasing proximal tubular phosphate reabsorption, which lowers serum phosphate and tends to raise serum calcium. Note that both PTH and FGF23 act to increase renal phosphate excretion, but they have the opposite effects on 1-α hydroxylase. In a feedback loop, secretion of PTH is inhibited by calcitriol acting on calcitriol receptors in the parathyroid gland. This feedback loop can be exploited physiologically and pharmacologically using calcitriol (or its analogues) to suppress PTH secretion. Several of the concepts above are illustrated in Figures 34.1 and 34.2.

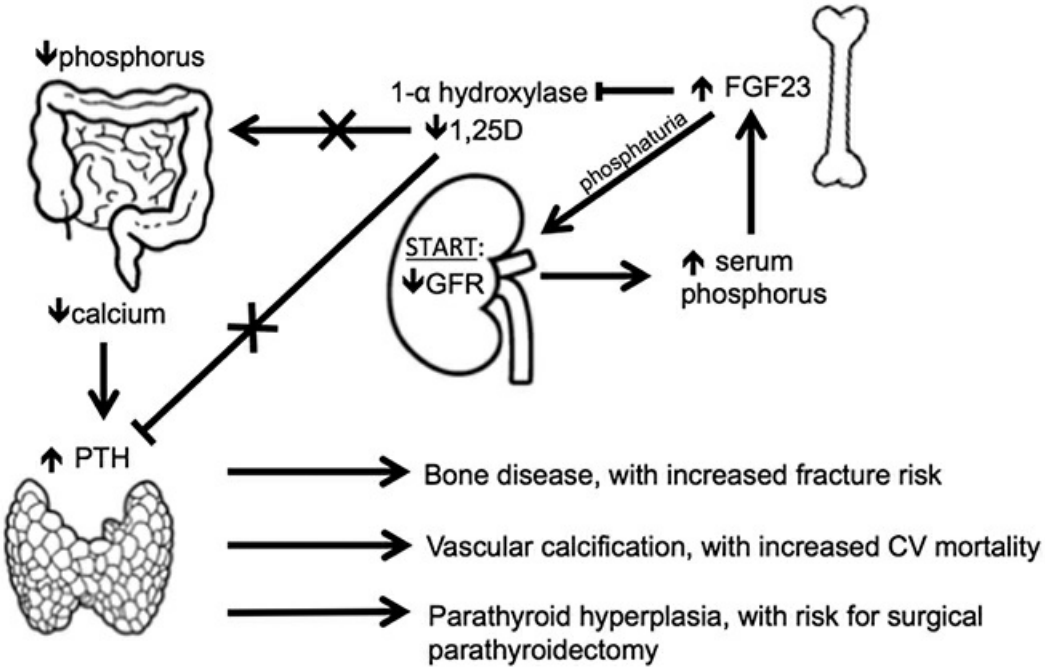


FIGURE 34.1: The decreased GFR in CKD leads to a predictable series of perturbations in FGF23, 1,25D, and PTH, which are able to maintain a relatively normal serum phosphate and calcium until dialysis dependency, though with multiple consequences elaborated above. The net effect of the increased FGF23, mildly suppressed calcitriol production, and elevated PTH during progressive CKD is the maintenance of serum calcium and phosphate within the normal range until stage 4 or 5. With onset of stage 5 CKD and initiation of dialysis, this elegant homeostasis system breaks down, leading to markedly elevated FGF23 and PTH levels, uniformly low calcitriol levels, hyperphosphatemia, and low or low-normal serum calcium. These abnormalities lead to bone diseases (see next section) generally referred to as CKD-MBD or renal osteodystrophy. 1,25D, 1,25-dihydroxyvitamin D; CKD, chronic kidney disease; CKD-MBD, chronic kidney disease–mineral bone disease; CV, cardiovascular; FGF23, fibroblast

growth factor-23; GFR, glomerular filtration rate; PTH, parathyroid hormone.

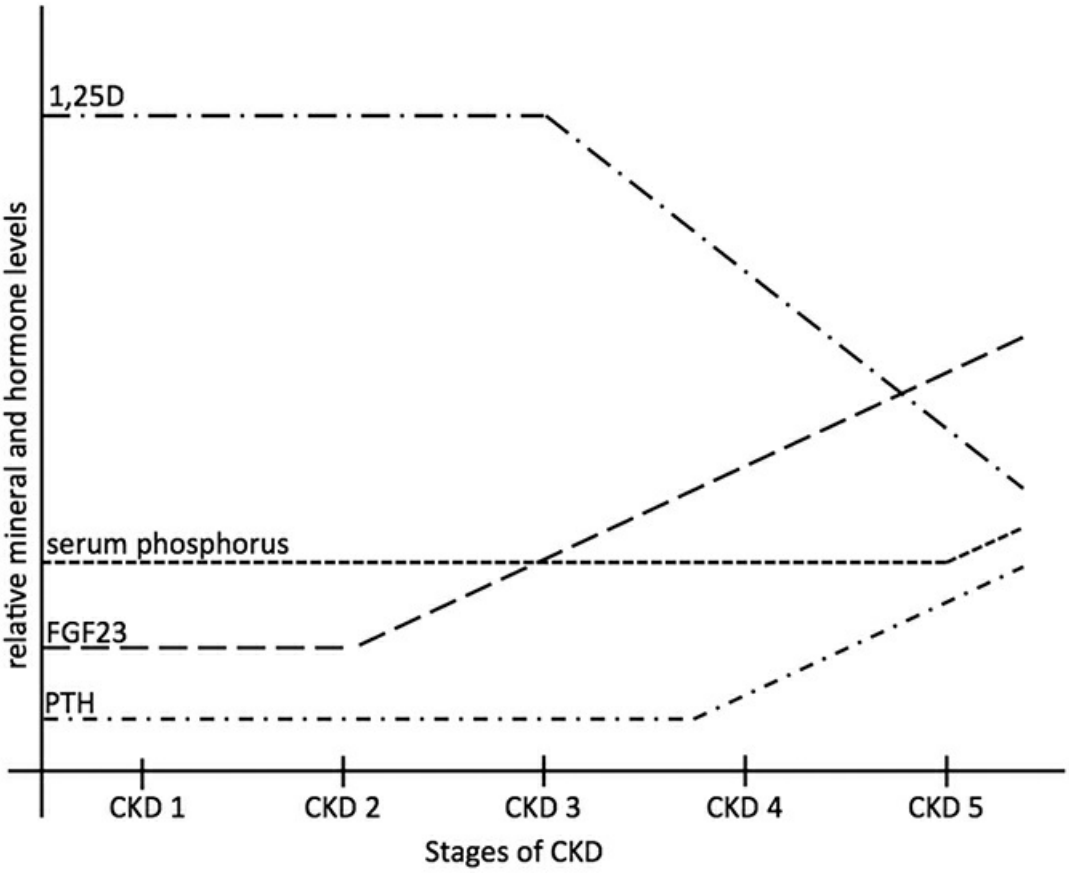


FIGURE 34.2: Timing of hormonal changes as CKD progresses, with relative preservation of normophosphatemia until late CKD. In the dialysis-dependent state, these changes will proceed along the same trend, unless otherwise intervened upon. The reactive elevation in PTH described above (as a response to low calcium, high phosphate, and low 1,25D) is termed secondary hyperparathyroidism. Concomitant with the increasing PTH, the parathyroid glands undergo progressive hyperplasia. After enough time and growth, the glands may lose their sensitivity to the physiologic negative feedback by elevated calcium and calcitriol, and thus develop autonomous PTH release. This is termed tertiary hyperparathyroidism, typically presents with markedly elevated PTH levels and hypercalcemia, and can lead to severe bone disease. 1,25D, 1,25-dihydroxyvitamin D; CKD, chronic kidney disease; PTH, parathyroid hormone.

II. BONE DISEASE IN CKD. Abnormalities in calcium, phosphate, vitamin D, and PTH lead to renal osteodystrophy. Under normal conditions, bone undergoes regular, coordinated turnover: the amount of bone resorbed by osteoclasts is matched with a new bone matrix (osteoid) created by osteoblasts, which then undergoes mineralization (promoted by vitamin D). The term renal osteodystrophy encompasses several pathologic lesions. Metabolic parameters (PTH, 25[OH]D, alkaline phosphatase, calcium) may be suggestive of certain pathologies, but ultimately do not correlate well. Radiographic findings may be present, but are often nondiagnostic until severe disease and not recommended for routine use. Bone densitometry does not reliably predict fracture risk in patients undergoing dialysis. Transiliac bone biopsy remains the gold standard for diagnosis.

Before obtaining a bone biopsy, a fluorescent bone-labeling compound such as tetracycline or demeclocycline is administered to the patient for 3 days, and then again, 2 weeks later. These drugs will deposit at the lines of mineralization; the amount of space

between the two fluorescent labels on biopsy suggests the rate of bone turnover (the larger the space, the higher the turnover). Each biopsy is assessed for both static and dynamic components in the "TMV" system, which assesses **T**urnover rate, **M**ineralization, and **V**olume of bone. Osteitis fibrosa and adynamic bone disease are disorders of high and low bone turnover rate, respectively. Osteomalacia is a disorder of osteoid mineralization, while osteoporosis is a disorder of low bone volume. Finally, although now rare, aluminum can accumulate on the bone surface and lead to a form of osteomalacia. It can be tested for by staining bone biopsies with acid solochrome azurine.

A. Osteitis fibrosa. This form of renal osteodystrophy occurs when PTH is persistently high. Continuous PTH stimulation leads to an increased number and activity of osteoblasts and osteoclasts, which causes increased bone turnover and marrow fibrosis. The severity of osteitis fibrosa is roughly proportional to the degree and duration of PTH elevation. Mild osteitis fibrosa is somewhat preferable to adynamic bone in that bone strength is greater. However, when osteitis fibrosa is severe, bone is laid down so rapidly that it is not properly mineralized or structured. This results in increased unmineralized bone (osteoid), inappropriately mineralized bone (as amorphous calcium phosphate rather than hydroxyapatite), and nonlamellar collage alignment. The resulting bone is more prone to fracture. Severe osteitis fibrosa can also be associated with erythropoietin-stimulating agent (ESA) resistance; this co-occurs with marrow fibrosis, as the hematopoietic niche is replaced with reticulin and collagen fibers.

The most prominent symptoms of severe osteitis fibrosa are bone and joint discomfort. Metastatic calcification with periarticular calcium deposits may lead to acute joint inflammation with pain and stiffness.

Biochemically, these patients have persistently elevated PTH levels and elevated alkaline phosphatase; calcium can be low, normal, or high. The degree of PTH elevation that predisposes a patient to osteitis fibrosa (vs adynamic bone disease) varies widely among patients. For example, at a PTH of 300 pg/mL (33 pmol/L), one patient who has been dialysis dependent for 3 months may have bone physiology consistent with osteitis fibrosa, while another patient who has been dialysis dependent for 3 years may have bone physiology consistent with adynamic bone disease.

Radiographic findings, though not recommended for diagnosis, may be present in moderate to severe disease. These can include subperiosteal resorption of the second and third phalanx, distal phalanx tuft erosions (sometimes with fingertip blunting), "salt-and-pepper" appearance of the skull or long bones, or "brown tumors" (noncarcinogenic lytic-appearing lesions) at sites of osteoclast activity. A technetium bone scan would show increased tracer uptake.

Treatment is directed at improving and stabilizing the PTH. In some cases, this may require a parathyroidectomy, after which bone architecture, tensile strength, and fracture risk all improve significantly.

B. Adynamic bone. In contrast to osteitis fibrosa, adynamic bone disease develops in the setting of a persistently suppressed PTH. Without the stimulus for osteoblast and osteoclast activity, these patients develop low bone turnover; osteoid thickness may be normal, distinguishing it from osteomalacia. Typically, these patients have a PTH less than 100 pg/mL (11 pmol/L), normal serum alkaline phosphatase level (with low bone-specific fraction), and sometimes an elevated serum calcium level. Bone densities tend to be normal or low.

Risk factors for the development of adynamic bone disease include female sex, advanced age, diabetes, and White race. It is also more common in patients undergoing peritoneal dialysis; however, the risk may be mitigated by the use of a 2.5-mEq/L (1.25 mM) calcium peritoneal dialysis solution. Aluminum is now a rare cause of adynamic bone disease.

Historically thought to be asymptomatic and not requiring treatment, adynamic bone is now known to be associated with an even higher fracture rate than osteitis fibrosa. Furthermore, the associated hypercalcemia (likely due to the impaired ability of the bone to buffer serum calcium) may predispose to increased vascular calcification. Symptoms, such as pain from nontraumatic fractures, are usually absent until the disease is advanced.

C. Osteomalacia. This is primarily a disorder of bone mineralization. Like adynamic bone disease, osteomalacia represents a state of low bone turnover. It is marked, however, by the presence of large amounts of unmineralized osteoid. The most common cause is vitamin D deficiency, and thus can be largely prevented and reversed with cholecalciferol or ergocalciferol supplementation. It can also develop from severe hypophosphatemia. Aluminum accumulation was historically a major cause of osteomalacia, but is now seldom seen. Rarely, osteomalacia has been ascribed to iron overload. Bone or joint-related symptoms are not usually seen. Osteomalacia most commonly presents with axial and proximal muscle weakness, often manifested by a waddling gait; these improve rapidly following vitamin D supplementation.

D. Osteoporosis. This is a disorder of low bone volume and can co-occur with—or independently of—any of the above bone disorders. As the age of patients at the time of starting dialysis continues to increase, many have preexisting osteoporosis documented with bone densitometry. Medical interventions used routinely for osteoporosis include bisphosphonates, the RANKL (receptor activator of nuclear factor kappa-B ligand) inhibitor denosumab, and PTH analogues (each described below in the section titled “Additional Therapies for Bone Disease”). Patients undergoing dialysis are typically excluded from clinical trials on these drugs, and thus safety and efficacy data are limited in this population. Caution should be used before prescribing these medications to patients with osteoporosis undergoing dialysis.

Maintenance of bone health in the dialysis population requires adequate management of the bone mineral axis and is tightly associated with modulation of vascular calcification and cardiovascular mortality.

III. CONTROL OF SERUM PHOSPHATE.

Hyperphosphatemia contributes to the development of hyperparathyroidism and bone disease and plays a pathologic role in the development and progression of cardiovascular disease. High serum phosphate levels may contribute to impaired bone mineralization and enhance vascular and other tissue calcification. High FGF23 levels, caused by hyperphosphatemia and other factors, have been shown to induce left ventricular hypertrophy in animal models.

The normal range for serum phosphate is 2.7 to 4.6 mg/dL (0.9-1.5 mmol/L). Hypophosphatemia may occasionally develop. It can be seen in patients receiving long or more frequent hemodialysis treatments, malnutrition with inadequate protein intake, or high residual kidney function. Hypophosphatemia should be managed by cessation of phosphate binders and encouraging higher phosphate intake. Rarely, daily administration of one or

more capsules or packets of Neutra-phos (Na/K phosphate) is needed. Each capsule or packet contains 250 mg (8 mmol) of phosphate.

In patients with CKD, hyperphosphatemia develops when dietary phosphate absorption exceeds the excretion capacity of the remaining nephrons—generally late CKD stage 4 or stage 5—and is usually mild. In patients undergoing dialysis, hyperphosphatemia develops in the vast majority of patients on thrice-weekly hemodialysis or peritoneal dialysis. In 2021, about 80% of patients undergoing hemodialysis in the United States were prescribed a phosphate binder, and mean predialysis serum phosphate was about 5.5 mg/dL (DOPPS Practice Monitor).

The 2017 *Kidney Disease: Improving Global Outcomes* (KDIGO) mineral bone disease guidelines recommend lowering elevated serum phosphate levels toward the normal range (2.7-4.6 mg/dL or 0.9-1.5 mmol/L), based on data that hyperphosphatemia is associated with vascular calcification and higher mortality. Use of the calcium phosphate product as a target is no longer recommended. In clinical practice, most physicians and dietitians strive to maintain predialysis phosphate between 3.0 and 5.5 mg/dL (1.0-1.8 mmol/L), which is achieved through provision of adequate dialysis, dietary restriction of phosphate intake, and use of phosphate binders with meals. Although lack of adherence to dietary restrictions and binders are causes of hyperphosphatemia, there are several important factors beyond patient control. These include differences among patients in GI phosphate absorption, efficiency of binders, efficiency of phosphate removal by dialysis, and severity of hyperparathyroidism.

A. Residual kidney function. This contributes substantially to phosphate removal from the body. Patients with higher urine volumes typically require lower doses of phosphate binders than other patients. Preservation of residual renal function should be a high priority in patients undergoing dialysis for this and other reasons.

B. Removal of phosphate by dialysis. The amount of phosphate removal during a dialysis session depends primarily on the predialysis serum phosphate level. A typical 4-hour hemodialysis treatment when predialysis serum phosphate is 5.3 mg/dL (1.75 mmol/L) removes about 900 mg of phosphate (Daugirdas, 2023); this equates to roughly 2.7 g removed per week for thrice-weekly dialysis. Increasing the amount of time on dialysis—either by extending treatment time or by adding treatment—can increase the amount of phosphate removed. Dialyzers with larger surface areas and use of hemodiafiltration can modestly increase phosphate clearance, resulting in slightly lower predialysis phosphate values. Without the use of phosphate binders, the average patient needs 18 to 30 hours of dialysis per week to achieve a predialysis serum phosphate of less than 4.5 mg/dL (1.45 mmol/L) (Daugirdas, 2015). Patients undergoing frequent and long nocturnal dialysis may require the addition of phosphate to the dialysis solution to prevent hypophosphatemia.

Peritoneal dialysis removes approximately 400 mg/d (or 2.8 g/wk) of phosphate (Rastogi, 2021). This is also far less than the amount of phosphate absorbed from the diet, and as a result, most patients undergoing peritoneal dialysis require the use of binders to control serum phosphate levels.

C. Dietary restriction. Restricting phosphate consumption is critical in controlling serum phosphate. However, quantifying the effective dietary phosphate exposure is difficult. Most foods do not provide phosphate content, and bioavailability varies greatly by food source. Inorganic phosphates, added as preservatives and flavor enhancers to processed foods, are the most bioavailable (90%-100%) and thus much more readily absorbed than

organic phosphates in natural food (Rastogi, 2021). The phosphate content of foods is related to their protein content and source: phosphate is more bioavailable in animal protein (60%-90%) than in plant protein (30%-50%) (Rastogi, 2021). Gastrointestinal absorption is further modulated by calcitriol use. Finally, certain medications may contain significant amounts of phosphate, though this may vary by manufacturer; notable examples include lisinopril (up to 115 mg per tablet), amlodipine (up to 120 mg), and paroxetine (up to 400 mg) (Sawin, 2020).

A standard American diet contains 1,000 to 1,600 mg of phosphate per day. In patients undergoing dialysis, phosphate in the diet should be restricted to 800 to 1,200 mg/d (notably, this is 5.6-8.4 g/wk, more than double what is removed by conventional hemodialysis). A dietitian with experience in counseling patients undergoing dialysis is essential for optimal management of hyperphosphatemia. See Table 34.1 and Appendix B (Tables B.9 and B.10) for foods high in phosphate (Rastogi, 2021; Sekar, 2018).

TABLE 34.1 Foods Especially High in Phosphate

Dairy products (milk, yogurt, cheese)
Organ and processed meat
Beans/peas
Nuts/seeds
Whole-grain breads, bran, and cereals
Many soft drinks (particularly colas)

See also Appendix B, Tables B.9 and B10.

D. Inhibition of the intestinal Na/H exchanger. Tenapanor is a minimally absorbed inhibitor of the sodium/hydrogen exchanger isoform-3 located on the apical surface of small intestinal cells. Inhibition of this exchanger reduces paracellular phosphate flux from the intestine. Trials in patients on hemodialysis and peritoneal dialysis have demonstrated a reduction in serum phosphorus of 0.7 to 1.0 mg/dL (Koiwa, 2023; Nakayama, 2024; Sprague, 2024). Although less efficacious than phosphate binders, tenapanor is sufficient in patients with mild hyperphosphatemia and can be used in addition to binders. It is administered orally as 30 mg twice daily with breakfast and dinner. The main side effect is diarrhea, which is dose related. Lower doses of 10 and 20 mg are available.

E. Phosphate binders. Because dietary phosphate typically exceeds the amount removed by dialysis and residual renal function, the majority of patients undergoing dialysis require the use of phosphate binders. These agents are taken with meals, and they work by binding phosphate in the GI tract, either by forming an insoluble complex or by binding it into a resin. Observational data suggest the use of phosphate binders correlates with longer survival and better nutritional status for patients on maintenance hemodialysis (Cannata-Andía, 2013; Lopes, 2012).

See Table 34.2 for a summary of commonly used phosphate-binding agents. There are two major categories of phosphate binders: those that contain calcium (either as calcium carbonate or calcium acetate) and those that do not (sevelamer, lanthanum, sucroferric oxyhydroxide, ferric citrate, and the rarely used aluminum-containing compounds).

TABLE

34.2 Selected Phosphate Binders

Product	Trade Names	Dose (mg) per Tablet	Elemental Calcium	Maximum Dose per Day	Comments
Calcium carbonate	(Generic, multiple names)	Multiple doses	40% elemental calcium	1.5 g of elemental calcium/d	Administered with meals as a binder; on an empty stomach as a supplement
	TUMS	500 mg	200 mg/tab	As above (7 tablets)	
	TUMS EX	750 mg	300 mg/tab	As above (5 tablets)	
	TUMS Ultra	1,000 mg	400 mg/tab	As above (3 tablets)	
	TUMS 500	1,250 mg	500 mg/tab	As above (3 tablets)	
	Os-Cal 500	1,250 mg	500 mg/tab	As above (3 tablets)	
	Os-Cal + D	1,250 mg	500 mg/tab	As above (3 tablets)	200 IU of vitamin D/tab
	Caltrate	600 mg	240 mg/tab	As above (6 tablets)	
Calcium acetate	PhosLo	667 mg	169 mg of elemental calcium/tab	As above (9 tablets)	More expensive than calcium carbonate. Prescription medication
Magnesium carbonate with calcium carbonate	MagneBind	200:200 mg $MgCO_3$ with 400 mg $CaCO_3$	160 mg/tab	Dose limited by serum Mg levels and diarrhea	85 mg of elemental magnesium/tab. Dialysate magnesium concentrations should be adjusted.
Magnesium carbonate with calcium carbonate	MagneBind	300:300 mg $MgCO_3$ with 250 mg $CaCO_3$	100 mg/tab	Dose limited by serum Mg levels and diarrhea	85 mg of elemental magnesium/tab. Dialysate magnesium concentrations should be adjusted.
Magnesium carbonate + calcium acetate	OsvaRen	435 mg of $MgCO_3$ and 235 mg of Ca acetate	60 mg/tab		Reduction of calcium load; Mg may have anticalcification properties; not available in the United States
Lanthanum carbonate	Fosrenol	250- and 500-mg tablets	0	1,250 mg t.i.d. Higher doses have not been tested long term.	Significantly more expensive than other products. Must be chewed
Sevelamer carbonate	Renvela	400- and 800-mg tablets and powder	0	Has been tested to 14 g/d in normal individuals. Dose may be limited by side effects of GI discomfort.	Significantly more expensive than other products
Sucroferric oxyhydroxide (PA21)	Velphoro	500 mg	0	3 g/d	Designed to minimize iron absorption from this iron-containing binder
Ferric citrate (JTT-751)	Not yet assigned	210-mg ferric iron	0	2.5 g/d ferric iron	210 mg elemental iron per tablet as 1 g ferric citrate. Associated with a significant increase in serum iron markers

GI, gastrointestinal; t.i.d., three times per day; IU, international units.

1. **Phosphate binder equivalent dose (PBED).** The dose of various phosphate binders that achieves an equivalent phosphate-binding capacity of 1 g of calcium carbonate is called the phosphate binder equivalent dose or PBED (Daugirdas, 2011). This allows comparison of dosages in patients taking different binders or multiple binders. In US patients undergoing dialysis with minimal residual kidney function, PBED averages 5.4 g/d (Kapoian, 2019). The average required PBED is somewhat less—around 4 g/d—in smaller patients, those with substantial residual renal function, and women, who tend to eat fewer phosphate-rich foods such as meats. This means patients typically would need 5 g/d of calcium carbonate to control their serum phosphate (Table 34.3).

TABLE 34.3 Dosages of Selected Phosphate Binders Required to Reach a Phosphate Binder Equivalent Dose (PBED) of 5.0 g/d

Phosphate Binder	Unit Dose Size (mg)	Phosphate Binder Equivalent Dose of One Tablet to 1-g Ca Carbonate	Approximate Number of Tablets to Reach PBED of 5 g/d	Gram of Calcium in a 5-g PBED Dose
Calcium carbonate	750	0.75	7	2.1
Calcium acetate	667	0.67	8	1.3
OsvaRen (Mg carbonate + Ca acetate)	435/235[a]	0.75	7	0.4
Lanthanum	500[b]	1.0	5	0
Sevelamer carbonate	800	0.7	8	0
Sucroferric oxyhydroxide (Velphoro)	500	1.4	3-4	0
Ferric citrate	210	0.60	8	0

[a]Each tablet contains 435-mg Mg carbonate and 235-mg Ca acetate. OsvaRen is not available in the United States.
[b]Tablets are sold by weight of lanthanum and not of lanthanum carbonate.
See https://www.ureakinetics.org/calculators/pbed.html

2. **Calcium load associated with calcium-based binders.** Calcium acetate, on a gram-per-gram basis, binds roughly an equivalent amount of phosphate as calcium carbonate, but contains only 25% calcium by weight (as compared to 40% in calcium carbonate). Attempting to manage the phosphate of a typical anuric patient solely with 5 g of calcium carbonate would result in the administration of 2.0 g (0.4 × 5.0) of elemental calcium per day. However, 5 g of calcium acetate provides only 1.25 g (0.25 × 5.0) of elemental calcium. Despite this, rates of hypercalcemia do not appear to differ between these binders.

   Although the 2017 KDIGO guidelines have removed the prior recommendation to limit elemental calcium to 1.5 g/day, there remain concerns that a net positive calcium balance is associated with worse survival (Palmer, 2016).

   For this reason, noncalcium-based binders are preferred. Of the patients who are managed with calcium-containing phosphate binders, many are treated with additional, noncalcium binders to decrease the calcium load. Another strategy to reduce calcium exposure is to use binders that combine calcium carbonate or calcium acetate with magnesium carbonate.

   Conversely, patients may derive a bone-specific benefit from increased calcium intake. Compared with patients who used noncalcium-based binders, patients who used calcium-based binders were retrospectively observed to have a lower risk of osteoporosis as measured by dual-energy x-ray absorptiometry (DEXA) (Hashimoto, 2021).

3. **Dosing relative to meals.** Phosphate binders are most effective when they are ingested with meals and when the number of binder pills is adjusted for the phosphate load of the meal. Some of the binders require the ingestion of multiple pills, and a high pill burden can reduce adherence. Reducing the number of pills by making them larger can make swallowing them more difficult. This has been addressed partially by making some binders chewable or by manufacturing them as

a powder that can be sprinkled over food.

IV. SELECTED PHOSPHATE BINDERS

A. Calcium-containing compounds. These agents are often used in the initial management of hyperphosphatemia due to their effective phosphate binding and low cost. They are also useful when some degree of calcium supplementation is desired. However, long-term use can be associated with vascular calcification, hypercalcemia, and increased mortality. Dialysate calcium concentration should be limited to 2.5 mEq/L (1.25 mM) to avoid a positive calcium balance during dialysis. The coadministration of calcium with active vitamin D preparations further predisposes patients to hypercalcemia, which would be an indication for changing the patient to a noncalcium-based binder.

1. **Calcium carbonate** (40% elemental calcium by weight) is available in a variety of preparations and dose sizes, including TUMS (200 mg of elemental calcium in the standard 500 mg tablet formulation), Caltrate (240 mg of elemental calcium/tab), and Os-Cal 500 (500 mg of elemental calcium/tab). Some tablets are chewed and others are swallowed. It best dissociates in an acidic environment, and consequently, its efficacy may be mitigated by medications such as proton pump inhibitors. A reasonable starting dose is 1 to 2 tablets with each meal. However, at full phosphate-binding doses (5 g of calcium carbonate or 2.0 g of elemental calcium per day), patients remain at high risk for excessive calcium loading. This binder has the benefit of easy accessibility and low cost. Common side effects include hypercalcemia, constipation, and nausea.
2. **Calcium acetate** (PhosLo, 25% elemental calcium by weight) is available in 667 mg tablets (169 mg of elemental calcium), and the recommended initial dose is two tablets with each meal. Upward titration may be necessary every 2 to 3 weeks to establish adequate phosphate control, with a typical required dose of two to three tablets per meal (5 g/d, which provides 1.3 g elemental calcium). Side effects include hypercalcemia, nausea, and constipation.
3. **Magnesium/calcium binders.** These include MagneBind (magnesium carbonate plus calcium carbonate), which is sometimes given off-label in the United States, and OsvaRen (magnesium carbonate plus calcium acetate), which has been approved for use in patients undergoing dialysis in Europe. As shown in Table 34.3, a 5-g/d PBED of OsvaRen would be associated with a daily elemental calcium load of only about 0.4 g/d. The risk of hypermagnesemia is small.

B. Sevelamer is an anion-exchange resin that comes in two forms, sevelamer carbonate (Renvela) and sevelamer hydrochloride (Renagel). Both trap phosphate in the bowel through ion exchange (of either bicarbonate or chloride, respectively) and hydrogen binding. Despite their anion exchange properties, the acid-base status of the patient is minimally affected. Both are available in a generic form; however, sevelamer carbonate is less expensive and most widely used. This drug is available in 800 mg tablets and 800 or 2,400 mg granule packets and should be started at 800 to 1,600 mg 3 times per day with meals. It can be titrated upward to a maximum of 14 g (17 tablets) per day to achieve phosphate control, though this involves a significant pill load and financial burden. Typical dose for phosphate control is 8 tablets per day. It is recommended to give other drugs 1 hour before or 3 hours after sevelamer administration. Sevelamer

may also have multiple, off-target anti-inflammatory effects (including lowering low-density lipoprotein [LDL], C-reactive protein, FGF-23, and possibly decreasing vascular calcification); however, data are mixed, and survival benefit has not been demonstrated (Sekar, 2018). The main side effects of sevelamer are nausea, dyspepsia, and diarrhea or constipation.

C. **Lanthanum carbonate** (Fosrenol) is a trivalent cation that binds phosphate ionically. It is available in 500, 750, and 1,000 mg tablets that must be thoroughly chewed or crushed. Because these tablets are relatively hard, the 1,000 mg tablet is best avoided. It should be used with caution in patients with poor dentition. They are also manufactured in 750 and 1,000 mg packets, though these may not be widely available. A reasonable starting dose is 500 mg 3 times per day with upward titration as needed, but not to exceed 1,250 mg 3 times per day. Only 2.5 g (five 500 mg tablets) are required to reach a PBED of 5, resulting in a relatively low pill burden. Very little lanthanum is absorbed, and to date there has been no evidence of toxic accumulation or adverse effects on bone metabolism (Hutchison, 2016). Its main side effects, similar to other phosphate binders, are GI-related and include nausea, vomiting, abdominal pain, and diarrhea.

D. **Sucroferric oxyhydroxide (SFO or Velphoro)** is an iron-containing phosphate binder. It shows comparable phosphate control to sevelamer in clinical trials, but the mean daily pill burden is 3 to 4 for SFO vs. 8 to 10 for sevelamer (Floege, 2014). It comes as a 500-mg chewable tablet; the starting dose is 1.5 g/d (1 tablet per meal, 3 tablets per day) with a maximum dose of 4 g (8 tablets) per day. In contrast to ferric citrate, which is another iron-based phosphate binder described below, SFO has only minimal oral iron absorption. Potential side effects include nausea, diarrhea, and black stool.

E. **Ferric citrate (Auryxia)** is an iron-based phosphate binder. In clinical trials, it has comparable phosphate control to sevelamer and calcium acetate with similar pill burden. Ferric citrate comes as a 210-mg tablet; the starting dose is 420 mg (2 tablets) per meal and can be titrated to its maximum dose of 12 tablets per day (2.5 g ferric iron per day). Patients treated with ferric citrate demonstrate significant improvement in serum iron measures (transferrin saturation, ferritin), with approximately 50% reduction in median weekly intravenous (IV) iron dose and approximately 25% reduction in median weekly ESA dose compared to patients on sevelamer or calcium acetate binders (Lewis, 2015). It should not be used in patients with iron overload and should be stopped if iron overload develops (TSAT > 50%-70%). Side effects include nausea and constipation.

F. **Aluminum carbonate and aluminum hydroxide.** These agents should no longer be used chronically and are rarely, if ever, used acutely for hyperphosphatemia. Co-ingestion with citrate (Shohl solution, calcium citrate, fruit juices, Alka-Seltzer) greatly enhances aluminum absorption and can lead to acute aluminum neurotoxicity.

G. **Use of more than one phosphate binder.** Combining a calcium-based binder with a noncalcium binder can be advantageous due to cost savings or the desire to supplement calcium. Combinations of two noncalcium binders have been reported and generally lead to slightly better phosphate control, though usually at the expense of higher pill burden (Molony, 2020). More complicated binder regimens increase nonadherence and therefore are better avoided. An aid to calculating the phosphate binder equivalent does with multiple binder regimens can be found at www.ureakinetics.org/calculators/pbed.html.

V. CONTROL OF SERUM CALCIUM.

Serum calcium circulates in a free (ionized) state and a protein-bound state. The ionized state is the biologically active form and is tightly regulated by PTH. The amount bound to protein varies in proportion to the concentration of albumin present. Total calcium reported on standard lab tests reflects the combination of both of these forms. Thus, in states of hypoalbuminemia, total calcium falls while ionized calcium may be unaffected. In these cases, *corrected calcium* can be used to predict ionized calcium and is calculated as follows:

Corrected calcium (in mg/dL) = total calcium + [0.8 × (4.0 − albumin [in g/dL])].
Corrected calcium (in mmol/L) = total calcium + [0.02 × (40 − albumin [in g/L])].

The normal range for total serum calcium is 8.4 to 10.2 mg/dL (2.10-2.55 mmol/L). The normal range for ionized calcium varies based on assay, but is typically 4.5 to 5.1 mg/dL (1.1-1.3 mmol/L) or 4.8 to 5.6 mg/dL (1.2-1.4 mmol/L). In new patients undergoing dialysis, due to low calcitriol levels, corrected and ionized calcium concentrations are usually slightly low or low-normal.

Use of corrected calcium in patients undergoing dialysis has been shown to be no more accurate than total calcium in predicting whether ionized calcium is high, normal, or low (Gauci, 2008; Yamaguchi, 2020). Therefore, use of uncorrected total calcium is recommended, with measurement of ionized calcium if the result could change management.

A. Hypercalcemia.

The 2017 KDIGO guidelines recommend avoiding hypercalcemia in all stages of CKD due to the risk for increased mortality and nonfatal cardiovascular events. Hypercalcemia may develop iatrogenically in the setting of excessive calcium intake, vitamin D receptor agonists, adynamic bone disease, or use of a high calcium bath. Investigation of ingested calcium should include dietary calcium, antacids, and phosphate binders; treatment is withdrawal of the offending agent. There are four case reports of hypercalcemia from the calcium-based cation-exchange potassium-binder patiromer (Rodriguez-Rojas, 2022). Endogenously, hypercalcemia may occur from tertiary hyperparathyroidism or from non-PTH-dependent causes (eg, sarcoidosis, malignancy).

B. Hypocalcemia.

Low serum calcium levels may be due to poor gastrointestinal absorption of calcium due to vitamin D deficiency, direct tissue deposition from severe hyperphosphatemia, use of a calcimimetic agent (cinacalcet or etelcalcetide), or use of an inappropriately low calcium dialysis solution. In addition to addressing the underlying etiology, daily oral calcium supplementation may be appropriate. Patients post parathyroidectomy often have high supplemental calcium requirements (more below).

C. Dialysate calcium concentration.

Dialysate calcium should be 2.5 mEq/L (or 1.25 mmol/L; equivalent to 5.0 mg/dL) for most patients on chronic hemodialysis. Because this is equal to a normal ionized calcium level, it will usually maintain a neutral calcium balance. Cautious use of a lower calcium bath (eg, 2.25 or 2.0 mEq/L) can be used to control chronically high serum calcium or to stimulate PTH secretion in patients with chronically low PTH. Use of these lower calcium baths can exacerbate hyperparathyroidism and lead to bone demineralization. Lower calcium baths increase QTc dispersion and are associated with an increased risk of sudden death; therefore, their use is generally discouraged.

Peritoneal dialysis fluid calcium concentration should be 2.5 mEq/L (1.25 mmol/L)

in most patients. A 3.5-mEq/L (1.75 mmol/L) dialysate is available, but should be reserved for patients with chronically low calcium that the clinician has determined warrants therapy. Higher dialysate calcium concentration can create a chronically positive calcium balance, suppress PTH, cause adynamic bone disease, and contribute to vascular and tissue calcification.

VI. CORRECTING 25(OH)D DEFICIENCY.

The liver synthesizes 25(OH)D (25-hydroxycholecalciferol) from cholecalciferol. The 25(OH)D levels reflect vitamin D stores. Without supplementation, most patients undergoing dialysis will have low 25(OH)D levels, in part due to inadequate dietary intake from the dairy restriction that accompanies a low phosphate diet. The primary and possibly sole reason for normalizing this level in patients with CKD is to prevent osteomalacia. Although treatment with vitamin D in early CKD will usually increase endogenous calcitriol levels, treatment in patients undergoing dialysis has not led to changes in PTH, serum calcium, or exogenous calcitriol use (Miskulin, 2016).

Deficiency of vitamin D can be treated with cholecalciferol (vitamin D_3) or ergocalciferol (vitamin D_2). Cholecalciferol is the endogenous, animal-based precursor to 25(OH)D; although it is not an FDA-approved pharmaceutical, it is widely available as a food supplement. Ergocalciferol, which is available as a prescription drug, is a plant-based sterol with a structure similar to cholecalciferol; it can be 25-hydroxylated to yield a biologically active compound similar to 25(OH)D. Most (but not all) assays of serum 25(OH)D levels detect both the 25(OH)D2 and 25(OH)D3 compounds. Studies show that cholecalciferol is more efficacious at raising 25(OH)D levels than ergocalciferol (Balachandar, 2021).

The goal of treatment is to replete and then maintain adequate stores. Given the fat-soluble nature of this vitamin, continued therapy—rather than a specific repletion dose—is more effective for long-term control. Either compound (D2 or D3) can be given as small daily doses or as larger weekly or monthly doses.

Levels of 25(OH)D less than 30 ng/mL (75 nmol/L) warrant repletion. In these patients, 50,000 international units (IU) weekly (or 4,000 IU daily) can be given for 2 to 3 months, depending on the magnitude of the deficiency and the size of the patient. Patients who are obese typically require higher doses. To maintain stores, 800 to 2,000 IU per day or 50,000 IU per month is sufficient and safe. Toxicity is rare and occurs at serum 25(OH)D levels greater than 120 ng/mL (300 nmol/L).

VII. PTH LEVELS

A. PTH assays.

PTH is an 84-amino-acid peptide hormone that activates a signaling cascade via the PTH1 receptor present on a variety of tissues. The N-terminal portion of the peptide is **essential** for binding and receptor activation, while large portions of the C-terminal are not. Fragments of PTH are rapidly cleared by the kidney and accumulate in renal failure. Most fragments cannot activate the PTH1 receptor owing to loss of portions of the N-terminus; however, these fragments were usually detected by single-antibody radioimmunoassays employed in the 1980s.

The so-called intact PTH (iPTH) assays use two separate antibodies to identify “intact” PTH molecules: these assays include a “capture” antibody that reacts to the mid-region of the molecule and a “detection” antibody that binds near the biologically active N-terminus. Use of such “intact” PTH assays greatly diminishes, but does not

eliminate, interference of PTH fragments. There are numerous commercial iPTH assays available, and the contribution of inactive PTH fragments to the total PTH measurement varies greatly. Consequently, in patients undergoing dialysis, different assays can lead to discrepant iPTH results (Cavalier, 2012; Souberbielle, 2006). This large interassay variability complicates interpretation of PTH in a single patient among different settings (such as a hospital test vs a dialysis center test).

B. PTH target range. The purpose of controlling PTH levels is 3-fold: (1) to limit parathyroid gland hyperplasia, (2) to prevent high values leading to severe osteitis fibrosa, while (3) avoiding oversuppression leading to adynamic bone disease. Poorly controlled hyperparathyroidism and consequent bone disease can lead to fractures, contribute to tissue calcification, and increase cardiovascular mortality. Medical management of hyperparathyroidism can improve these comorbidities, as well as reduce the need for surgical parathyroidectomy.

The 2017 KDIGO bone guidelines recognize the lack of sufficient outcome trials to make firm recommendations on the management of hyperparathyroidism. In patients with CKD not on dialysis, guidelines recommend avoiding routine use of active vitamin D compounds, except for patients with severe hyperparathyroidism. In patients undergoing dialysis, they recommend the use of vitamin D compounds and calcimimetics as PTH-lowering therapy. Typically, the goal is to maintain a stable PTH level over time, generally in the range of 2 to 9 times the upper limit of normal (for most assays, this is ~150 to 600 pg/mL [16-64 pmol/L]), while avoiding hypercalcemia and hypocalcemia.

Patients undergoing chronic dialysis should not have an iPTH maintained below 150 pg/mL (16 pmol/L), as there is a high likelihood of inducing adynamic bone disease. Persistently low PTH values are more likely with overuse of active vitamin D, calcimimetics, calcium-based phosphate binders, and use of high calcium dialysate (eg, ≥3.0 mEq/L [1.5 mM]).

In an individual patient, PTH in a given range does not always correlate with the expected bone disease. Adynamic bone disease has been found in patients with PTH values above the target range, osteitis fibrosa is not uncommon in patients with PTH levels maintained in the target range (although its severity is usually mild), and osteomalacia is due to vitamin D deficiency and has little correlation with PTH. Clinical events (eg, fractures, hypercalcemia) that do not correlate with the results of repeated PTH measures warrant further evaluation.

C. Serum bone-specific and total alkaline phosphatase. Alkaline phosphatase is produced in multiple organs, predominantly the bones and liver. Bone-specific alkaline phosphatase becomes elevated in the setting of increased bone turnover in uncontrolled hyperparathyroidism (osteitis fibrosa); however, routine measurement is cost prohibitive. Total serum alkaline phosphatase can be used as a surrogate marker, with caution in patients with liver disease. In settings of uncertainty, a hepatic etiology of elevated alkaline phosphatase can be elucidated by concomitant measurement of γ-glutamyl transferase (GGT), which is elevated in biliary processes. The 2017 KDIGO guidelines recommend monitoring serum alkaline phosphate levels at least annually.

D. Methods of lowering or raising serum PTH. As discussed in the opening pages of this chapter, the reasons for hyperparathyroidism in CKD are (1) low 1,25D levels (1,25D suppresses the parathyroid gland), (2) low serum calcium, and (3) high serum

phosphate. Accordingly, PTH can be lowered by activating the vitamin D receptor, raising the serum calcium (or activating the CaSR by other means), and reducing serum phosphate. Raising the serum calcium to the upper limit of the normal range, once popular, is no longer recommended for fear of precipitating or worsening vascular calcification.

If the serum PTH is below the desired level, reducing the dose of PTH-suppressing drugs (such as vitamin D receptor activators or calcimimetics) or lowering the serum calcium slightly (eg, by lowering dialysis solution calcium or avoiding calcium-containing phosphate binders) can be expected to increase PTH levels.

E. Vitamin D receptor activators. Active vitamin D (calcitriol) and vitamin D receptor agonists (see Table 34.4) suppress serum PTH in a dose-dependent fashion: the higher the pretreatment PTH, the larger the dose required to suppress PTH into the desired range. Dose adjustments of active vitamin D products for PTH control are based on subsequent PTH determinations, which initially should be performed up to monthly to establish control, then reassessed quarterly. If hypercalcemia (calcium >10.2 mg/dL [2.55 mmol/L]) develops (and persists despite discontinuation of calcium supplementation), the dose should be decreased by 30% to 50%, or held until the hypercalcemia resolves and then restarted at a lower dose. Because these drugs can increase gut absorption of phosphate, they should be given cautiously to patients with hyperphosphatemia and preferably only after elevated serum phosphate levels have been somewhat controlled.

TABLE 34.4 Characteristics of Commonly Used Vitamin D Analogues

Medication	Trade Name	Route	Dosing Information	Comments
Calcitriol	Rocaltrol	PO	Starting dose: 0.25 mcg daily or 0.5 mcg 3 times per week Dose range: 0.25-2 mcg daily Available in 0.25- and 0.5-mcg tablets	Monitor calcium and phosphorus at least monthly.
	Calcijex	IV	0.02 mcg/kg (or 1-2 mcg) given 3 times weekly Titrate by 0.5-1 mcg every 2-4 wk.	
Doxercalciferol	Hectorol	PO	Starting dose: 2.5-5.0 mcg 3 times per week Titrate by 2.5 mcg q8 wk. Available in 2.5-mcg tablets	A vitamin D prohormone that is metabolized in the liver to active $1,25(OH)_2$ vitamin D_2. Oral administration in patients on dialysis is more hypercalcemic and hyperphosphatemic than IV administration.
	Hectorol	IV	Starting dose: 2.5-5.0 mcg 3 times per week Titrate by 1-2 mcg q8 wk.	
Paricalcitol	Zemplar	PO	Dosing: 1-2 mcg daily or 2-4 mcg on a thrice-weekly regimen. Titrate by 1-mcg increments on the daily schedule or by 2 mcg on the thrice-weekly schedule.	Causes minimal alterations in calcium and phosphorus, comparable to placebo
	Zemplar	IV	0.04-0.1 mcg/kg or give the dose in mcg equal to biPTH/40 or iPTH/80 3 times per week Titrate by 30%-50% at 4-wk intervals.	The IV preparation can also be administered on a once-weekly regimen based on the cumulative weekly dose.

biPTH, bio-intact parathyroid hormone; iPTH, intact parathyroid hormone; IV, intravenous; mcg, micrograms; PO, orally.

For patients on in-center hemodialysis, these medications are usually given thrice weekly during each dialysis session. This directly observed therapy improves adherence. For patients on home dialysis modalities, these drugs can be given daily or thrice weekly.

1. **Calcitriol** (Calcijex; Rocaltrol) or 1,25(OH)2D3 is a synthetic form of the natural compound with the same name. The dose is typically started as low as 0.25 mcg or as high as 2 mcg 3 times per week (depending on the starting PTH, calcium, and phosphate) and titrated to achieve the desired PTH goal, while avoiding hypercalcemia. It can be administered either IV or orally (PO), with a 1:1 dose conversion. This drug is usually the least expensive formulation of the active vitamin D compounds.
2. **Paricalcitol** (Zemplar) or 19-Nor-1,25(OH)2D2 is a vitamin D analogue that has a lower incidence of hypercalcemia and hyperphosphatemia in animal studies. In humans, however, the evidence of superiority over calcitriol is limited. Equivalent PTH control has been achieved with low rates of hypercalcemia and hyperphosphatemia with both drugs (Coyne, 2014; Thadhani, 2020). The IV and PO formulations are dosed differently. Recommended initial IV dosing is weight based and ranges from 0.04 to 0.10 mcg/kg IV thrice weekly. Recommended thrice-weekly oral dosing is based on the starting PTH level and can be calculated by dividing the PTH (in pg/mL) by 80. The dose can be titrated every 2 to 4 weeks.
3. **Doxercalciferol** (Hectorol) or 1α(OH)D2 is a vitamin D prohormone, similar in structure to ergocalciferol with an added 1α hydroxylation, which is metabolized by the liver to active 1,25(OH)2D2. Initial dosing is 4 mcg intravenously (or 10 mcg orally) 3 times per week with each hemodialysis treatment and can be titrated in 1 to 2.5 mcg increments every 8 weeks to a maximum of 18 mcg IV (or 20 mcg orally). Lower daily doses administered orally are reasonable for patients undergoing peritoneal dialysis. PTH control and rates of hypercalcemia and hyperphosphatemia appear to be similar to the other vitamin D analogues (Park, 2014).

F. Calcimimetics are synthetic peptides that bind to the calcium-sensing receptor on the parathyroid gland, making it more responsive to the ambient ionized calcium. This results in decreased release of PTH and—in contrast to active vitamin D products—a marked decrease in serum calcium with a slight decrease in serum phosphate. These drugs are best used in patients with a high serum calcium level as a bridge to parathyroidectomy (or in patients who are not surgical candidates) and typically after active vitamin D compounds have been maximized.

1. **Cinacalcet** (Sensipar) is a pill available in 30, 60, and 90 mg. Maximal PTH suppression of 60% to 80% occurs 2 to 4 hours after each dose, and 30% to 50% suppression at 24 hours is typically observed. Serum PTH should be measured 12 to 24 hours after a dose. The initial dose of cinacalcet should be 30 mg daily regardless of serum PTH and should not be initiated if the calcium is less than 8.4 mg/dL (2.1 mmol/L). The dose should be increased by 30-mg increments to a maximum of 180 mg/d, based on monthly or quarterly PTH results, provided the corrected calcium remains greater than 7.8 mg/dL (1.95 mmol/L).

   A fall in serum calcium accompanies PTH suppression, and hypocalcemia of

less than 7.5 mg/dL (1.87 mmol/L) occurs in about 5% of patients. In this case, the cinacalcet dose should be decreased or a calcium supplement should be provided.

Nausea and vomiting are common dose-limiting side effects. Thus, these drugs are frequently administered thrice weekly with dialysis to increase adherence. However, this dosing strategy may be suboptimal due to the short pharmacodynamic PTH response to cinacalcet.

A large outcomes trial of cinacalcet versus placebo (with all patients eligible for continued conventional therapy) achieved substantial PTH control (median PTH about 300 vs 700 pg/mL [32 vs 74 pmol/L] at 6 months) and lower serum calcium levels (median calcium 9.1 vs 9.9 mg/dL; 2.27 vs 2.47 mmol/L). However, cinacalcet did not reduce cardiovascular events or deaths (EVOLVE Trial Investigators, 2012). Cinacalcet use in pretransplant patients often portends continued need posttransplant and may be associated with increased need for posttransplant parathyroidectomy (Wang, 2023). Transplant candidates with PTH greater than 1,000 ng/mL may be better managed with parathyroidectomy than intensive use of calcimimetics and vitamin D receptor activators.

2. **Etelcalcetide** (Parsabiv) is an IV calcimimetic agent. Compared to cinacalcet, it appears to have more potent PTH suppression, a longer half-life, and improved adherence due to directly observed therapy. However, etelcalcetide also carries a higher risk of hypocalcemia, as well as a higher cost (Palmer, 2020; Wetmore, 2020). Both drugs have high rates (~10%-30%) of nausea and vomiting. Unlike vitamin D receptor activators, etelcalcetide decreases levels of FGF23. This drug is administered intravenously thrice weekly after dialysis, with a starting dose of 5 mcg, and titrated by 2.5 to 5 mcg every 4 weeks to a maximum of 15 mcg thrice weekly.

VIII. PARATHYROIDECTOMY.

Surgical parathyroidectomy continues to be beneficial and necessary in patients with hyperparathyroidism that is unable to be medically controlled. After parathyroidectomy, patients undergoing dialysis should have marked improvement in their bone density and hypercalcemia, hyperphosphatemia, and tissue calcification. Parathyroidectomy has been associated with increased survival by 15% to 57% and improved quality of life (Lau, 2018). These benefits (specifically bone mineral density) may be attenuated if the parathyroidectomy is performed post transplant. Parathyroidectomy rates are higher among patients who are younger, have been dialysis dependent longer, and are receiving peritoneal dialysis (Danese, 2022).

A. Indications.

Failure of high-dose active vitamin D and calcimimetic therapy to improve findings of hyperparathyroidism suggests the presence of parathyroid gland hyperplasia with loss of calcium-sensing and vitamin D receptors. Hypercalcemia, uncontrolled bone disease, and calciphylaxis in the setting of a very high PTH (frequently >1,000 pg/mL [106 pmol/L]) are common scenarios in which patients benefit from parathyroidectomy. Indications are listed in Table 34.5.

TABLE 34.5 Interactions for Parathyroidectomy

1. Severe progressive symptomatic osteitis fibrosa (skeletal pain and/or fractures) despite adequate medical management, including serum phosphorus control and calcitriol therapy

2. Very high levels of PTH plus any of the following:
- Persistent hypercalcemia if other causes have been excluded
- Severe intractable pruritus
- Persistent severe soft-tissue calcification despite attempts to control the serum phosphorus level
- Idiopathic disseminated skin necrosis (calciphylaxis)
- Incapacitating arthritis, periarthritis, and spontaneous tendon ruptures

PTH, parathyroid hormone.

B. Surgical strategy. Parathyroid surgery is a complex endeavor and requires an experienced surgeon. Parathyroid gland localization—an already difficult task—can be further complicated by aberrantly located glands or by an atypical number of glands (may range from 3 to 6). Surgical options include (1) total parathyroid resection with autotransplantation of a small portion into a surgically accessible area (eg, the forearm) or (2) subtotal parathyroidectomy, which involves resection of all but part of one gland (eg, 3.5 glands, typically). Both procedures carry the risk of removing too much or too little tissue, resulting in either permanent hypoparathyroidism or recurrent (vs persistent) hyperparathyroidism, respectively; the latter occurs in roughly one-third of patients and may require additional surgery (Wetmore, 2016). Autotransplantation has the advantage of facilitating an easier and safer repeat surgery; however, it increases the risk of postsurgical of hypoparathyroidism (Lau, 2018).

C. Chemical ablation. Percutaneous injection of ethanol or calcitriol under ultrasound guidance into the parathyroid glands of patients with severe hyperparathyroidism has been shown to cause regression of the glands and decreased PTH secretion. It may be advantageous for those who are poor surgical candidates. However, this procedure is not routinely performed in most hospitals and is rarely used in the United States.

D. Postoperative management. Immediately after a parathyroidectomy done for severe hyperparathyroidism, profound hypocalcemia can develop; this is called hungry bone syndrome and tends to occur in approximately 25% of patients undergoing dialysis post parathyroidectomy (Lau, 2018). The more severe the underlying osteitis fibrosa, the more severe the postparathyroidectomy hypocalcemia. The mainstay of management is oral calcium; most patients will require 2 to 6 g of elemental calcium per day (this translates into, eg, 10-30 TUMS per day). Calcium should be administered in split doses between meals to enhance absorption. When calcium intake is this high, the majority of intestinal absorption occurs paracellularly; however, concomitant calcitriol administration may enhance the small transcellular component. Some patients may require additional IV calcium in the immediate postoperative period. After stabilization on oral supplementation, calcium should initially be monitored weekly as an outpatient. The target total calcium level is in the low-normal range; excursions above 9.0 mg/dL should prompt a reduction in oral calcium intake. Most patients will experience transient resolution of hyperphosphatemia after parathyroidectomy due to phosphate uptake into bone. However, as bone healing subsides, hyperphosphatemia will recur. At that time, oral calcium can be moved to mealtime as a binder, or a noncalcium-based binder can be started.

IX. CALCIPHYLAXIS.

Calciphylaxis (also known as calcific uremic arteriolopathy) is a rare and unusual disorder of microvascular calcification and occlusion leading to necrotic soft-tissue lesions. It is seen predominately in patients undergoing dialysis, although it can also

occur in CKD and rarely in acute kidney injury. In the United States, calciphylaxis is observed in 35 patients per 10,000 annually (Nigwekar, 2016). Early signs and symptoms include livedo reticularis and extremely painful, indurated, red nodules that progress to ulcerative and necrotic lesions. Typical survival is less than 1 year (usually due to wound-related sepsis), and quality of life is greatly compromised by pain and limited mobility (Nigwekar, 2018). Risk factors include diabetes, obesity, female sex, dialysis dependency for more than 2 years, peritoneal dialysis, elevated calcium and phosphate levels, and warfarin use (or other vitamin K deficiency, eg, malabsorption) (Nigwekar, 2016). Warfarin increases the risk of calciphylaxis 3- to 13-fold, and use is present in 40% to 50% of patients with the disease undergoing dialysis (Nigwekar, 2018).

A high index of suspicion is necessary to identify the disease as early as possible. The differential diagnosis includes vasculitis, warfarin-associated skin necrosis, cryoglobulinemia, calcinosis cutis, and panniculitis. Skin biopsies are the gold standard for diagnosis and show characteristic arteriolar calcifications in the medial layer. Imaging usually does not play a role; however, when a biopsy is inconclusive, lacy net-like calcifications on plain films or heterogeneous radiotracer uptake on nuclear bone scan can be suggestive (Nigwekar, 2018; Paul, 2017).

Once the diagnosis is made, calcium-containing supplements (including phosphate binders) and vitamin D compounds should be discontinued. Aggressive phosphate control should be pursued with dialysis intensification, dietary modification, and the use of noncalcium-based phosphate binders. Patients undergoing peritoneal dialysis should be switched to hemodialysis. Warfarin should be discontinued whenever possible. Parathyroidectomy, previously common in calciphylaxis management, is now being questioned (Nigwekar and Sprague, 2016).

Sodium thiosulfate (STS), a vasodilator that also prevents adipocyte-mediated vascular calcification (Chen, 2014), is currently the mainstay of therapy, though data are limited. STS has been retrospectively observed to completely resolve the lesions in a quarter of patients and to improve the process in an additional half (Nigwekar, 2013). However, a more recent meta-analysis of 19 retrospective studies—which included 422 patients with CKD experiencing calciphylaxis—showed neither STS-associated improvement in skin lesions nor a survival benefit (Wen, 2023). A multicenter, randomized, double-blind, placebo-controlled trial is ongoing. The typical dose is 25 g IV 3 times per week, administered in the final 30 to 60 minutes of dialysis. Limited alternative treatments are available; one small case series (N = 34) of hyperbaric oxygen use showed wound improvement in half of the patients, with complete wound healing in one-third (An, 2015). Wound care is critically important in ulcerative lesions, and surgical debridement may be necessary.

X. ADDITIONAL THERAPIES FOR BONE DISEASE

A. Bisphosphonates. Bisphosphonates decrease bone resorption by binding to bone and inhibiting osteoclasts. Although these agents are typically first-line therapy in osteoporosis, because they are cleared by the kidney, there remain safety concerns in patients undergoing dialysis for drug accumulation and toxicity. Furthermore, the induced reduction in bone turnover in this population may be deleterious, creating a form of adynamic bone disease.

B. RANKL inhibitor, denosumab (Prolia). This is a monoclonal antibody against

RANKL, a mediator of osteoclast differentiation and activity. Thus, denosumab has similar osteoclast inhibition as bisphosphonates and can have similar downstream effects on bone. This drug is administered every 6 months as a subcutaneous injection. Unlike bisphosphonates, a lapse in administration can result in rapid reversal of bone density improvement (Reid and Billington, 2022). Denosumab is not cleared by the kidneys, and it appears to be safe to use in patients undergoing dialysis, as supported by a post hoc analysis of the FREEDOM trial (Simonini, 2024). The main side effect tends to be hypocalcemia (potentiated in patients undergoing dialysis and accompanied by an increased PTH); this can be managed with calcium supplements, increased calcitriol, or a high calcium dialysate bath (Khairallah and Nickolas, 2018). Notably, the hypocalcemic effect of denosumab can be used intentionally in cases of malignancy-induced hypercalcemia.

C. Synthetic forms of PTH. At present, there are two forms of FDA-approved synthetic PTH: teriparatide (Forteo) and abaloparatide (Tymlos). Teriparatide is synthetic human PTH and abaloparatide mimics PTH-related peptide (PTHrP), both for the first 34 amino acids. In contrast to the two antiresorptive agents above, these drugs are anabolic agents that have the potential to build new bone. Both are administered as a daily subcutaneous injection for up to 2 years, and both result in similar, marked increases in bone density (Reid and Billington, 2022). These drugs are not cleared by the kidney. Data for use in patients undergoing dialysis are limited; however, small studies have shown beneficial results without increased adverse events in patients undergoing dialysis (including in a patient with adynamic bone disease) (Khairallah and Nickolas, 2018). Side effects include transient hypotension and hypercalcemia; the risk of hypercalcemia is lower with abaloparatide.

D. Anti-sclerostin antibody, romosozumab (Evenity). This drug, FDA approved in 2019, is the most recent addition to osteoporosis treatment. By blocking sclerostin, it prohibits Wnt signaling, which simultaneously decreases bone resorption and promotes bone formation. Studies thus far show robust improvements in bone density, exceeding the drugs mentioned previously (Reid and Billington, 2022). It is administered as a monthly subcutaneous injection. Case reports show potential safety in patients undergoing dialysis. However, until further safety analyses are performed, it does carry a black box warning for increased risk of myocardial infarction, stroke, and cardiovascular death, thus potentially limiting its use in a large portion of patients undergoing dialysis.

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35 Dialysis in Infants and Children

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The choice of dialysis treatment for infants and children is broad and includes the full range of therapies used in adult patients. There are indications and complications of the dialysis procedure that are unique to children, and there are important technical and anatomic considerations. Chronic care of children undergoing dialysis is complex and requires attention to growth and cognitive development, age-appropriate nutritional interventions, consequences of metabolic disorders, and psychosocial adaptation to achieve the goal of comprehensive rehabilitation.

I. ACUTE DIALYSIS

A. Definition of acute kidney injury (AKI) in children.

AKI is a common condition that affects about one-third of children who are hospitalized and is linked to higher rates of morbidity and mortality in both critically ill and noncritically ill pediatric populations. The ability to accurately identify AKI is therefore crucial in pediatric inpatients to obtain a good renal outcome.

The concept of AKI for the pediatric population has evolved with the introduction of the definition of pRIFLE (pediatric Risk, Injury, Failure, Loss, and End-stage kidney disease), an adaptation of the global AKI definitions released by AKIN (the Acute Kidney Injury Network) and by KDIGO (Kidney Disease: Improving Global Outcomes) (Table 35.1). pRIFLE classifies AKI based on decreased estimated glomerular filtration rate (eGFR), increased serum creatinine, and/or decreased urine output. When recent serum creatinine measurements and glomerular filtration rate (GFR) estimates from the previous 3 months are not available, a previously normal GFR of 100 mL/min/1.73 m^2 can be assumed (Table 35.2). The pRIFLE classification is more sensitive than AKIN in identifying mild cases of AKI in children from 1 month of age (Table 35.1).

TABLE 35.1 Definition and Criteria for AKI Stages: AKIN/KDIGO Versus Pediatric RIFLE (pRIFLE) Classification

	pRIFLE	AKIN/KDIGO	Urine Output
Stage 1 or Risk	eGFR decreased by ≥25% or 50%-99% serum creatinine rise from baseline with 7 d	Increase in creatinine by >50%-99% from baseline (based on previous blood test) within 7 d or ≥0.3 mg/dL to ≥ 26 mcmol/L increase within 48 h	<0.5 mL/kg/h for more than 8 h
Stage 2 or Injury	eGFR decreased by ≥50% or 100%-199% serum creatinine rise from baseline within 7 d	Increase of creatinine of >100%-199% from baseline within 7 d	<0.5 mL/kg/h for more than 16 h
Stage	eGFR decreased by 75%	Increase of creatinine of ≥200% from baseline	<0.3 mL/kg/h for more

3 or Failure	or eGFR <35 mL/min/1.73 m^2 or ≥200% serum creatinine rise from baseline within 7 d	within 7 d or Any requirement for renal replacement therapy	than 24 h or anuria for 12 h

AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; RIFLE, risk, injury, failure, loss, and end-stage kidney disease.

Thomas et al. (2014)—eGFR is estimated using the revised Schwartz equation.

TABLE 35.2 Schwartz Bedside Equation for GFR Estimation in Children

Revised Schwartz equation
GFR (mL/min/1.73 m^2) = 0.413 × (length or height) (cm)/serum creatinine (mg/dL) or = 36.5 × (length or height) (cm)/serum creatinine (mcmol/L)

GFR, glomerular filtration rate.

B. Acute dialysis indications. The indications for acute renal replacement therapy in pediatrics are like those in adults, which can be remembered using the mnemonic, AEIOUT:

A. Acidosis (pH < 7.2) which cannot be safely corrected with sodium bicarbonate administration because of the risk of sodium or volume overload

E. Electrolytes. Hyperkalemia (*K* > 6.5 mmol/L) with electrocardiographic abnormalities

I. Ingestions of drugs and toxins

Inborn error of metabolism with severe organic acidemia or hyperammonemia

O. Overload of fluid. Volume overload with congestive heart failure, pulmonary edema, or severe hypertension not manageable with diuretics or conservative measures: fluid overload greater than 20% body weight in the setting of critical illness is an independent indication for dialysis.

Oliguric acute renal failure where optimal nutritional and medical support will require fluid and/or electrolyte removal

U. Uremia. Progressively rising blood urea nitrogen (BUN) level in a situation where recovery is not anticipated and uremic consequences are likely

Uremic encephalopathy (symptomatic) with particular attention to seizures

Uremic pericarditis

T. Tumor lysis syndrome or severe hyperuricemia complicating chemotherapy for malignancy

Toxin ingestion. Guidelines for extracorporeal therapy for poisoning are provided in Chapter 18.

C. Choice of acute dialysis modality. The choice of dialysis modality in children with AKI is determined based on the patient's characteristics, the goals of the dialysis, the level of local expertise, and the availability of the necessary equipment.

1. **Acute peritoneal dialysis (PD)** allows gradual, continuous removal of solute and water through diffusion and ultrafiltration. PD is most frequently chosen in infants and is even successfully performed in low-weight infants (from 1.5 to 1.8 kg body weight) where extracorporeal dialysis meets anatomic barriers. The method

has several advantages and does not require sophisticated equipment or technical expertise. Continuous PD provides efficient clearance in small children. As an added benefit, PD eliminates the need for anticoagulation and vascular access maintenance, which are required for other methods. In neonates postcardiac bypass surgery, the initiation of PD has been shown to be more effective than passive fluid drainage and diuretics. However, the difficulty to precisely predict and achieve ultrafiltration rates is a drawback of PD in the AKI setting.

2. **Intermittent hemodialysis (IHD)** is preferentially used in hemodynamically stable patients. It is a highly effective technique to achieve solute removal by clearance and fluid removal by ultrafiltration. IHD is the preferred choice in children suffering from acute life-threatening electrolyte abnormalities (eg, hyperkalemia), drug toxicity, tumor lysis syndrome, and hyperammonemia. However, the feasibility of performing IHD is limited in neonates and infants because of the required large extracorporeal blood volumes that may cause cardiovascular instability.
3. **Continuous kidney replacement therapy (CKRT)** has been utilized in pediatric patients ranging from preterm infants to older adolescents, and is especially useful for critically ill patients. Continuous procedures (hemofiltration, hemodialysis, and hemodiafiltration) allow for a more uniform rate of fluid removal that engenders less hemodynamic stress. Devices with high balance accuracy for precise control of fluid removal and the option of using low blood flow rates are available that allow the use of continuous extracorporeal procedures even in premature newborns. CKRT permits better phosphate clearance than IHD or PD and is thus frequently employed for tumor lysis syndromes. However, maintaining vascular access with adequate flow in small vessels can be problematic and is often the limiting factor in children (Table 35.3).

TABLE 35.3 Overview of Indications and Contraindications for Acute Peritoneal Dialysis (PD), Intermittent Hemodialysis (IHD) and Continuous Kidney Replacement Therapy (CKRT) in the Pediatric Population

	Indications	Contraindications	Relative Contraindications

PD	• Overhydration
	• Hemodynamic instability
	• Electrolyte imbalance
	  • Hyperphosphatemia
	  • Hyponatremia
	  • Hyperkalemia
	• Metabolic acidosis
	• Need for a gentle detoxification
		• Abdominal wall defects
		  • Omphalocele
		  • Gastroschisis
		  • Bladder exstrophy
		  • Diaphragmatic hernia
		• Major contemporary abdominal surgery
		• Intra-abdominal adhesions
			• Freshly operated abdomen
			• Ileus/pancreatitis
			• Ureterostomy, pyelostomy, or loop ileostomy
			• Rapid detoxification
			  • Severe hyperammonemia
			  • Severe hyperphosphatemia
			  • Severe hyperkalemia
			• Dialysate leakage with risk of peritonitis may limit acute PD.

IHD	• Acute kidney failure in hemodynamically stable patients (with/without hypervolemia and oligo-anuria) • Diuretic-resistant volume overload • Uremia • Therapy-refractory electrolyte imbalance	• No central venous access • Incompatibility to treatment component • Technical and	

	(hyperkalemia)
	• Metabolic crises in inborn errors of metabolism (hyperammonemia, maple syrup urine disease)
	• Intoxications with dialyzable exogenous and/or endogenous toxins
	  • Rhabdomyolysis
	  • Ethylene glycol, etc
	  • Other dialyzable toxins
	• Drug overdose
	• Gadolinium or x-ray contrast media exposure of patients with reduced GFR
		personnel requirements

CKRT	• Acute kidney failure in hemodynamically unstable patients with hypervolemia, oliguria/anuria • Diuretic-resistant volume overload • Uremia • Patient with catabolic metabolism and high fluid requirements (parenteral nutrition, postoperative, high blood product requirements) • Electrolyte and/or acid-base imbalance that cannot otherwise compensate • Multiple organ failure • Contraindications for PD (abdominal surgery and wall defects) • Neonatal metabolic crises in inborn errors of metabolism (hyperammonemia, maple syrup urine disease, methylmalonic acidemia, and propionic acidemia)	• No central venous access • Technical and personnel requirements

D. Peritoneal dialysis (PD).

1. **Catheter choice and configuration.** Surgically placed permanent tunneled catheters (eg, flexible double-cuff Tenckhoff; Figure 35.1) should be used in AKI whenever possible. Alternatively, temporary PD catheters can be placed at the bedside using the Seldinger technique. However, temporary catheters have a high failure rate (due to obstruction and leakage) and can usually only be used for a few days. In very-low-weight premature neonates who are too small for the placement of a regular PD catheter, an angiocatheter or a multipurpose drainage catheter (eg, Mac-Loc Locking Multipurpose Drainage Catheter, Cook Medical, Bloomington, IN) can be used.

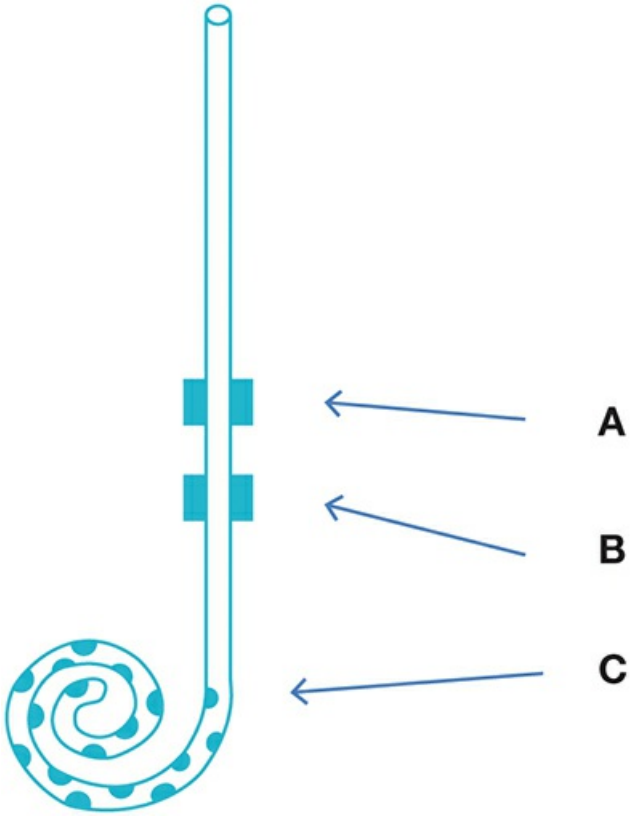


FIGURE 35.1: Flexible double-cuff Tenckhoff catheter showing the outer (A) and inner (B) cuffs and the coiled tip (C).

The length of the peritoneal catheter should be chosen according to the patient's body size. The catheter cuffs can be placed and attached with silicone glue at the desired position on the catheter. The distance between the inner cuff and the coil end should equal the umbilicus-symphysis distance minus 2 cm (Figure 35.2). The desired positions of the inner cuff, outer cuff, and skin outlet should be marked preoperatively on the skin.

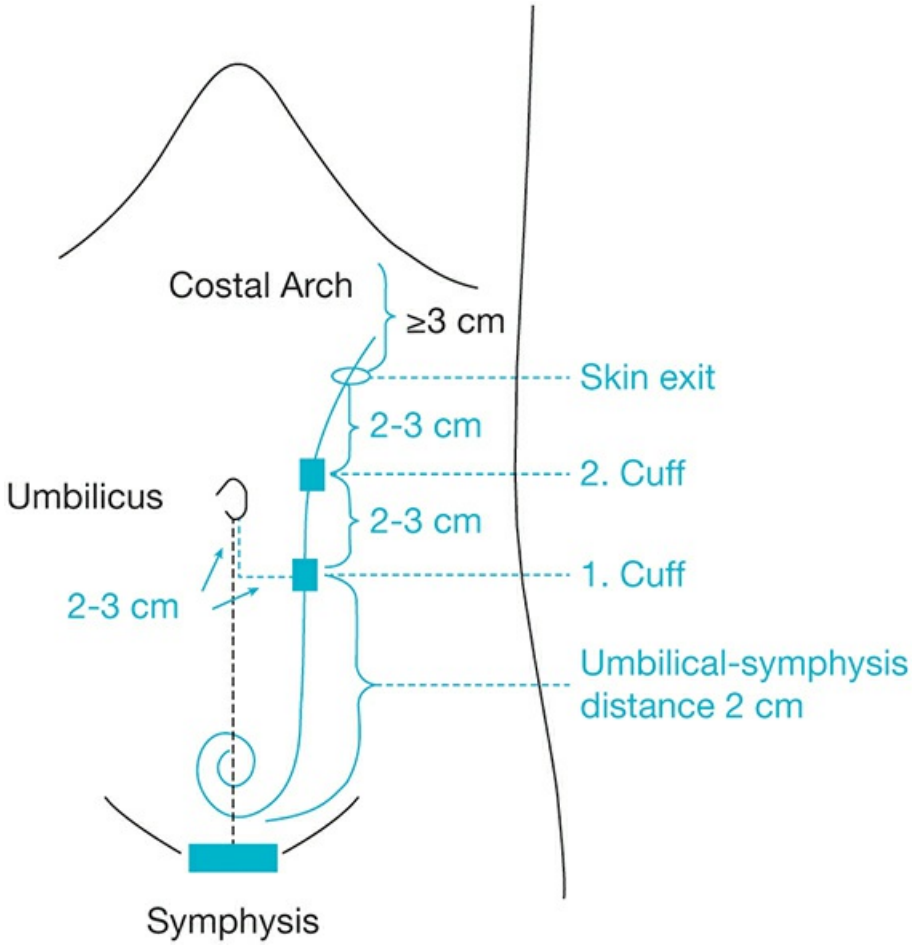


FIGURE 35.2: Schema showing the manner in which the catheter insertion site and deep cuff location are determined in order to achieve a proper pelvic position of the catheter tip. As shown, the distance between the inner cuff and the coiled portion of the catheter should be equal to the distance from the umbilicus to the pubic symphysis minus 2 cm.

a. **Measurements**
   1. Distance from symphysis to the umbilicus (required for positioning of the inner cuff).
   2. Distance from symphysis to costal arch (to make sure that the distances between the outer cuff, skin exit, and ribcage are not too short).
      The catheter at the exit site should point laterally.

b. **Positioning the cuffs on the catheter**
   1. **Distance from coiled end to inner cuff.** umbilicus to symphysis distance minus 2 cm
   2. **Distance from inner cuff to outer cuff.** 2 to 3 cm
   3. **Distance from outer cuff to skin exit.** at least 3 cm
   4. **Distance from skin exit to costal arch.** at least 3 cm

2. **Catheter placement.** The catheter can be inserted depending on local procedural expertise either by percutaneous placement or by surgery (laparoscopy or laparotomy). Surgical implantation is considered the gold standard for PD catheter placement in children, although percutaneous placement is an alternative and may be

the only option when surgery is not available. In young male infants, the inguinal canals should be ligated to prevent tracking of dialysis fluid into the scrotum. Partial omentectomy should be performed in children 3 years of age and older. The subcutaneous path to the catheter outlet is created by tunneling. To prevent cuff protrusion and infection, the catheter outlet should be at least 2 cm from the outer cuff. The catheter exit should be placed as remotely as possible from feeding gastrostomy tubes and colostomies and out of the diaper area.

A test exchange with 20 mL/kg body weight fill volume should be performed intraoperatively to ensure that no fluid is leaking out. The catheter should be secured at the exit site with a transparent nonocclusive dressing. Perioperative antibiotic prophylaxis with a first-generation cephalosporin should be administered during and for 48 hours after surgery. Bed rest for 3 to 5 days is recommended to allow undisturbed wound healing and to avoid strain on the catheter. Postoperative pain must be treated assiduously with analgesics to avoid intraperitoneal pressure peaks.

Dialysis treatment can be started immediately after surgery if required for AKI, although it is preferable to start dialysis only after the catheter has completely healed (2 weeks after placement; Table 35.4).

TABLE 35.4 Typical Complications in Children Undergoing Acute or Chronic Peritoneal Dialysis

Peritoneal Dialysis Complications

	Problem	Solution
Surgical	• Hydrothorax (dialysate leakage) • Hernia	• Surgical correction • 12- to 24-h dialysis break if possible
	• Bleeding after catheter insertion	• Surgical revision
	• Perforation of gut	• Discontinue PD • Antibiotic treatment • Switch to CKRT if possible
Infective	• Peritonitis • Exit-site infections	• Calculated antibiotic treatment
Mechanical	• Catheter malfunction	Sonographic and/or radiologic check of catheter position • Constipation? → Enema • Fibrin in dialysate? → Heparin 200-400 IU/L • Surgical revision

	• Leakage of peritoneal fluid at exit site	• Early leakage (<72 h after placement):
		  • 12- to 24-h dialysis break if possible
		  • Fibrin glue
		If unsuccessful:
		• Surgical revision
		• Late leakage (>72 h after placement):
		  • Surgical revision

Biochemical	Electrolyte imbalance • Hyponatremia • Hypotension	• Oral or intravenous administration of electrolytes • Modify ultrafiltration/increase fluid intake.
	Protein loss	• Increase dietary protein intake.
Metabolic	• Hyperglycemia/diabetes	• Choose the correct peritoneal solution. • Treatment with insulin

CKRT, continuous kidney replacement therapy; PD, peritoneal dialysis.

3. PD: prescription and administration. The PD prescription in critically ill

neonates and infants is based on continuous frequent exchanges with low dialysate volume. The initial fill volume should be 300 mL/m^2 body surface area or 10 mL/kg body weight. Larger fluid loads may provoke leakage and compromise respiration due to pressure on the diaphragm.

With such small fill volumes, solute equilibration and glucose absorption occur rapidly, necessitating frequent exchanges with initial dwell times of 45 to 60 minutes if ultrafiltration is needed, using at least 2.3% dialysate dextrose concentration. Exchange volumes can be gradually increased, and the dwell times expanded after the initial healing phase, usually in the second week after catheter placement.

For fill volumes less than 100 mL, exchanges are performed using a closed-circuit dialysis system with an in-line sterile graduated cylinder to which the dialysis fluid bags, the patient catheter, and a drainage line for effluent dialysate are attached. Equipment examples include the Dialy-Nate system/Gesco Dialy-Nate (Utah Medical Products, Midvale, Utah, USA) or the PD-Paed Plus (Fresenius Medical Care, Bad Homburg, Germany). Both the desired inflow volume and the effluent dialysate can be quantitated precisely in the burette, and the process is repeated without opening the system. This allows one to perform closed-circuit, low-volume, manual continuous PD in infants and neonates. When larger fill volumes are applied and inflow and outflow are problem-free, automated peritoneal dialysis (APD) using a cycler device can be utilized to limit nursing effort.

Heparin (200-500 IU/L) may be added to the dialysate to avoid or reverse the formation of fibrin exudates.

It is important to note that anuric neonates and infants with large ultrafiltration volumes may require sodium supplementation because substantial amounts of sodium (>100 mmol/L) are lost with the ultrafiltrate (Table 35.5).

TABLE 35.5 Dialysis Prescription in Critically Ill Children

Dialysis Dosage	
Initial	• Inflow volume: 10 mL/kg (or 300 mL/m^2) • Dwell time: 60 min • PD fluid: Dextrose 2.3% To adjust the desired UF rate: optimize glucose concentration or dwell time. Note: Dwell time <45 min is usually not effective.
>5-7 d post-op	• Inflow volume can be increased by 10%-20% every 24 h up to 800 mL/m^2 in infants and 1,000 mL/m^2 in older children. Note: Volume should be increased according to intra-abdominal pressure.
Dialysis Management	
Perioperative antibacterial prophylaxis	• Cefazolin 20 mg/kg IV preoperatively and intraperitoneal for 48-h postcatheter implantation
Exchange volume	• Manual exchange: always initially • Cycler: when PD stable and from >100 mL of effluent volume
Protein flakes	• Heparin 200-500 IU/L dialysate
Postoperative	• At least 3 d bed rest
Monitoring	

Documentation	Documentation of dialysis therapy plan (dwell time, dialysate concentration, UF per cycle, cumulative values, etc) Documentation of fluid intake
Laboratory	Check laboratory parameters daily (arterial blood gases, Hb, K, Na, Ca, urea, blood glucose, etc).
Weight	Weigh twice a day.

IV, intravenous; PD, peritoneal dialysis; UF, ultrafiltration.

a. PD fluids. Commercial biocompatible PD solutions should be used by default. Whenever available, biocompatible PD fluids (Baxter Physioneal, Fresenius Balance, or BicaVera) should be used in children to enhance the chance to preserve a viable peritoneum for their long expected lifetime.

E. Extracorporeal kidney replacement therapy

1. Vascular access. A large variety of temporary vascular catheters in different lengths and sizes are available for the pediatric population. The vascular access should allow a blood flow rate of 5 to 10 mL/kg per minute. Typically, acute hemodialysis (HD) access is accomplished using a nontunneled, uncuffed central venous catheter. In terms of location, as a first choice, the catheter should be implanted in the brachiocephalic (innominate vein) trunk via the internal jugular vein and preferably on the right side, as the course of that blood vessel is straight and in axial continuity with the superior vena cava. The left internal jugular vein would be the first choice for an alternative access route. Another option is the subclavian/axillary vein, but this blood vessel has a smaller caliber and there is greater risk of secondary complications (eg, pneumothorax). The femoral vein should be chosen only if there is no alternative because of the increased risk of bacterial infection; plus, there is an increased risk of iliac-femoral thrombosis, which could compromise the patient's suitability for transplantation.

For short-term hemodialysis, central venous catheters should have the tip located in the vena cava, while for long-term dialysis, the tip should be placed within the right atrium. For long-term dialysis, the catheter should be tunneled under the skin to avoid infections. Both temporary and permanent catheters are available.

In small infants and neonates, single-lumen catheters may be more appropriate considering vessel size. If the available dialysis device does not allow for operation in single-needle mode, placement of two single-lumen catheters is an option. In neonates, a catheter can be inserted into the vena cava through the umbilical vessel if the vessel is still patent. Most of these catheters can be left in place for several weeks (Table 35.6).

TABLE 35.6 Selection of Temporary Central Venous Catheter Sizes for Hemodialysis According to Patient Body Weight

Patient Weight (kg)	Catheter Options (Dual Lumen)
Neonate	6F or 7F (Gambro, Medcomp)
3-6 kg	7F (Medcomp)
6-30 kg	8F (Medtronic, Teleflex, Gambro)
>15 kg	9F (Medcomp)
>30 kg	10F-13F (Medtronic, Teleflex)

Please check manufacturers' specifications due to unforeseen changes.
Data from "Vascular Access" as suggested by PCRRT/ICONIC. Accessed April 11, 2024. https://www.pCRRT.com

2. Equipment

a. Dialysis devices. Several commercially available devices permit blood flow rates within ranges suitable for neonates and infants: These include the Baxter Prismaflex, the Asahi Plasauto Sigma, Baxter Aquarius, and the Fresenius MultiFiltrate. Carpediem (Medtronic), a miniaturized device specifically designed for use in neonates, has recently become available (Table 35.7).

TABLE 35.7 Main Characteristics of Commercially Available Monitors for Neonatal and Pediatric CKRT

Monitor	Neonatal Lines	Pediatric Lines	Total Extra-corporeal Volume (mL)	Blood Flow Range (mL/min)	Blood Flow Steps (mL/min)	Fluid Turn-over Range (mL/h)
Medtronic CARPEDIEM	Y	Y	27-42	2-50	1	10-300
Plasauto Sigma	Y	Y	70-87	1-400	1	10-12,000
Gambro Prismaflex	-	Y	60	20-100	2	50-2,500
Fresenius MultiFiltrate	-	Y	72	10-100	2	10-7,000
Baxter Aquarius	-	Y	82	10-200	2	50-11,000

CKRT, continuous kidney replacement therapy.
Prismaflex equipped with HF20 circuit, others with FX Paed.
Data from Nissenson AR and Fine RN. *Handbook of Dialysis Therapy.* 5th ed. Elsevier; 2017.

b. Blood lines. Use of infant or child tubing systems and small dialyzers is essential to reduce the extracorporeal blood volume, which should not exceed 10% of the blood volume, that is, 0.8% of the body weight.

If the extracorporeal (ie, tubing + filter) volume exceeds 10% of the blood volume, the extracorporeal system should be primed with blood or a 5 to 10% albumin solution.

Cooling of the blood circuit is a concern in infants; a **blood warmer** may be used in-line, although with some models this increases the circuit volume.

c. Dialysate and replacement solutions. The safest option is to use commercially available bicarbonate-based dialysate or replacement solutions. Errors associated with the local preparation of solutions in hospital pharmacies are well-documented and are no longer acceptable given the availability of standardized solutions, such as PrismaSol, PrismaSATE (Gambro Lundia AB, Lund, Sweden), Accusol (Baxter Healthcare, Deerfield, IL), Pureflow (NxStage Medical, Inc., Lawrence, MA), Normocarb (Dialysis Solutions Inc., Whitby, ON), or Hemosol B0 (Gambro Lundia AB, Lund, Sweden).

d. Dialyzers are available in a range of sizes suitable from small infants through older adolescents (Table 35.8).

TABLE 35.8 Selection of Filters Suitable for Pediatric Dialysis

Patients	Filter	Surface	Priming Volume	Membrane
Neonatal	Gambro-Lundia Miniflow 10	0.04 m^2	3.5 mL	AN69
	Minifilter Minntech	0.07 m^2	6 mL	Polysulfone
	Bellco CARPEDIEM 1	0.07 m^2	27.2 mL (circuit)	Polysulfone
	Bellco CARPEDIEM 3	0.2 m^2	41.5 mL (circuit)	Polysulfone
	Baxter Polyflux 2H Dialyzer	0.2 m^2	17 mL	Polyamide
	Fresenius FX Ped	0.2 m^2	18 mL	Helixone
	Gambro-Lundia HF 20	0.2 m^2	60 mL (circuit)	AN69
Pediatric	Nipro Sureflux-03L	0.3 m^2	22 mL	Polypropylene
	Nipro Sureflux-05L	0.5 m^2	35 mL	Polypropylene
	Baxter Polyflux 6H Dialyzer	0.6 m^2	52 mL	Polyamide
	Nipro Sureflux-07L	0.7 m^2	45 mL	Polypropylene
	Fresenius FX 40	0.6 m^2	32 mL	Helixone
	Fresenius Ultraflux AV 400 S	0.75 m^2	52 mL	Polysulfone
	Nipro Sureflux-07L	0.7 m^2	45 mL	Polypropylene
	Nipro Sureflux-09L	0.9 m^2	56 mL	Polypropylene
	Fresenius FX 50	1.0 m^2	53 mL	Helixone
	Baxter Evodial 1.0	1.05 m^2	66 mL	HeprAn—Polyurethane (Heparin-free HD)
	Nipro Sureflux-11L	1.1 m^2	68 mL	Polypropylene
	Baxter Evodial 1.3	1.3 m^2	83 mL	HeprAn—Polyurethane (Heparin-free HD)
	Fresenius FX 60	1.4 m^2	74 mL	Helixone
	Fresenius Ultraflux AV 600 S	1.4 m^2	100 mL	Polysulfone
	Baxter Evodial 1.65	1.65 m^2	100 mL	HeprAn—Polyurethane (Heparin-free HD)
	Fresenius Ultraflux AV 1000 S	1.8 m^2	130 mL	Polysulfone
	Fresenius FX 80	1.8 m^2	95 mL	Helixone

The filter surface area should approximately match the patient's body

surface area. Generally, polysulfone dialyzers are preferred due to their biocompatibility and lower anticoagulation requirements.

3. **Prescription**
   a. **The target blood flow rate** should be at least 100 mL/min/m^2 body surface area, corresponding to 3 mL/min/kg body weight, and if possible should be increased to 6 mL/min/kg. In IHD and continuous venovenous hemodialysis (CVVHD), dialysate flow should be 1.5 to 2 times the blood flow. In continuous venovenous hemofiltration (CVVH), filtration rate should equal 50% of the body weight per day (ie, 20 mL/kg/h).
   b. **Ultrafiltration.** Usually, a net fluid withdrawal of 10 to 15 mL/kg (ie, 1%-1.5% of body weight) per hour is well tolerated during extracorporeal treatment. However, this depends on several factors such as hemodynamic stability, blood pressure, intravascular filling/blood volume, and hemoconcentration. Ultrafiltration rates in infants and small children may be as low as 5 to 30 mL/h without replacement fluid (hemodialysis or slow continuous ultrafiltration [SCUF]) or as high as 100 to 600 mL/h with replacement fluid (CVVH); larger children can tolerate ultrafiltration and replacement rates near those of adults. Ultrafiltration is controlled by volumetric pump or automated weighing to avoid errors in replacement fluid, which, if compounded over days of therapy, could be substantial in a small patient with anuria.
4. **Anticoagulation.** Both heparin and citrate-based protocols for circuit anticoagulation are available for children. The use of regional citrate anticoagulation is increasingly preferred over heparin-based systemic anticoagulation for pediatric renal replacement therapy in children as it yields longer circuit running times at reduced complication rates. Citrate should always be used in patients with increased bleeding risks such as neonates or postoperative trauma patients (Table 35.9).

TABLE 35.9 Regional Citrate Anticoagulation: Initial Citrate and Calcium Flow Rate Setting

	Solutions	Initial Flow Rate
Citrate solutions	Trisodium citrate 4%[a] (138 mmol/L citrate)	Citrate flow rate (mL/h) = Blood flow (mL/min) × 1.7
	ACD-A solution[b] (113 mmol/L citrate)	Citrate flow rate (mL/h) = Blood flow (mL/min) × 2
Calcium solutions	Calcium chloride 5.5% (0.5 mmol calcium/mL)	Calcium flow rate (mL/h) = Blood flow (mL/min)/8
	Calcium gluconate[c] 10% (0.23 mmol calcium/mL)	Calcium flow rate (mL/h) = Blood flow (mL/min)/4

a Contains 40 g/L trisodium citrate.

b ACD-A: anticoagulant citrate dextrose solution A; contains 22 g/L trisodium citrate, 8 g/L citric acid, 24.5 g/L glucose.

c An advantage of using gluconate is the absence of chloride in the infusate.

Since the citrate infusion rate is scaled to circuit blood flow, which is relatively large in infants and small children, citrate accumulation may occur after prolonged therapy, resulting in “citrate lock” or persistently low ionized calcium levels despite calcium infusion. The combination of fixed-concentration bicarbonate-containing

replacement fluid and citrate anticoagulation may result in metabolic alkalosis after several days of therapy. In children with compromised hepatic function, metabolization of citrate to bicarbonate may be impaired, resulting in metabolic acidosis (Table 35.10).

TABLE 35.10 How to Adjust Citrate and Calcium Infusion Rates to Achieve Desired Extracorporeal and Patient Serum Ionized Calcium Levels

Measured extracorporeal serum ionized calcium	Suggested change in citrate infusion rate	Measured patient serum ionized calcium levels	Suggested change in calcium infusion rate
<0.2 mmol/L	↓ by 20%	<1.0 mmol/L	↑ by 20%
0.2-0.3 mmol/L[a]	**none**	**1.0-1.3 mmol/L[a]**	**none**
>0.3 mmol/L	↑ by 20%	>1.3 mmol/L	↓ by 20%

[a]These are the desired ionized calcium levels. No adjustment in citrate or calcium infusion rates required.

Doses for systemic heparin anticoagulation in infants are larger than those reported for adults, and monitoring the system by activated clotting times (ACTs) is recommended. A priming bolus of 20 to 50 IU/kg (300-1,000 IU/m^2) followed by a continuous infusion of 400 IU/m^2 is recommended. ACT should be targeted to 150 to 220 s with hourly monitoring (Table 35.11).

TABLE 35.11 Regional Citrate Anticoagulation: Procedures for Specific Complications

Problem	Sign	Cause	Solution
Citrate accumulation/intoxication	• Metabolic acidosis • Increasing anion gap • Decreasing Ca++, increasing quotient (total Ca/Ca++ >> 2.5) • Increasing lactate	• Liver failure • Poor muscle prefusion	Stop citrate temporarily, increase turnover/dialysate flow; if necessary, start HDF with predilution.
	• Metabolic alkalosis • Decreasing Ca++, increasing quotient (total Ca/Ca++)	• Overdose/reduction of blood flow without reduction of citrate perfusor	
Hypocalcemia	• Ca++ < 1.0 mmol/L	• Citrate accumulation • Increased loss • Hypocalcemia of the critically ill patient	Calcium substitution, target Ca++ 1.0 mmol/L
Metabolic alkalosis	• ↑pH • ↑HCO_3 (>35 mEq/L)	• Bicarbonate substitution too high relative to blood flow	Reduce bicarbonate concentration in dialysate.
		• Metabolization of citrate in liver	Adjust bicarbonate concentration in dialysate.
		• Overdose of citrate	Stop citrate temporarily, increase turnover/dialysate flow; if necessary, start HDF with predilution.
Metabolic acidosis	• ↓ pH • ↓ HCO_3	• Inability of the liver to metabolize citrate	See citrate intoxication.

		• Insufficient buffer in dialysate • Disease-related metabolic acidosis	Adjust bicarbonate concentration in dialysate.
Hypernatremia	• Accumulation with use of trisodium citrate solution	• Dialysate flow/UF rate too low	1. Increase dialysate flow. 2. Decrease sodium content in dialysate/adjust conductivity. 3. Predilution with G5 % (as HDF)

HDF, hemodiafiltration; UF, ultrafiltration.

II. CHRONIC DIALYSIS

A. Indications. Optimal management of chronic kidney disease (CKD) avoids or delays some of the historical indications for initiation of dialysis. Early dialysis initiation, for example, at eGFR greater than 10 mL/min/1.73 m^2, is not associated with better outcomes in children but expands the duration of their risk for dialysis and transplant-related complications. Hence, there is consensus that renal replacement therapy should not be initiated based on a specific eGFR threshold but rather, whenever symptomatic uremia or metabolic disturbances such as hyperkalemia, hyperphosphatemia, malnutrition, or growth failure occur that cannot be managed conservatively. Pediatric nephrologists must be able to spot the subtle signs of uremia, such as decreased energy (less vigorous play), resumption of napping, anorexia (with the absence of expected weight gain), inattention in school, or failure to meet anticipated developmental milestones, to determine when to start dialysis.

B. Chronic PD. PD is often the therapy of choice for pediatric patients since it offers several benefits as a chronic dialysis modality. It is technically simple and avoids the need for chronic vascular access (which is particularly difficult to achieve and maintain in infants and small children). Blood pressure and volume status may be better controlled with PD than with hemodialysis. Much less time is spent in the hospital and in the dialysis unit, with more time spent at school and engaged in other age-appropriate activities. Parents often feel they have greater control over their child's care when they perform PD. The risk of bacterial peritonitis as a critical technique complication has markedly decreased in recent years, thanks to advances in connection technology, and is now lower than the risk of catheter infections in children undergoing chronic hemodialysis.

Dialysis efficacy in terms of transperitoneal solute exchange appears to be as efficient in children as in adults. Since peritoneal surface area is correlated with body surface area, small children have a relatively large surface for solute exchange compared with adults, which makes PD an effective modality.

Peritoneal equilibration testing (PET) shows that very young children are more likely to fall into the category of high or high-average transporters whereas adolescents have PET results similar to those in adults. Enhanced glucose absorption will result in relatively rapid attainment of osmotic equilibrium between dialysate and plasma, limiting ultrafiltration during long dwells.

1. PD modalities. Automated forms of PD (APD) utilizing short dwells are almost universally used in children to accommodate the high-average peritoneal transport typically found in young infants and to improve treatment adherence in older children. The initial prescription is guided by transport characteristics determined by PET, typically ranging from four to eight exchanges per night with dwell times of 1

to 2 hours. Fill volumes are determined by patient comfort, but most children can tolerate 40 to 50 mL/kg or 800 to 1,100 mL/m^2 without discomfort or leakage once their catheter exit site is well healed. The choice of glucose concentration depends on ultrafiltration needs (fluid intake minus urine output and insensible losses). PD can be performed without a daytime dwell (nightly intermittent peritoneal dialysis [NIPD]), with a daytime dwell (continuous cycling peritoneal dialysis [CCPD]), or with a daytime dwell and midday exchange if needed for solute clearance or fluid removal. Use of a daytime dwell is recommended to improve phosphate and middle molecule clearance in patients without residual renal function. NIPD avoids the discomfort of having a full abdomen during daytime, but clearance will likely be adequate only in patients with high or high-average peritoneal transport characteristics or those with residual renal function. The day dwell of CCPD may allow shortening of the nightly treatments (this is often desirable in older children) or improved clearance for low and low-average transporters. High transporters usually absorb most of their long dwell if it is left in all day. This can be prevented using PD fluid containing the slowly resorbed oncotic agent icodextrin for the daytime dwell. The use of icodextrin may also avoid the feeling of permanent satiety that often accompanies continuous peritoneal glucose absorption during daytime. Tidal dialysis, an APD variant where several partially drained "tidal" dwells are incorporated into three to four completely drained main cycles, can make PD more comfortable in children with abdominal pain at the end of a drain. The original modality of continuous ambulatory peritoneal dialysis (CAPD) with four long manual exchanges within 24 hours has been largely abandoned in children.

2. **PD adequacy.** Dialysate and urine collections are required to assess the delivered dialysis dose at a given prescription. Collections are repeated whenever the prescription is changed and at regular intervals to assess changes in residual kidney function and peritoneal transport function. Outcome data to define adequate clearance in children are not available. A total (peritoneal and renal) weekly *Kt*/*V* urea of 1.8 has been recommended as a minimal target clearance. Total body water (TBW), that is, the distribution volume of urea, can be calculated using the Morgenstern equations that have been validated in children on chronic PD:

   For boys, TBW (L) = $0.10 \times (\text{height [cm]} \times \text{weight [kg]})^{0.68} - 0.37 \times \text{weight (kg)}$.

   For girls, TBW (L) = $0.14 \times (\text{height [cm]} \times \text{weight [kg]})^{0.64} - 0.35 \times \text{weight (kg)}$.

   These equations can be simplified, with slightly less precision, to the following:

   For boys, TBW (L) = $20.88 \times \text{body surface area } (m^2) - 4.29$.

   For girls, TBW (L) = $16.92 \times \text{body surface area } (m^2) - 1.81$.

   In practice, young children with PET-defined high or high-average permeability peritoneal membranes will almost always exceed the *Kt*/*V* target values, particularly if there is residual renal function. Older children with low-average permeability peritoneal membranes and without residual renal function often require a midday exchange to achieve acceptable clearances.

C. Chronic hemodialysis. Chronic hemodialysis is the appropriate modality for children with families not capable of providing reliable home care. Hemodialysis is the next step therapeutic option for children with PD technique failure due to abdominal

adhesions following severe peritonitis episodes, children failing to achieve adequate ultrafiltration due to high transporter status after long-term PD, and large adolescents with low-permeability peritoneal membranes who may not achieve adequate clearance on PD without a burdensome exchange schedule. Because hemodialysis treatments take children out of usual activities (school and play), a hemodialysis unit treating children must provide intensive nursing, tutoring, and play therapy during dialysis treatments.

1. **Setting and equipment**
   a. **Vascular access.** Vascular access remains a major limitation to the successful maintenance hemodialysis of small children. Placing and maintaining permanent accesses in small vessels requires experienced and dedicated surgeons and radiologists. Vascular catheters can be placed by interventional radiologists or surgeons, depending on the best experience available in an institution. A conservative strategy for permanent access is critical because of the lifelong need for renal replacement therapy. Some young adults leave pediatric dialysis units after many years of hemodialysis treatment, and one must ensure they have not depleted all options for long-term vascular access.
   b. **Fistulas and grafts.** An arteriovenous fistula between the radial artery and cephalic vein of the nondominant arm with an end-to-side anastomosis is a common mode of vascular access in children. Since fistulas save central veins and have much better long-term functional survival than central venous catheters, the "fistula-first" approach is strongly recommended in children. Depending on the surgeon's expertise, fistulas can be created from around 6 years of age or 20 kg of body weight. When blood vessel size is too small for constructing an adequate fistula, a polytetrafluoroethylene (Gore-Tex or Impra) graft can be placed between an extremity artery and vein. Children with myelomeningocele may prefer a graft placed in the thigh because of the absent sensation there if the vasculature is sufficiently developed to support that. Lower extremity grafts allow unimpeded play or schoolwork during dialysis treatments, but risk leg edema and hypertrophy.
   c. **Catheters.** Available double-lumen hemodialysis catheters range from 6F to 14F in caliber, with lengths appropriate for small children through older adolescents. Both temporary and permanent catheters are available, and precurved models for internal jugular cannulation are available in larger sizes (see Tables 35.6, 35.12, and 35.13).

TABLE 35.12 Commercially Available Short-Term Dual-Lumen Hemodialysis Catheters

Company	Catheter	Size (F)	Tip to Cuff Insertion Lengths (cm)	Tip Type
Gambro	Gamcath pediatric double lumen	6 8	7.5, 10, 12.5 10, 12.5, 15	Tapered
	Gamcath double lumen	11 12	15, 17.5, 20, 25	Tapered
Medcomp	Duo-flow side × side short-term hemodialysis catheter	9 11 12 14	9, 12, 15 12, 15, 20, 24 13, 15, 20, 24 13, 15, 20, 24 (tip-to-hub)	Tapered
	Soft-line short-term hemodialysis	7 9 11.5	7, 10, 12, 15, 20 (tip-to-hub)	Tapered
	Hemo-cath short-term hemodialysis catheter	8, 11.5 13.5	12, 15, 20, 24, 27 (tip-to-hub) 15, 20, 24, 28, 35	Tapered
Medtronic	Mahurkar curved extension dual-lumen catheter kits	8 10 11.5	12, 15, 19.5	Tapered
	Mahurkar straight extension dual-lumen catheter	10 11.5	12, 15 13,5, 16, 19.5, 24	Tapered
Teleflex	Arrow pediatric two-lumen hemodialysis catheter for high volume infusions	8, 9	11, 13	Staggered tip
	Arrow Arrowg+ard Blue hemodialysis catheterization kits[a]	12	15, 20, 25	Staggered tip
	Arrow Arrowg+ard Blue hemodialysis catheterization Kits[a]	15	15, 20, 25	V-tip

Please check the manufacturer's specification due to unforeseen changes.

[a]Coated.

Resource: Endovascular Today. Dialysis catheters. Accessed April 11, 2024. https://evtoday.com/device-guide/us/dialysis-catheters

TABLE 35.13 Commercially Available Long-Term Dual-Lumen Hemodialysis Catheters

Company	Catheter	Size (Fr)	Tip to Cuff Insertion Length (cm)	Tip Type
BD Interventional	GlidePath	7 10	15, 19, 23, 27, 31, 35 10, 12, 15, 19, 23	Symmetric
	HemoSplit	14.5	15, 19, 23, 27, 31, 35	Symmetric
Medcomp	Hemo-Cath	8	15, 18, 24, 28, 32	Step
	Long-term HD catheter	12.5	(tip-to-hub)	
	Split Cath long-term HD catheter	10 14 16	15, 18, 24, 28, 32, 36, 40, 55 (tip-to-hub)	Split

HD, hemodialysis.

Please check manufacturer's specification due to unforeseen changes.

Resource: Endovascular Today. Dialysis catheters. Accessed April 11, 2024. https://evtoday.com/device-guide/us/dialysis-catheters

d. Blood flow rate. Desired blood flow rate is targeted to urea clearance specifications for a chosen dialyzer. Smaller blood vessels cause higher venous resistance than in adults, which eventually limits flow, typically in the range of 50 to 150 mL/min in small children and 200 to 350 mL/min in older children. Small catheters often limit flow to 25 to 100 mL/min because of limited arterial inflow.

e. **Dialyzers.** A list of dialyzers that are appropriate for small patients is provided in Table 35.8.

f. **Blood lines.** Appropriately sized blood lines should be used to limit the extracorporeal circuit volume to 10% of blood volume.

g. **Dialysis machines.** Dialysis machines that provide volumetric ultrafiltration control are required. Small errors in ultrafiltration volume (of a few hundred milliliters) may cause symptomatic hypotension or chronic volume overload. Blood flows must be accurate within the range of 30 to 300 mL/min, and the blood pump calibrated to different size lines. Many available dialysis machines are not designed nor approved for use in young children.

h. **Dialysis solution.** Bicarbonate dialysis solution is standard for pediatric hemodialysis.

i. **Anticoagulation.** The strategy for heparin administration to infants and children is similar to that for adults. Clotting is infrequent when the ACT is prolonged to approximately 150% of the population baseline value. A "low-dose" heparin protocol can be used to prolong the clotting time to 125% of the population baseline value. The initial loading dosage is usually 10 to 20 units/kg, with higher dosages being used for infants and children weighing less than 15 kg. The initial maintenance heparin infusion rate (for the first 20-30 minutes) can be set at 0.3 to 0.5 units/kg/min, with further adjustments based on changes in the ACT. Low-molecular-weight heparin has been used in children receiving chronic hemodialysis. Heparin-induced thrombocytopenia occurs in children, and anticoagulation has been successful with danaparoid, hirudin, and argatroban, although published reports are few. In older children, heparin-free dialysis can be performed successfully. Different dialyzer membrane types have not been systematically compared with regard to clotting. Clotting will be more likely in smaller children, in whom the blood flow rate is usually low relative to the size of the dialyzer. Intermittent saline flushes of the dialysis circuit will result in excessive volume administration in small children unless removal of excess fluid by ultrafiltration is carried out simultaneously.

2. **Hemodialysis prescription.** Small patients require a cautious approach to avoid disequilibrium by limiting urea clearance to 3 mL/min per kg, which is calculated from the specifications of the chosen dialyzer and the blood flow attainable through the patient's access. Early treatments may be programmed even more slowly if the patient is very uremic; repeated short treatments are usually advisable during the initiation of hemodialysis when the serum urea nitrogen level is extremely elevated. Once a stable, chronic dialysis regimen is attained, higher efficiency in urea clearance is generally well tolerated. At this stage, intradialytic symptoms are more frequently related to fluid removal than to urea clearance. With conditioning and distraction, most children can tolerate hemodialysis sessions lasting 2 to 4 hours.

   a. **Kinetic modeling of hemodialysis.** Formal three-point urea kinetic modeling of hemodialysis has been performed in children, and results are useful in assessing the efficiency of the dialysis treatment as well as dietary protein intake (as a function of urea generation rate) during the interdialytic period. Recommended dietary protein intake in children is greater than that in adults, and the long-term effects of inadequate intake on growth and neurologic

development are of even greater concern. The slow-flow technique for blood sampling is important for accurate measurement, and the duration of slow flow is determined by the volume of the blood line from the needle or catheter to the sampling port. Pediatric blood lines can be adequately cleared by a slow-flow rate (60 mL/min) for 17 seconds; we predict infant lines will require 12 seconds at a slow-flow rate of 20 mL/min. The greater reliance on catheters in pediatric dialysis raises concern that recirculation will diminish treatment efficiency.

b. Adequacy of hemodialysis. When small patients receive efficient clearance (ie, relatively high *K*/*V*), there is a greater amount of postdialysis urea rebound with reequilibration of urea from either the intracellular space or relatively underperfused tissues. Thus, single-pool modeling overestimates the dose of dialysis and urea generation rate. The National Kidney Foundation's (NKF) Kidney Disease Outcome Quality Initiative (KDOQI) 2006 recommendation in adults is for a minimum delivered dialysis dose of a single-pool *Kt*/*V* = 1.2. The guidelines recommend using single-pool *Kt*/*V* to guide therapy, but to increase the minimum dose for smaller patients, including children. A minimum sp*Kt*/*V* value of 1.4 to 1.5 would seem to be appropriate for children, and in practice, such a minimum value is easily achievable. Equilibrated *Kt*/*V* is recommended by the European Best Practice Guidelines, and this can be derived from single-pool *Kt*/*V* and the rate of dialysis using the Tattersall equation described in Appendix C. Yet another approach is to extrapolate from a postdialysis sample taken 15 minutes after dialysis (Goldstein, 1999). Whether sp*Kt*/*V* or equilibrated *Kt*/*V* is used to target dose, it is prudent to err on the side of providing more therapy when treating this vulnerable population. Small children have a high surface area to TBW ratio, and alternative scaling of hemodialysis dose to body surface area would require even higher doses of *Kt*/*V*. Residual renal function can significantly impact the hemodialysis prescription, especially in very small patients. Regular measurements are needed to ensure overall treatment adequacy as the GFR falls. If patients are unable to perform urine collections, they should be assumed to have no residual GFR to avoid inadvertent underdialysis.

3. Complications of chronic hemodialysis

a. Disequilibrium and seizures. Infants and small children develop seizures as a manifestation of the disequilibrium syndrome more commonly than adults. For this reason, the blood flow rate and session length are usually limited for the first few treatments. Overly rapid urea removal is generally avoided by choosing an appropriately sized dialyzer and blood flow rate to provide 3 mL/min/kg urea clearance for the initial treatments; often, blood flows are limited by the caliber of the dialysis access. Other measures sometimes utilized to help prevent disequilibrium syndrome include keeping the dialysate sodium at or slightly above the plasma level and the prophylactic infusion of mannitol (0.5-1.0 g/kg body weight) during the hemodialysis session.

b. Hypotension. Intradialytic hypotension and cramping are common with fluid removal greater than 1% of body weight per hour or 5% in total, yet interdialytic weight gains can be large in children with anuria on largely liquid diets and in noncompliant adolescents, resulting in sustained interdialytic hypertension.

Infants and very young children are prone to precipitous falls in blood pressure with no warning and no ability to communicate distress. Blood volume monitoring systems, which allow continuous adjustment of the ultrafiltration rate to the dynamic changes of circulating blood volume, have proven highly efficient in preventing intradialytic hypotension. Also, isolated ultrafiltration or lower dialysate temperature may make fluid removal more tolerable. In highly fluid-sensitive children, repeated treatments may be the only way to remove fluid safely, and small children often require four or five treatments per week for fluid and blood pressure management.

c. **Hypothermia with isolated ultrafiltration.** If the circulated dialysis solution is not warmed, the extracorporeal blood circuit will act as a radiator, leading to cooling of the blood and the child. Body temperature should be monitored throughout dialysis, especially during isolated ultrafiltration.

III. CARE OF THE PEDIATRIC PATIENT WITH END-STAGE KIDNEY DISEASE (ESKD)

A. Nutrition. Comprehensive nutritional management is important for the achievement of growth and physical development. The recommended energy intakes for pediatric patients undergoing dialysis depend on their ages and should be the same as the estimated energy requirement for healthy children. For infants, the estimated energy requirement is approximately 100 kcal/kg/d. Such high intakes usually require supplementation, and enteral feeding via nasogastric or gastrostomy tubes is standard practice to avoid undernutrition and growth failure. In older children, obesity has become a greater concern and can adversely affect posttransplant outcomes; thus, nutrition counseling in this age group will be markedly different than in infants and toddlers.

Protein requirements for children depend on their age and are greater than those in adults. The daily recommended intake of protein for pediatric patients undergoing dialysis is the same as that for healthy children, with an additional allowance to account for the amino acids and protein lost during the dialysis process.

Supplementation of water-soluble vitamins is routine practice for children treated with chronic PD or hemodialysis. Fat-soluble vitamins should not be supplemented as clearance of vitamin A metabolites is impaired, risking hypervitaminosis A.

Fluid, sodium, phosphate, and potassium restrictions are usually required in pediatric patients, although usually less so in children undergoing PD. Potassium and phosphate binders are almost always required for adolescents, yet some infants receiving efficient dialysis will require supplementation. For patients undergoing hemodialysis, restrictions depend on the amount of residual urinary output but always require individual dietary guidance to optimize fluid, sodium, and potassium intake. Infants pose a particular challenge; daily fluid intake in an infant with anuria on hemodialysis should be limited to 600 to 700 mL/m^2, and formula should be concentrated and appropriately supplemented to achieve nutritional goals. Conversely, infants with polyuria, which is frequently observed with dysplastic kidneys even in ESKD, will require supplemental fluid and sodium to maintain volume status and permit growth. In infants with anuria on PD, ultrafiltration-related sodium losses must be compensated through supplements to avoid hyponatremia and dehydration.

Special infant formulas with reduced phosphate and potassium content are available. Oral hypersensitivity and food avoidance are common in infants and young children, and carefully timed solid food introduction with speech therapy is usually necessary.

B. Hypertension. Hypertension is a particular concern, given the accelerated rate of cardiovascular disease in children with CKD. Attention is directed to the maintenance of normal volume status and age-appropriate blood pressure. High blood pressure in children undergoing PD is usually the result of incorrect dialysate glucose concentrations chosen at home coupled with excessive sodium and fluid intake; it is usually managed with dietary counseling, parent education, and close monitoring of weight and blood pressure at home. In patients undergoing hemodialysis, hypertension may be the result of inadequate fluid removal during dialysis and nonadherence to sodium and fluid restrictions. In patients who remain hypertensive despite increased dialysis time, lowered dialysate temperature or isolated ultrafiltration may make volume removal more tolerable. Dietary and psychological counseling for the patient and family is advisable in cases of repeated nonadherence as this may reflect more serious difficulties in coping with the chronic disease process.

If a patient remains hypertensive despite apparent euvolemia, dry weight should be reassessed. Routine longitudinal monitoring of bioelectrical impedance along with weight and blood pressure can help uncover subclinical fluid overload. Pharmacologic antihypertensive therapy is often applied but of limited efficacy if fluid overload is the root cause of hypertension. Doses should be titrated to age-appropriate blood pressure targets and reassessed frequently. Since both white-coat and masked hypertension are common in children on dialysis, regular ambulatory blood pressure monitoring is indispensable in pediatric blood pressure management.

C. Anemia. Children undergoing hemodialysis tend to be anemic more often than adults and have lower hemoglobin at the initiation of dialysis. Children respond well to erythropoiesis-stimulating agents (ESAs); the indications, route of administration, and potential complications are similar for children and adults. Long-acting ESAs such as darbepoetin-alfa (administered every 7-14 days) and Mircera (administered every 28 days) have largely replaced short-acting α- and β-erythropoietin. The ESA dosage requirement per kilogram body weight is 2 to 3 times higher in young infants than in adolescents and adults.

Iron deficiency and frequent or persistent subclinical infections (eg, catheter-related or affecting the urinary tract) may adversely affect the ESA response, and nonadherence to home therapy is occasionally a problem. Another common cause of apparent ESA nonresponsiveness is due to unrecognized fluid overload causing dilutional anemia. Iron supplementation, either intravenous or oral, is usually necessary in pediatric patients with ESKD; blood loss in the hemodialysis circuit is an important cause of iron deficiency in very small patients, especially when more than three treatments per week are prescribed.

D. Growth. During the first 1 to 2 years of life, body growth primarily depends on adequate energy supply. Therefore, the introduction of enteral feeding techniques has contributed to much improved growth rates in infants requiring dialysis at this young age, where anorexia is very common. However, increasing energy intake above the estimated energy requirements will not usually be of benefit in patients with failing

growth despite adequate nutritional intake.

Inadequate dialysis may be one cause of reduced growth. When children dialyzed on a 3/week schedule were changed to a 6/week hemodiafiltration regimen, marked catch-up growth was noted (Fischbach, 2010). It was not clear if the benefit was due to more frequent extracorporeal treatment or to the effects of removal of larger-molecular-weight uremic toxins.

When growth rates are poor despite good nutrition, **recombinant human growth hormone (rhGH) therapy** should be initiated. rhGH treatment increases growth rates in children receiving chronic dialysis, although not as effectively as in children with nondialysis CKD. The usual dosage is 0.05 mg/kg/d or 30 IU/m^2/wk as a nightly subcutaneous injection. In children on hemodialysis with compromised adherence to home therapy, in-center thrice weekly administration of the same weekly dose is an acceptable alternative. Apart from accelerating longitudinal growth, rhGH also induces a welcome gain of lean body mass and is lipolytic. Use of hemodiafiltration has been suggested to increase the effectiveness of rhGH on increasing growth (Paglialonga, 2023).

rhGH is generally very well tolerated; slipping of capital femoral epiphyses may occur in patients with poorly controlled bone disease. Benign intracranial hypertension is another complication that occurs at an increased frequency (~1%) in patients undergoing dialysis on rhGH treatment. Growth hormone therapy is often paused at the time of renal transplantation, and growth velocity is reassessed with a functioning allograft. Glucocorticoid minimization or withdrawal is integral to successful growth after transplant.

E. Acidosis. Metabolic acidosis is common in children with ESKD and is more problematic in those receiving hemodialysis than those treated with PD. Chronic acidosis may impair growth by affecting bone mineralization through the growth hormone/insulin-like growth factor-1 axis, as well as exerting a catabolic effect on lean body mass. Some pediatric patients benefit from oral sodium bicarbonate or sodium citrate therapy or higher dialysate bicarbonate concentrations to maintain a serum bicarbonate concentration greater than or equal to 22 mmol/L.

F. Renal osteodystrophy. Renal osteodystrophy can rapidly develop in children undergoing dialysis treatment but can be ameliorated by good control of serum calcium, phosphate, bicarbonate, intact parathyroid hormone, and alkaline phosphatase levels. Calcitriol and vitamin D analogues are used to treat hyperparathyroidism and associated bone disease. Cinacalcet is used as second-line treatment in children, but there is little guidance regarding dosing or outcomes in the youngest patients. Hyperphosphatemia should be controlled by dietary manipulation and by oral administration of phosphate binders to an age-appropriate serum phosphate level. Phosphate intake is targeted at or below the daily recommended intake for age, with greater restriction in patients with hyperphosphatemia or hyperparathyroidism. Calcium carbonate and calcium acetate have long been used as phosphate binders, but sevelamer is a good alternative in children of any age at risk of calcium overload. Calcium acetate is available in a liquid formulation, and sevelamer is available in powder, which have facilitated dosing in infants and young children. Sucroferric oxyhydroxide is a new powerful calcium-free phosphate binder that also provides a supply of iron. It was recently approved for use in children from 2 years onward and is available in tablet and powder formulations.

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36 Cardiovascular Disease

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Among individuals receiving maintenance dialysis, mortality due to cardiovascular disease (CVD) is 10 to 30 times higher than in the general population. For example, a 30-year-old patient receiving dialysis has a similar CVD mortality risk to that of an 80-year-old in the general population. This very elevated risk likely reflects the very high prevalence of CVD, increased prevalence and severity of diabetes, hypertension and left ventricular hypertrophy, and the presence of nontraditional risk factors such as chronic volume overload, hyperphosphatemia, anemia, and other aspects of the uremic milieu (Table 36.1). In this chapter, we focus on epidemiology and management of traditional and nontraditional CVD risk factors and on ischemic heart disease, heart failure, pericardial effusion, valvular disease, and arrhythmia.

TABLE 36.1 Traditional and Nontraditional Cardiovascular Risk Factors in Maintenance Dialysis

Traditional Risk Factors	Nontraditional Factors
Older age	Extracellular fluid volume overload
Male gender	Abnormal calcium/phosphate metabolism
Hypertension	Vitamin D deficiency
Diabetes	Anemia
Smoking	Oxidant Stress
Dyslipidemia	Inflammation
Left ventricular hypertrophy	Malnutrition
Physical inactivity	Thrombogenic factors
Menopause	Sleep disturbances
Family history of cardiovascular disease	Altered nitric oxide/endothelin balance
	Other uremic toxins

I. TRADITIONAL CARDIOVASCULAR RISK FACTORS

A. Blood pressure. Data on optimal assessment of blood pressure, including home versus in-center hemodialysis measures, optimal blood pressure targets, and optimal strategies and agents for blood pressure management in dialysis, remain insufficient (Flythe, 2020). One major challenge is balancing volume control with pharmacologic therapies that lower blood pressure, a challenge that requires individualizing the dialysis prescription while incorporating key treatment goals, including potential utilization of guideline directed medical therapy in patients with CVD receiving dialysis.

B. Diabetes. Patients with diabetes receiving dialysis are at higher risk for acute coronary syndromes and have worse outcomes following coronary interventions than those without diabetes. Additionally, there is increased prevalence of heart failure. Poor blood glucose control is associated with increased mortality. Limited data suggest that a hemoglobin A1c threshold of 8% may be a reasonable target in many patients receiving dialysis for cardiovascular risk reduction, with even less stringent targets in those with very extensive comorbidity (Rhee, 2014); critically, however, the ideal hemoglobin A1c

target remains unknown (de Boer, 2022).

C. Smoking. Smoking is associated with progression in patients with early stage chronic kidney disease (CKD) and may well adversely impact residual kidney function in patients receiving dialysis. Smoking is strongly associated with all-cause mortality in patients with dialysis and is likely associated with CVD. In observational data, former smokers have a far lower risk than current smokers, suggesting a benefit of smoking cessation and a role for directed intervention (Bek, 2023).

D. Dyslipidemia

1. Lipid profiles.

Dyslipidemia is very common in all stages of kidney disease, including both hemodialysis and patients receiving peritoneal dialysis. Dyslipidemia, particularly high low-density lipoprotein (LDL) cholesterol and high triglyceride levels, is particularly common in peritoneal dialysis, where the glucose-enriched milieu predisposes to a more atherogenic lipid profile. Total cholesterol and, in particular, high-density lipoprotein (HDL) cholesterol levels, may be reduced, whereas atherogenic lipoprotein remnants and lipoprotein (a) are often increased. In hemodialysis, similarly to many advanced chronic disease states, the relationship of total or LDL cholesterol to mortality is "U"-shaped; higher cholesterol levels, likely via increased atherogenic risk, and lower levels, likely caused by associated malnutrition, are both associated with a heightened risk of mortality (Kaysen, 2018).

Nearly one-third of patients receiving dialysis have hypertriglyceridemia, defined by levels above 200 mg/dL (2.26 mmol/L), with levels occasionally 600 mg/dL (6.8 mmol/L) or higher. The predominant underlying cause is downregulation of functional lipoprotein lipase, resulting in reduced lipolysis of triglyceride-rich very low-density lipoproteins (VLDL) and yielding high quantities of atherogenic remnant lipoproteins (Vaziri, 2009). Enrichment of LDL particles with triglycerides also suggests partial deficiency of hepatic lipase. These basic defects may be enhanced by β-adrenergic blockers, high-carbohydrate diets, absorption of glucose from peritoneal dialysate, the use of heparin, and decreased hepatic blood flow from cardiac disease. Hypertriglyceridemia is associated with adverse outcomes in patients receiving peritoneal dialysis.

2. Measurement.

If not previously assessed, it may be worthwhile to evaluate a lipid profile at least once in all patients receiving dialysis. This can establish a diagnosis of severe hypercholesterolemia or hypertriglyceridemia that may prompt focused treatment or evaluation for secondary causes of dyslipidemia (Miller, 2011).

The current KDIGO (Kidney Disease Improving Global Outcomes) lipid guideline, similar to the recent American Heart Association guideline, notes limited data to support dose escalation of lipid-lowering therapies and therefore favors a "fire-and-forget" strategy (KDIGO Lipid Work group, 2013). Accordingly, among patients already treated with a high potency statin, there is no indication to routinely measure cholesterol. Similarly, in patients receiving dialysis not currently treated with a statin, given the data discussed later regarding statin efficacy for CVD prevention, there is also no indication to routinely measure cholesterol.

3. Treatment

a. Principles.

Treatment strategies for dyslipidemia include medications and lifestyle modifications. As in the general population, first-line therapy for most

patients is dietary and lifestyle modification, including exercise whenever feasible. While the utility of lifestyle modifications for changing the lipid profile remains uncertain, there is little drawback to this strategy, particularly given other potential benefits, minimal risk, and a lack of benefit on hard outcomes associated with pharmacologic therapy.

Dietary prescriptions are best accomplished with guidance from a dietician with experience in management of patients with kidney diseases. In patients with hypertriglyceridemia, mild restriction of total carbohydrate intake and limitation of the use of refined carbohydrate may be indicated. Additionally, alcohol ingestion should be discouraged. Despite the risk of malnutrition in many patients receiving dialysis, there may be a minority where overall calorie restriction is indicated to achieve ideal body weight, especially among those receiving peritoneal dialysis. In patients receiving peritoneal dialysis, sodium restriction may reduce the need for higher dialysate glucose concentrations; this would yield less glucose absorption and decrease the stimulus for hypertriglyceridemia. If possible, physical training and regular exercise are recommended as they may result in an improved cardiovascular risk profile and an improved sense of well-being.

b. Statin therapy. Although patients receiving dialysis are in the highest risk group for CVD events, several large clinical trials have failed to show a significant benefit with statin therapy among patients receiving hemodialysis, despite substantial LDL-C lowering with therapy in these trials. Accordingly, the 2013 KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease suggests that statins or a statin/ezetimibe combination not be initiated in adults with dialysis-dependent CKD.

In patients receiving incident dialysis and already being treated with statin therapy, these medications likely should be continued. This conclusion is based on results from the Study of Heart and Renal Protection (SHARP), which enrolled not only patients receiving dialysis but also more than 6,000 individuals with stage 3b and 4 CKD, more than 2,000 of whom progressed to require dialysis or kidney transplant. In general, simvastatin/ezetimibe was continued during kidney replacement therapy, and, in analyses of SHARP participants who at baseline did not require dialysis, including those who subsequently initiated dialysis, statin/ezetimibe therapy was associated with significant cardiovascular event reduction. Although no studies evaluate patients receiving dialysis who have coronary artery disease and were not previously treated with a statin, it also seems reasonable to initiate statin therapy in patients receiving dialysis with a relatively good longer-term prognosis, such as those listed for transplant.

One area of insufficient knowledge is peritoneal dialysis. SHARP included 496 patients receiving peritoneal dialysis, but, aside from SHARP, patients receiving peritoneal dialysis have not been included in large clinical trials of lipid-lowering therapy. In SHARP, there was a trend toward a benefit with lipid-lowering therapy versus placebo among those participants receiving peritoneal dialysis Some observational data also suggest a benefit with statins in the peritoneal dialysis population; however, potential biases in these studies make confidence in this conclusion low.

In sum, based on available data, statins should be continued in those individuals already using these agents, with attention paid to dose and drug-drug interactions (Table 36.2). Additionally, among patients undergoing dialysis who have not previously been prescribed a statin, the authors suggest that statin treatment may be appropriate for individuals with longer life expectancies, such as those listed for transplantation or those who have experienced acute coronary syndromes. Given the paucity of data in peritoneal dialysis but physiology that suggests higher atherosclerosis risk, a "fire-and-forget" approach may also be beneficial among patients undergoing peritoneal dialysis.

TABLE 36.2 Suggested Lipid-Lowering Medication Dose Adjustments for Reduced GFR and Dialysis

Agent	Dose Adjustment in Dialysis	Notes
Statins[a]		
Atorvastatin	None	4D trial used a dose of 20 mg daily
Fluvastatin	↓ to 50%	Decrease dosage by half at GFR <30
Lovastatin	↓ to 50%	Decrease dosage by half at GFR <30
Pravastatin	No	Starting dose of 10 mg/d recommended for GFR <60
Rosuvastatin	↓	Decrease to a maximum of 10 mg/d at GFR <30; recommended starting dose is 5 mg/d
Simvastatin	See note	If GFR <10, start at 5 mg/d and use doses above 10 mg daily with caution; may interact with amlodipine and other calcium channel blockers
Bile Acid Sequestrant		
Cholestyramine	No	Not absorbed
Colestipol	No	Not absorbed
Colesevelam	No	Not absorbed
Fibrates[b]		
Bezafibrate	See note	Concurrent use of fibrates and statins contraindicated in advanced CKD.
Ciprofibrate	See note	
Clofibrate	See note	
Fenofibrate	See note	
Gemfibrozil	See note	
Miscellaneous		
Ezetimibe	No	None
Nicotinic acid	↓ to 50%	May worsen glycemic control and cause orthostasis, hyperuricemia, and flushing; may have phosphate lowering effects

GFR, Glomerular filtration rate.

[a]Statins may interact with other medications used in patients receiving dialysis, including calcineurin inhibitors, several antibiotics, and, potentially, calcium channel blockers.

[b]Based on package inserts, all fibrates are contraindicated in patients receiving dialysis. Small short-term studies have safely utilized fibrates in patients receiving dialysis, with one study using gemfibrozil 600 mg twice daily and another using fenofibrate 100 mg daily without any serious adverse effects. The FIELD trial of 9,795 patients with type 2 diabetes evaluated fenofibrate 200 mg daily versus placebo and noted no adverse safety signals in the 519

patient subset with stage 3 CKD.

While statin use is generally safe in the dialysis population, a number of medications increase blood levels of statins via co-metabolism by hepatic cytochrome P450 enzymes; these include calcineurin inhibitors, macrolide antibiotics, azole antifungal agents, calcium channel blockers, fibrates, nirmatrelvir/ritonavir, and nicotinic acid; this has been most often documented with simvastatin. Potential drug-drug interactions should be assessed in each patient. Statins may cause myopathy, and the risk of myopathy may be increased in advanced CKD. This is particularly apparent with concurrent use of fibrates, and this combination should be avoided in advanced CKD.

c. **Hypertriglyceridemia management.** Statins have some effect in lowering serum triglyceride levels, although they are less effective than fibrates and/or nicotinic acid for this purpose. In contrast, bile acid resins may actually increase triglyceride levels. There are no data supporting a benefit of fibrates or nicotinic acid on outcome improvement in patients receiving dialysis, particularly in those with only modest elevations in serum triglyceride level (<500 mg/dL [<5.7 mmol/L]), and these agents should not be first-line therapy in this setting. Based on this paucity of data, the 2013 KDIGO guidelines state: “Fibric acid derivatives are not recommended to prevent pancreatitis or reduce cardiovascular risk in adults with CKD and hypertriglyceridemia.” There are no data to guide treatment decisions in patients receiving dialysis with very high triglyceride levels (>500 mg/dL [>5.7 mmol/L]); accordingly, treatment decisions need to balance potential risks associated with severe hypertriglyceridemia with the risks and benefits associated with therapy. Of note, adequate data do not exist to guide fibrate dosing in patients receiving dialysis as the safety of this class has not been assessed sufficiently. Small studies and reports suggest that fibrates may be safe, although some dose reduction may be prudent if these agents are used in dialysis (Table 36.2) and concurrent use with a statin is contraindicated. Available fibrates include gemfibrozil, bezafibrate, ciprofibrate, clofibrate, and fenofibrate.

d. **Other lipid-lowering agents.** Alternatives to statins and fibrates include bile acid sequestrants (including the phosphate binder, sevelamer), nicotinic acid, and ezetimibe. Bile acid sequestrants can interfere with absorption of other medications; bile acid sequestrants should not be used when triglycerides are >400 mg/dL (>4.5 mmol/L), and their use is relatively contraindicated when triglycerides are >200 mg/dL (>2.3 mmol/L) since they may increase triglycerides in some patients. Doses do not need to be reduced in patients receiving dialysis (Table 36.2). Sevelamer acts by the same mechanism to lower both total and LDL cholesterol and may be a good choice when phosphate lowering is also desired.

While not as effective for LDL lowering, niacin itself or as nicotinic acid or nicotinamide has favorable effects on HDL cholesterol levels and also lowers serum triglyceride levels and serum phosphate levels. However, there are no trial data to support a benefit of nicotinic acid on CVD or mortality outcomes in dialysis. Dosage should be reduced by about 50% in end-stage kidney disease (ESKD), given its substantial kidney excretion. Adverse effects can include

hyperglycemia and hepatotoxicity in individuals with underlying liver disease or when high doses are used. Flushing may be attenuated with concurrent aspirin use or by giving longer-acting preparations. Nicotinic acid is more often used as a first-line therapy when severe hypertriglyceridemia (>500 mg/dL, or 5.8 mmol/L) needs to be treated to protect against pancreatitis or when a statin is contraindicated.

Ezetimibe is a drug that inhibits cholesterol absorption. There are few data available on its use in kidney failure, although its use in conjunction with simvastatin in SHARP suggests safety.

Newer options for treating dyslipidemia include proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. To date, there have been no trials of these agents among the dialysis population.

E. Left ventricular hypertrophy

1. **Epidemiology.** Left ventricular hypertrophy (LVH) is highly prevalent in patients with CKD, frequently developing prior to the need for kidney replacement therapy and likely reflecting both pressure and volume overload (Kidney Disease Outcomes Quality Initiative [KDOQI] Clinical Practice Guidelines for Cardiovascular Disease [CVD], 2005). Over 30% of participants in the Frequent Hemodialysis Network studies, a group that overall was healthier than the general dialysis population, had LVH at study entry (defined using cardiac magnetic resonance imaging), with other studies showing prevalence rates of 50% to 75%. LVH in patients receiving dialysis is an independent risk factor for subsequent adverse cardiovascular events and death.

   Most LVH is initially concentric, characterized by a uniform increase in wall thickness secondary to pressure overload from hypertension, stiffened blood vessels, or aortic stenosis. Anemia and volume overload resulting from chronic inability to effectively remove ingested sodium and fluid may each result in eccentric or asymmetric hypertrophy. The end point may be a dilated cardiomyopathy with eventual reduction in systolic function. Individuals with advanced heart failure may have low blood pressure; this may in part be responsible for the “J”-shaped (or “U”-shaped) relationship observed between blood pressure and mortality in patients receiving dialysis (with low blood pressures also being associated with reduced survival).

   LVH is most often diagnosed with echocardiography, an inexpensive, noninvasive widely available test. Cardiac function should be assessed in the euvolemic state, as both significant volume depletion and overload may reduce left ventricular inotropy. Accordingly, in patients receiving dialysis, two-dimensional echocardiography is likely to be most informative if performed on a day during the interdialytic interval. While three-dimensional echocardiography may be useful to assess left ventricle (LV) structure as it avoids the use of geometric assumptions of LV shape that are required to estimate LV mass and volume, the increasing availability of cardiac magnetic resonance imaging likely provides the most accurate assessment of LV structure. While screening echocardiography is currently recommended for patients incident to dialysis, there is no evidence that this improves clinical outcomes.

2. **Prevention and management.** Some data suggest that with modification of risk factors, including anemia and elevated systolic blood pressure, strict management of

volume, management of mineral and bone disorder, and use of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy, regression of LVH may occur in patients receiving dialysis. Data are inconsistent on whether high-flow arteriovenous (AV) fistulas may lead to maladaptive cardiac remodeling, although a small clinical trial suggested that elective ligation of AV access following successful kidney transplantation was associated with LV mass reduction (Rao, 2019). That regression of LVH results in reduced CV events and decreased mortality risk appears likely, as multiple post hoc analyses have shown a lower risk of adverse events in participants in whom LVH regressed over the course of clinical trials.

With regard to renin-angiotensin-aldosterone system (RAAS) inhibition, the largest outcomes study to date evaluating the effect of RAAS blockade in patients with LVH receiving dialysis was the Fosinopril in Dialysis Study, which randomized 397 patients receiving hemodialysis to fosinopril versus placebo and showed no benefit on cardiovascular events over a 2-year period (Zannad, 2006). In a small randomized clinical trial comparing atenolol to lisinopril in patients with LVH receiving maintenance hemodialysis, LVH improved over time with either agent, although cardiovascular outcomes were better with atenolol (Agarwal, 2014). Randomized trials in CKD targeting normalization of hemoglobin levels with recombinant human erythropoietin had no effect on left ventricular mass. In patients enrolled in the Frequent Hemodialysis Network study, those receiving more frequent hemodialysis showed a significant improvement in LV mass; whether this benefit was mediated through improved control of blood pressure, volume, phosphate, or other factors is uncertain.

II. NONTRADITIONAL RISK FACTORS.

Several nontraditional risk factors are listed in Table 36.1. In-depth discussion of some of these is beyond the scope of the Handbook, but we briefly summarize the most pertinent issues.

A. Mineral and bone disorder.

Mineral and bone disorders may affect the cardiovascular system in multiple ways (Lau and Ix, 2013). First, both elevated parathyroid hormone (PTH) and reduced 1,25-vitamin D levels may directly affect the myocardium, promoting hypertrophy. Second, hyperphosphatemia, positive calcium balance in the setting of impaired bone buffering, and other factors in the uremic milieu, including loss of calcification inhibitors, can combine to promote vascular calcification. Third, other hormones, including FGF23, may promote LVH and may also act independently or through other calcification promoters to increase vascular calcification. Vascular calcification occurs at both the arterial media and the intima, with medial calcification generally more pronounced among patients receiving dialysis. Medial calcification is associated with stiffer blood vessels, as evidenced by increased pulse wave velocity. This increases cardiac afterload and promotes LVH. Furthermore, during the cardiac cycle, the systolic pressure wave normally reflects back onto the heart during early diastole, promoting coronary filling. With stiffened arteries and increased pulse wave velocity, this reflected wave returns to the heart prematurely—during late systole. This results in loss of the coronary filling effect and increased afterload, because the heart has to pump against the reflected pressure wave from the previous contraction.

Vascular calcification may be diagnosed in several ways. Plain radiographs are

specific but insensitive, while electron beam and spiral computed tomography are sensitive and specific but expensive and associated with significant radiation exposure on repeated use. Ultrasound, most commonly of the carotid arteries, is relatively inexpensive and noninvasive but requires a trained operator and may lack the precision to closely track changes over time. Use of such tests needs to be justified by their impact on clinical decision-making. Currently, there is no reliable method of reversing vascular calcification, although some studies have suggested that use of non–calcium-containing binders results in more favorable calcium balance. Dialysis prescriptions resulting in negative phosphate balance may also slow progression of calcification. A reasonable strategy may be to limit the use of calcium-containing phosphate binders in patients in whom extensive vascular calcification has been documented.

B. Anemia. Anemia is common in patients with CKD, especially at dialysis initiation, and its severity correlates with the extent of LVH. In observational studies, patients with higher hemoglobin levels have fewer CVD events; however, treatment with erythropoiesis stimulating agents (ESAs) to raise hemoglobin levels to the normal range appears associated with increased cardiovascular risk. Hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs) seem to have at least the same magnitude of cardiovascular risk as do ESAs.

C. Sleep. Sleep abnormalities are highly prevalent in patients receiving dialysis and are associated with adverse cardiovascular outcomes. Nocturnal hypoxemia associated with sleep apnea is associated with increased CVD events and may represent a potentially modifiable risk factor.

D. Oxidant stress and inflammation. Numerous factors in the patient receiving dialysis increase oxidant stress and inflammation burden. These include the use of dialysis catheters, underlying illness and infection, malnutrition, and perhaps the dialysis procedure itself. Many protective mechanisms against inflammation are impaired, including reduced serum levels of free thiols such as glutathione. Retained, failed AV grafts or kidney allografts may also be a source of continued inflammatory stimulus. At this time, specific treatment strategies to reduce inflammation or oxidant stress are neither widely used nor adequately supported by randomized trials, and results of studies investigating the potential benefit of antioxidant therapies in the dialysis population have been disappointing. Ziltivekimab and clazakizumab, monoclonal antibodies targeting the interleukin-6 ligand, are being evaluated in patients with advanced CKD and those receiving dialysis, respectively, with the hope that reducing chronic inflammation will have CVD benefits in this population (Chertow, 2024; Pergola, 2024).

III. ISCHEMIC HEART DISEASE

A. Overview. Acute myocardial infarction (MI) and acute coronary syndromes are exceedingly common in the ESKD population and associated with poor outcomes. One study in Taiwan demonstrated a 30% 1-year mortality following acute coronary syndrome in patients with dialysis. In the United States from 2018-2020, 1-year mortality among patients with dialysis after a percutaneous intervention (PCI) was approximately 35% and 1-year mortality after a coronary artery bypass graft (CABG) surgery was approximately 28%. These mortality rates are 2 to 3 times higher than among those with no history of coronary artery disease (USRDS, 2022).

Both vascular stiffness and atherosclerosis contribute to pathogenesis; vascular stiffness, manifesting as a loss of arterial elasticity, may result in LVH with subsequent increased myocardial oxygen demand and altered coronary perfusion, followed, ultimately, by subendocardial ischemia (Sarnak, 2019). Small vessel coronary artery disease also plays a role: in one study, up to 50% of patients receiving dialysis who were nondiabetic with symptoms of myocardial ischemia did not have significant large caliber coronary artery disease, implicating isolated small vessel disease as a cause of ischemia.

B. Diagnosis. Routine screening is not currently recommended for patients undergoing dialysis, and even screening of asymptomatic transplant candidates, although widely performed, has uncertain benefits. There are no preoperative screening guidelines specific to patients receiving dialysis, and it is reasonable to use general population guidelines, recognizing that the extent of comorbid conditions prevalent in the dialysis population is likely to place them in the highest cardiovascular risk group. Because many patients receiving dialysis are unable to achieve adequate exercise levels for valid stress tests, pharmacologic stress tests should be used in this population. Furthermore, because of the high incidence of baseline electrocardiogram abnormalities, either nuclear or echocardiographic imaging should be utilized in stress testing. There is no absolute contraindication to cardiac catheterization in patients treated with dialysis, although preservation of existing kidney function is an important consideration, especially in those treated with peritoneal dialysis, and the associated risk of contrast nephropathy should be kept in mind. Cardiac catheterization approaches include the femoral artery and the radial artery; if using a radial artery approach, this should be done in discussion with the treating nephrologist, incorporating the lifelong vascular access plan into decision-making.

Diagnosis of acute MI can be challenging, as cardiac biomarker levels, including troponins, are often chronically elevated (deFilippi, 2017). Chronic troponin elevation itself is a marker of worse prognosis, likely representing ongoing injury and subclinical ischemia. The Fourth Universal Definition of Myocardial Infarction (2018) suggests that if chronic, elevations in cardiac biomarkers in kidney failure should not be classified as acute injury; however, rising and/or falling cardiac biomarker levels in the appropriate clinical setting are likely consistent with acute MI (Thygesen, 2018).

C. Prevention. There are few clinical trials evaluating primary and secondary prevention strategies in patients receiving dialysis. If hemorrhagic risk and blood pressure permit, aspirin, β-blockers, ACE inhibitors or ARBs, and nitrate preparations may all be appropriate for secondary prevention.

D. Treatment. The optimal treatment of coronary artery disease in patients undergoing dialysis remains uncertain. Medical management, PCI, including angioplasty with use of either drug eluting or bare metal stents, and CABG surgery, all have roles in individualized care. Equipoise between an initial invasive intervention therapy, consisting most often of PCI, and an initial medical management strategy was demonstrated in the ISCHEMIA-CKD trial, which enrolled 777 individuals with stable coronary disease, moderate or severe coronary ischemia, and advanced kidney disease, including 411 receiving dialysis. There was no evidence that an initial invasive strategy was preferential to medical management, recognizing that approximately 20% of individuals assigned to medical management underwent revascularization in the

subsequent 3 years following randomization (Bangalore, 2020).

1. **Pharmacologic management of stable coronary artery disease.** The pharmacologic approach to stable coronary artery disease in patients receiving dialysis is likely similar to that in the general population. The progressive introduction of sublingual nitrates, oral long-acting nitrates, β-blockers, and calcium channel blockers in those with angina is appropriate. Usual dosages of sublingual and oral nitrates can be given to patients receiving dialysis.

   The role of aspirin use in the dialysis population remains uncertain. There is strong evidence supporting low-dose aspirin for secondary prevention of atherosclerotic CVD events in individuals with coronary artery disease in the general and nondialysis CKD populations, whether or not ischemic cardiomyopathy is present; however, there are no clinical trial data in patients receiving dialysis evaluating the use of aspirin for secondary CVD prevention. Limited observational data in patients receiving dialysis have not shown a beneficial effect on cardiovascular outcomes associated with low-dose aspirin, although clinical trials examining aspirin use and use of other antiplatelet agents for access patency also suggest no evidence of harm. At this time, given the significant CVD benefits of aspirin use in patients with known atherosclerotic cardiovascular disease not receiving dialysis, it is likely reasonable to use aspirin in patients with coronary artery disease receiving dialysis.
2. **Revascularization.** Given the high periprocedural risks associated with CABG, if anatomy permits and symptoms persist despite medical management, PCI, most likely with a drug eluting stent, may be a good approach for many patients receiving dialysis, particularly those who are not transplant candidates or who are at high perioperative risk with CABG (Pan, 2023). Of note, there are no high-quality data to assess the preferred revascularization therapy for those with 3-vessel disease or left main disease. For PCI, a key determination for stent type may be whether a patient receiving dialysis can safely use dual antiplatelet therapy for 1 year or more. As with most procedures, those done on an emergent basis are associated with worse outcomes. Thrombolytics and glycoprotein IIb/IIIa antagonists are likely beneficial, particularly when interventional cardiology is unavailable, but may be associated with a higher risk of bleeding complications.
3. **Chest pain during the hemodialysis session.** Chest pain during dialysis may represent acute or chronic coronary artery disease (in addition to arrhythmia and noncardiac causes). For patients who develop recurrent chest pain primarily during the hemodialysis sessions, a number of potential therapeutic options are available. Nasal oxygen may be beneficial in this setting. If the anginal episode is associated with hypotension, initial treatment should include raising the blood pressure by elevating the feet and by cautiously administering saline. Sublingual nitroglycerin can be given if the blood pressure has increased to a clinically acceptable value. Possibly, the blood flow rate should be reduced and ultrafiltration should be stopped until the anginal episode subsides. Cooling the dialysate may also help maintain cardiac perfusion, particularly in individuals prone to intradialytic hypotension. Predialysis administration of 2% nitroglycerin ointment may be of benefit when applied 1 hour prior to a hemodialysis session, assuming that the blood pressure will tolerate this intervention. Predialysis administration of β-blockers and oral nitrates

may be of benefit but must be done cautiously because the risk of hypotension during the dialysis session may be increased. Of note, several β-blockers require dose reduction in patients receiving dialysis, including atenolol, which has extensive kidney clearance. Among commonly used β-blockers, atenolol and metoprolol are extensively cleared with hemodialysis, while carvedilol and labetalol do not have substantial dialysis-related clearance. Calcium channel blockers could be of use in situations where β-blockade is contraindicated or inadequate; however, given the negative cardiac inotropy associated with this class and the high prevalence of systolic dysfunction in patients receiving dialysis, caution should be exercised with regard to calcium channel blockers, particularly the nondihydropyridines (diltiazem and verapamil).

IV. CARDIOMYOPATHY AND HEART FAILURE

A. Pathophysiology. Heart failure is highly prevalent and related to many common factors in the dialysis population. Although there is no universally accepted definition, heart failure is generally characterized by volume overload, pulmonary edema, and dyspnea. Heart failure may occur as a result of left ventricular dysfunction (systolic dysfunction), diastolic dysfunction in which the LV has a normal ejection fraction but impaired filling, or a combination of these. These are broadly classified as heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HfpEF). Right ventricular failure and pulmonary hypertension are also common in people with kidney failure. HfpEF is often associated with LVH and systemic hypertension, both of which are extremely common in patients receiving dialysis. Systolic dysfunction is frequently a result of ischemic disease and dilated cardiomyopathy. For obvious reasons, patients receiving dialysis are particularly vulnerable to fluid overload, and pulmonary edema in the setting of marked fluid overload may not represent overt cardiac dysfunction. However, frequent pulmonary edema with minimal intradialytic weight gain may be an important clue to cardiac dysfunction. An additional clue may be dialysis-related hypotension, as dysfunctional hearts likely have reduced capacity for adaptation to intravascular volume loss. Furthermore, ultrafiltration may never allow accumulation of excess fluid, rendering hypotension the sole manifestation of heart failure.

Although the diagnosis of heart failure is clinical, echocardiography is invaluable for diagnosing systolic and diastolic dysfunction. Echocardiography may also suggest the cause of disease, identifying wall motion abnormalities that may indicate ischemia and infarcts, LVH that may predispose to diastolic dysfunction and valvular disease with its effects on cardiac morphology. The 2005 KDOQI CVD guidelines recommended obtaining echocardiograms at dialysis initiation after dry weight is established and every 3 years thereafter; this recommendation is opinion-based.

B. Treatment. Chronic therapy for heart failure in patients undergoing dialysis has not been adequately studied; therefore, most recommendations are either extrapolated from the general population or based on smaller trials (Heidenreich, 2022). Restriction of sodium intake, including avoidance of routine sodium modeling if this is associated with a positive sodium balance, is important, since, with most thrice-weekly hemodialysis schedules, the ability to remove excess fluid is limited. More frequent dialysis therapies, including daily hemodialysis and peritoneal dialysis, may help optimize volume status

(Sarnak, 2022). Maintaining a balance between fluid overload, on the one hand, and symptomatic hypotension, on the other, may be extremely difficult in some patients receiving dialysis. In the future, newer technologies, including intradialytic blood volume monitoring and bioimpedance analysis, may have more clearly delineated roles for optimizing volume management.

1. **Medical therapy**
    a. **ACE inhibitors** are beneficial in individuals with chronic HFrEF and may be beneficial in patients receiving dialysis, with one prior meta-analysis showing a reduction in LV mass. There are limited data showing a survival benefit with these agents. One small Italian study did show a mortality benefit with dual ACE inhibitor and ARB therapy versus ACE inhibitor therapy alone in patients with a left ventricular ejection fraction below 40% receiving hemodialysis, a strategy that is not routinely recommended (Cice, 2010). On the other hand, one relatively large randomized trial of olmesartan versus placebo failed to show any improvement in terms of cardiovascular event rate or death (Iseki, 2013). Major limitations associated with use of these agents include hypotension and hyperkalemia. If there is a contraindication to ACE inhibitor use, it seems reasonable to extrapolate from data in the general population and substitute ARBs. Most ACE inhibitors are cleared during dialysis while ARBs are not dialyzable.
    b. **β-Blockers,** another mainstay of heart failure therapy in the general population, are also of uncertain benefit in the dialysis population. In an Italian study, carvedilol, well studied for heart failure in the general population, reduced mortality in patients receiving dialysis with left ventricular dysfunction (Cice, 2003). Carvedilol dosing is the same as in the general population. Several β-blockers, including atenolol, have markedly reduced elimination rates in kidney failure and should be used with great caution (Chapter 31), although atenolol was safely used in a clinical trial comparing lisinopril with atenolol in patients with LVH receiving hemodialysis. In general, non–kidney-metabolized β-blockers, such as metoprolol and carvedilol, can be safely titrated to heart rate and blood pressure. Dialysis clearance also varies for specific β-blockers, with atenolol and metoprolol both extensively cleared with high-flux hemodialysis while carvedilol and labetolol have minimal hemodialytic clearance.
    c. **Aldosterone blocking agents,** including spironolactone and eplerenone, and possibly finerenone, are beneficial in the general population and kidney disease population with or at risk of heart failure. Given the known adverse effects of aldosterone on arterial stiffness and cardiac remodeling, aldosterone blocking agents could be beneficial in the dialysis population. There are no data showing that clinical outcomes are improved with these agents among patients receiving dialysis, although trials of carefully selected patients receiving dialysis suggest that these agents can be used with close attention to serum potassium levels (Charytan, 2019).
    d. **Cardiac glycosides,** namely digoxin, are sometimes used in heart failure in the general population, where it has been shown that they improve morbidity but not mortality. Digoxin, when used in patients receiving dialysis, should be utilized judiciously, with careful attention to dosage and drug levels.

Maintenance dosing should begin at low doses (0.0625 or 0.125 mg) every other day. A loading dose should generally not be used. Care should be taken in complex drug regimens as many other medications affect digoxin levels.

e. **Sacubitril/valsartan** is an angiotensin receptor II blocker–neprilysin inhibitor that reduces mortality and heart failure hospitalizations, most notably in individuals with HFrEF. Sacubitril inhibits the breakdown of natriuretic peptides, with likely substantial kidney effects but possibly effects elsewhere in the body. There are no clinical trial data and only minimal observational data to date to recommend use of this agent in patients receiving dialysis at the current time.

f. **Sodium-glucose cotransporter-2 (SGLT2) inhibitors** appear extremely effective in both the general population and in the advanced CKD population for reduction in heart and kidney risk. There are no data on their use in dialysis. Short-term pharmacokinetic studies suggest that they might be used with minimal dose adjustment (Barreto, 2023), and randomized trials evaluating cardiovascular outcomes with this class of agents in the dialysis population are in progress.

2. **Nonmedical therapy**

   a. **Left ventricular assist devices** (LVADs) have major implications for dialysis in outpatient settings, as many freestanding hemodialysis facilities do not have personnel trained for management of patients with LVAD (Roehm, 2018). In these individuals, peritoneal dialysis may be a preferred dialysis modality due to less profound hemodynamic shifts and no need for blood stream access. Patients with LVADs can have AV fistulas and AV grafts. Anticoagulation is imperative in these patients, particularly with older LVAD models, and is typically accomplished with warfarin.

   b. **Cardiac resynchronization therapy** is indicated when there is significant electrical dyssynchrony between the right and left ventricles in an individual with HFrEF. Cardiac resynchronization involves pacing the LV while simultaneously or nearly simultaneously pacing the right ventricle to restore ventricular synchrony and improve LV function. The benefits of cardiac resynchronization therapy in the general heart failure population are only supported by moderate evidence. Many current cardiac resynchronization devices require multiple transvenous leads; in patients receiving dialysis, who are highly dependent on central venous patency and who have a high incidence of blood stream infection, the risk of central vein stenosis and thrombosis and bacteremia may exceed potential benefits with this intervention. Leadless devices may be more widely available in the next several years.

3. **Role of arteriovenous (AV) fistulas and grafts.** Although limited data exist, if there is a concern that AV access may be playing a role in heart failure, flow reduction procedures may be useful in addressing potential concerns with high-flow fistulas while maintaining fistula patency. This problem is more often encountered with upper arm *high*-flow fistulas, and close attention to the size of the AV fistula is an essential part of longitudinal dialysis patient care. Slowing of the heart rate during fistula or graft occlusion (by finger pressure) suggests that the AV shunt is importantly and pathologically contributing to an increased cardiac output (Branham

sign). The test is specific, but absence of heart rate slowing with fistula or graft occlusion by no means exonerates the AV communication as a contributory cause of the heart failure.

V. PERICARDIAL DISEASE. Pericardial disease most commonly manifests as acute uremic or dialysis-associated pericarditis although chronic constrictive pericarditis may also be seen. Clinically significant pericardial effusions are fairly rare.

A. Uremic pericarditis. Uremic pericarditis describes patients who develop clinical manifestations of pericarditis prior to or within 8 weeks of initiation of kidney replacement therapy. In the current era, uremic pericarditis is rare, but remains an indication for and responds extremely well to initiation of kidney replacement therapy.

B. Dialysis-associated pericarditis. Clinically significant dialysis-associated pericarditis is also a rare syndrome, although it is more common than uremic pericarditis. It may occur long after a patient has been stabilized on dialysis. The etiology of dialysis-associated pericarditis remains unknown but may be at least in part dependent on inadequate dialysis and volume overload. Certain medications may also contribute, such as hydralazine and minoxidil. Other causative factors are likely present, given that intensification of dialysis frequently does not result in resolution.

1. **Pericarditis manifestations and diagnosis.** The most common symptom of pericarditis is chest pain, generally pleuritic in nature and exacerbated by reclining and reduced with leaning forward. Pericarditis may be accompanied by nonspecific symptoms, including fever, chills, malaise, dyspnea, and cough, with respiratory symptoms potentially reflecting a pericardial effusion. Physical examination may reveal a pericardial friction rub. When hemodynamically significant, pericardial disease accompanied by an effusion may be characterized by hypotension, particularly during hemodialysis. Jugular venous distension, elevated pulsus paradoxus, and distant heart sounds may also be present. Chest radiograph may reveal an enlarged cardiac silhouette that may be difficult to distinguish from other causes of cardiomegaly. Dialysis-related pericarditis often does not manifest with the classical electrocardiogram finding of diffuse ST segment elevation because there may only be minimal inflammation of the epicardium. Echocardiography is useful in identifying pericardial effusions, but effusions may be absent in patients who have adhesive, noneffusive pericarditis.
2. **Treatment**
   a. **Monitoring.** Small (<100 mL), asymptomatic pericardial effusions are fairly common in patients receiving dialysis and require no acute intervention. Larger effusions present a risk of tamponade and should be monitored closely using serial echocardiograms. Hemodynamic and even echocardiographic signs of impending tamponade are not always reliable.
   b. **Intensification of hemodialysis** is the mainstay of therapy but is effective only approximately 50% of the time. This may be accomplished by increasing dialysis frequency to 5 to 7 days per week, with careful attention to electrolytes, including phosphate and magnesium, avoidance of overalkalinization, and volume status. Heparin during dialysis has traditionally been avoided out of concern for hemorrhagic tamponade.
   c. **Adjuvant medical therapies,** including oral and parenteral glucocorticoids

and nonsteroidal anti-inflammatory medications, have generally not been effective and are not indicated. Colchicine may be an option for pericarditis due to inflammatory conditions, although this agent has a narrow therapeutic window in patients receiving dialysis.

d. Surgical drainage. Failure to recognize the need for timely surgical drainage of large pericardial effusions may have significant consequences as the onset of tamponade may be rapid and without premonitory signs. Hence, regular echocardiographic monitoring of the size of an effusion is vital. Surgical drainage by subxiphoid pericardiostomy should be considered whenever the effusion size is estimated by echocardiography to exceed 250 mL (posterior echo-free space larger than 1 cm) even when hemodynamic compromise is absent. Drainage is mandatory when overt tamponade appears. **Subxiphoid pericardiostomy** may be the surgical drainage procedure of choice (ie, insertion under local anesthesia of a large-bore tube into the pericardial space). The tube is left in place to close drainage for several days until drainage ceases. Instillation of locally acting steroids has not been proven necessary and increases the risk of infection. **Pericardiocentesis** using a blindly inserted needle is dangerous and not indicated except as an emergency therapy for patients with life-threatening tamponade. *Guided pericardiocentesis* is the most common method used for pericardial fluid removal and can be performed under fluoroscopic, echocardiographic, or computed tomography guidance. Of note, hemorrhagic effusions may be poorly evacuable through typically used pericardiocentesis needles. **Anterior pericardiectomy** has been favored by some, but general anesthesia and thoracotomy are unnecessary risks given the uniformly successful response to drainage by subxiphoid pericardiostomy.

C. Constrictive pericarditis. Constrictive pericarditis can appear as an unusual complication of dialysis-associated pericarditis or as the first manifestation of pericardial disease. Constrictive pericarditis may also masquerade as congestive cardiac failure; the best means of differentiation is by right heart catheterization. Even then, the diagnosis may be in doubt and can be proven only by a favorable response to total pericardiectomy.

D. Purulent pericarditis. Occasionally, patients are found to have purulent pericarditis as a complication of septicemia, often as a result of access site infection. These patients often require anterior pericardiectomy in addition to antimicrobial therapy.

VI. VALVULAR DISEASE

A. Endocarditis. Infective endocarditis is a relatively uncommon complication of hemodialysis but is far more common in this population than in most other groups. Central venous hemodialysis catheters, in particular, are associated with a high risk of bloodstream infection and subsequent endocarditis; cardiovascular implantable electronic devices may also be associated with increased risk. An additional factor predisposing to endocarditis is cannulation of AV fistulas using a buttonhole technique.

The majority of infective endocarditis cases are due to gram-positive organisms (*S. aureus*, *S. epidermidis*, and *Enterococcus*). The presence of underlying valvular disease, including calcification, may increase the risk. Prevention is focused on avoiding use of central venous catheters as much as possible, prolonged antimicrobial therapy for

staphylococcal bacteremia when it occurs, and reinforcement of proper vascular access technique, including exit site and cannulation site care.

1. **Symptoms and signs.** Patients with endocarditis receiving dialysis usually, but not always, have fever. Murmurs, leukocytosis, and septic emboli may also be present; however, the clinical evaluation of murmurs may prove difficult because cardiac murmurs are common in the general dialysis population owing to anemia, valvular calcification, and the presence of AV fistulas. Because a substantial percentage of patients receiving dialysis are normally hypothermic, the body temperature with infection may be elevated to only slightly above the normal range or not at all.
2. **Diagnosis** is chiefly dependent on positive blood cultures and clinical suspicion. Transthoracic and, if echocardiography windows are limited, transesophageal echocardiography may be critical to making the diagnosis.
3. **Treatment** of endocarditis in patients receiving hemodialysis will usually be directed at gram-positive organisms, and regimens should be tailored to bacterial sensitivities. In most locations, empiric therapy in individuals with fever and a dialysis catheter will be initiated with vancomycin, because of both the high incidence of methicillin-resistant *S. aureus* and the ease of administration. Some practitioners will add empiric gram-negative coverage with a third- or fourth-generation cephalosporin. In the presence of methicillin-sensitive *S. aureus*, antistaphylococcal penicillins like oxacillin or first-generation cephalosporins like cefazolin are preferable. First-generation cephalosporins that can be dosed at hemodialysis are often used to avoid the need for additional vascular access, recognizing the ongoing infection risks associated with vascular catheters as well as the need to preserve veins for AV fistulas and grafts. Bacteremia therapy may include an additional agent for synergistic therapy (eg, gentamicin, rifampin) and should be continued for at least 4 to 6 weeks. Such prolonged antimicrobial therapy may reduce the likelihood of a valvular sequestration of infection. Newer antistaphylococcal agents such as daptomycin have been developed, but use should be judicious and aided by input from an infectious disease specialist to avoid development of widespread resistance. In all cases, there should be a high degree of suspicion for line and access infections and a low threshold for removal of potentially infected central venous catheters.
4. **Valve replacement.** Dialysis dependence is not a contraindication to valve surgery. Indications for surgery are the same as in the general population: progressive valvular destruction, progressive heart failure, recurrent embolization, and failure to respond to appropriate antibiotic therapy. Based on United States Renal Data System (USRDS) data, in-hospital mortality following aortic or mitral valve replacement for bacterial endocarditis is approximately 14%, and 6-month survival is approximately 60% and does not differ between tissue and prosthetic valves (Leither, 2013).

B. Valvular Calcification and Stenosis

1. **Mitral annular calcification.** Mitral annular calcification may occur in as many as 50% of patients on dialysis. It is recognized on echocardiography as a uniform echodense rigid band located near the base of the posterior mitral leaflet and may progressively involve the posterior leaflet. Complications include conduction

abnormalities, embolic phenomena, mitral valve disease, and increased risk of endocarditis. There are no proven preventive or treatment strategies.

2. **Aortic calcification and stenosis.** Aortic valve calcification occurs in 25% to 55% of patients receiving dialysis. Risk factors are similar to those for other forms of vascular calcification. Calcification may result in progressive immobilization of the aortic leaflets, eventually restricting flow. Functional aortic stenosis exists when the valve leaflets thicken to the extent that a pressure gradient develops across the aortic valve. The aortic stenosis appears to progress far faster in the dialysis population than in the general population.
    a. **Symptoms and signs.** Angina, congestive heart failure, and syncope are the cardinal symptoms of critical aortic stenosis. Frequent episodes of intradialytic hypotension may be a clue as the heart has difficulty in adapting to conditions of reduced filling. The classical systolic murmur that radiates to the carotid arteries may be present; this typically begins after S1 and ceases prior to S2; additionally, S2 may be fixed or paradoxically split. However, it is often difficult to differentiate the murmur of aortic stenosis from that heard in aortic sclerosis or from benign flow murmurs.
    b. **Diagnosis** is by echocardiography and cardiac catheterization and mirrors diagnostic methods in the nondialysis population.
    c. **Valve replacement** is the therapy of choice. Timing depends on perceived risks versus anticipated benefits. Studies from the USRDS have not demonstrated any difference in survival based on the use of tissue versus nontissue bioprosthetic valves. The mortality rate for valve replacement (with or without concurrent CABG) is relatively high for patients receiving dialysis; however, in most cases, the prognosis is worse if clinically indicated surgery is not performed or if emergent surgery rather than elective surgery is performed. Multiple observational studies report successful transcatheter aortic valve implantation procedures in patients receiving dialysis, with data suggesting low 30-day mortality (4%), with 1-year mortality of 31% with this less invasive approach (Ogami, 2021).

VII. ARRHYTHMIAS, CARDIAC ARREST, AND SUDDEN CARDIAC DEATH

A. Risk factors.

Many comorbid conditions that are highly prevalent in patients receiving dialysis are also associated with arrhythmias. These include LVH, chamber enlargement, valve abnormalities, and ischemic heart disease. Additionally, serum levels of cations that can affect cardiac conduction, including potassium, calcium, hydrogen, and magnesium, are often abnormal and undergo rapid fluctuation during hemodialysis.

B. Cardiac arrest and acute arrhythmias.

Cardiac arrest and arrhythmia are the most common cause of death among patients receiving dialysis, with rates of 61 per 1,000 patient years from 2018 to 2020, accounting for 43% of deaths with a known cause in the hemodialysis population and 41% of deaths with a known cause in the peritoneal dialysis population. Outcomes following cardiac arrest remain poor. At one hospital system, from 2006 to 2014, 28% of patients on dialysis receiving in-hospital cardiopulmonary resuscitation did not survive the initial event, and another 42% died during that hospitalization; only 10% were discharged home (Saeed, 2021). Potential

strategies to reduce the risk of fatal cardiac risk include careful attention to fluid and electrolyte shifts. The risks of arrhythmias and cardiac arrest are higher in patients being dialyzed using a dialysate potassium level of less than 3 mM and are most notable at low dialysate potassium concentrations; many nephrologists believe that low potassium dialysate (<2 mM) should be avoided if possible. One trial showed a reduction in arrhythmias when a 3 mM potassium dialysate was used in conjunction with sodium zirconium cyclosilicate to control the serum potassium level as compared with a 2 mM potassium dialysate (Charytan, 2024). Calcium balance may also be a factor. One study suggested an increased risk of sudden death associated with the use of a low dialysis solution calcium concentration, particularly in individuals with higher serum calcium levels. Finally, multiple studies demonstrate a higher risk of sudden death following the long interdialytic interval among patients treated with thrice-weekly hemodialysis, further suggesting that electrolyte or volume abnormalities may be complicit.

For acute arrhythmias that occur during dialysis, the dialysis session should be terminated and blood returned cautiously. Urgent cardioversion per advanced cardiac life support (ACLS) guidelines is indicated for all patients with an unstable rhythm, and all dialysis facilities should have automated external defibrillators available and staff trained in their use. Amiodarone, currently the first-line pharmacologic intervention for ventricular tachycardia in the general population, is dosed identically in patients receiving dialysis. Airway management and cardiac monitoring is essential. Administration of procainamide and other class Ia antiarrhythmics should be undertaken with caution as they may cause QT prolongation and torsades de pointes in patients receiving dialysis.

Adequate data on the benefits of implantable cardioverter defibrillators (ICD) are lacking in patients receiving dialysis. While, intuitively, given the high risk of ventricular arrhythmia, ICD use appears sensible, ICDs with transvenous leads are associated with an increased risk of infection and central vein stenosis (Hickson, 2014). One randomized trial, evaluating patients receiving dialysis with an LV ejection fraction ≥35% was stopped early for futility, with no difference in outcomes between those receiving and not receiving an ICD and a high number of adverse events associated with device implantation (Jukema, 2021). Newer, leadless subcutaneous devices may be a better option in the dialysis population.

C. Atrial fibrillation. Atrial fibrillation is the most common arrhythmia in both the general and the dialysis population and often occurs in patients with structural heart disease and, in particular, left atrial enlargement. Prevalence estimates for paroxysmal and permanent atrial fibrillation are as high as 30% in individuals with advanced CKD, including patients receiving dialysis.

1. **Drug therapy.** The benefits of rhythm versus rate control remain uncertain at this time. Several medications have traditionally been used for rate control in atrial fibrillation, including digoxin, β-blockers, nondihydropyridine calcium channel blockers, and amiodarone. β-Blockers or nondihydropyridine calcium channel blockers such as diltiazem are good choices for rate control in patients with intact systolic function, but the latter may be contraindicated in subjects with reduced cardiac function due to their negative inotropic effects. In these individuals, there is clearly a trade-off, as chronic control of tachycardia may be offset by a drug-related decrease in cardiac inotropy.

Although it is a less effective agent for rate control, digoxin is frequently used in patients with reduced systolic function. Paradoxically, digoxin use is also associated with a high risk of arrhythmias. When digoxin is used in patients receiving dialysis, extreme care must be taken to minimize electrolyte shifts and, in particular, hypokalemia. These patients should generally be dialyzed using a 3 mM potassium bath. Use of dialysis solution containing a lower concentration of bicarbonate may be helpful to prevent potassium shifts. Amiodarone may be the drug of choice when rate control is not adequate with β-blockers or calcium channel blockers. Importantly, owing to drug interactions among warfarin, amiodarone, and digoxin, combinations of these drugs should be used with caution.

2. **Anticoagulation.** Two questions remain unanswered in the dialysis population regarding anticoagulation in atrial fibrillation. The first is whether patients receiving dialysis should receive anticoagulation for primary prevention of thromboembolism in atrial fibrillation, and the second is which agent should be used if the decision is made to anticoagulate.

   The risks and benefits of anticoagulant therapy should be considered on an individual basis in all patients with chronic and paroxysmal atrial fibrillation receiving dialysis. There is a higher risk of both stroke and bleeding complications in patients receiving dialysis, and risk scores are not validated in this population. Warfarin use may increase the risk of vascular medial calcification, including calcific uremic arteriolopathy (calciphylaxis). Apixaban is increasingly used as an alternative to warfarin in the dialysis population. Apixaban, although not cleared by the kidney, does accumulate in patients receiving dialysis, and dosing remains uncertain. US and European dosing recommendations differ, with the US package insert suggesting a dose of 5 mg twice daily unless the patient is 80 years old or older or less than 60 kg, in which case the dose would be 2.5 mg twice daily. European guidance is more hesitant about the use of apixaban in the dialysis population but suggests a dose of 2.5 mg twice daily when this agent is utilized. The 2019 AHA/ACC/HRS Focused Update of the 2014 Guideline for the Management of Patients With Atrial Fibrillation states that “use of warfarin or apixaban might be reasonable in dialysis-dependent patients with atrial fibrillation, but further study is warranted.”

3. **Left atrial appendage occlusion.** The left atrial appendage is the primary source of thromboemboli in individuals with atrial fibrillation, making percutaneous left atrial appendage occlusion a potentially attractive alternative option to anticoagulation in patients with atrial fibrillation. In the general population, this procedure is considered for patients at increased risk of stroke with contraindications to long-term anticoagulation, a description that may apply to many patients dependent on dialysis, particularly those with clinically significant bleeding histories. Most procedures use transesophageal echocardiography to guide placement of the occlusion device that is placed via a femoral access. Most centers require anticoagulation with warfarin or a direct oral anticoagulant for at least 6 weeks after the procedure, followed by dual antiplatelet therapy for as long as 6 months. Many centers will also prescribe bacterial endocarditis prophylaxis following device placement.

VIII. STROKE. Cerebrovascular disease is very common in individuals with CKD, with a high incidence of both ischemic and hemorrhagic events. Even in the absence of clinically evident strokes, silent lesions and substantial brain white matter disease may be present. The presence of cardiovascular disease is associated with cerebrovascular manifestations in individuals with CKD, including worse cognitive function. As discussed previously, given the frequency with which atrial fibrillation occurs in individuals with kidney failure, the use of warfarin and other anticoagulants for stroke prophylaxis in the dialysis population urgently requires an adequately powered clinical trial to inform optimal treatment decisions.

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37 Obstetrics and Gynecology in Patients Undergoing Dialysis

Kavitha Vellanki and Susan Grossman

Derangements of the hypothalamic-pituitary-ovarian axis in the uremic milieu contribute to sexual dysfunction, dysmenorrhea, infertility, and abnormal uterine bleeding in women with end-stage kidney disease (ESKD). Fertility is decreased, but the possibility of conception is high enough and pregnancy risky enough that conception needs to be prevented when not wanted, planned when desired, and managed carefully by a multidisciplinary team when it does occur.

I. SEXUAL DYSFUNCTION

A. Incidence, etiology, and management. Data on sexual dysfunction in female patients undergoing dialysis are limited when compared to their male counterparts. Available literature reports a high prevalence of sexual dysfunction in dialysis-dependent women, as high as 85% to 100% in some studies (Strippoli, 2012). A multitude of reasons have been proposed for sexual dysfunction, including hyperprolactinemia, dyspareunia, gonadal dysfunction, comorbid conditions, medication side effects, fatigue, depression, and altered body image from catheters or fistula/grafts. Decreased libido and inability to achieve orgasm are most observed. Currently, there are no tested treatment options for the management of sexual dysfunction in dialysis-dependent women.

B. Hyperprolactinemia. Elevated circulating levels of biologically active prolactin hormone are seen in patients undergoing dialysis from increased production, and to a lesser extent, decreased metabolic clearance. Historical data from the 1970s and 1980s report hyperprolactinemia in 75% to 90% of dialysis-dependent women, with more recent data reporting no change in serum prolactin levels with more frequent dialysis compared to the regular 3× weekly schedule (Lo, 2017). Clinical manifestations and indications of treatment for hyperprolactinemia include hypogonadism and galactorrhea. Since some medications can cause high prolactin levels, a careful review of medications should be done prior to initiating workup. Several uncontrolled studies have reported improvement in sexual function in patients undergoing dialysis when treated with dopamine agonists (bromocriptine and cabergoline) for hyperprolactinemia. These agents have not been widely used in patients undergoing dialysis, as they are particularly prone to causing hypotension and need higher doses to suppress prolactin levels when compared to the general population.

C. Dyspareunia. Dialysis-dependent women can experience vaginal dryness and dyspareunia from estrogen deficiency as in the general population. Available treatment options include vaginal lubricants, moisturizers, estrogen therapy, and the selective estrogen receptor modulator ospemifene. Vaginal lubricants and moisturizers are effective in relieving symptoms associated with mild to moderate vaginal dryness, including dyspareunia, and are particularly suitable for women who cannot or do not

wish to use hormonal therapy. Both decrease the friction related to thin, dry vaginal tissue, and the main difference is how and why they are used (Edwards and Panay, 2016). Vaginal moisturizers are routinely used 2 to 3 times per week and not just during sexual intercourse. They rehydrate the vaginal mucosa and mimic natural vaginal secretions. Lubricants are only used during sexual activity to provide short-term relief from symptoms during sex. A wide variety of over-the-counter and prescription products are available and should be effective in dialysis-dependent women as in the general population. Estrogen supplementation may improve sexual function, but studies assessing the safety and efficacy in the dialysis population are lacking. As per the North American Menopause Society guidelines, local estrogen therapies (creams/rings/intravaginal tablets) can be prescribed for the treatment of vaginal symptoms associated with estrogen deficiency in postmenopausal patients undergoing dialysis; simultaneous progestin use is not recommended. Oral estrogen is rarely necessary in patients undergoing dialysis, and when needed, the risks versus benefits for the individual patient should be assessed. The lowest effective dose should be used, as the metabolism of orally administered estrogen is altered in patients undergoing dialysis; its metabolites are highly protein bound and therefore are poorly removed with dialysis. In rare circumstances when used, monitoring estradiol levels may be beneficial as side effects correlate with serum concentrations; the latter are not always dose dependent. Ospemifene at 60 mg daily dosing is effective in treating moderate to severe symptoms of vaginal dryness associated with menopause including dyspareunia and does not need any dose adjustment in ESKD. The major concern with long-term use is the potential risk for endometrial cancer, as it has an estrogen agonist effect on the endometrium. No data are available on its use in dialysis-dependent women.

II. BIRTH CONTROL

A. Indications. In a study of 76 women under the age of 55 at the start of dialysis, 50% were sexually active, 42% had menstrual cycles, and 36% used birth control. Only 13% reported discussions with their nephrologist about pregnancy and contraception (Holley, 1997). The absence of luteal hormone and estradiol peak in the second half of the menstrual cycle leads to anovulation, and secondary amenorrhea is common. Although infertility is considered the rule in dialysis-dependent women, accumulating evidence points to increasing fertility rates with increasing dialysis intensity. Conception occurred in 15% of the women receiving dialysis for 36 hours or more per week in the nocturnal dialysis program at the University of Toronto (Barua, 2008). Better management of anemia and fluid overload are cited as other plausible factors playing a role (Ankawi, 2024). It is often difficult to identify women with high risk for conception, as pregnancies have occurred in dialysis-dependent women following years of amenorrhea. In general, women who have become pregnant with renal insufficiency prior to starting dialysis and women who have regular menstrual cycles while receiving dialysis care are at increased risk of conception. Safe and effective contraception should be offered to all patients undergoing dialysis who do not wish to conceive, but also to women who choose to conceive, so pregnancy can be planned with appropriate prepregnancy counseling and optimization of maternal care, so that when pregnancy does occur, the chances of a successful outcome will be increased.

B. Methods of contraception. There are several different categories of contraceptive

devices available, the choice to be guided by the patient's preference, underlying comorbid conditions, and timing of conception (Burgner and Hladunewich, 2020).

1. **Barrier methods:** Diaphragms and condoms can be used by patients undergoing dialysis in the same manner as by women with normal renal function. In terms of pregnancy prevention, high failure rates, 25% to 29% per year, have been reported with these methods in normal women, although much of this may be related to improper use. The failure rates might be lower in patients undergoing dialysis as fertility is decreased, but no estimates are available for comparison. Spermicides can be used along with these barrier methods.
2. **Intrauterine devices** are good birth control methods for women treated with either hemo- or peritoneal dialysis (PD). Although there are concerns that intrauterine device use might increase the risk of peritonitis in women treated with PD, available data are limited to a few case reports.
3. **Combined estrogen-progestin contraceptive formulations and devices** are the most widely used contraceptives in the general population. They are available as oral pills, transdermal patches, transvaginal rings, and injectables. They contain estrogen and progestin in various amounts. Since dialysis-dependent women are at increased risk of cardiovascular disease, thrombotic events, and uncontrolled hypertension, combined hormonal agents should generally be avoided. Progestin-only contraception could be a good alternative, with spotting being the most common side effect. The injectable form of progestin is not a good option for women who wish to conceive soon, as it may take up to 18 months for fertility to be restored after stopping the medication.
4. **Sterilization** should be considered in women who have completed their families or who choose to never conceive again. Appropriate counseling about permanent sterility should be provided and where applicable, partner sterilization is advised if the woman has significant surgical or anesthetic risk.

   Many women on dialysis have prolonged period of anovulatory bleeding due to the unopposed effect of estrogen on endometrium. Estrogen-progesterone cycling can reduce the risk of endometrial cancer associated with unopposed estrogen. The risk-benefits of such an approach in dialysis-dependent women are not known. The provision of estrogen also provides the theoretical benefit of preventing bone loss from the effects of estrogen deficiency in ESKD but estrogen is no longer considered a first-line agent for the prevention of bone loss in all women. Treatment of infertility in dialysis is generally not attempted, as pregnancy is dangerous to the mother and outcomes are still poor.

III. PREGNANCY

A. Frequency.

As pregnancy cannot lend itself to randomization and fertility is diminished in dialysis-dependent women, available data are almost exclusively derived from case reports, case series, or surveys. The first successful conception in a patient undergoing dialysis was reported in 1971 (Confortini, 1971). The woman had been on chronic hemodialysis for more than 2 years before conceiving and delivered a viable infant. Since then, various estimates of pregnancy in dialysis-dependent women of childbearing age from various parts of the world over different time frames have ranged from 0.3% in Belgium to 0.5% in the United States (Okundaye, 1998) to 1.4% in Saudi

Arabia to as high as 15% in women receiving nocturnal hemodialysis. Rates of pregnancy are 2 to 3 times higher in women on hemodialysis compared to PD. The exact reasons for this are unclear. Proposed explanations have included presumed adverse effects of hypertonic peritoneal dialysate or prior episodes of peritonitis, leading to adhesions interfering with the transport of ova to the fallopian tube.

B. Outcomes. Despite the risks of prematurity and low birth weight being high, the likelihood of pregnancy in ESKD resulting in a surviving infant has steadily increased over the years, from 23% in the 1980s to around 50% in the 1990s and as high as 86% with more than 36 hours per week of intensive dialysis in 2013. Unsuccessful pregnancies are not often reported, and many women find it hard to adhere to long and frequent dialysis treatments, so the incidence of successful pregnancies in the current period of more intense dialysis could be lower than some of the optimistic published experience. In an Italian cohort followed from 2000 to 2012, women on dialysis had a 10-fold lower probability of delivering a live-born baby than those who had a kidney transplant, who in turn had a 10-fold lower probability of delivering a live-born baby when compared to the overall population (Piccoli, 2014). The likelihood of having a successful outcome is higher for women who start dialysis after conception (90%) compared to women who conceive on chronic dialysis. Early pregnancy losses before 20 weeks in women on dialysis contribute to poor outcomes in this group (Jesudason, 2013).

C. Diagnosis. A high index of suspicion is required to make a timely diagnosis of pregnancy in ESKD, as amenorrhea is common and symptoms of early pregnancy such as nausea are often attributed to metabolic or gastrointestinal problems. Urine pregnancy tests are not reliable even if the woman is not anuric. Blood tests for beta-human chorionic gonadotropin (β-HCG) levels should be checked prior to imaging studies for abdominal complaints. Serum β-HCG levels should be interpreted with caution in ESKD, as levels tend to be slightly elevated even in nonpregnant patients undergoing dialysis due to impaired renal excretion. Occasionally, such borderline elevations in serum β-HCG levels have led to the cancellation of elective surgery. In pregnant women undergoing dialysis, β-HCG levels are elevated to a degree that is greater than expected for gestational age, so gestational age is best assessed by ultrasound. Fetal heartbeat is first detected by 5 to 6 weeks whereas β-HCG appears in the maternal circulation 8 to 10 days after ovulation and peaks at 8 to 10 weeks in normal pregnancies. Elevated β-HCG levels in ESKD can lead to the mistaken impression of pregnancy being more advanced than it is (Potluri, 2011). Failure to appreciate the higher β-HCG levels in pregnant patients undergoing dialysis can lead to a mistaken diagnosis of hydatidiform mole and nonviable pregnancy. When a nonviable pregnancy is suspected early in the first trimester, the diagnosis should be confirmed by measuring serial β-HCG levels as levels decrease in a nonviable pregnancy, albeit more slowly than in a woman with normal renal function. Similarly, serum tests of α-fetoprotein done for screening of Down syndrome may be falsely elevated in pregnant women undergoing dialysis; amniocentesis with karyotyping is often done to confirm abnormal results.

D. Management of hypertension during pregnancy. The major maternal risk associated with pregnancy in patients undergoing dialysis is severe hypertension, and 80% of pregnant women on dialysis have some degree of hypertension (blood pressure [BP] > 140/90 mm Hg). The first step toward BP control, as in a nonpregnant patient

undergoing dialysis, would be to make sure the woman is euvolemic. With more frequent hemodialysis, complications related to hypertension have decreased significantly because fluid overload is then less of an issue. Regardless, pregnant women on dialysis should be taught to check their BP on nondialysis days at home and report promptly any increase or decrease. Home monitoring of BP should continue for at least 6 weeks postpartum.

1. **Superimposed preeclampsia.** Pregnant women receiving chronic dialysis are at increased risk of superimposed preeclampsia; 20% of pregnancies in patients with ESKD are complicated by preeclampsia. The diagnosis is difficult to make in the absence of HELLP (Hemolysis, Elevated Liver Enzymes, Low Platelets) syndrome. Worsening hypertension in a euvolemic, pregnant, anuric woman on dialysis may be the only sign of preeclampsia and should lead to prompt patient assessment when that happens. Emerging evidence on the use of angiogenic factors in the diagnosis of preeclampsia is highly promising, with the major limitation being the availability and standardization of the tests for routine clinical practice (Andronikidi, 2024). The National Institute of Health and Care Excellence (NICE) guidelines from the UK suggest offering specific testing for placental growth factor (PIGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) between 20 and 37 weeks of gestation when preeclampsia is clinically suspected. A low PIGF (<100 pg/mL or <5th percentile for gestational age) and an increased sFlt-1 to PIGF ratio greater than 38 have been shown to be highly predictive of preeclampsia and related adverse maternal/fetal outcomes. These cut-off values have not been specifically studied in pregnant women with ESKD. Low-dose aspirin should be considered for the prevention of preeclampsia, preferably initiated before 16 weeks and discontinued by 36 weeks.
2. **Drug therapy for hypertension.** Several first-line agents can be used safely if BP remains higher than 140/90 mm Hg when the patient is euvolemic, including methyldopa, labetalol, and calcium channel blockers. There is less experience with other β-blockers and clonidine but, except for atenolol, these are considered safe. Hydralazine can be added to any of these first-line drugs but does not work efficiently as a single agent when given orally. Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers are contraindicated in pregnancy. Contradictory data exist on the risk of congenital anomalies with first-trimester exposure to ACE inhibitors, and pregnancy does not need to be terminated in such a case.
    a. **Severe hypertension.** Intravenous hydralazine is the drug of choice for hypertensive crisis in pregnant women and should be given in doses of 5 to 10 mg every 20 to 30 minutes. Labetalol is a good alternative. It can be given as a 20-mg bolus repeated every 30 minutes to a maximum dose of 220 mg or as a continuous infusion with 1 to 2 mg/min followed by 5 to 10 mg/h to a maximum of 300 mg.
    b. **Magnesium.** Magnesium is superior to anticonvulsants for seizure prophylaxis in preeclampsia. It is to be used with caution in patients undergoing dialysis. A loading dose can be given safely. Additional magnesium doses should not be given until after dialysis or until a decrease in the serum magnesium level has been demonstrated. Magnesium potentiates the hypotensive effects of calcium channel blockers, and any calcium channel blocker should be stopped if

magnesium is required.

E. Dialysis regimen during pregnancy

1. **Dialysis modality.** Prior reports have shown no difference in pregnancy outcomes with dialysis modalities. However, in a recent systematic review of available data, the prevalence of small for gestational age babies was twice as higher in women on PD compared to those on hemodialysis (67% vs 31%, respectively; Piccoli, 2016). It is easier to increase the amount of dialysis delivered with hemodialysis, and the higher pregnancy success rates with intensified dialysis have been achieved in women on hemodialysis. Although dialysis modality should not be changed due to pregnancy, it may be easier to start hemodialysis in a pregnant woman than PD. If PD is elected, the placement of the peritoneal catheter is possible only at an early stage of pregnancy, but immediate use and increased intra-abdominal pressure may increase the risk of leaking around the catheter. There have been instances of mechanical problems with peritoneal catheters with changes in fetal position. For pregnant women already receiving PD, additional dialysis can be provided as needed with hemodialysis, especially in those with no residual renal function, when pregnancy is near term, rather than switching the modality completely. Continuing PD can decrease the frequency and associated travel burden with in-center hemodialysis.
2. **Intensive dialysis.** There is growing evidence that the likelihood of a surviving infant is increased with intensive dialysis (Oliverio and Hladunewich, 2020). The ideal number of hours of dialysis has not been established. There was a marked improvement in the outcomes of women dialyzed for more than 20 h/wk with a corresponding decrease in severe infant prematurity compared with less intense regimens (Hou, 2010). Infant survival was 75% for pregnancies in the group dialyzed more than 20 h/wk compared to less intensively dialyzed groups, with mean gestational ages of 34 weeks versus 30 weeks in the respective groups. Even better outcomes are seen in women undergoing nocturnal hemodialysis for 48 hours weekly, with most infants surviving and born close to term (Nadeau-Fredette, 2013). In a comparison of pregnancy outcomes in the United States versus Canada, there was a suggestion of a “dose-response” relationship between the duration of weekly dialysis and pregnancy outcomes (Hladunewich, 2014). There may be some amount of dialysis between 20 and 48 hours a week that will lead to satisfactory outcomes in women with no residual renal function. Daily dialysis decreases the fluid removal at each treatment, decreasing the risk of hypotension during dialysis. Daily dialysis also allows the patient to eat a high-protein diet to ensure that the needs of pregnancy are met.

   Typically, no dietary restrictions are required, and every pregnant woman undergoing dialysis should be assessed by a dietitian for adequate caloric and protein intake to meet maternal and fetal needs. A midweek serum urea nitrogen less than 35 mg/dL (12.5 mmol/L) is targeted in pregnant women on dialysis with residual renal function (Luders, 2018).
3. **Dialysis solution calcium.** It is estimated that an average full-term fetus contains approximately 30 g calcium, 20 g phosphorus, and 0.8 g magnesium, and about 80% of these minerals are accreted during the third trimester; calcium transfers from mother to infant at a rate of 300 to 350 mg/d during the final 6 weeks (Kovacs,

2015). Total and free calcitriol levels increase during normal pregnancy and may reach triple the nonpregnant values. Conversely, calcitriol levels have been reported to be low in pregnant anephric women on dialysis. In pregnant women on dialysis, a positive calcium balance of 200 mg per treatment can usually be achieved with 2.5 mEq/L (1.25 mmol/L) calcium concentration in the dialysate. Since both maternal hypercalcemia and hypocalcemia are associated with adverse neonatal outcomes, predialysis serum calcium and phosphate levels should be checked weekly, and dialysate calcium/vitamin D analogues adjusted promptly. Additional oral calcium supplementation can be prescribed if needed. Phosphate binders are not required with increasing intensity of dialysis during pregnancy, hypophosphatemia is more common, and phosphate can be added to the dialysate. If phosphate binders are required, calcium-containing binders are the only group known to be safe in pregnancy. There is limited experience with sevelamer or lanthanum carbonate in pregnancy. Vitamin D analogues are considered safe in pregnancy. Experience with cinacalcet is limited to a few case reports of use in primary hyperparathyroidism.

4. **Dialysis solution bicarbonate.** Serum bicarbonate in normal pregnancy is 18 to 20 mmol/L. More frequent dialysis with a standard dialysis bath of 35 mEq/L carries a theoretical risk of alkalosis. A 25-mEq/L bicarbonate bath is usually effective in avoiding alkalosis. When this bicarbonate concentration is not available, bicarbonate can be removed by increasing ultrafiltration and replacing the losses with normal saline.
5. **Dialysis solution sodium.** Normal serum sodium is decreased during pregnancy to approximately 134 mmol/L. Since thirst is normal, the pregnant woman will take in enough water to keep serum sodium at these levels, even if a higher dialysate sodium is used. As this could lead to fluid overload, dialysate sodium can be adjusted down to match serum sodium in such patients.
6. **Monitoring weight gain.** Determination of optimal estimated dry weight is problematic in a regular nonpregnant patient undergoing dialysis; this becomes even harder during pregnancy. Recommended weight gain over the course of their pregnancy for women initially at their ideal body weight is 11.5 to 16 kg. Only 1.6 kg of this weight gain occurs in the first trimester. It is often difficult to assess how much of the intradialytic weight gain is from pregnancy-associated weight gain or due to excess fluid gain unrelated to pregnancy. Estimated dry weight should be increased gradually during pregnancy after carefully assessing for signs of fluid overload, with the understanding that pedal edema in a pregnant woman on dialysis is not always synonymous with fluid overload. A 1- to 2-kg increase in dry weight during the first trimester and 0.5 kg/wk in the second and third trimesters is reasonable, depending on the prepregnancy body mass index. Serial ultrasound imaging for the determination of amniotic fluid volume can help in determining the optimal dry weight. With daily dialysis, volume-related hypertension is minimized, and preeclampsia should be considered if BP is found to be elevated during dialysis.
7. **Heparinization.** Clotting of the extracorporeal circuit of the dialysis access occurs frequently during pregnancy. Heparin does not cross the placenta and unless there is vaginal bleeding it is not necessary to lower the dose.
8. **Management of anemia.** Anemia in pregnant women is associated with premature birth and low birth weight. The hemoglobin level at which anemia

contributes to these problems is not well established. Patients undergoing dialysis who become pregnant usually experience worsening anemia as plasma volume increases, but the increase in red cell mass is limited by erythropoietin deficiency. Target hemoglobin levels for pregnant women on dialysis have not been established, but a target hemoglobin of 10 to 11 g/dL (100-110 g/L) is usually aimed for as in the nonpregnant population undergoing dialysis. Increasing requirements of iron and erythropoietin are expected during pregnancy.

a. **Erythropoiesis-stimulating agents (ESAs).** It has been usual practice to continue erythropoietin during pregnancy. Recombinant erythropoietin does not cross the placenta, but it is not known whether darbepoetin crosses the placenta. There are a few case reports of the use of darbepoetin in pregnancy without problems. ESAs have been originally classified as Category C for use during pregnancy by the United States Food and Drug Administration (FDA) based on animal data. Multidose vials or bacteriostatic saline vials contain benzyl alcohol; this chemical is contraindicated in pregnancy and should be avoided. Single-dose vials (not mixed with bacteriostatic saline) should be used. Erythropoietin use has been associated with hypertension in nonpregnant patients, but it is difficult to determine what factors influence hypertension in pregnancy.
b. **Iron therapy.** Normal women require 700 to 1,150 mg of iron during pregnancy. Daily dialysis increases iron losses compared with losses associated with three-per-week dialysis treatments. An increase in iron requirements is observed in pregnant women on dialysis. There is a little-known downside to treating iron deficiency. The optimal transferrin saturation and ferritin levels for pregnant women on dialysis are not known, and the cut-offs used are the same as in the nonpregnant population on dialysis. Because of the high rate of transfer to the fetus, especially after 30 weeks' gestation, we limit individual intravenous iron doses to 62.5 mg. The FDA has labeled ferric gluconate and iron sucrose as category B risk for pregnancy.
c. **Folate.** Folate requirements are increased in normal pregnancy, and deficiency is associated with an increase in neural tube defects. Due to increased loss with intensive hemodialysis, folate supplementation of 4 to 5 mg daily is required in pregnant women treated with hemodialysis.

IV. LABOR AND DELIVERY.

Premature birth is common and occurs in up to 80% of infants born to patients undergoing dialysis. Multiple factors, including maternal hypertension, fetal distress, and premature labor, play a role. Serial measurements of cervical length with cerclage as needed, terbutaline, magnesium, nifedipine, and indomethacin have all been used in attempts to prevent or treat premature labor. Magnesium has been given intravenously in hemodialysis and added to PD solution in PD. When additional magnesium is given, serum magnesium levels should be monitored frequently to avoid hypermagnesemia. The use of magnesium in combination with nifedipine should be avoided due to the risk of profound hypotension. Although drugs used to prevent premature labor are intended for short-term use, premature labor recurs and repeated use of such drugs can be problematic. Planned induction at or just after 37 weeks, involving a multidisciplinary team of high-risk obstetricians, neonatologists, and nephrologists, is considered standard of practice. When needed, cesarean section can be done extraperitoneally in patients

undergoing PD, leaving the catheter in place and resuming dialysis 24 hours after delivery, starting with small exchange volumes and increasing the fill volume over the next 48 to 72 hours. If there is leakage or incision-site complications, patients can be transitioned to hemodialysis for several weeks.

Infants born to dialysis-dependent women are frequently small for gestational age, and even those that appear normal should be monitored in a high-risk nursery. An infant at birth whose kidneys are normal for gestational age will have serum urea nitrogen and creatinine levels similar to those of the mother. A solute diuresis can occur, requiring close monitoring of electrolyte and volume status. There does not appear to be an increased risk of congenital anomalies, but information regarding growth and development in children born to dialysis-dependent women is limited.

V. ABNORMAL UTERINE BLEEDING

A. Incidence.

Many women develop amenorrhea when the glomerular filtration rate falls to less than 10 mL/min. Menstruation returns in as many as 60% of patients once dialysis is started. Regular menstruation has become more common in premenopausal women with ESKD than it was in the early days of dialysis; however, over 70% of women on renal replacement therapy report irregular cycles and/or heavy menstrual bleeding (Lin, 2016). Women on hemodialysis and those on PD report similar menstrual abnormalities. Uterine bleeding is common and is of concern because it may be an early sign of endometrial cancer. In addition, heavy blood loss may lead to severe anemia even in women treated with ESA, although the introduction of ESAs has made the management of abnormal uterine bleeding substantially easier.

B. Management

1. **Screening for malignancy.** Management depends on age and perceived cancer risk. The incidence of cancer in general is higher among patients with ESKD on dialysis than in the general population as is the overall cancer death rate (Au, 2019), but whether the incidence rates of endometrial, ovarian, or cervical cancer are higher is unclear.
    a. **Women older than 40 years** who have abnormal uterine bleeding should have endometrial sampling. There is an excellent correlation between the histopathology of endometrial specimens taken by biopsy in the office and D&C (dilatation and curettage) performed in the operating room. If the endometrial biopsy is nondiagnostic, or if bleeding persists after a negative biopsy, then further diagnostic testing should be done.
    b. **Women younger than 40 years.** The cancer risk is relatively small, and routine screening, either cytology every 3 years (Pap test) or high-risk human papillomavirus testing every 5 years, can be continued. Women with systemic lupus or on chronic immunosuppressive therapy should follow a more intense protocol, such as cervical cancer screening for HIV-positive women: either annual Pap testing or combined testing by Pap test plus high-risk human papillomavirus testing. If both are negative, then repeat testing can be done in 3 years.
2. **Anticoagulation.** The lowest possible dosage of heparin should be used to perform hemodialysis when a woman is menstruating. Heparin-free techniques are available as described in Chapter 13.

3. **Bloody peritoneal fluid during PD.** During menstruation or ovulation, the peritoneal fluid can become bloody (Lew, 2007). There is no specific management, except perhaps to avoid the addition of heparin to the PD solution (which sometimes is added in patients with impaired drainage). In some cases, frank hemoperitoneum may occur, requiring suppression of ovulation (Harnett, 1987). An aseptic peritonitis picture during menstruation or ovulation has been reported (Poole, 1987). Bloody peritoneal fluid frequently occurs after gynecologic procedures.
4. **Management of anemia.** Anemia should be managed with erythropoietin, as in other patients undergoing dialysis. Heavy uterine bleeding will result in increased iron requirements, and additional intravenous iron may have to be given.
5. **Hormonal therapy.** Given the evidence that hormonal replacement therapy may increase the incidence of cardiovascular events, and the excess cardiovascular mortality among women with ESKD, the risks associated with hormone replacement therapy may outweigh the benefits (see discussion below).
    a. **Intrauterine delivery of progesterone** using the levonorgestrel-releasing intrauterine system (LNG-IUD 52) is the first-line treatment for patients with ESKD who are experiencing abnormal uterine bleeding. This system is highly effective and, in most cases, will obviate the need for systemic hormonal therapy. Once the intrauterine device has been implanted, scanty menstruation should develop within 3 months. Peritonitis has been reported after placement of intrauterine devices in patients on PD, so these patients should receive prophylaxis prior to insertion. (American College of Cardiology guidelines do not recommend routine antibiotic prophylaxis prior to intrauterine device insertion to prevent endocarditis.)
    b. **Oral contraceptives** are a second-line treatment but should be avoided if BP control or risk of thrombotic disease is a problem.
    c. **Medroxyprogesterone acetate (Depo-Provera).** Progesterone can be given either intramuscularly as Depo-Provera 100 mg once a week for 4 weeks or orally as 10 mg daily for the first 10 days of the menstrual cycle. This drug is best reserved for patients with chronic hypermenorrhea who do not respond to more conservative intrauterine or oral hormonal therapy. Because many patients on dialysis have a bleeding tendency, intramuscular injections on a regular basis are undesirable. Moreover, the half-life of intramuscular medroxyprogesterone acetate in patients undergoing dialysis is unpredictable. Progestins work best in the setting of anovulatory bleeding.
6. **Other drugs**
    a. **Tranexamic acid.** This antifibrinolytic is a synthetic lysine derivative that can be used by women who want to avoid hormonal therapy or are trying to conceive. It decreases heavy menstrual bleeding by about 50%. One advantage is that it only needs to be taken while the woman is menstruating. Tranexamic acid therapy is contraindicated in women with seizure disorders or a history of thrombosis. Suggested doses for patients with ESKD are 12.5 mg/kg every 12 to 24 hours orally or 5 mg/kg every 12 to 24 hours intravenously.
    b. **Gonadotropin-releasing hormone agonists.** These can be given as an intramuscular injection once a month (leuprolide acetate) or as a daily intranasal dose. These drugs are extremely expensive and should be reserved for patients

who continue to have excessive menstrual bleeding despite treatment with intrauterine progesterone, oral contraceptives, progestins, or tranexamic acid. They may be particularly helpful in patients who will be undergoing chemotherapy or who require ongoing anticoagulation therapy. There is one report of ovarian hyperstimulation in a patient on chronic dialysis who received two doses of leuprolide acetate (Hampton, 1991).

c. **High-dosage intravenous estrogens.** In the case of acute excessive blood loss, high-dosage estrogen therapy can be used, giving 25 mg of conjugated estrogens IV every 6 hours. Bleeding usually subsides within 12 hours.
d. **Desmopressin.** In a setting of acute blood loss when bleeding time is prolonged, desmopressin should be given in a dosage of 0.3 pg/kg in 50 mL of saline every 4 to 8 hours for three to four doses.
e. **Nonsteroidal anti-inflammatory agents** have been shown to be effective in women who ovulate. These agents may be less effective in the setting of ESKD because of the increased incidence of anovulatory cycles. Also, women with ESKD are at increased risk for gastrointestinal complications.

7. **Surgical treatments**
   a. **Endometrial ablation.** Endometrial ablation can be performed by several surgical techniques: hysteroscopic endometrial ablation with laser, photocoagulation, roller ball, or loop resection. Patients are pretreated with either danazol or gonadotropin-releasing hormone for 3 to 4 weeks before the procedure to thin the endometrium. The procedure leads to permanent infertility.
   b. **Hysterectomy.** For postmenopausal women with significant uterine bleeding, hysterectomy may be the approach of choice. Laparoscopic hysterectomy is now an option, and for leiomyomata too large for laparoscopic surgery, gonadotropin-releasing hormones can be given to reduce the size of fibroids enough to make laparoscopic hysterectomy possible. The proposed operation should be carefully discussed with the patient, and concomitant medical problems and the risks of surgery should be taken into consideration. With the advent of endometrial ablation with laser, hysterectomy will now probably be reserved for women who have bleeding secondary to uterine fibroids or to other uterine or pelvic pathology that in itself warrants the surgery. Hysterectomy should be done only as a life-saving procedure in a premenopausal woman who is a candidate for renal transplantation because the latter will frequently restore fertility.

VI. HORMONE REPLACEMENT THERAPY.

Women with ESKD experience menopause on average 5 years earlier than women without renal failure (Garg and Ramalakshmi, 2020). The role of hormone replacement therapy in patients undergoing dialysis has never been clear. About 10% of postmenopausal women on dialysis take hormonal replacement therapy (Kramer, 2003). Most report that hormonal replacement therapy was started before the initiation of dialysis. Of women not taking hormone replacement therapy, a majority say they would not start if advised to do so by their doctors. Evidence of the risk of hormonal replacement therapy raises concern about its use in patients with ESKD. The Women's Health Initiative Study demonstrated an increased risk of breast cancer, pulmonary embolism, deep vein thrombophlebitis, and coronary and cerebrovascular disease after long-term replacement of estrogen and progesterone in normal postmenopausal women. The only

health advantage for women in the treatment group was reduced fractures. Women with ESKD have more than a 20-fold increased incidence of cardiovascular disease compared to women without ESKD. Multifactorial bone disease is more common and more severe in patients undergoing dialysis than in healthy people of the same age and sex. The risk of hip fracture is also higher. When young women on dialysis who have regular menses are compared with young women with amenorrhea, the group with amenorrhea has a significantly lower bone mineral density. Raloxifine 60 mg daily has been used successfully to prevent bone loss in estrogen-deficient patients undergoing dialysis, and this drug provides a safe alternative to hormone replacement therapy.

Given this background, the use of hormone replacement therapy should be limited to the relief of symptoms of estrogen deficiency that cannot be relieved by other treatments. Only the patient can decide the importance of relieving these symptoms after understanding the risks. The increased risk of cardiovascular disease and breast cancer in healthy women taking hormone replacement therapy was small enough that many women have continued them. Unfortunately, the specific risk of hormone replacement therapy in patients with ESKD has not been determined, and we can only extrapolate from the data in healthy women and women with preexisting heart disease when advising patients of the risk.

It is still general practice to treat women with premature ovarian failure or early surgical menopause with hormonal replacement therapy. It may be difficult to know whether a woman is postmenopausal since even women with serum levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in the postmenopausal range may normalize their values after transplant. A very small study (n = 13) of premenopausal patients undergoing dialysis taking hormonal replacement therapy found an improvement in sexual function and general well-being as well as an improvement in L2-L4 bone density (Matuszkiewicz-Rowiñska, 1999). Hormone replacement therapy is contraindicated in women with active liver disease and deep vein thrombophlebitis. Estrogen may make lupus flares more likely and may worsen hepatic cystic disease in women with polycystic kidney disease. If hormone replacement therapy is prescribed, the dose should be adjusted in women on dialysis. Estrogen levels increase more in patients undergoing dialysis than in normal controls when estrogen is administered. If oral estrogen is given, the dose used should be about half of what would be given to a woman without renal failure. Transdermal estrogen may have less effect on clotting factors than oral estrogen.

VII. GYNECOLOGIC NEOPLASMS

A. Benign. Uterine fibroids are extremely common, occurring in as many as 80% of women over the age of 30, with approximately 25% of them being symptomatic. There is no information about the incidence of fibroids in patients with chronic renal failure. Uterine fibroids usually present with either menometrorrhagia or symptoms related to the enlarging uterus pressing on nearby organs, that is, pain, pressure, and constipation. Small, asymptomatic fibroids can be managed with observation. Indications for therapy include symptomatic bleeding, pain or pressure, urinary retention, torsion, degeneration with acute abdominal pain, prolapse through the cervix, and increase in size after menopause. Women still in the childbearing age range who are potential candidates for transplant should have a myomectomy performed rather than a hysterectomy if that is surgically feasible, to preserve childbearing potential. Recently, several treatments other than hysterectomy have become available, including medical therapy with the

abortifacient mifepristone, gonadotropin-releasing hormone agonists, laparoscopic myomectomy, myolysis, and uterine artery embolization. Laparoscopic myomectomy should not be done in women who plan childbearing because of the increased risk of uterine rupture with pregnancy.

B. Cancer screening

Women treated with dialysis are less likely to get regular mammograms and Pap smears than women in the general population. The incidence of cervical cancer may be increased in women with ESKD, while the incidence of breast cancer is similar to that in women without kidney disease. Several recent studies suggest that screening for malignancies in women with ESKD results in a negligible increase in life expectancy because of the shortened survival of women with ESKD (Kajbaf, 2002). Such an outlook does not allow for the possibility that strides are being made in the care of patients with ESKD, leading to prolonged survival.

Young women, women awaiting transplantation, and women with increased risk for breast or cervical cancer should be screened. Women with the highest risk for cervical cancer include women who have been treated with immunosuppressive therapy or who are currently on immunosuppressive therapy, either for previous transplant or for their underlying disease, and also, women with human immunodeficiency virus (HIV). These women should have Pap tests performed every year or combined testing with Pap smears and high-risk human papillomavirus testing; if negative, this test should be repeated in 3 years as discussed earlier.

C. Evaluation of cancer for women who are symptomatic.

Endometrial cancer usually presents as abnormal uterine bleeding, the investigation and management of which have been discussed above. Ovarian cancer usually presents with vague abdominal symptoms and later as an ovarian mass. Abdominal discomfort, nausea, and weight loss induced by ovarian cancer may initially be misinterpreted as symptoms of uremia or underdialysis. In patients on PD, ovarian cancer may present as bloody peritoneal fluid, an abnormal peritoneal cell count, or a change in the color of the fluid. A high index of suspicion is necessary to detect ovarian cancer at an early and potentially curable stage. The use of the tumor marker CA-125 to screen for or follow ovarian cancer is of limited value in patients undergoing dialysis. This marker is not efficiently removed by dialysis and is also produced by mesothelial cells, giving rise to elevated levels, especially in patients undergoing PD.

D. Diagnostic procedures

1. **Lower gastrointestinal series.** When performing the lower gastrointestinal examination, the amount of water used to dilute the contrast material can be reduced to one-fourth the normal amount.
2. **Computed tomography (CT).** Intravenous contrast infusion, if needed to perform a CT scan or angiography, is not contraindicated in patients undergoing dialysis. Although the administration of contrast involves increasing intravascular volume and osmolality, immediate dialysis following the study can be performed in the rare instances of associated symptoms. Dialysis can be done the following day if the patient is asymptomatic. A patient on PD requiring an abdominal CT scan should present for the examination with dialysis fluid in the abdomen.
3. **Pelvic and abdominal ultrasonography.** The patient on PD with a suspected pelvic or ovarian lesion should undergo ultrasound scanning of the involved area. In

those instances where pelvic pathologic changes cannot be visualized without distending the bladder, the bladder can be filled via a Foley catheter.

4. **Transvaginal versus transabdominal ultrasound.** It is possible to delineate pelvic abnormalities more clearly using transvaginal ultrasound, because of the proximity of the probe to the pelvic organs and the relatively thin vaginal vault, which enables the use of higher sound frequencies and therefore higher resolution. On the other hand, the transabdominal probe will give a more panoramic view of the pelvis, showing the interrelationship of the major anatomic structures in the pelvic organs and their possible pathology. The transvaginal probe is able to furnish a more focused image of the organ of interest but only permits effective imaging to no more than 7 to 10 cm in depth. Unlike transabdominal pelvic ultrasound, it is best for the patient to have the transvaginal ultrasound study done while the bladder is empty. Since many patients on dialysis are not able to fill their bladders unless a Foley catheter is placed and fluid instilled into the bladder, it makes sense to first perform a transvaginal ultrasound if pelvic pathology is suspected and proceed to transabdominal pelvic sonogram if the information needed cannot be obtained with the transvaginal approach. Patients undergoing PD should have the abdomen full for transabdominal ultrasound and empty for transvaginal ultrasound.
5. **Magnetic resonance imaging (MRI).** For women who are on PD, an MRI of the peritoneal cavity can be done without any contrast, using the dialysate as a contrast medium, making MRI of the abdomen and pelvis the best modality to evaluate potential anatomic abnormalities. The use of gadolinium as a contrast agent to enhance MRI should be done only after considering the potential risk of nephrogenic systemic fibrosis. There is some evidence that when dialysis is done after an MRI to help remove infused gadolinium, the risk of nephrogenic systemic fibrosis is not as high as once thought (Schieda, 2018).
6. **PET-CT (positron emission tomography-computed tomography) scanning.** There does not need to be any adjustment in the performance of PET-CT scans; although there may be slight differences in readings for patients with ESKD (Toriihara, 2015).

E. Management. The management of gynecologic cancers and nonmalignant tumors in women with chronic renal failure includes surgical excisions and chemotherapy.

1. **Surgery.** In patients undergoing PD, any gynecologic procedure more invasive than a Pap smear (eg, endometrial or cervical cone biopsy) should be performed with an empty peritoneal cavity (Ma, 2012). The patient should receive prophylactic antibiotics as described below. In patients with peritoneal catheters undergoing pelvic or abdominal operations, we leave the catheter in place unless there is bacterial contamination of the peritoneal cavity. When there is a low but measurable risk of peritoneal contamination as in a vaginal hysterectomy, we administer 1.0 g of vancomycin hydrochloride and 1.0 g of cefoxitin prophylactically IV just prior to surgery. If the patient is known to be colonized with *Pseudomonas*, tobramycin 2.0 mg/kg IV should be added to the prophylactic regimen. Postoperatively, the catheter is irrigated with 500 mL of PD solution 3 times daily to maintain patency. Irrigations are decreased to once daily when the fluid is no longer bloody. We wait 10 to 14 days before using the catheter again, maintaining the patient by hemodialysis during the interim.

2. **Chemotherapy.** The use of chemotherapeutic agents in patients undergoing dialysis is beyond the scope of this handbook.

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38 Nervous System and Sleep Disorders

Christopher W. McIntyre

Patients with chronic kidney disease (CKD) are subject to a wide variety of pathophysiologic processes that challenge the structural and functional integrity of both central and peripheral nervous systems. Neurologic dysfunction can be episodic or chronic and can reflect a wide range of humoral, metabolic, inflammatory, and vascular insults. These may be attendant to the underlying conditions that have led to end-stage kidney disease (ESKD), advanced uremia itself, or to the dialysis procedure (on a variety of levels). The integrated product of these factors contributes to neurocognitive performance, depression, health-related quality of life, and the ability of the patient to tolerate the dialysis procedure while leading a full and independent life in the hours spent not actually receiving dialysis. This chapter is limited to a discussion of the brain and the peripheral nervous system and encompasses sleep disorders and combination pathologies such as restless legs syndrome.

I. CENTRAL NERVOUS SYSTEM. When considering dysfunction of the central nervous system (CNS) in patients with uremia undergoing dialysis, it's important to consider the range of structural abnormalities that can occur, as well as the impact of the uremic milieu. Many of these considerations are often present together and may result in compound effects.

A. Intracranial bleeding and ischemic stroke. Spontaneous subdural hemorrhage is common. The rate has been increasing over recent years, possibly associated with increased use of anticoagulation in patients with atrial fibrillation in an attempt to reduce the risk of stroke (Dimitrijevic, 2024). Intracranial or subarachnoid bleeds are not uncommon (even during the dialysis procedure itself). They are a particular problem in patients with polycystic kidneys who may have intracranial aneurysms. Headache occurs in both disequilibrium and early cerebral hemorrhage, but the pattern of recovery is different, and new onset headache may need to be investigated for possible intracranial bleeding by computed tomography (CT) or magnetic resonance imaging (MRI), embracing the limitations of contrast use in this population. Anticoagulation free dialysis should be used. Both ischemic and hemorrhagic strokes are common and catastrophic events but usually present little diagnostic challenge. Both short- and long-term management are controversial with there being very little data relating to the application of intracerebral thrombolysis or primary/secondary preventive measures in patients receiving hemodialysis. The efficacy and safety profile of all of these interventions may well be very different in patients receiving dialysis compared with the general population, where they were developed (Zamberg, 2022).

B. Subclinical brain structural abnormalities. There are several pathologies detectable by brain MRI in the brain of patients receiving dialysis. These may be entirely asymptomatic or linked to more subtle defects in neurocognitive function, often only apparent on specific testing. They are often progressive. Many of these changes do

not appear to be associated with classical cardiovascular risk factors and instead seem to be predominantly driven by other factors such as microvascular disease, inflammation, and challenged perfusion (both in general and episodically during hemodialysis) (Miglinas, 2020). These abnormalities range from silent cerebral infarct to changes in both the white matter (leukoaraiosis) and gray matter (cortical atrophy).

1. **Silent cerebral infarcts.** Nakatani and coworkers examined the hypothesis that patients receiving hemodialysis develop silent cerebral infarcts (SCI). These silent infarcts are mainly subcortical and lacunar without causing any neurologic deficit but are thought to be a risk factor for developing symptomatic infarct or hemorrhagic strokes. Nakatani and coworkers (2003) examined a group of 50 patients receiving hemodialysis and found that in those who developed SCI, associated risk factors were smoking, lower high-density lipoprotein (HDL) cholesterol, higher uric acid levels, and higher levels of hepatocyte growth factor. Echocardiographically, the group who developed SCI had higher interventricular septal thickness at the end of diastole, higher posterior wall thickness at the end of diastole, and higher left ventricular mass index. On 24-hour blood pressure monitoring, the group with silent infarcts was not more hypertensive, in general, but did not evidence the healthy pattern of a nocturnal fall in blood pressure. One possible mechanism in the causation of SCI might be microbubbles generated during the hemodialysis procedure and, undetected by the air alarms, may find their ways into the cerebral circulation and cause ischemic damage (Forsberg, 2010; Erdoes, 2017).
2. **Cerebral atrophy.** Cerebral (cortical) atrophy has been identified in patients receiving hemodialysis through both CT- and MRI-based studies. The degree of cerebral atrophy is associated with duration of dialysis. Cerebral blood flow is lower in between dialysis sessions and higher during hemodialysis. These hemodynamic changes and changes in cerebral oxygenation are less pronounced in patients receiving peritoneal dialysis, suggesting that there may be iatrogenic cerebral effects of hemodialysis (Prohovnik, 2007).
3. **Leukoaraiosis.** Leukoaraiosis describes nonspecific changes in the brain white matter caused by loss of axons and myelin. This is usually associated with ischemic injury. The MRI appearance is that of high signal intensity on T2-weighted images. Leukoaraiosis is a risk factor for developing dementia, mobility problems, and strokes and has been described in the literature primarily as an age-related phenomenon. In the non-CKD population, leukoaraiosis is associated with reduction in cognitive function and with increased prevalence and severity of depression.

   Several studies have identified this pattern of structural brain injury as being common in patients receiving hemodialysis; in fact, it is a universal finding after only 3 months of hemodialysis. The severity of reduction in cognitive function was proportional to the distribution and amount of white matter injury, and, in turn, this was proportional to the degree of cardiovascular instability during hemodialysis sessions (Eldehni, 2015).

C. Humoral abnormalities influencing brain function

1. **Uremic encephalopathy.** Encephalopathy is a cardinal feature of untreated uremia. Initial manifestations are subtle: flattened affect, irritability, and poor rapport with others. Formal evaluation at this stage may reveal patchy cognitive or

psychomotor behavior. Event-related brain potentials (stimulus-evoked averaged electroencephalogram [EEG] waveforms) may be abnormal. As uremia advances, lassitude gives way to disorientation, confusion, delirium, stupor, and, preterminally, coma. There are accompanying motor disturbances: tremulousness, myoclonus, and asterixis (flapping tremor). These major signs of uremic encephalopathy will reliably regress within a week or so of initiation of regular dialysis; failure to do so should lead to an alternative or additional diagnosis. Chorea athetoid movement disorders may present rarely (particularly during dialysis treatment), in particular in patients with diabetes. This is thought to represent basal ganglia changes with MRI evidence of osmotic injury and may respond to intensification of dialysis treatment to limit the time between successive treatments and modulate the degree of solute movement during the treatment itself.

2. **Metabolic and electrolytic causes.** Hypercalcemia from any cause (often relating to CKD mineral bone disorder or its treatments) can present as an acute confusional state or coma. Severe low or high serum sodium levels can also result in a predominantly neurologic presentation. The presence of cerebral atrophy often makes the patient receiving dialysis remarkably resistant to the development of severe cerebral edema as a result of abnormal tonicity. Hypoglycemia may present in patients with diabetes due to inappropriate hypoglycemic therapy or to further reductions in residual renal function with reduced insulin metabolism. In patients without diabetes, hypoglycemia may occur as a result of reflex hyperinsulinemia after exposure to hemodialysis solutions containing higher glucose concentrations or as a hypoglycemic response to glucose-free dialysate.

   Acute aluminum intoxication can present with an acute neurotoxicity syndrome characterized by agitation, confusion, seizures, myoclonic jerks, and coma. This is quite uncommon now compared with the bygone era when there were less stringent water treatment standards and heavy reliance on aluminum-containing salts for oral binding of phosphate. Still, even today, the acute syndrome can be seen when dialysis solution becomes highly contaminated with aluminum for some reason, or in the course of deferoxamine therapy. In this setting, the plasma aluminum level is usually more than 500 mcg/L (19 mcmol/L), and typical EEG changes (multifocal bursts of slow or delta wave activity, often accompanied by spikes) are present.

3. **Infection and inflammation.** Both systemic and local infection and inflammation can affect the brain in patients receiving dialysis. Sepsis in this patient group not uncommonly presents without a typical pyrexial response (especially in the older adults), and the initial manifestation can be central obtundation. Patients receiving dialysis are immunosuppressed as a consequence of both the uremic state and of immunomodulatory therapy given as part of treatment of their underlying disease. They also are at higher risk of a wide range of encephalitic or meningitic processes, especially those with more “slow burning” presentations such as tuberculous meningitis.

   Endotoxemia is another important factor that could be implicated in the pathogenesis of hemodialysis-induced brain injury. Endotoxemia is well described in patients with stage 5 chronic kidney disease on dialysis (CKD5D), and it induces a systemic proinflammatory state (McIntyre, 2011). These patients experience gut hypoperfusion and increased bowel permeability, resulting in bacterial and

endotoxin translocation to the circulation. The level of resultant circulatory stress is associated with the severity of endotoxemia. Patients receiving hemodialysis are in a chronic state of endotoxemia, with acute exacerbations from recurrent mesenteric ischemia accompanying each hemodialysis session. The repeated endotoxemic insult may also aggravate the effects of hemodialysis on cerebral perfusion with secondary ischemic white matter subcortical brain injury.

D. Acute episodic dysfunction

1. **Disequilibrium syndrome.** Rapid correction of advanced uremia is sometimes complicated by a characteristic syndrome of neurologic dysfunction appearing in the last part of dialysis or shortly afterward. Hemodialysis is usually involved, but disequilibrium can also occur with peritoneal dialysis. In its mildest form, the syndrome is limited to restlessness, headache, nausea, and vomiting; more severe manifestations include confusion and major seizures. The syndrome is believed to be caused by brain swelling due to a lag in osmolar shifts between blood and brain during dialysis, but changes in brain pH may also play a role. Disequilibrium occurs in a major form in patients who have not previously undergone dialysis, but minor features may complicate chronic therapy. Disequilibrium is more likely to occur when patients with advanced states of uremia are dialyzed for excessive lengths of time during their first treatment sessions, especially in the era of using higher-efficiency dialyzers in this setting. The initial dialyses should be relatively short and given at a markedly reduced blood flow rate as discussed in Chapter 10. The goal is to reduce elevated serum urea levels slowly over the course of several days. The routine use of anticonvulsants in this setting should be avoided.
2. **Other factors affecting tonicity.** Rapid shifting of other osmotically active substances (glucose and sodium) may also contribute to presentation with acute obtundation, and further consideration may need to be given to glucose level correction and careful individualization of dialysate conductivity to minimize these additional insults.
3. **Dialysis-induced reduction in cerebral perfusion/oxygenation.** Failure to maintain blood pressure during dialysis may also precipitate an acute reduction in consciousness levels. Diagnosis and management of intradialytic hypotension is dealt with in more detail in other sections of this handbook, but immediate recognition and corrective measures are essential to restore normal functioning and reduce the risk of a watershed area cerebral infarct. Such episodes may also be important in driving chronic subclinical white matter injury. Hemodialysis results in acute reductions in cerebral perfusion and results in the development of acute brain injury—in the form of cytotoxic edema. This injury is repetitive and cumulative, leading to fixed white matter injury (Anazodo, 2023).
4. **Coning.** Uncal and cerebellar tonsillar herniation can occur without other coexisting pathologic lesions. This can present with a severe dialysis-induced headache and a reduced level of consciousness and result in death. More commonly, this presentation occurs in the setting of either inherited abnormalities predisposing to coning (such as the so-called Chiari malformation, where there is partial hindbrain herniation through the foramen magnum, sometimes seen in spina bifida) or after neurosurgery. Cerebrospinal fluid diversion and, in particular, shunt malfunction can also increase the risk of dialysis-induced brainstem herniation.

Limitation of ultrafiltration rate and careful matching of dialysate tonicity to plasma are the essentials of management in this setting.

5. **Nonconvulsive status epilepticus.** *Status epilepticus* may present with confusion or more severe reductions in the level of consciousness. When occurring without obvious convulsive activity (Iftikhar, 2007), it may mimic collapse from either a catastrophic intracerebral event (although with normal brain imaging) or acute cardiovascular insufficiency.

   Typically, the EEG in nonconvulsive *status epilepticus* shows generalized spike-and-wave complexes at 3 Hz or repetitive generalized or focal spikes, sharp-waves, and spike-and-wave complexes at >4/s. Events that can precipitate nonconvulsive status include alcohol, drug withdrawal, infection, hypoxia, cerebrovascular accident, menstruation, cyclosporine A therapy, malignancy, and antibiotic neurotoxicity. Antibiotics that have been reported to cause seizures in patients with decreased renal function include penicillins, cephalosporins, imipenem/cilastatin, and quinolones. Management is focused on dealing with precipitating causes and use of standard anticonvulsant drugs for the management of acute epilepsy.

E. Differential diagnosis of acute obtundation syndrome, dialysis disequilibrium, and chronic dementia. The differential diagnosis for each of these conditions is large. A partial list to consider when confronted with a patient with acute obtundation is given in Table 38.1. Mimics of dialysis disequilibrium are given in Table 38.2, and those for chronic dementia in Table 38.3. Proposed management strategies for acute obtundation are shown in Figure 38.1 and for chronic obtundation in Figure 38.2.

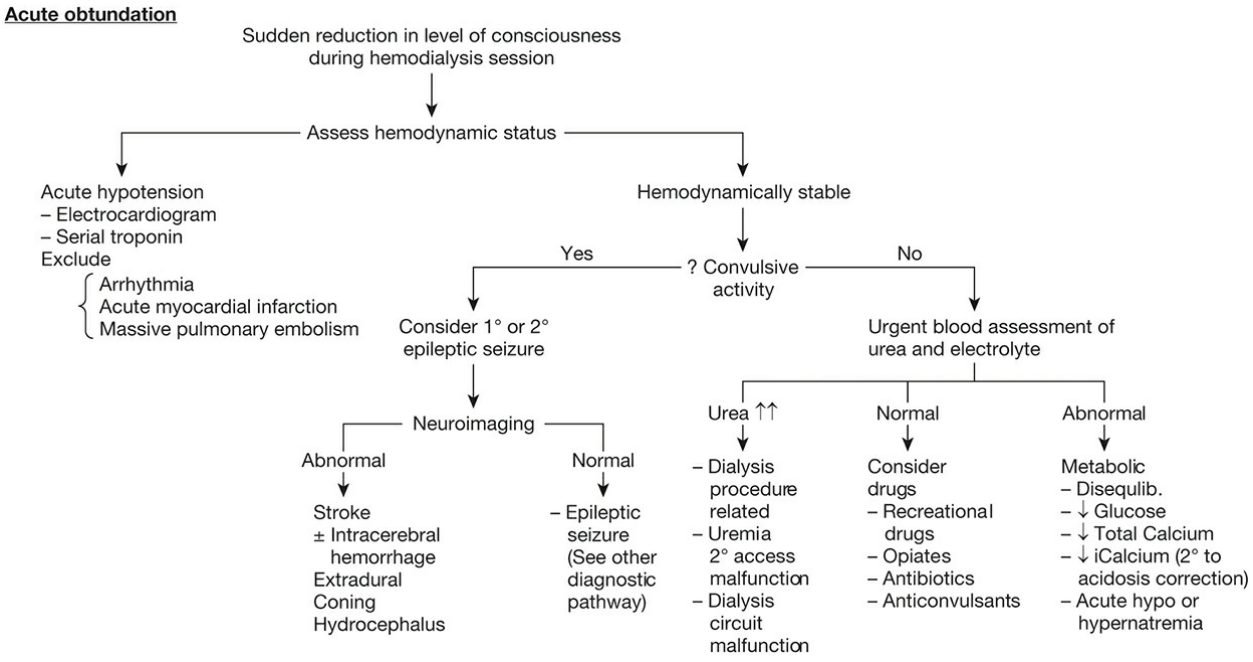


FIGURE 38.1: Evaluation and management of acute obtundation.

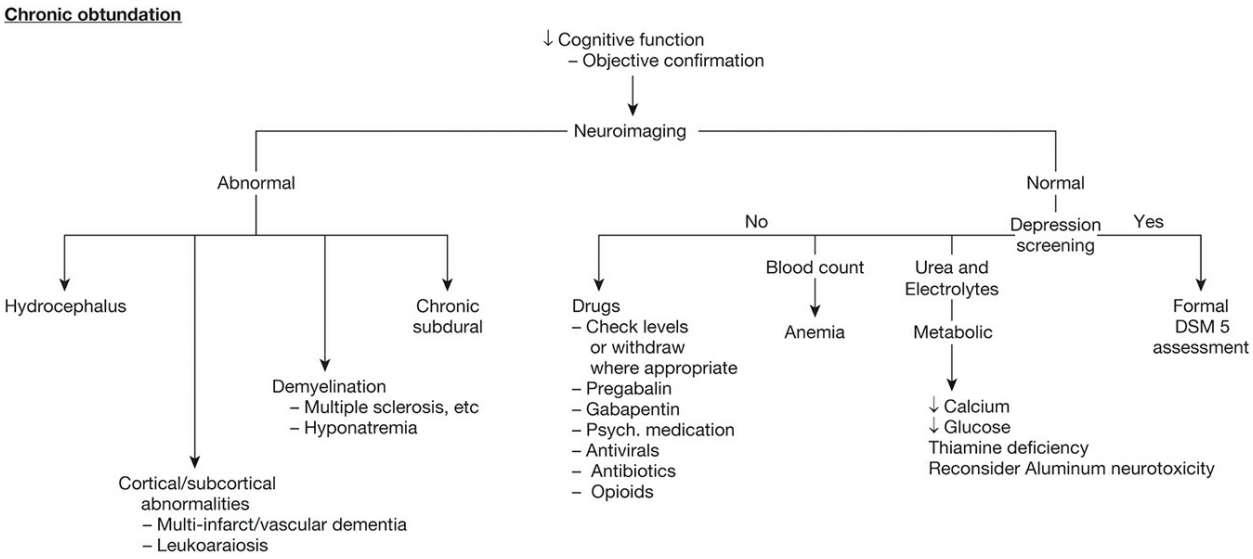


FIGURE 38.2: Evaluation and management of chronic obtundation. DSM 5, *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition.

TABLE 38.1 Partial Differential Diagnoses of Acute Obtundation in Patients Receiving Maintenance Dialysis

Uremic encephalopathy
Drug intoxication (by drugs renally excreted)
Antibiotics
Antiviral agents
Opiates
Anticonvulsants
Central nervous system infection
Meningitis
Encephalitis
Endocarditis
Hypertensive encephalopathy
Hemorrhage
Subarachnoid
Subdural
Intracranial
Acute aluminum toxicity (coingestion of citrate, highly contaminated dialysate)
Wernicke encephalopathy (in patients with vomiting, poor food intake)

TABLE 38.2 Conditions That May Mimic Dialysis Disequilibrium Syndrome

Intracranial bleeding
Subdural
Subarachnoid
Intracranial
Metabolic disorders
Hyperosmolar states

Hypercalcemia
Hypoglycemia
Hyponatremia
Cerebral infarction
Hypotension
Excessive ultrafiltration
Cardiac arrhythmia
Myocardial infarction
Anaphylaxis
Aluminum intoxication (subacute)

TABLE 38.3 Partial Differential Diagnoses of Chronic Dementia in Dialysis Patients

Idiopathic presenile dementia
Vascular dementia
Depression
Chronic subdural hematoma
Drug intoxication
Metabolic disorders
Hypercalcemia (autonomous hyperparathyroidism or iatrogenic)
Hypoglycemic brain damage
Demyelination syndrome secondary to hyponatremia
Uremia (underdialysis)
Hydrocephalus (possibly secondary to subarachnoid hemorrhage)
Anemia
Thiamine deficiency (chronic Wernicke–Korsakoff syndrome)
Chronic infection
Aluminum encephalopathy (dialysis dementia)

F. Diagnosis and management of epileptic seizures

1. **Etiology.** Seizures are not uncommon in patients receiving dialysis. Generalized seizures are an integral feature of advanced uremic encephalopathy. Seizures can also be a manifestation of severe disequilibrium syndrome, as discussed previously. Table 38.4 lists the most common associated conditions. Intracranial hemorrhage commonly leads to focal seizures, while most of the other causes lead to generalized seizures.

TABLE 38.4 Seizures in Patients Receiving Dialysis

Etiology
Disequilibrium syndrome
Hypertensive encephalopathy
Intracranial hemorrhage
Drug-induced reduction in fit threshold
Alcohol withdrawal
Metabolic
Hypoglycemia
Hypocalcemia
Hyperosmolality due to peritoneal dialysis

Hypernatremia (accidental due to hemodialysis machine malfunction) or hyponatremia
Severe hypotension
Anoxia
Arrhythmia
Uremic encephalopathy (unlikely in dialysis patients)
Toxins (star fruit ingestion)
Anaphylaxis
Aluminum encephalopathy
Air embolism
Prevention
Identification of susceptible subgroups
Predialysis serum urea nitrogen level >130 mg/dL (46 mmol/L)
Severe hypertension
Previous seizure disorder
Alcoholism
Predialysis hypocalcemia (<6 mg/dL, 1.5 mmol/L) with acidosis
Limiting initial dialysis session blood flow rate, length, and ultrafiltration rate
Maintenance of dialysis solution sodium concentration at or above plasma level
Use of 3.5 mEq/L (1.75 mM) or 4.0 mEq/L (2.0 mM) calcium bath in hypocalcemic patients; administration of IV calcium during dialysis if necessary
Scrupulous attention to blood pressure control during EPO therapy
Limiting exposure to ethanol and to “epileptogenic” drugs
Penicillins
Fluoroquinolones
Cyclosporine
Meperidine (Demerol)
Theophylline
Metoclopramide
Lithium
Therapy
Stopping dialysis
Maintenance of airway patency
Drawing blood for glucose, calcium, and other electrolytes
If hypoglycemia is suspected, administration of IV glucose
Administration of IV diazepam or lorazepam, and also phenytoin if required
Treatment of metabolic disturbance if present

EPO, erythropoietin

Seizures characterize both aluminum-induced encephalopathy and severe hypertension. In children with renal failure, the incidence of seizures is higher than in adults. Predialysis hypocalcemia can result in seizures during or soon after dialysis because of the fall in serum ionized calcium level associated with rapid correction of acidosis. As in any patient with hypocalcemia, associated (and often causal) hypomagnesemia should be excluded. Hypoglycemia can occur if glucose-free dialysis solution is used.

Seizures tend to be more common in patients taking a variety of “epileptogenic” drugs. Penicillins and cephalosporins are common offenders, especially if high doses are given or when provision for dose reduction in the setting of CKD has not been made. A selection of other epileptogenic drugs is given in Table 38.4. A variety of poisonings in patients receiving dialysis can also present with seizures, including star fruit ingestion (numbness, weakness, obtundation, seizures). Some

anticonvulsant drugs may have enhanced removal by high-efficiency hemodialysis (eg, carbamazepine), and this may result in precipitation of seizures due to reduction of drug plasma levels below the therapeutic threshold.

2. **Diagnosis.** Electroencephalography is of somewhat limited value in the evaluation of seizures in patients receiving dialysis. Patients with renal failure rarely have a normal EEG, the most common abnormal findings being reduced voltage, loss of alpha activity, and the appearance of periodic, symmetric, and usually frontal, delta wave slowing. In any case, the EEG is unlikely to distinguish between the various causes of seizures listed in Table 38.4, and a search for aluminum poisoning, an underlying metabolic cause, a complication of the dialysis procedure, or a structural intracranial lesion is important not to neglect.
3. **Prevention.** Patients who are susceptible can often be identified (see Table 38.4). The prevention of dialysis disequilibrium has already been discussed. Patients with low serum ionized calcium levels can be given intravenous calcium at the start of dialysis, and a dialysis solution with a higher calcium concentration can be used. Blood pressure needs to be carefully regulated.
4. **Management.** One suggested algorithm is shown in Figure 38.3. The emergency treatment of convulsions should begin by stopping dialysis and ensuring patency of the airway. Blood should be sampled immediately and serum glucose, calcium, and other electrolyte values determined. IV glucose should be administered if hypoglycemia is suspected. If seizures persist, benzodiazepines are appropriate drugs for initial use. Further management of refractory seizure activity needs to be performed with appropriate full monitoring of the cardiovascular status of the patient in a higher-dependency clinical area. Additional agents can be utilized. Phenytoin is effective but must be used with caution and appropriate monitoring of cardiac rhythm. A loading dosage of phenytoin, 10 to 15 mg/kg, can be given by slow IV infusion at a rate no greater than 50 mg/min, during constant electrocardiographic monitoring to guard against phenytoin-induced bradycardia, atrioventricular conduction block, or other arrhythmias. Other agents that may be appropriate include IV valproate.

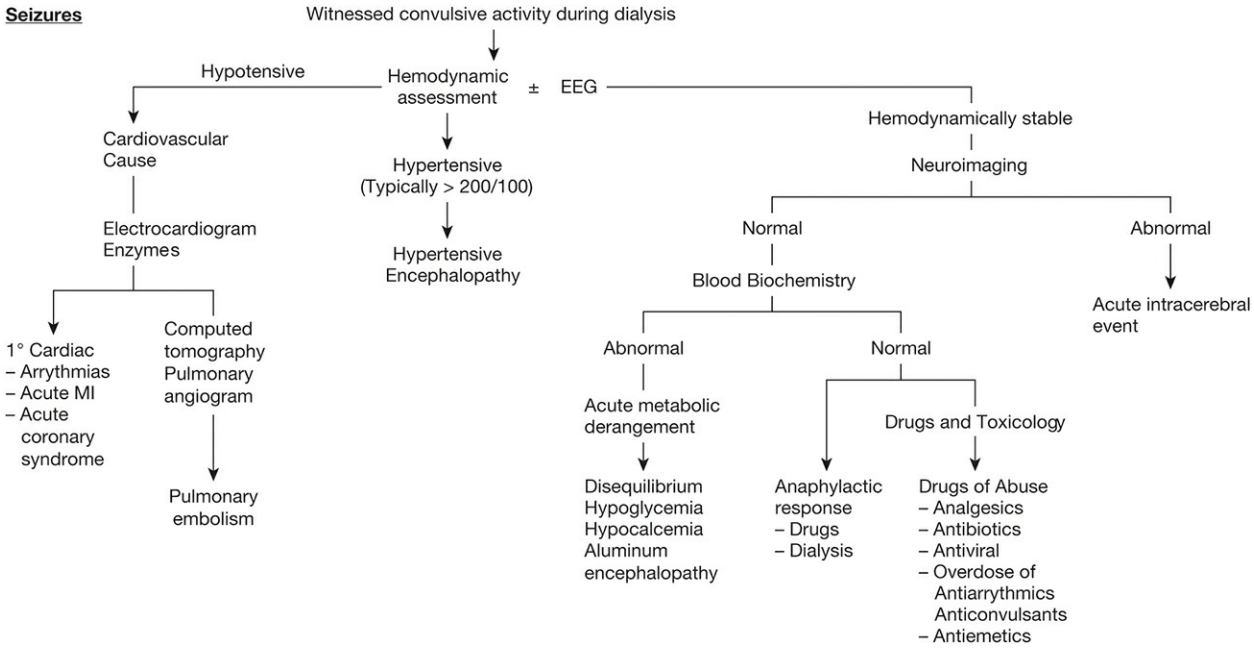


FIGURE 38.3: Evaluation and management of seizures.

5. **Drug prophylaxis.** The prophylaxis of recurrent convulsions is usually effective with administration of phenytoin, carbamazepine, or sodium valproate. Fits relating to dialysis encephalopathy respond best to benzodiazepines, particularly clonazepam.
   a. **Phenytoin.** Phenytoin absorption is slow and erratic. Its hepatic metabolism is concentration dependent and saturable, and distribution and elimination vary. Phenytoin protein binding is decreased and the distribution volume increased in renal failure. With any given total serum phenytoin level, the concentration of active, free drug is higher in patients with uremia than in those with normal renal function. Most clinical laboratories measure the total serum drug concentration, and a low total phenytoin level in a patient with renal failure should not be misinterpreted as subtherapeutic. Physical findings such as nystagmus may be helpful in deciding not to increase the dose. Seizures are also a manifestation of phenytoin excess, and small dosage increases may result in disproportionately large increases in the serum drug level. Dose increments should be small, sufficient time should be allowed for the patient to reach steady-state drug levels, and measurement of free serum phenytoin concentration should be done frequently in patients with uremia who are not responding to therapy.
   b. **Other agents.** Other newer anticonvulsants may also be suitable (with less risk of sedation, wider therapeutic windows, or as part of multiple drug regimens). Dialysis clearance of many of these drugs has not been subjected to rigorous patient-based evaluation. This is especially true when managing acute kidney injury and adding in alternative dialysis/CKRT (continuous kidney replacement therapy) schedules. Reference to up-to-date dose modification guidelines and sources is strongly recommended. Table 38.5 is provided as initial guidance to some of the therapeutic challenges posed utilizing this group of drugs in patients undergoing dialysis.

TABLE 38.5 Pharmacokinetics of Anticonvulsants in Patients Receiving Dialysis

Drug	Renal Excretion (%)	Nonuremic Dosage Range (mg/d)	Usual Dosage for ESKD Patients (% of Nonuremic Dose)	Plasma Half-life (h)			Notes
				Nonuremic Patients	ESKD Patients	Removed by Hemodialysis	
Carbamazepine	3	600-1,600	100	10-20	Same[a]	No	NU-TPL = 4-12 mg/L
Clonazepam	<1	0.5-20.0	100	17-28	Same[a]	No	
Diazepam	<1	5-10 (IV)[b]	?50	20-70	Same[a]	No	Active metabolites may accumulate in renal failure
Ethosuximide	>30	750-2,000	100	50-60	Same[a]	Yes	NU-TPL = 40-100 mg/L
Phenobarbital	10-40	60-200	75	100	120-160	Yes	
Phenytoin	<5	300-600	100	10-30	Same[a]	±	NU-TPL = 10-20 mg/L ESKD-TPL = 4-10 mg/L due to decreased protein binding
Primidone	40[c]	500-2,000	Caution	5-15	Same[a]	Yes	Avoid in ESKD patients
Valproic acid	<4	750-2,000	75-100	6-16	Same[a]	±	NU-TPL = 50-120 mg/L
Vigabatrin	50	2,000-4,000	25	7	14	Unknown	New drug; little experience in dialysis patients

ESKD, end-stage kidney disease; ESKD-TPL, therapeutic plasma concentration in patients receiving dialysis; NU-TPL, therapeutic plasma concentration in subjects without uremia.

[a]Inferred (estimated) from pharmacokinetic considerations.

[b]Initial dose.

[c]Extensive metabolism to phenylethylmalonamide (PEMA) and phenobarbital. Primidone and PEMA are excreted unchanged, and 10% to 40% of phenobarbital is excreted by the kidneys.

Carbamazepine, ethosuximide, and valproic acid can be given in 75% to 100% of the usual dosage to patients receiving dialysis. Protein binding of valproic acid may be reduced in uremia. Carbamazepine is not well removed by dialysis. Valproic acid is dialyzable when high-flux dialyzers are used. Ethosuximide is substantially dialyzable, and a posthemodialysis supplement may be required. Primidone is 40% renally excreted and is moderately dialyzable. Primidone should be used with extreme caution in patients receiving dialysis; the need for a substantially reduced dosage should be anticipated, and a posthemodialysis supplement may be required. Phenobarbital can be given in 75% to 100% of the usual dosage. Phenobarbital is dialyzable, and a dose should be scheduled after the dialysis treatment. Vigabatrin, a gamma-aminobutyric acid-transaminase inhibitor, is eliminated by the kidney; major dosage reduction is necessary in patients receiving dialysis (see Table 38.5).

G. Chronic neurologic states

1. **Neurocognitive decline and dementia.** Reduced cortical function and dementia are common in patients receiving dialysis, with characteristic patterns of memory loss and impaired cognition. This is in part due to a predominantly older adult population with a high burden of comorbid conditions and all of the recognized risk factors for the development of dementia. Widespread atheromatous plaques are found commonly in patients receiving dialysis, predisposing them to multi-infarct dementia. At autopsy, the brains of these patients are seen to contain multiple lacunar infarcts in the basal ganglia, thalamus, internal capsule, pons, and

cerebellum. Clinically, these patients present with a progressive stepwise decline in intellectual and neurologic functioning and may have a variety of neurologic signs according to the site of the infarcts. The diagnosis of chronic subdural hematoma as a complication of anticoagulant treatment should always be borne in mind as the disease may present with pseudodementia, drowsiness, and confusion. The diagnosis is made by appropriate neuroimaging. Both aluminum and iron can be found deposited in the brain in an accelerated fashion, and this can be associated with progressive reduction in cortical function. Metabolic disorders, including drug intoxication, are excluded by simple laboratory tests and a careful drug ingestion history. Lastly, thiamine deficiency has been described in a group of patients from Taiwan (Hung, 2001) and one small randomized pilot study, which still needs confirmation, has claimed improvement in cognitive tests in patients given thiamine and folic acid supplements (Lu, 2021).

2. **Subclinical cognitive dysfunction and depression.** Subclinical uremic encephalopathy may be present in patients receiving chronic dialysis if inadequate dialysis is delivered. Severe depression (and sometimes anxiety) can impair cognitive function, but these may be detected only if detailed and regular neuropsychological assessment is undertaken.

   A more common pattern, however, is as the result of widespread subcortical white matter brain injury. Leukoaraiosis has been described as a risk factor for developing dementia, mobility problems, and strokes and represents accelerated vascular aging. It is common in patients receiving dialysis and, as with other forms of brain injury, is associated with inflammation, hypertension, and vascular disease. This form of subcortical injury occurs precisely in the vascular watershed area of the brain, where episodic intradialytic reduced perfusion would be expected to have its maximal effect. The few studies that have fully assessed cognitive loss in patients receiving hemodialysis have identified relative preservation of memory and vocabulary (cortical pattern) but have shown significant loss of primarily subcortical functions relating to decision making and executive functioning.

   Of even more potential impact is the recent realization that subcortical subclinical ischemic white matter changes are associated with the interruption of intracerebral circuits, the loss of “thymic balance,” and the development of clinical depression. These circumstantial data, in combination with the temporal colocalization of significant increase in social dependency, clustered around initiation and the first 6 months of dialysis, raise the fascinating possibility of a new biologic basis for depression and increasing social dependency in patients receiving hemodialysis.

II. SLEEP-RELATED DISORDERS.

Surveys of patients receiving dialysis report that 40% to 50% have one or more sleep complaints and that more than 50% studied in a sleep disorders laboratory have a sleep disorder objectively documented by polysomnography (Lyons, 2024). Patients receiving dialysis complain frequently of “insomnia” independently of anxiety or depression. They may have difficulty falling asleep or staying asleep. Patients often complain of awakening frequently during the night without apparent cause. Excessive daytime sleepiness is a frequent complaint. It is common to enter a dialysis unit during the daytime and find many patients fast asleep while undergoing dialysis. Chronic daytime

sleepiness may affect cognitive functioning, interfere with activities of daily living, and decrease quality of life. Daytime sleepiness may also interfere with the patient's ability to work and place them in danger while driving or operating heavy equipment.

A. Sleep apnea. Studies have found sleep apnea in 50% to 75% of patients with sleep-related complaints receiving dialysis. Sleep apnea can be classified as obstructive, central, or mixed. **Obstructive sleep apnea** is a very common medical disorder resulting from a collapse of the upper airway during sleep in the presence of continuing respiratory effort. It is often associated with loud snoring, gasping, and snorting sounds during sleep. It is reported to occur in 4% of normal men and 2% of women 30 to 60 years of age. As many as 81% of older adults in nursing home are reported to have sleep apnea. Obstructive sleep apnea has been reported to be associated with increased morbidity and mortality. This morbidity is most often related to cardiovascular (often associated with sympathetic overdrive) and cerebrovascular pathophysiologic processes, as well as accidents due to sleepiness. This obstruction appears to be largely due to upper airway edema and congestion/distortion of the nasopharynx. While patients receiving dialysis may have obstructive sleep apnea, they also commonly have **central sleep apnea**. In central apnea, neither respiratory effort nor airflow is present, suggesting a malfunction in the respiratory centers of the brain. **Mixed apneas**, which refer to central sleep apnea with an obstructive component, are not uncommon in the dialysis population.

B. Restless legs syndrome and periodic leg movements in sleep

1. **Restless legs.** One of the most common complaints among patients with ESKD is restless legs syndrome (RLS). RLS is a subjective complaint for which there is no objective test. Patients often describe an irritating sensation deep in the muscles of the lower leg, particularly in the calf muscle. Patients can relieve this sensation only by moving their legs and feet. The irritating sensation typically appears when patients are at rest, often in the hours prior to the patient's usual bedtime. RLS may significantly delay sleep onset.
2. **PLMS.** Periodic leg movements in sleep (PLMS) is a common sleep disorder occurring with increased incidence with age and is common in the older adults of the general population. It generally consists of a dorsiflexion of the foot or movement of the lower limb lasting 2 to 4 seconds and repeating every 20 to 40 seconds numerous times. It occurs primarily in the first third of the sleep period during non–rapid eye movement sleep. Each movement may result in a brief arousal from sleep and can be the source of complaints about unrefreshing sleep and daytime fatigue. PLMS occurs in approximately 80% of patients who complain of RLS. PLMS is found in a very high percentage in patients with ESKD. Patients receiving dialysis with PLMS have a much higher number of movements per hour of sleep than those in the general population with PLMS. In one case series of 45 patients receiving dialysis, 71% had significant PLMS, and several of them had more than 1,500 leg movements in a single night. Many of the PLMS incidents were associated with repetitive arousals, resulting in very poor-quality sleep, daytime complaints of fatigue, and increased mortality. Both presence of sleep apnea and a high PLMS index (eg, more than 35 leg movements per hour of sleep) are associated with elevated mortality rates. It is not known whether this is causal or merely associative, and whether treatment will improve survival in such patients has also not been

determined.

3. **Diagnosis**
   a. **History.** A sleep history can easily be obtained using a questionnaire or brief interview. Patients or bed partners should be questioned regarding quantity and quality of nocturnal sleep, number of awakenings from sleep, whether sleep is restorative, snoring, gasping, breathing pauses during sleep, lower limb movements (kicking) while awake or asleep, daytime fatigue, or inappropriate napping. Ingestion of medications and social habits (eg, excess caffeine) associated with excess irritability should be reviewed.
   b. **Polysomnography.** Sleep disorders such as sleep apnea and PLMS in sleep are easily identifiable via standard diagnostic polysomnography (sleep studies). These studies are usually performed in specially equipped laboratories found in many hospitals. Polysomnography generally encompasses simultaneous electroencephalography, electrooculography, electromyography, and electrocardiography, as well as monitoring of breathing sounds, respiratory effort and airflow, arterial oxygen saturation, and leg movements during the patient's usual sleep period.
4. **Treatment of sleep apnea**
   a. **Medication** has not been shown to be effective in the treatment of obstructive sleep apnea. Benzodiazepines are contraindicated for obstructive sleep apnea, as are other CNS depressants, because they may result in longer apneas, greater O_2 desaturation, and more severe sleep fragmentation with consequently greater daytime fatigue.
   b. **Nocturnal dialysis.** Both nocturnal hemodialysis and nocturnal cycler-assisted peritoneal dialysis (Tang, 2006) have been reported to bring about improvement in sleep apnea. The responsible mechanisms have not been established, but probably the provision of nocturnal ultrafiltration and improved volume control improves upper airway edema (directly measured by MRI), and this impacts on the obstructive element of sleep apnea (Elias, 2013).
   c. **Continuous positive airway pressure (CPAP).** CPAP consists of the administration of positive air pressure via the mouth or nares. The positive air pressure splints the upper airway open, effectively preventing obstruction. This has been shown to be an effective treatment for sleep apneas in the dialysis population, whether the cause is obstructive, central, or mixed. Noncompliance is a problem, however, in patients who use CPAP treatment for obstructive sleep apnea.
   d. **Supplementary O_2.** Administration of low-flow supplemental O_2 has been reported to be a successful treatment for central sleep apnea in some recent studies. However, if obstructive sleep apnea is also present, low-flow O_2 may result in a lengthening of apnea duration.
   e. **Surgery.** Various surgical approaches have been used for the treatment of obstructive sleep apnea. These usually involve the surgical reduction or removal of the uvula and tissues of the soft palate. Surgeries for obstructive sleep apnea have been reported to have an overall success rate of 50%.
5. **Treatment of RLS/PLMS**
   a. **Conservative measures.** Iron repletion is helpful in the general population

but is very rarely a problem in patients receiving dialysis owing to continual monitoring of iron status. Nonetheless, iron deficiency should be avoided. General advice about caffeine, alcohol, and nicotine avoidance is sometimes helpful. Regular stretching, exercise, massage, and either hot or cold baths may ameliorate symptoms. Chronic insomnia from restless legs adds to the burden of mood disturbance, which may perpetuate a cycle of poor sleep. Aerobic exercise and intradialytic exercise have both been reported to have some benefit, as has cooled dialysate.

b. Medication. Dopamine precursors or agonists such as L-dopa have been shown to reduce the number and severity of both disorders and are considered the treatment of choice by many. Benzodiazepines, such as clonazepam, have been used for many years. Controversy exists as to whether benzodiazepines actually reduce the number of movements or simply suppress arousal. Longer-acting dopamine agonists such as ropinirole are now available but should be used cautiously in patients with ESKD. Both gabapentin and pregabalin appear to have some efficacy for the treatment of RLS.

c. Dialysis clearance. Enhanced clearance of middle molecules, either by high volume hemodiafiltration or the newer generation of mid cut-off dialyzers, have initial data to support their use to treat RLS.

d. Transplantation. Complete resolution of both sleep apnea and RLS/PLMS has been reported following kidney transplantation.

III. PERIPHERAL NEUROPATHY

A. Uremic neuropathy.

Uremic neuropathy is a distal, symmetric, mixed motor and sensory polyneuropathy. It typically involves the legs more than the arms. Clinical manifestations include paresthesia in the feet, painful dysesthesia, ataxia, and weakness. The sense of position and the vibratory threshold are often impaired. Physiologic studies show slowing of motor nerve conduction and sensory action potentials. The condition is due to one or more toxins retained in uremia and inadequately removed by dialysis. In patients with coexisting diabetes, the development of disabling neuropathy can be rapid, and unraveling the contribution of each cause may be difficult.

With effective dialysis, clinical uremic neuropathy is unusual, but subclinical manifestations can be detected in over 50% of patients. Serial electrophysiologic monitoring has been used to assess the adequacy of dialysis schedules but is not routinely employed. If clinical signs of peripheral neuropathy appear, then the adequacy of the dialysis treatment should be carefully evaluated using urea kinetic modeling. A switch to a high-flux membrane or hemodiafiltration to increase the removal of middle molecules may be of benefit. More frequent hemodialysis, and especially nocturnal hemodialysis 6 times per week, may improve neuropathy, but solid data on neuropathy are not yet available. Neuropathy is most reliably reversed by successful renal transplantation.

1. Differential diagnosis. Uremic neuropathy has to be distinguished from disturbed peripheral nerve function owing to an underlying systemic disease (eg, amyloidosis or diabetes mellitus). Table 38.6 gives an abbreviated list of disorders to be considered in the differential diagnosis. Pyridoxine supplementation has been reported to improve peripheral polyneuropathy in a group of older Japanese adult

patients receiving dialysis; however, this was not a controlled study, and baseline pyridoxal 5′-phosphate levels were not decreased (Moriwaki, 2000).

TABLE 38.6 Principal Differential Diagnoses of Uremic Polyneuropathy

Diabetes mellitus
Ethanol abuse
Amyloidosis
Malnutrition
Polyarteritis
Lupus erythematosus
Multiple myeloma
Thiamine deficiency

B. Mononeuropathies (carpal tunnel syndrome). Occasionally, prolonged recumbency during the hemodialysis procedure leads to ulnar and peroneal nerve palsies; however, the most common neuropathy is carpal tunnel syndrome, which is due to compression of the median nerve at the wrist, where it passes through a narrowed carpal tunnel. Prevalence increases with years on dialysis and is as high as 73% in patients who have been receiving hemodialysis for 10 years or longer. The pathogenesis appears to be multifactorial. Deposits of β_2-microglobulin amyloid may compress the median nerve as it passes through the carpal tunnel; however, amyloid is not present in all biopsy specimens. Some patients report exacerbation of symptoms during hemodialysis, perhaps due to a fistula-induced arterial steal phenomenon causing median nerve ischemia. Also, the increase in extracellular fluid volume between dialysis treatments may lead to edema and median nerve compression.

1. **Symptoms.** Most often, patients complain of numbness, tingling, burning, or a sensation of “pins and needles” in the fingers of the affected hand. The hand may feel stiff or swollen. Although symptoms are usually present in the distribution of the median nerve (over the thumb, index and middle fingers, and radial aspect of the ring finger), patients sometimes complain of sensory disturbance over the entire hand. Aching pain may be referred to the forearm. Symptoms are often worse at night or during hemodialysis and are exacerbated by activities involving repeated flexion and extension at the wrist. They occur more frequently on the side of the longest functioning vascular access. However, some patients have developed symptoms in an arm that never had been used for a graft or fistula.
2. **Examination.** In early cases, there may be no objective loss of sensation or muscle strength. Symptoms can often be provoked by tapping over the palmar aspect of the carpal tunnel (Tinel sign) or by having the patient hold their wrists in a flexed position for 1 minute (Phalen sign). In more advanced cases, perception of light touch, pinprick, temperature, or two-point discrimination may be diminished in the distribution of the median nerve. The abductor pollicis brevis muscle may be weak, and, in long-standing cases, there may be atrophy of the thenar eminence.
3. **Diagnosis.** The differential diagnoses of carpal tunnel syndrome include spondylosis of the lower cervical spine, thoracic outlet syndrome, sensorimotor polyneuropathy or mononeuropathy, and radial arterial steal syndrome in patients with an arteriovenous access. Except in early cases, the diagnosis can usually be

established definitively by electromyography and nerve conduction velocity studies.

4. **Treatment.** Splinting the affected wrist in a neutral resting position, especially at night and during dialysis treatments, may relieve symptoms temporarily. If splinting is unsuccessful or poorly tolerated, injection of the carpal tunnel with microcrystalline corticosteroid esters will provide about 30% of patients with permanent relief. If symptoms improve inadequately after injection, or if there is significant objective loss of motor or sensory function, surgical decompression of the carpal tunnel yields improvement in more than 90%, but symptoms often recur within 2 years.

C. Finger flexion contractures. β_2-Microglobulin amyloid can deposit along the flexor tendons of the hands. These deposits may make the digital flexor tendons of the hand adhere to one another, creating a subcutaneous soft tissue mass in the palm and irreducible flexion contractures of the fingers. Surgical debridement of amyloid deposits from the flexor tendon sheaths may allow greater finger extension, but these deposits frequently recur within several years.

D. Atlanto-cervical spondylopathy. Progressive neck instability and cord compression due to destructive β_2-microglobulin–derived amyloidosis have been described in patients receiving long-term dialysis. The condition can be diagnosed by MRI. Early decompression is vital to avoid major disability. Radiographic features include narrowing of the intervertebral disk spaces and erosion of the vertebral end plates without appreciable formation of osteophyte. The lower cervical spine is most often affected, but similar changes may also occur in the dorsal and lumbar spine. Cystic deposits of β_2-microglobulin amyloid can be seen within the odontoid process and the vertebral bodies of the upper cervical spine. Also, peri-odontoid soft tissue masses of β_2-microglobulin amyloid, termed “pseudotumors,” may be present. The initial symptom of destructive spondyloarthropathy is pain, typically in the neck when the cervical spine is involved. However, most patients with radiographic abnormalities have no neck pain. Although neurologic compromise occurs infrequently, significant myelopathy has been reported, especially in patients who have received hemodialysis for 20 years or longer. Severe destructive spondyloarthropathy must be differentiated from vertebral osteomyelitis by MRI.

IV. MANAGEMENT OF CHRONIC PAIN.

Chronic pain is very challenging to manage in patients receiving maintenance dialysis. Standard hierarchical escalation of analgesic type and choice may not be appropriate. Effective and consistent analgesia without unacceptable side effects is difficult to achieve from the point of view of both drug type choice and dose and frequency. Intermittent drug removal by hemodialysis provides an additional dimension to consider. Considerable trial and error is often required to achieve this balance, and availability of a specialist pain relief team with relevant experience with patients receiving dialysis is highly desirable. Access to additional measures such as selective nerve blocks, regional anesthesia, and intra-articular injection may provide optimal pain relief with minimized use of potentially toxic medication with a narrow therapeutic window.

Regular simple analgesics (such as paracetamol [called acetaminophen in the United States]) are the bedrock of chronic pain management. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) may be appropriate in patients without kidneys, but the risk

of sudden loss of residual renal function needs to be carefully considered in patients with some degree of retained renal function. If NSAIDs are used, doses at the lower end of the potential range and lower potency agents such as ibuprofen are preferred. Opiates characteristically accumulate in this setting and may be markedly dialyzed out, precipitating acute pain relating to hemodialysis sessions. Even the use of weaker agents such as codeine can result in severe obtundation and respiratory arrest. Opiates, however, are often necessary to provide adequate symptom relief. In general, dosing intervals need extending rather than doses limited, slow release preparations should be avoided, and access to "top up" doses may need to be limited. Transdermal release patches can be useful, especially utilizing drugs such as fentanyl, which rely on hepatic disposal. The lowest dose formulation should be utilized initially. Adequate time should be allowed for any of these opioid agents to achieve steady state before escalation of the analgesic algorithm. Co-analgesic drugs such as antidepressants (eg, tricyclic antidepressants) or anticonvulsants (eg, gabapentin) are often considered in intractable pain, particularly with a neuropathic element. These can be especially troublesome to utilize without excessive sedation and poor quality of life. Again, doses should be started at the lowest possible level, with very careful dose escalation. Combination of these agents should be avoided if possible. Use of cannabis-derived products, either as cannabidiol (CBD) oil as a co-analgesic or tetrahydrocannabinol (THC) administration, appears to be effective in many patients who have access to them. Synthetic cannabinoids such as nabilone and dronabinol may be used in pain management. It should be noted, however, that rigorous study of these agents is lacking and that the optimum place for individual agents and issues such as optimal CBD/THC ratios are still unclear. Finally, it is important not to neglect nonpharmaceutical strategies in pain management. Patients should be closely involved in decision making, and efforts should be made to explain the challenges and manage expectations. Additional interventions such as psychological interventions should be given due consideration. Management of chronic pain with a palliative care specialist is often warranted.

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39 Patient-Reported Outcomes and Experience Measures in Dialysis

Mark Unruh

Patient-reported outcomes (PROs) are self-reported data for outcomes such as well-being, social functioning, physical functioning, and mental health. Patient-reported outcome measures (PROMs) are tools to reliably collect such patient data.

PROs provide an opportunity for patients with end-stage kidney disease (ESKD) to report their symptoms and experiences that might otherwise be overlooked. Observational studies have demonstrated a marked mismatch between the patient's experience of symptoms and the nurse and renal providers' assessment of those symptoms. A number of recent interventions and drug trials have used PROs as primary outcomes in the evaluation of potential benefit of the intervention or drug in question. PROs may be used as a marker in the evaluation of population health management. Using PROs in clinical practice provides an important opportunity to address patient-centered concerns and enhance the quality of care.

Patient-reported experience measures (PREMs) assess the patient's perception of the health care experience. PREMs may focus on the in-center hemodialysis experience or the broader experience of patients with chronic kidney disease (CKD).

In the United States, one widely used PREMs is called the ICH-CAHPS (https://ichcahps.org), which stands for "The In-Center Hemodialysis Survey Consumer Assessment of Healthcare Providers and Systems." This is designed to measure the experiences of people receiving in-center hemodialysis care at Medicare-certified dialysis centers.

Table 39.1 lists a number of domains covered by the ICH-CAHPS. These domains measure important aspects of the dialysis experience and performance of the in-center dialysis team. These questionnaires are administered twice a year using a combination of mail and telephone surveys, and the results are published in a "Care Compare" section on the Medicare.gov website. This PREM is also used as part of a quality incentive program and is a key component of value-based purchasing. A more inclusive Kidney PREM has been used in the United Kingdom to assess patient experience with kidney care.

TABLE 39.1 PROMs and PREMs Used in the Care for Patients With ESKD

PROMs	DOMAINS	Items	Time	Use
SF-12	Physical and mental well-being	12	5-10 min	Overall generic quality of life
KDQOL-36	SF-12 core, burden, symptoms/problems, and effects of kidney disease	36	15-20 min	Kidney disease–specific quality of life
EQOL-5D	Physical and mental functioning	6	5 min	General function and well-being
Patient Health Questionnaire-9	Depressive symptoms	9	5-10 min	Depression screening
Integrated Palliative Outcome Scale-renal (IPOS-Renal)	General well-being and quality of life; symptom burden	26	10-15 min	Kidney disease symptoms and well-being
Edmonton Symptom Assessment Survey-renal (ESAS-r)	Physical and mental symptoms related to kidney disease	12	5-10 min	Kidney disease symptoms
Dialysis Symptoms Index	Physical and mental symptoms associated with hemodialysis	30	10-15 min	Kidney disease symptoms
PREMs				
ICH-CAHPS	Nephrologists communication and caring, quality of dialysis center care and operations, providing information to patients, global rating	62	20-30 min	Patient experience in-center hemodialysis
Kidney PREM	Patient experience (13 themes)	39	15-20 min	Patient experience with renal care for any CKD stage or treatment

CKD, chronic kidney disease; EQOL-5D, 5-dimension quality of life scale devised by the Euroqol group; ESKD, end-stage kidney disease; ICH-CAHPS, In-Center Hemodialysis Survey Consumer Assessment of Healthcare Providers and Systems; KDQOL-36, Kidney Disease Quality of Life; PREM, patient-reported experience measure; PROM, patient-reported outcome measures; SF-12, Short Form 12.

The PROMs in dialysis have evolved with improvements in the therapy of ESKD and the expectations of patients and providers. For example, survival was the most prominent outcome in the early treatment of ESKD with hemodialysis. Survival could be measured in days, weeks, months, or years. As expertise with dialysis improved, measurements of patient functioning and functional status were more widely adopted. The Karnofsky Index, a measure of functional status that could be completed by proxy or by the patient, measured patient functioning. The index ranged from normal, with no complaints nor evidence of disease, to moribund. Subsequently, measures were developed that assessed various symptoms and moods to more fully capture outcomes important to the patient. Fatigue was a domain of quality of life that was positively impacted by anemia treatment among patients with ESKD. Over time, the field moved beyond a one-dimensional view of symptoms to include multidimensional measures of health-related quality of life (**HRQOL**). PROMs were developed that echoed the World Health Organization's (WHO) view of health as being multidimensional, reflecting wellness rather than the absence of sickness or disease. Multidimensional tools in use today often assess physical, social, and emotional functioning.

Table 39.1 demonstrates general HRQOL instruments and multidimensional tools that are widely used. The **Short Form-36 (SF 36)** and the **Sickness Impact Profile (SIP)** were instruments used to capture a more holistic view of patients with ESKD. The subsequent Kidney Disease Quality of Life (**KDQOL**) measure assesses both physical and mental health and also the burden and symptoms of kidney disease. These multidimensional quality-of-life measures have drawbacks that we should be aware of, such as a limited vocabulary for severity. The SF-36 measures tend to measure moderate activities and may not capture the extent to which the functional status of patients on dialysis may be limited. Also, domains measured by these tools may not reflect the values of the person completing the survey. For instance, a patient with a profound chronic illness may not be as concerned about their moderate level of social functioning when they are just trying to get by with their activities of daily living. Finally, the weighting of the response by the patient may not be consistent over time. This is called response shift and may reflect the coping of patients with ESKD with their changing health status. For instance, a patient may change their expectations for their physical role if they are chronically limited in that domain by needing a walker or wheelchair. The limitations of the PROs are important when interpreting longitudinal change in this medically frail population.

Novel approaches to PROs provide the opportunity to incorporate patient voices in their care. PROMs that leverage item-response theory in the scoring of responses facilitate the measurement of a PRO domain with fewer questions and therefore create less work for staff and patients. PROMs have also become integrated into the electronic health record. These tools allow patients to enter their own data using a variety of input devices such as tablets or mobile phones. The data are then scored and integrated into the electronic health record, allowing for tracking changes over time. This approach allows physicians and dialysis teams to incorporate PROs into their usual workflow.

In order to best understand and apply findings from PROMs to the care of patients undergoing dialysis, it is important to understand the instrument measurement characteristics. Human beings can be relatively reliable and capable of giving a numeric assessment of qualities for which there is no physical scale. For example, we know that humans are able to accurately

assess physical stimuli and assign numerical values to the loudness of sound, brightness of light, or intensity of pressure. The field of psychometrics demonstrates that humans can reliably report perceptions of pain and depressive symptoms.

The psychometric measurement issues of PROMs that nephrologists and dialysis teams should be aware of when examining data generated by their patients include the **reliability** of the measure being used. The reliability reflects how stable the measure is and the reproducibility of the measure for that specific domain of PROMs. The test-retest reliability can be ascertained by looking at how much the measure changes in a patient whose health is otherwise stable over time. The **internal consistency** assesses the extent to which items in a domain such as fatigue are correlated with each other.

Another key property of psychometric measurement for PROMs is **validity**. Validity reflects whether one is measuring what one thinks is being measured. For example, when considering a patient-reported outcome tool that is trying to assess fatigue, it would be important to ensure that the content of questions around that measurement captures the severity of a patient being worn out, tired, and unable to do activities because of that tiredness. The validity of a PROM may be shown with construct validity, which examines the degree to which the measure aligns with other measures in the same domains and diverges from other unrelated concepts.

Another characteristic of PROs that is critical to their clinical use is **responsiveness**, which is the sensitivity of the score to change. For instance, in a patient with ESKD who has a hip replacement, one would expect the score of their physical functioning to dramatically improve after a successful surgery. Measures that are not responsive to changes in health are of limited utility.

The selection of patients by their ability to complete a given survey is a key consideration when examining results in a population of patients undergoing dialysis. PROs may be measured by patient self-report using paper and pencil, in-person or phone interviews, or by patient responses entered into a mobile phone or a tablet computer. Completing surveys may be a challenge for those patients for whom English is a second language, for patients with a relatively low level of health literacy, and for patients with chronic conditions that may limit vision or the ability to use an arm. PROs measured by self-report may thus miss a substantial proportion of patients. Still, other methods such as observation or informant ratings have been shown to be not as reliable as patient self-report. In addition, attempts to use information present in the electronic health record to capture patient well-being have yielded mixed results.

The PROM results for patients with ESKD have demonstrated low physical well-being compared to scores for other chronic health conditions. As an illustration, the physical well-being of patients undergoing dialysis as measured by the SF-36 was lower than that of nondialysis patients with heart failure, chronic lung disease, or angina. Measures of PROs in the patients with CKD have been shown to be very predictive of other key outcomes, such as hospitalization and death. Outcome scores on the physical and mental well-being assessment scales were nearly as strong predictors of hospitalization or death as the level of serum albumin, which in turn has been demonstrated to be a very important predictor of outcomes among patients with ESKD. It is perhaps with this in mind that, in the United States, the Centers for Medicare and Medicaid Services (CMS) requires that measures of HRQOL be incorporated annually in the care of patients with ESKD.

The frequency of collecting PROMs and PREMs depends on the rationale for data collection. There have been studies measuring PROs at various frequencies, from several times a day to every 3 to 12 months. The frequent assessment of symptoms may be problematic, given

the underlying variability of scores from day to day. In addition, some of these tools have a relatively high acquisition burden, requiring completion of a form that may take up to 30 minutes, which many patients and providers find burdensome. Most commonly, PREMs are measured once or twice a year. This frequency permits dialysis units and dialysis organizations to develop action plans to address any issues of concern found related to a given PREM prior to the next survey.

Patient symptoms collected using PROMs have an impact on HRQOL, as they are associated with limitations related to work, family, and social life. Highly prevalent and severe symptoms among patients with ESKD include fatigue, sleepiness, pain, and dry skin (Murtagh, 2007). Other frequently reported symptoms that have been noted as severe include changes in appetite, muscle cramps, mood disorders, cognitive disorders, and sexual dysfunction. Adverse symptoms among patients with ESKD have been shown to be negatively associated with HRQOL, hospitalization, and survival. For instance, itchiness was strongly associated with adverse changes in mental and physical well-being. Among patients and providers, symptom relief has been identified as a top research priority. The "Standardized Outcomes in Nephrology" (SONG) initiative identified core outcomes that are important to consider for clinical trials in ESKD. The core outcomes that should be reported in all trials as delineated by the SONG initiative (Tong, 2018) include fatigue. The middle tier that was clinically important and should be reported in some trials includes the ability for travel, work, impact on family and friends, mobility, and feeling washed out after dialysis. Additional outcomes important to patients identified by the SONG initiative to be considered for clinical trials include anxiety, cognition, cramps, itching, nausea, restless legs, sexual function, and sleep.

Depression among patients with ESKD may be measured using standard tools for depression, such as the Beck Depression Inventory and the Patient Health Questionnaire. The tactic of measuring depression and then having an action plan to address scores that are at levels associated with depression has been a focus among dialysis organizations due to changes in US policy.

The use of PROMs to systematically improve symptoms may be an important opportunity to improve HRQOL and other outcomes. The Symptom Management Involving End-Stage Renal Disease (SMILE) study (Weisbord, 2010, 2013) was a randomized controlled trial of patients undergoing maintenance hemodialysis that assessed the symptoms of patients undergoing hemodialysis and then provided feedback to the provider for more active management by a nurse trained in palliative care. This study focused on depression, pain, and sexual dysfunction. Although there were no significant differences between the feedback and nurse manager groups, both nurse management and feedback had statistically significant, but perhaps not clinically meaningful, improvements in erectile dysfunction and depression scores compared to a baseline observation period. The SMILE study highlighted an approach to provider treatment strategies where one can attempt to improve patient outcomes by measuring and addressing key symptoms. Other areas of clinical interest that may be addressed using this approach would include physical activity, anxiety, fatigue, and sleep disorders.

Various approaches to symptom assessment and management were highlighted in a KDIGO Controversies Conference (Davison, 2015). The conference concluded that symptom assessment and management should be viewed as a key component of quality care for patients with ESKD. Patients undergoing dialysis should have routine screening using validated tools, and this screening should be integrated into the normal workflow of the dialysis organization or practice. The conference was aware of the use of multiple medications by patients with ESKD. Therefore,

it was recommended that first-line treatment of symptoms should focus on nonpharmacologic approaches, which then could move toward pharmacologic therapy using a shared decision-making model involving the patient and the dialysis team. Finally, there are patient-level strategies that may be considered to address patient-reported symptoms. These include efforts to enhance social support, tactics to address social drivers of health, and strategies to increase a sense of spirituality and self-efficacy.

The symptoms experienced by patients on dialysis may coexist as clusters. Such symptom clusters can include fatigue, depression, and pain. Emerging literature suggests that patients with ESKD have a higher frequency of symptom clusters compared to nondialysis patients with CKD or malignancy. The Technology-Assisted Stepped Collaborative Care (TACcare) study (Jhamb, 2023) identified fatigue, depression, and pain as a key symptom cluster, which may be associated with poor adherence to medication, dialysis treatments, and diet and fluid restrictions as well as other adverse health behaviors associated with hospitalization and cardiovascular morbidity and mortality. The study was implemented in the dialysis unit using telehealth and demonstrated an improvement in the key outcomes of depression as measured by the depression index, pain as measured by the Brief Pain Inventory, and fatigue as measured by the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) The use of screening PROMs and telehealth facilitates the implementation of TACcare-type interventions into the real-world workflow of dialysis units including settings where behavioral health providers are scarce.

In conclusion, PROMs provide the opportunity to improve the physical and mental health of patients with ESKD. The use of PREMs provides insight into the patient experience with kidney care. The measurement of symptoms and other PROs should be integrated into the clinical workflow at a frequency that provides important patient-reported data, while limiting the burden on the dialysis team and patient. Nephrologists may consider targeted measurement of symptoms to complement the US regulatory requirement that HRQOL be measured annually. PROMs and PREMs should sharpen the focus on patient-centered care and treat symptoms as part of shared decision-making to improve patient outcomes. The measurement of PROMs has been shown to improve communication, and using the multidisciplinary team in dialysis units provides mechanisms to improve quality of life among patients with ESKD.

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APPENDIX A

TOOLS FOR ESTIMATING GLOMERULAR FILTRATION RATE AND DAILY CREATININE EXCRETION

I. NORMALIZING GLOMERULAR FILTRATION RATE (GFR) TO BODY SURFACE AREA (BSA).[1]

The proper size denominator to use in adjusting GFR to body size is a matter of debate, but traditionally, GFR is normalized in adults to BSA—usually per 1.73 m^2 of BSA (the average BSA in early 20th-century adults). BSA is usually calculated from an equation proposed by Gehan and George (1970) that depends on height and weight only. It is not dependent on age or gender. A number of Web calculators are available to help with this calculation.

$$BSA = 0.0235 \times W^{0.51456} \times H^{0.422446}$$

where

W = weight in kg and H = height in cm.

When GFR is normalized to BSA, GFR/1.73 m^2 values in young adult men and women are similar and are in the range of 110 to 120 mL/min. In children as young as 2 years of age, GFR/1.73 m^2 also remains close to 110 to 120 mL/min.

Example: How to normalize GFR to 1.73 m^2 BSA:

Assume raw GFR is 100 mL/min.

If BSA = 1.5 m^2, multiply 100 by 1.73/1.50.

GFR/1.73 m^2 = **115** mL/min.

If BSA = 2.0 m^2, multiply 100 by 1.73/2.0.

GFR/1.73 m^2 = **86** mL/min.

The example shows two subjects with a GFR of 100 mL/min. One has a BSA of 1.5 m^2 and the other of 2.0 m^2. The BSA-normalized GFR is 115 mL/min/1.73 m^2 in the smaller person and 86 mL/min/1.73 m^2 in the larger person. Of note, most of the recent GFR estimating equations already calculate a value that is normalized to 173 m^2 BSA, so such corrections are not required.

II. CALCULATING ESTIMATED CREATININE CLEARANCE (eCrCl) USING THE Ix EQUATION.[2]

An equation to predict 24-h creatinine excretion rate was developed and validated by Ix *and colleagues* (2011). This equation was validated in a number of large

databases and is based on creatinine that was measured using an isotope dilution mass spectrometry (IDMS)-calibrated assay. The Ix equation is calculated as follows:

When creatinine excretion rate is in mg/24 h and SCr is in mg/dL:

eCrCl = [(24-h excretion rate in mg per day)/1,440]/(0.01 × SCr),

where

24-h excretion rate in mg = 880 − 6.2 × Age + 12.5 × (Wt in kg) + (35 if Black) − (380 if female),

or when SCr is measured in mcmol/L:

eCrCl = [(24-h excretion rate in mcmol per day)/1,440]/(0.001 × SCr)

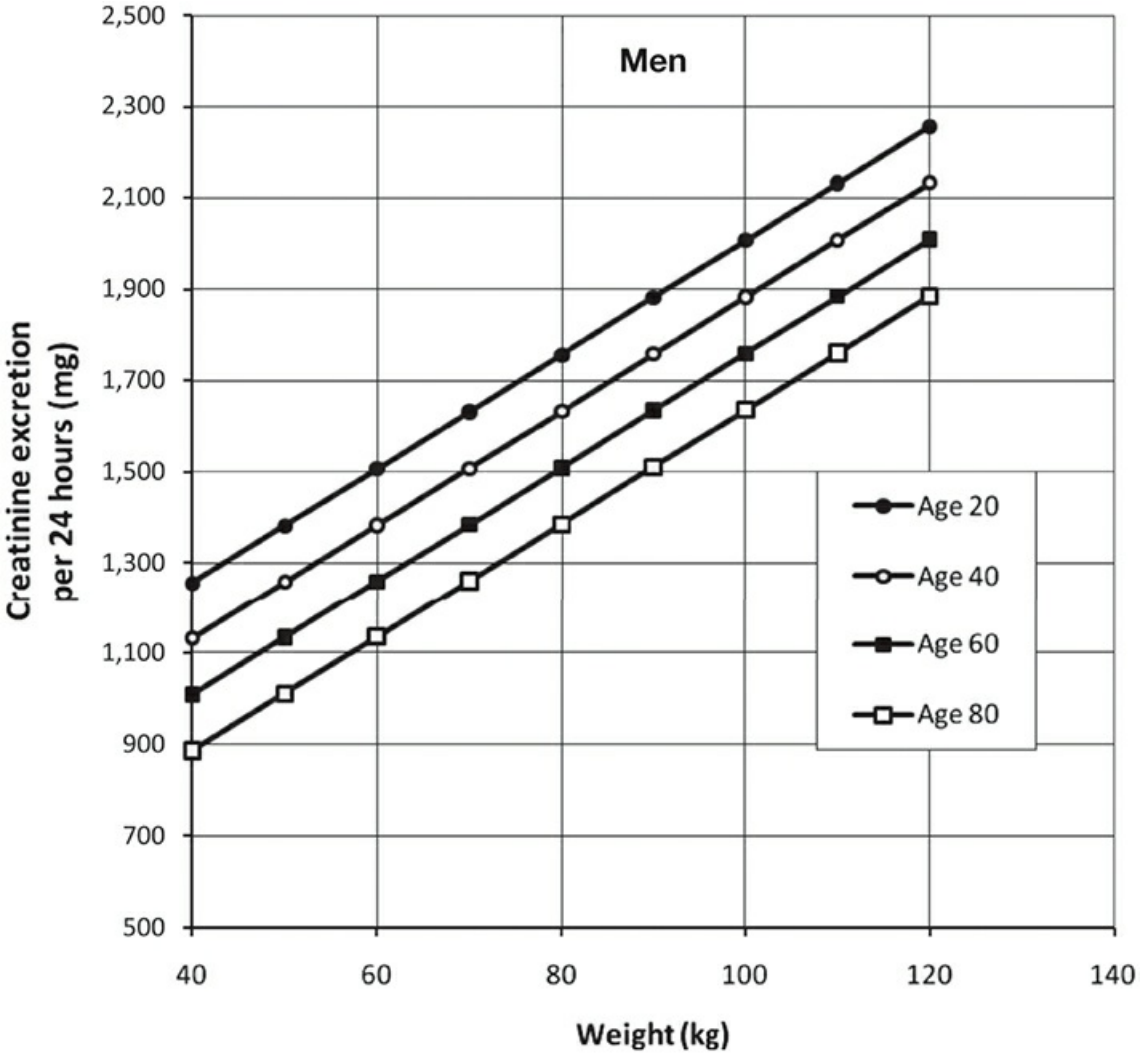
24-h excretion rate in mcmol = 8.84 × [880 − 6.2 × Age + 12.5 × (Wt in kg) + (35 if Black) − (380 if female)]

Note that the age correction for this new equation by Ix (2011) has a much less steep age correction than the commonly used Cockcroft and Gault equation, and the correction for female sex is more severe than the 0.85 term used in the Cockcroft and Gault equation. Weight is included in both the Ix and the Cockcroft and Gault prediction equations for creatinine clearance since the result of these equations is the "raw" creatinine clearance, uncorrected for BSA.

There is a recent trend to avoid race adjustments in anthropometric equations. For a race-neutral version of the Ix equation, simply add 17 mg/d to the equation for a person of any race (the average of 0 for White race and 35 mg for Black race in the original equation.).

III. EQUATIONS CALCULATING ESTIMATED GLOMERULAR FILTRATION RATE (eGFR).

Equations for estimating GFR have been based on serum levels of either creatinine or cystatin (sometimes both) and typically have output results as mL/min/1.73 m^2 and so they have not required inputting patient weight or height. Up until around the year 2020, one equation that was popular was the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey, 2009). More recently (Inker, 2021), it was found that the CKD-EPI equation overestimated GFR in patients of the Black race, and a number of other creatinine and cystatin-based equations were evaluated, focusing on bias in different race-based groups. Cystatin-based equations have been shown to be the least biased between Black and White race individuals (Inker, 2021; Yan, 2024); although equations that incorporate both serum creatinine and serum cystatin levels had somewhat higher accuracy levels than cystatin-only equations, the price was a slightly reduced accuracy in Black race individuals (Figure A.1).


Men
Creatinine excretion per 24 hours (mg)
2,500
2,300
2,100
1,900
1,700
1,500
1,300
1,100
900
700
500
40
60
80
100
120
140
Weight (kg)
Age 20
Age 40
Age 60
Age 80

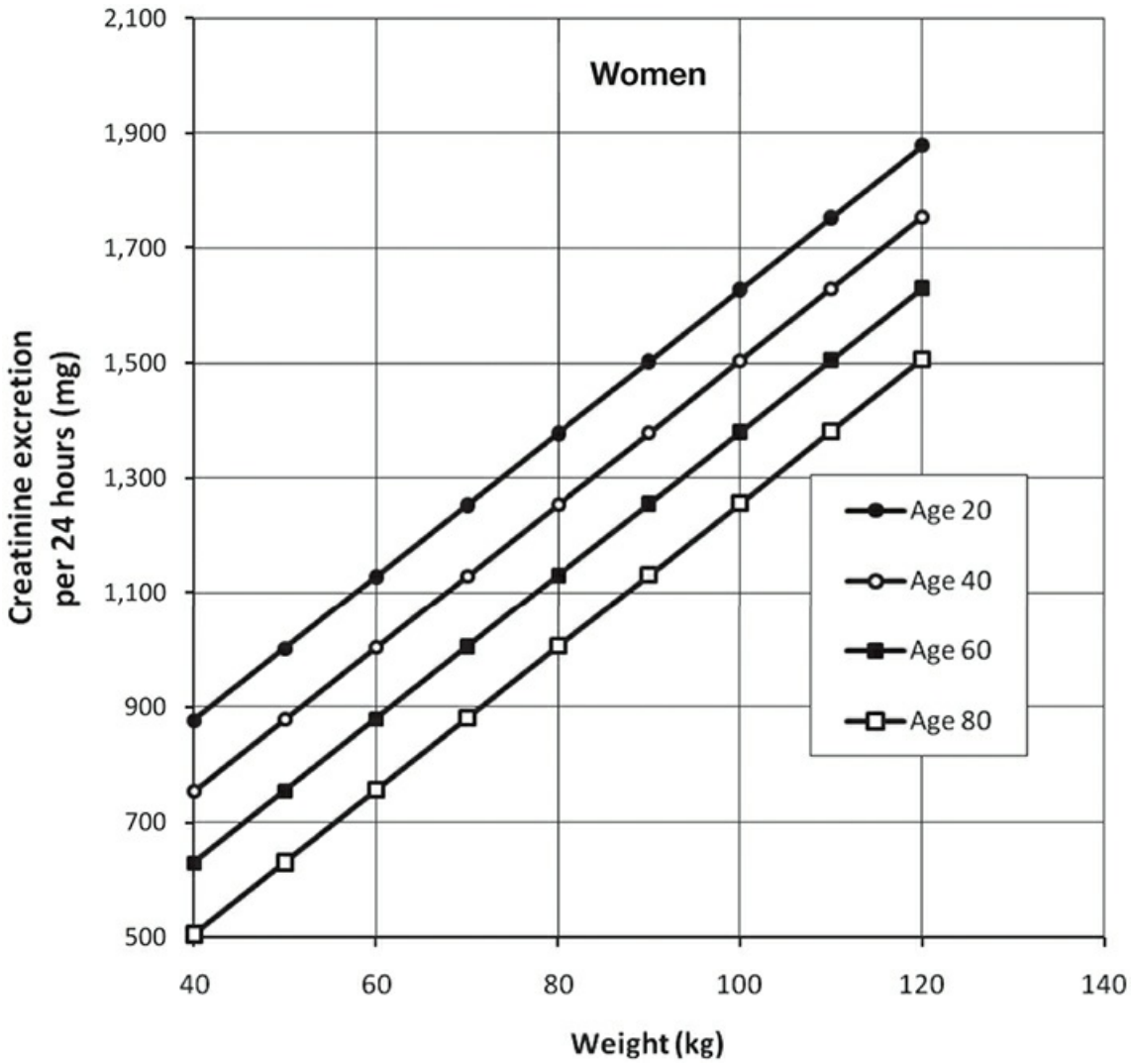


FIGURE A.1: The expected 24-hour creatinine excretion rate according to the Ix equation (Ix, 2011). Estimates for men are shown in the top panel and for women in the bottom panel. For Black race males or females, add 35 mg/24 h. (Reproduced with permission from Daugirdas JT. *Handbook of Chronic Kidney Disease Management*. 2nd ed. Wolters Kluwer; 2018.)

IV. CORCORAN-SALAZAR EQUATION. This equation is a modification of the Cockcroft and Gault equation and can be used to estimate creatinine clearance (not indexed to BSA) in people who are obese (Figure A.2).

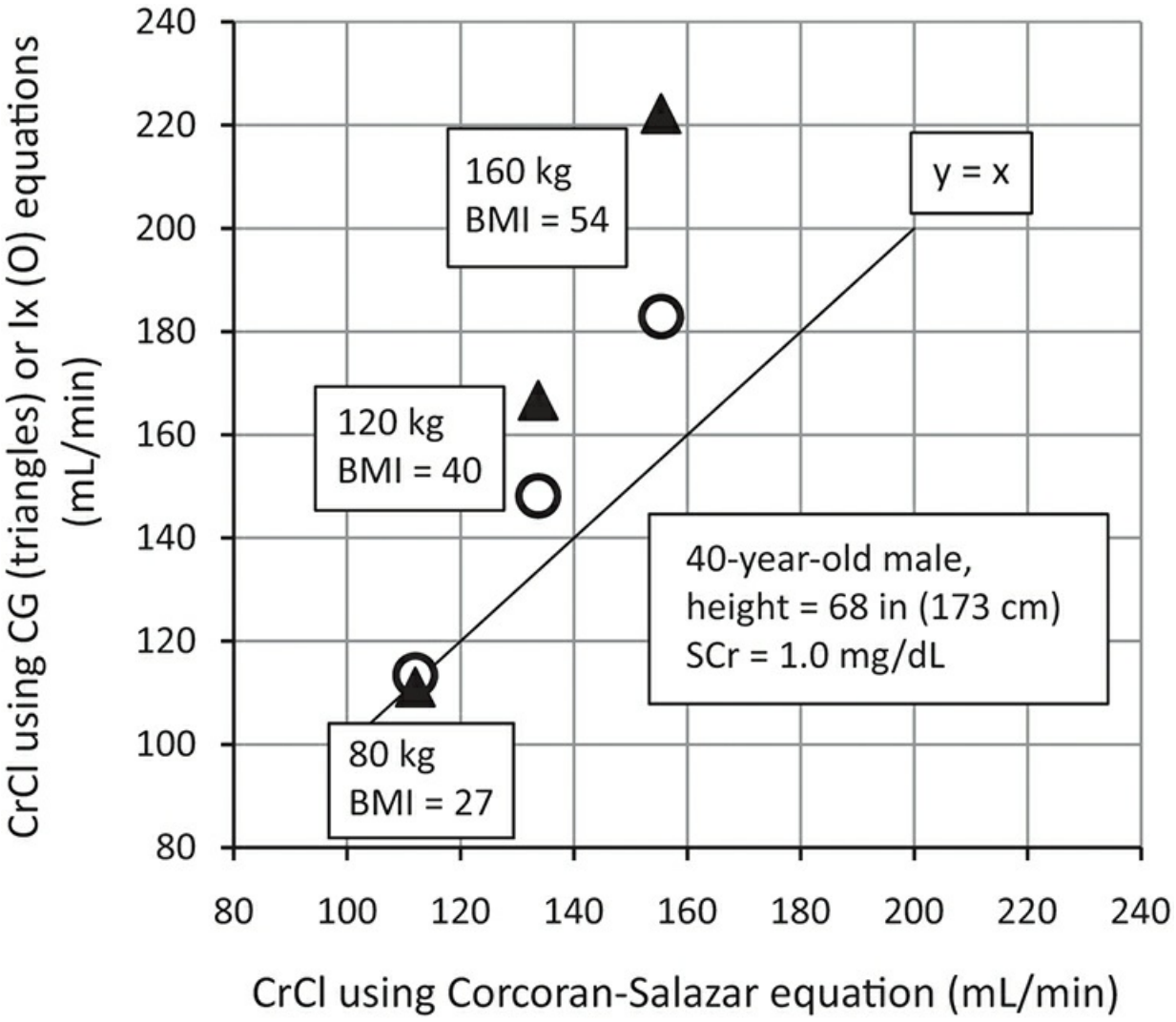


FIGURE A.2: Differences in three CrCl estimating equations in three 40-year-old male subjects all having an SCr of 1.0 mg/dL (88.4 mcmol/L) and all being of the same height but weighing 80, 120, or 160 kg. Both the Cockcroft and Gault (CG) and Ix equations tend to overestimate CrCl in markedly obese subjects. (Reproduced with permission from Daugirdas JT. *Handbook of Chronic Kidney Disease Management*. 2nd ed. Wolters Kluwer; 2018.)

Male:

$$\text{eCrCl} = \frac{(137 - \text{age}) \times \left[(0.285 \times W) + (12.1 \times H^2) \right]}{51 \times \text{SCr}}$$

Female:

$$\text{eCrCl} = \frac{(146 - \text{age}) \times \left[(0.287 \times W) + (9.74 \times H^2) \right]}{60 \times \text{SCr}}$$

where eCrCl = estimated creatinine clearance, W = actual body weight in kg, H = height in meters, and SCr = serum creatinine in mg/dL.

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[1]Text in sections I and II in this appendix is cited with permission from MacGregor MS, Methven S. Assessing kidney function. In: Daugirdas JT, ed. *Handbook of Chronic Kidney Disease Management*. 2nd ed. Wolters Kluwer; 2018

[2]Text in sections I and II in this appendix is cited with permission from MacGregor MS, Methven S. Assessing kidney function. In: Daugirdas JT, ed. *Handbook of Chronic Kidney Disease Management*. 2nd ed. Wolters Kluwer; 2018

APPENDIX B

NUTRITIONAL TOOLS

I. IDEAL, LEAN, MEDIAN STANDARD, AND ADJUSTED BODY WEIGHTS

A. Ideal body weight equations (kg)

1. Method of Devine (1974)

Men: 50 + 2.3 kg for each inch over 5 feet

Women: 45.5 + 2.3 kg for each inch over 5 feet

2. Method of Robinson (1983)

Men: 52 + 1.9 kg for each inch over 5 feet

Women: 49 + 1.7 kg for each inch over 5 feet

B. Adjusted body weight (kg).

There are two methods of computing adjusted body weight in widespread use.

1. Kidney Disease Outcome Quality Initiative (KDOQI) method

The first, used for protein and calorie recommendations by KDOQI, is:

$$adjBW = edfreeBW + (stdBW - edfreeBW) \times 0.25$$

where edfreeBW is the edema-free actual body weight and stdBW is the median standard weight from Tables B.1 and B.2.

TABLE B.1 Median Standard Weights for Men and Women in the United States by Age, Height, and Frame Size (Used to Compute Adjusted Body Weight)

Height		Median Standard Weight (kg)						Ideal Body Weight (kg) (Robinson)
		Age 25-54			Age 55-74			
		Frame Size[a]						
In	cm	S	M	L	S	M	L	
				Men				
62	157	64	68	82	61	68	77	55.8
63	160	61	71	83	62	70	80	57.7
64	163	66	71	84	63	71	77	59.6
65	165	66	74	84	70	72	79	61.5
66	168	67	75	84	68	74	80	63.4
67	170	71	77	84	69	78	85	65.3
68	173	71	78	86	70	78	83	67.2
69	175	74	78	89	75	77	84	69.1
70	178	75	81	87	76	80	87	71
71	180	76	81	91	69	84	84	72.9
72	183	74	84	91	76	81	90	74.8
73	185	79	85	93	78	88	88	76.7
74	188	80	88	92	77	95	89	78.6
				Women				
58	147	52	63	86	54	57	78	45.6
59	150	53	66	78	55	62	78	47.3
60	152	53	60	87	54	62	78	49
61	155	54	61	81	56	64	79	50.7
62	157	55	61	81	58	64	82	52.4
63	160	55	62	83	58	65	80	54.1
64	163	57	62	79	60	66	77	55.8
65	165	60	63	81	60	67	80	57.5
66	168	58	63	75	68	66	82	59.2
67	170	59	65	80	61	72	80	60.9
68	173	62	67	76	61	70	79	62.6
69	175	63	68	79	62	72	85	64.3
70	178	64	70	76	63	73	85	66

Data for median standard weight derived from the combined National Health and Nutrition Examination Survey (NHANES) I and II datasets (Frisancho, 1984).

Ideal body weight computed according to Robinson (1983).

[a]Frame size as defined in Table B.2.

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TABLE

B.2 Frame Size as Determined by Elbow Breadth in cm

	Frame Size		
Age (y)	**Small**	**Medium**	**Large**
Men			
18-24	≤6.6	>6.6 and <7.7	≥7.7
25-34	≤6.7	>6.7 and <7.9	≥7.9
35-44	≤6.7	>6.7 and <8.0	≥8.0
45-54	≤6.7	>6.7 and <8.1	≥8.1
55-64	≤6.7	>6.7 and <8.1	≥8.1
65-74	≤6.7	>6.7 and <8.1	≥8.1
Women			
18-24	≤5.6	>5.6 and <6.5	≥6.5
25-34	≤5.7	>5.7 and <6.8	≥6.8
35-44	≤5.7	>5.7 and <7.1	≥7.1
45-54	≤5.7	>5.7 and <7.2	≥7.2
55-64	≤5.8	>5.8 and <7.2	≥7.2
65-74	≤5.8	>5.8 and <7.2	≥7.2

Derived from the US population in the NHANES 1 and NHANES 2 datasets.

Data from Frisancho (1984).

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2. **Based on ideal body weight.** Another version, commonly used in drug dosing, is:

   Adjusted body weight = IBW + 0.4 × (edfreeBW – IBW),

   where IBW = ideal body weight calculated according to Devine or Robinson as described earlier.

C. Lean body weight equations (kg)

1. **Janmahasatian (2005)**

   Men: 9,270 × wt(kg) / (6,680 + 216 × BMI)

   Women: 9,270 × wt(kg) / (8,780 + 244 × BMI)

II. BODY SURFACE AREA EQUATIONS.

SA = surface area, W = postdialysis weight in kg, H = height in cm.

A. Gehan and George (1970). This can be used in all patients, but should especially be used when age is less than 18 years.

$$SA = 0.0235 \times W^{0.51456} \times H^{0.422446}$$

B. Dubois and Dubois (1916)

(not as good as Gehan and George in children or in adults with obesity)

$$SA = 0.007184 \times W^{0.425} \times H^{0.725}$$

III. TOTAL BODY WATER ANTHROPOMETRIC EQUATIONS (FIGURES B.1 AND B.2)

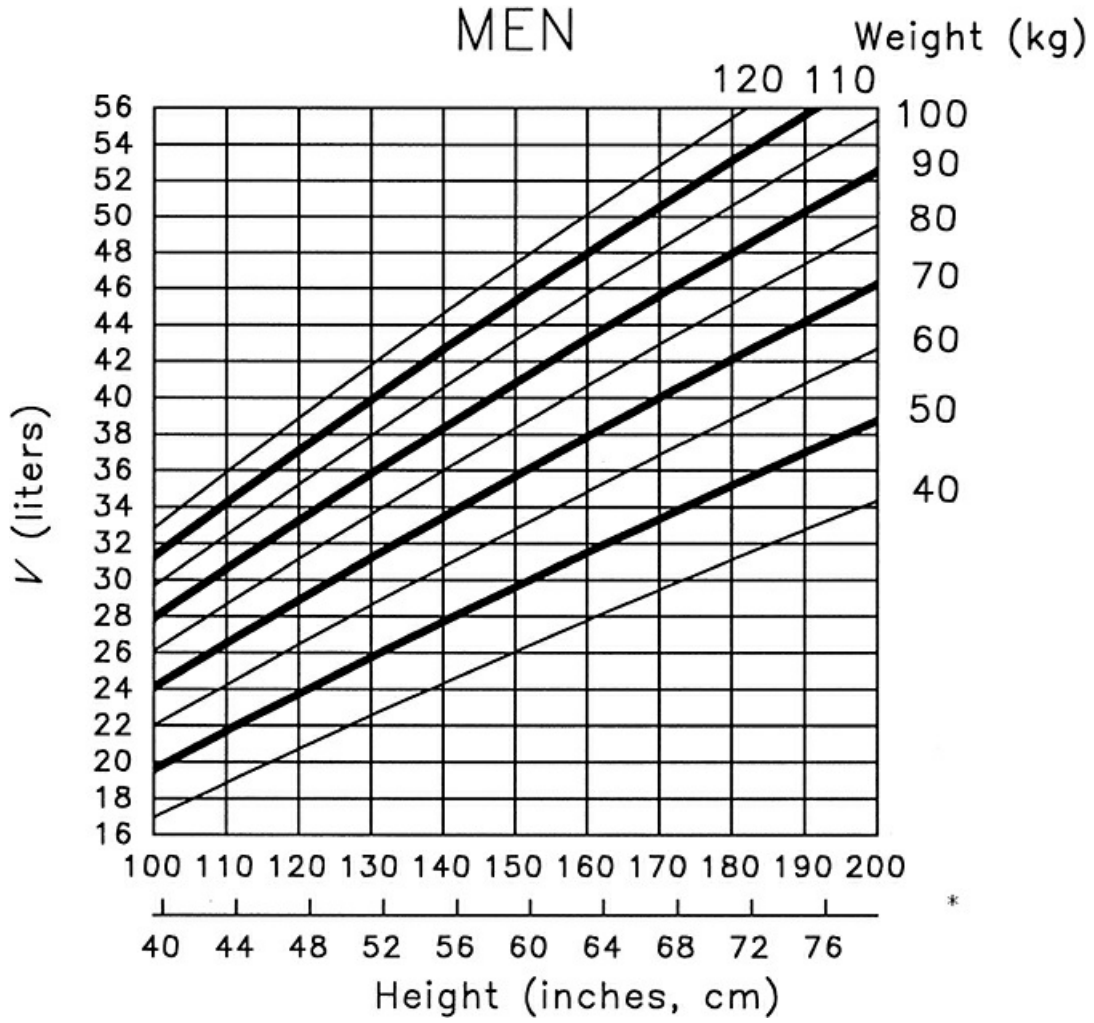


FIGURE B.1: Estimated total body water urea (***V***) in males as a function of weight and height. To use, find the height on the horizontal axis, rise until the appropriate weight line has been reached, and read ***V*** off the vertical axis. For urea modeling, use the postdialysis weight. The modeled ***V*** is usually 90% of the anthropometric ***V***. The values are calculated from the Hume and Weyer equation. (Reprinted from Daugirdas JT, Depner TA. A nomogram approach to hemodialysis urea modeling. *Am J Kidney Dis*. 1994;23:33-40, with permission from Elsevier.)

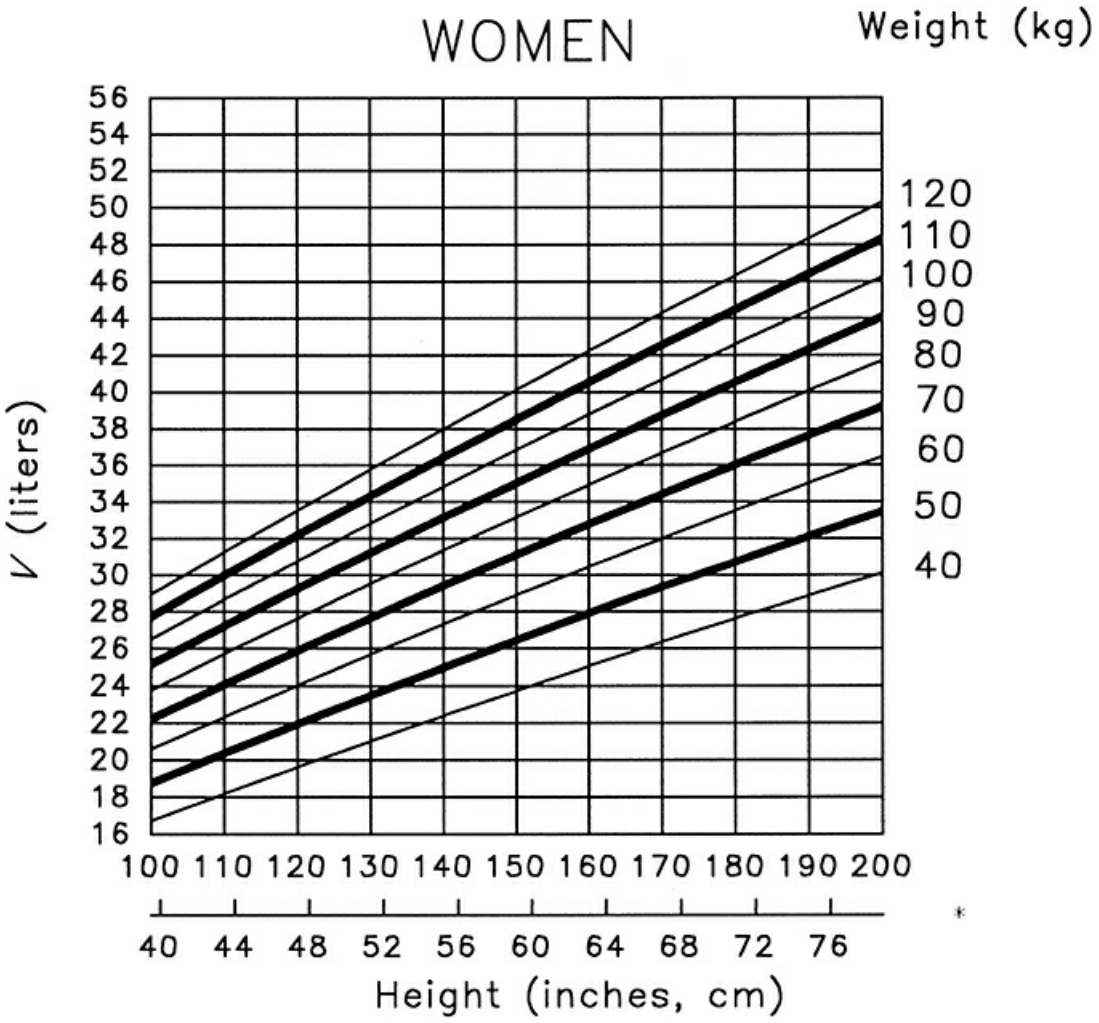


FIGURE B.2: Estimated total body water urea (***V***) in females as a function of height and weight. To use, find the height on the horizontal axis, rise until the appropriate weight line has been reached, and read ***V*** off the vertical axis. For urea modeling, use the postdialysis weight. The modeled ***V*** usually is 90% of the anthropometric ***V***. The values are calculated from the Hume and Weyer equation. (Reprinted from Daugirdas JT, Depner TA. A nomogram approach to hemodialysis urea modeling. *Am J Kidney Dis*. 1994;23:33-40, with permission from Elsevier.)

TBW = total body water, W = postdialysis weight in kg, H = height in cm.

A. Watson (1980)

$$\text{TBW_male} = 2.447 - 0.09516 \times \text{Age} + 0.1074 \times H + 0.3362 \times W$$

$$\text{TBW_female} = 0 - 2.097 + 0.1069 \times H + 0.2466 \times W$$

B. Morgenstern (2006). Use in patients less than 19 years of age.

$$\text{HW} = H \times W$$

$$\text{TBW_male} = 0.10 \times (HW)^{0.68} - 0.37 \times W$$

$$\text{TBW_female} = 0.14 \times (HW)^{0.64} - 0.35 \times W$$

C. Hume and Weyers (1971)

$$\text{TBW_male} = (0.194786 \times H) + (0.296785 \times W) - 14.012934$$

$$\text{TBW_female} = (0.344547 \times H) + (0.183809 \times W) - 35.270121$$

IV. SELECTED DIET COMPOSITION TABLES

A. Potassium

Table B.3 to Table B.8

TABLE B.3 Potassium Content of Salts, Salt Substitutes, and Baking Powders

Product	Sodium (mg per ¼ teaspoon)	Potassium (mg per ¼ teaspoon)
No salt	0	650
Morton's salt substitute	0	610
Adolph salt substitute	0	600
McCormick's unseasoned salt substitute	0	585
Diamond crystal salt substitute	0	550
Co-Salt	0	495
Morton's lite salt	245	375
Table salt	590	0
Sea salt	560	0
Salt sense	390	0
Lessalt	310	170
Baking soda	250-300	0
Baking powder[a]	80	0
Monosodium glutamate	125	0

[a]There are many different types of baking powders, and the sodium content varies widely.

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TABLE B.4 Potassium Content of Foods Considered to Be High in Potassium

Food	Typical Serving	Potassium (mg)	Content (mmol)
Banana	1 small, 6″-7″ long	360	9.3
Cantaloupe	1 cup diced	420	11
Orange juice	½ cup from frozen, reconstituted with water	240	6.1
Prunes	5, dried, uncooked	350	8.9
Avocado	Raw, ½ cup sliced	350	9.0
Potato	Baked, 2¼″ to 3″ diameter, peel eaten	920	23
Potato	Baked, 2¼″ to 3″ diameter, peel not eaten	510	13
Spinach	1 cup cooked	840	21
Brussels sprouts	1 cup cooked	490	13
Broccoli	1 cup cooked flowerets	290	7.4

Milk	1 cup, whole milk	350	8.9
Yogurt	Fruit variety, from low-fat milk, 1 cup	440	11
Dried beans	1 cup cooked, most varieties	880	23

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TABLE B.5

Fruits: Potassium Content per 250 g Serving (About 1 Cup)

mg	**75-300**	**301-650**	**>800**
mmol	**1.9-7.7**	**7.7-16.7**	**>20.5**
In each column, fruits are listed from lowest to highest potassium content	cranberries, sauce cranberries, dried cranberries, raw blueberries, raw pears, bartlett, raw apples, red delicious raw fruit cocktail, canned watermelon, raw pineapple, canned in syrup rhubarb, cobbler peach, raw	pineapple, raw strawberries, frozen cantaloupe, raw plums, raw strawberries, raw blackberries, raw oranges, raw navel tangerines, raw mango, raw kiwi, raw grapes, raw honeydew, raw cherries, raw apricot, raw	banana, raw guava, raw avocado, raw plantain, raw trail mix with nuts and fruit prunes, dried raisins, dried currants, dried apricot, dried

Data from U.S. Dept. of Agriculture's Food Data Central. Survey Foods (FNDDS). Accessed February 12, 2025. fdc.nal.usda.gov/food-search

TABLE B.6

Potassium in Fruit and Vegetable Juice

Fruit Source	**mg per cup (~240 mL)**	**mmol per 240 mL**
Cranberry	195	5.0
Apple	275	7.0
Grapefruit	400	10
Orange	465	12
Tomato	500	13

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TABLE B.7

Potassium Content of Vegetables

Lower Potassium Content	**Higher Potassium Content**

Asparagus	Artichokes
Beans (green beans or wax beans)	Bamboo shoots
Cabbage	Beans and lentils
Carrots	Beets
Cauliflower	Broccoli, Brussels sprouts
Celery	Chinese cabbage, greens
Corn	Kohlrabi
Cucumber	Mushrooms
Eggplant	Parsnips
Kale	Potatoes (white or sweet)
Lettuce	Pumpkin
Mixed vegetables	Rutabaga
Okra	Spinach
Onions	Squash (Hubbard)
Peas	Tomatoes
Peppers	
Radish	
Rhubarb	
Squash (summer)	
Watercress	
Water chestnuts	
Zucchini	

TABLE B.8 Potassium Content of Foods Other Than Fruits or Vegetables

Lower Potassium Content	Higher Potassium Content
Rice	Whole-grain pasta and breads
Noodles	Cereals containing bran
Pasta	Milk, yogurt, cheese
Refined breads	Nuts and seeds
Pies without chocolate or high-potassium fruit	Some salt-free broths and soup stocks
Cookies without nuts or chocolate	Salt substitutes

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B. Phosphorus

Table B.9 to B.11

TABLE B.9 Milligrams of Phosphorus per g Protein Content of Common Protein-Rich Foods

Protein Range (mg phosphate per g)	Food Source and Value
<5.0	Egg white (1.4)

5.1-7.0	Cod (6.0) Chicken, dark meat (6.5) Shrimp (6.5)
7.1-10.0	Turkey (7.1) Beef, tenderloin (8.3) Rabbit, wild (7.3) Beef, bottom round (8.5) Chicken, white meat (7.4) Pork (8.9) Goat (7.4) Lobster (9.0) Lamb, leg (7.4) Venison, loin steak (9.1) Crab, Dungeness (7.8) Tuna, canned (9.2) Ground beef, 95% lean (7.8) Ground beef, 80% lean (9.6) Beef, brisket (8.1) Haddock (10.0) Tuna, yellow fin (8.2)
10.1-11.9	Halibut (10.7) Cottage cheese, 2% low fat (10.9) Salmon, farm raised (11.4)
12-14.9	Catfish (13.0) Peanut butter, crunchy (13.0) Egg, whole (13.2) Crab, Alaska King (14.5) Peanut butter, smooth (14.5)
15.0-20.0	Peanuts (15.0) Salmon, canned (15.8) Pinto beans (16.3) Soy nuts (16.4) Liver, beef, and chicken (17.5) Soy milk, regular, not enriched (17.9)
>20.0	Cheddar cheese (20.6) Swiss cheese (21.3) Almonds (25.3) Milk, 2% low fat (27.6) American cheese (30.7) Cashews (32.3)

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TABLE B.10 Foods Containing High Amounts of Organic or Inorganic Phosphate

Organic Phosphate	Inorganic Phosphate
Dairy products	*Beverages*
Nuts and seeds	Colas, “Pepper”-style sodas, some fruit punches, some flavored waters, plastic bottled iced teas, plastic bottled fruit beverages, some energy drinks, premixed diet shakes, bottled coffee beverages, liquid nondairy creamers

Chocolate	*Processed Meats*
Meat	"Enhanced" meat products, self-basting frozen turkeys, sausages, luncheon meats, restructured meats (chicken nuggets), hot dogs
Fish	*Dairy Products with Additives*
Eggs	Processed cheese products, half and half, evaporated milk, pudding, whipped topping
Legumes (soy, peanuts, peas, beans, lentils)	*Calcium Phosphate–Fortified Products*
Whole-grain cereals	Juices, breakfast cereals, breakfast bars, protein bars, "instant" hot cereals, mineral supplements
	Refrigerated and Frozen Bakery Products
	Biscuits, crescent rolls, rolls, cake, Danish, cheese cake
	Calcium or Magnesium Phosphate in Vitamins or Osteoporosis Mineral Supplements

Data from Murphy-Gutekunst L. Hidden phosphorus in popular beverages: part 1. *J Ren Nutr*. 2005;15:e1-e6. Murphy-Gutekunst L, Barnes K. Hidden phosphorus at breakfast: part 2. *J Ren Nutr*. 2005;15:e1-e6. Reproduced with permission from Daugirdas JT. *Handbook of Chronic Kidney Disease Management*. Lippincott Williams & Wilkins; 2011.

TABLE B.11 Specialty Products and Supplements

Company	Product and Product Analysis
Ross Nutrition www.abbottnutrition.com	Suplena Per 8 oz can: 425 calories 185 mg sodium 10.6 g protein 165 mg phosphorus 265 mg potassium
Nestle Nutrition www.nestlenutritionstore.com	Resource Benecalorie Per 1.5 oz carton: 330 calories 15 mg sodium 7 g protein 55 mg phosphorus 0 mg potassium
Ener-G foods www.ener-g.com	Whole line of low-protein breads, pasta, flour, cereals, and egg products Available in stores and on the website
Med Diet, Inc www.med-diet.com	Offers low-protein bread, cookies, baking mixes, and condiments Available online only
Maddy's low-protein store www.dietforlife.com	Whole line of low-protein snacks, cereals, and bakery products Available online only
Cambrooke Foods www.cambrookefoods.com	Offers low-protein breads, pasta products, meat products, and cheese products Available online only

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APPENDIX C

UREA KINETIC MODELING

I. ESTIMATING DIALYZER BLOOD WATER CLEARANCE FROM K_0A, Q_b, AND Q_d

Step 1. Get the in vitro K_0A urea for the particular dialyzer being used from the manufacturer specification sheet. If this is not readily available, input the urea clearance from the dialyzer specification sheet into the K_0A calculator at ureakinetics.org.

Step 2: Calculate in vivo K_0A from industry-reported in vitro K_0A.

$$K_0A_\text{in vivo} = 0.537 \times K_0A_\text{in vitro}$$

The 0.537 term adjusts the in vitro K_0A from dialyzer specification sheets to an in vivo K_0A value that, when used, estimates dialyzer clearances that correspond more closely with clinically found clearances. If this 0.537 adjustment is used, for validation checking, the modeled median patient urea distribution volume should be close to 0.9 × the median Watson estimate of total body water. We did compare dialyzer clearances estimated using the 0.537 K_0A adjustment with conductivity-based clearances, using data from around the year 2020 in patients being dialyzed with modern, high-efficiency dialyzers. Even with this strong 0.537 downward adjustment, calculated in vivo dialyzer clearance was about 5% to 8% higher than measured conductivity clearances (Raimann, 2020). Some of the discrepancies may have been due to recirculation. When checking the ratio of modeled to anthropometric volume using conductivity clearance, the modeled urea distribution volume was 0.87 × Watson volume, which is close to the value determined in the Hemodialysis (HEMO) study (Daugirdas, 2003). If one uses an in vivo K_0A multiplier of 0.43 instead of 0.537, then the estimated dialyzer clearance will be very close to the measured conductivity clearance.

Step 3: Adjust K_0A_invivo downward if the dialysate flow rate is less than 500 mL/min (because of poor penetration of dialysis solution in the fiber bundle). We no longer recommend making this adjustment for Q_d greater than 500 mL/min, as manufacturers have improved penetration of dialysate into the fiber bundle at high dialysis solution flow rates. When Q_d is less than 500 mL/min, the following adjustment can be used, which lowers the effective in vivo K_0A. However, when Q_d is less than 350 mL/min, K_0A can decrease very substantially; there are no good data to help quantify the adjustment needed. The minor adjustment in the equation below does not fully account for the reduction in K_0A when very low Q_d values are used.

$$K_0A_{\text{invivo}} = K_0A_{\text{invivo}} \times \left(1 + 0.0549 \times \frac{Q_d - 500}{300}\right)$$

Step 4: Compute diffusive blood water clearance (Kdifw) from estimated in vivo K_0A, Q_b, and Q_d.

$$Z = \exp[K_0A / (0.894 \times Q_b) \times (1 - 0.894 \times Q_b / Q_d)]$$

$$\text{Kdifw} = 0.894 \times Q_b \times (Z - 1) / (Z - 0.894 \times Q_b / Q_d)$$

Step 5: Add convective clearance to diffusive clearance to calculate dialyzer clearance (K_d).

$$Q_f = \text{Wtlosskg} \times 1{,}000 / \text{TD_min}$$

$$K_d = \left[1 - \frac{Q_f}{0.894 \times Q_b}\right] \times \text{Kdifw} + Q_f$$

In step 5, the sign of the Q_f term in mL/min is positive; ie, >0.

The estimated in vivo dialyzer clearance values shown in Figure 3.6 were derived using the above equations. An ultrafiltration (Q_f) value of 11.7 mL/min (about 2.8 L weight loss for a 4-hour treatment) was used. We assumed that the whole blood flow rate on the horizontal axis of Figure 3.6 was the true whole blood flow rate and that it is not diminished by tubing collapse due to flattening of the pump segment at high prepump pressures.

II. HOW TO CALCULATE THE STANDARD *KT/V* (STD *KT/V*).

This can be done using a urea kinetic program such as Solute Solver (ureakinetics.org), which is available free of charge to not-for-profit organizations (Daugirdas, 2009; 2025). A simplified approach using estimating equations can also be done as follows:

Step 1: Compute single pool *Kt/V* (sp*Kt*/*V*).

This can be done by inputting the urea reduction ratio (URR), weight change, and dialysis session length into the Daugirdas *Kt/V* estimating equation described in Chapter 3, or by using the nomogram derived from this equation shown in Figure 3.14. When using other than 3/week schedules, one should ideally modify the urea generation coefficient of the Daugirdas *Kt/V* estimating equation to adjust for frequency and interdialytic interval (Daugirdas, 2013). Alternatively, sp*Kt*/*V* can be calculated using a urea modeling program such as the one available at ureakinetics.org.

Step 2: Compute equilibrated *Kt/V* (e*Kt*/*V*).

A formula modified from an equation suggested by Tattersall (1996) can be used to predict the amount of rebound based on the sp*Kt*/*V* and the dialysis session length in minutes (*Td*):

$$e\mathit{Kt}/\mathit{V} = sp\mathit{Kt}/\mathit{V} \times \mathit{Td}/(\mathit{Td} + 30.7)$$

The 30.7 number is a time constant. The constant that we recommend, 30.7 minutes, is based on data from the HEMO study (Daugirdas, 2009, 2013) and is slightly different from the value of 35 minutes originally suggested by Tattersall.

Step 3: Use the Leypoldt equation to get a fixed-volume standard *Kt/V* (*S*).

$$S = \frac{10{,}080\dfrac{1-e^{-eKt/V}}{t}}{\dfrac{1-e^{-eKt/V}}{eKt/V}+\dfrac{10{,}080}{N\times t}-1}$$

Step 4: Adjust the standard *Kt/V* fixed volume value (*S*) for volume removal using the Frequent Hemodialysis Network (FHN) equation (Daugirdas, 2010c).

$$\text{std}Kt/V = S/\left[1-(0.74/F)\times \text{UF_week}/V\right]$$

where *S* is the simplified, fixed volume value from the Leypoldt equation, *F* is the frequency (sessions per week), UF_week is the volume of fluid removed by dialysis over the entire week, in liters. *V* is the estimated urea volume, which can be entered as 90% of the Watson volume.

Example: *S* = 2.0, *F* = 3 times per week, UF_week = 10 L, *V* = 35 L.

$$\begin{aligned}\text{std}Kt/V &= 2.0/\left[1-(0.74/3.0)\times 10/35\right]\\ &= 2.0/(1-0.247\times 0.286)\\ &= 2.0/(1-0.070)\\ &= 2.0/0.93 = 2.15\end{aligned}$$

Thus, after adjusting for volume change, the std*Kt/V* is 2.15 instead of 2.0. The old 2.0 minimum value of std*Kt/V* suggested by the Kidney Disease Outcome Quality Initiative (KDOQI) 2006 guidelines should therefore be 2.15 when the volume-adjusted std*Kt/V* is used; the latter should be used as it corresponds very closely to the std*Kt/V* calculated using formal urea kinetic modeling (Daugirdas, 2010c).

III. HOW TO CALCULATE SURFACE AREA–NORMALIZED STD *KT/V* (*SAN_stdkt/V*)

Step 1: Calculate the median *V/S* ratio for your region's population, where *V* = estimated total body water using the Watson equation and *S* = estimated body surface area using the Gehan and George equation or the Dubois equation (these equations are listed in Appendix B). Call this variable "*M*." For the US population, this value is close to 20.0 for adults when *V* is computed using Watson and *S* using Dubois (Ramirez, 2012). The median ratio is close to 17.5 in children when *V* is computed using Morgenstern and *S* is computed using the Gehan and George equation (Daugirdas, 2010b).

$$M = \text{median ratio of } (V/S)$$

Step 2: Calculate the adjustment factor for the patient in question. Compute *V* and *S* using the same equations that were used to calculate the global value of "*M*." The patient-specific adjustment factor is simply (*V*/*S*)/*M* where *V* and *S* are patient-specific values, and *M* is the global value for the population.

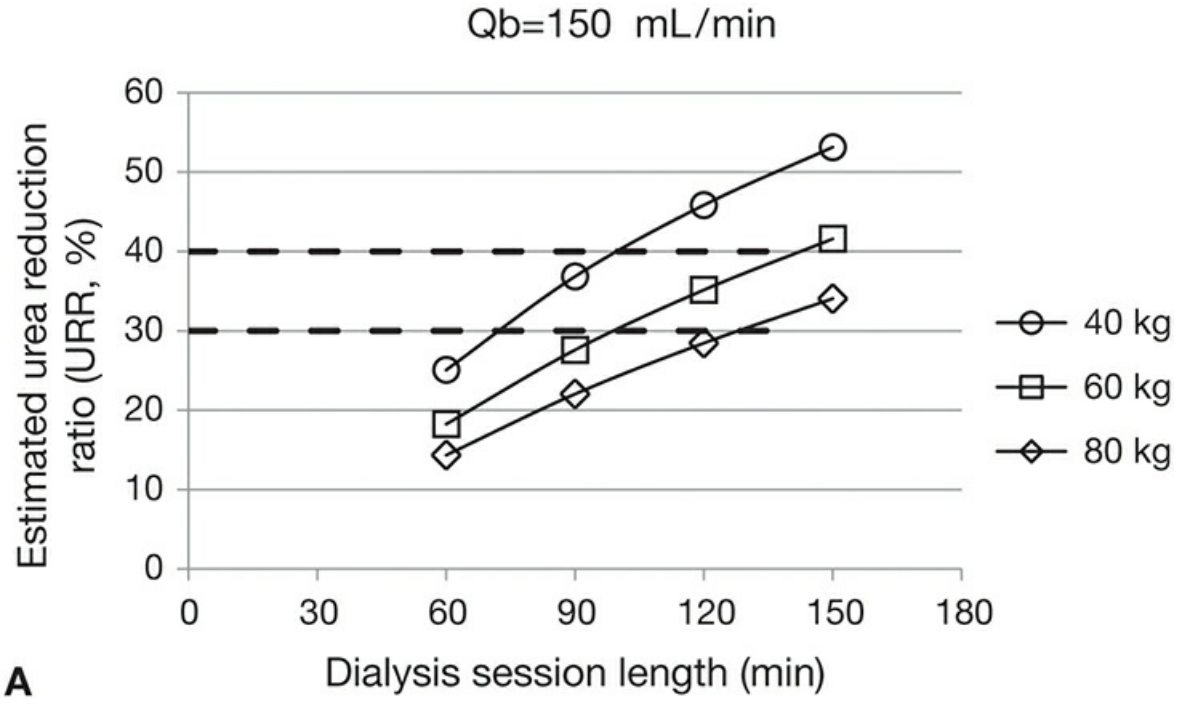
$$SAN_stdKt/V = stdKt/V \times (V/S)/M$$

For more information, see Ramirez (2012). The target *SAN_stdKt/V* is opinion based. Probably a value of at least 2.2 is appropriate. Values of 2.5 and 2.4, respectively, were the

mean doses given to women in the high-dose arm of the HEMO trial and to men in the conventional dose arm (Daugirdas, 2010a).

IV. DIALYSIS PRESCRIPTION FOR INITIAL DIALYSIS TREATMENTS.

As discussed in Chapters 10 and 12, to reduce the chances of disequilibrium syndrome, the initial few dialysis sessions should target a URR no greater than 30% to 40%, with the lower value (30%) used when the predialysis serum urea nitrogen value is greater than 100 mg/dL. Dialyzer efficiency has increased dramatically, to the point that lower efficiency dialyzers (eg, K_0A <1,000 mL/min) are sometimes not available. One can use Figure C.1 to estimate the dialysis session length that should result in a URR in the 30% to 40% range. Note that in smaller patients, even a dialysis session length of 2 hours can result in a URR value outside of the desired range. To remove additional fluid and reduce the ultrafiltration rate, the dialysis session can be extended with the dialysate in bypass, for example, using isolated ultrafiltration.



A

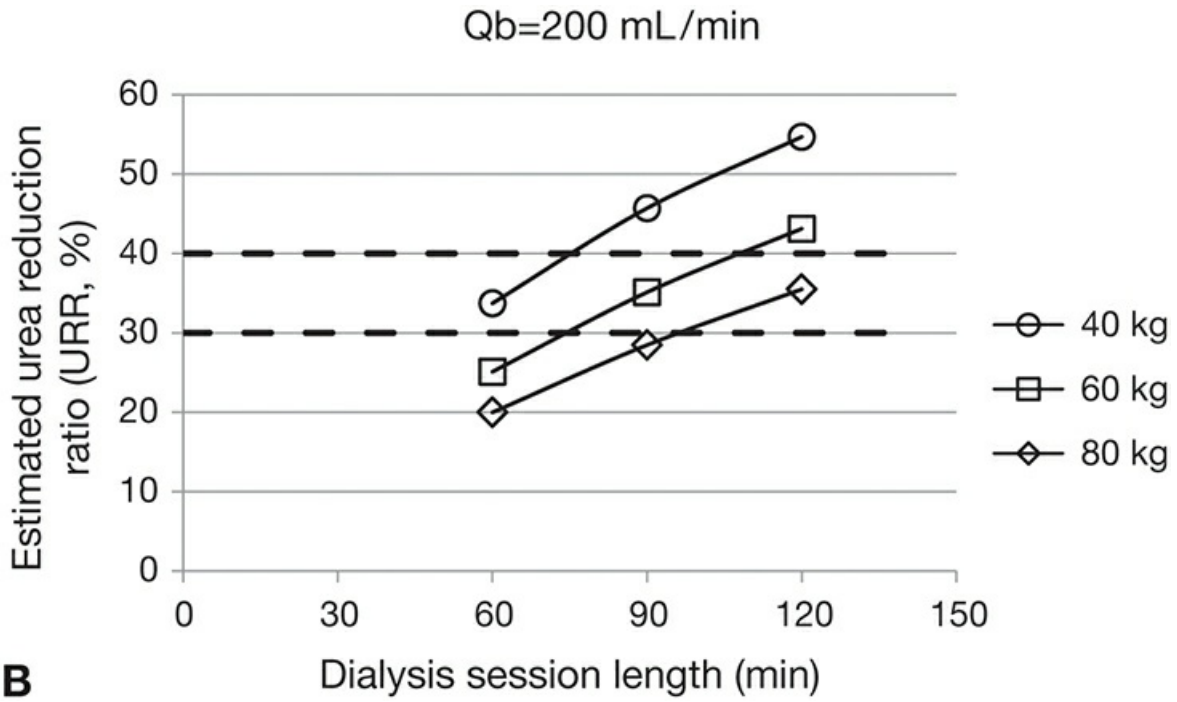


FIGURE C.1: Estimated urea reduction ratio as a function of body weight and dialysis session length using a blood flow rate (Q_b) of 150 mL/min (panel A) or 200 mL/min (panel B). These values were based on the "What-if" model of urea kinetics available at ureakinetics.org. Assumptions made were Q_d = 500 mL/min, dialyzer K_0A = 1,000 mL/min, and urea distribution volume = 50% of body weight.

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APPENDIX D

SPECIFICATIONS OF SELECTED DIALYZERS

Manufacturer	Model		Surface Area (m^2)	Membrane	Sterilization	KUF (mL/h/mm Hg)	Urea Clearance (mL/min) Q_b = 300 mL/min	Urea Clearance (mL/min) Q_b = 400 mL/min	K_oA-Urea Q_b = 300 mL/min	Blood Compartment Volume (mL)
Asahi Kasei Medical										
	ViE-A	15A	1.5	VitabranE (Vit-E Polysulfone)	γ-Irradiation	68.0	268	314	1,103	86
		18A	1.8	VitabranE (Vit-E Polysulfone)	γ-Irradiation	77.0	272	323	1,190	103
		21A	2.1	VitabranE (Vit-E Polysulfone)	γ-Irradiation	89.0	279	333	1,382	117
	Rexeed-L	13L	1.3	Rexbrane (Polysulfone)	γ-Irradiation	10.0	255	291	888	76
		15L	1.5	Rexbrane (Polysulfone)	γ-Irradiation	12.0	265	305	1,045	86
	Rexeed-A	15A	1.5	Rexbrane (Polysulfone)	γ-Irradiation	72.0	272	317	1,190	86
		18A	1.8	Rexbrane (Polysulfone)	γ-Irradiation	81.0	280	330	1,415	103
		21A	2.1	Rexbrane (Polysulfone)	γ-Irradiation	90.0	284	340	1,569	117
B. Braun Avitum AG	Diacap Pro	13H	1.3	α-Polysulfone	γ-Irradiation	70.0	263	303	1,010	82
		16H	1.6	α-Polysulfone	γ-Irradiation	85.0	270	322	1,145	100
		19H	1.9	α-Polysulfone	γ-Irradiation	97.0	280	332	1,415	120
		13L	1.3	α-Polysulfone	γ-Irradiation	11.0	257	295	916	82
		16L	1.6	α-Polysulfone	γ-Irradiation	14.0	269	310	1,123	100
		19L	1.9	α-Polysulfone	γ-Irradiation	17.0	276	321	1,292	120
		Lo12	1.2	Amembris (Polysulfone)	γ-Irradiation	9.0	249		812	68
		Lo15	1.5	Amembris (Polysulfone)	γ-Irradiation	10.0	267		1,083	90
		Lo18	1.8	Amembris (Polysulfone)	γ-Irradiation	12.0	276		1,292	103
		Lo20	2.0	Amembris (Polysulfone)	γ-Irradiation	14.0	281		1,450	119
		500	2.0	PAES and PVP blend	Steam	59.0	285	351	1,614	105

	Revaclear	Revaclear	1.4	PAES and PVP blend	Steam	50.0	271	321	1,167	84
		Revaclear Max	1.8	PAES and PVP blend	Steam	60.0	282	339	1,487	100
		300	1.4	PAES and PVP blend	Steam	48.0	272	323	1,190	74
		400	1.8	PAES and PVP blend	Steam	54.0	281	338	1,450	93
		500	2.1	PAES and PVP blend	Steam	65.0	284	345	1,569	106
	Polyflux	14L	1.4	Polyamix (Polyamide)	Steam	10.0	252	293	849	81
		17L/R[a]	1.7	Polyamix (Polyamide)	Steam	12.5	264	310	1,027	104
		21L/R[a]	2.1	Polyamix (Polyamide)	Steam	15.0	275	328	1,265	123
		140H	1.4	Polyamix (Polyamide)	Steam	60.0	262	309	993	94
		170H	1.7	Polyamix (Polyamide)	Steam	70.0	270	321	1,145	115
		210H	2.1	Polyamix (Polyamide)	Steam	85.0	281	339	1,450	125
	Nephral	ST200	1.1	AN 69ST	γ-Irradiation (wet)	33.0	216	241		64
		ST300	1.3	AN 69ST	γ-Irradiation (wet)	40.0	231	261		81
		ST400	1.7	AN 69ST	γ-Irradiation (wet)	50.0	250	287		98
		ST500	2.2	AN 69ST	γ-Irradiation (wet)	65.0	265	310		126
Fresenius	F	3	0.4	Polysulfone	Ethylene oxide	1.7	125[b]		188	24
		4	0.7	Polysulfone	Ethylene oxide	2.8	183		364	42
		4HPS	0.8	Polysulfone	Steam	8.0	170		316	51
		5HPS	1	Polysulfone	Steam	10.0	227		606	63
		6HPS	1.3	Polysulfone	Steam	13.0	243		746	78
		7HPS	1.6	Polysulfone	Steam	16.0	247		789	96
		8HPS	1.8	Polysulfone	Steam	18.0	252	290	849	113
		10HPS	2.2	Polysulfone	Steam	21.0	259	300	945	132
		180NRe	1.7	Polysulfone	E Beam	76.0	277	328	1,321	102
		200NRe	1.9	Polysulfone	E beam	74.0	280	333	1,415	113
		HF80S	1.8	Polysulfone	Steam	55.0	248	285	801	110
		HdF100S	2.3	Polysulfone	Steam	60.0	271	285	1,167	132
	FX	600	1.5	Helixone	Steam	52.0	268		1,103	97
		800	1.8	Helixone	Steam	63.0	276		1,292	118
		100	2.1	Helixone	Steam	75.0	278	332	1,351	138
		60	1.4	Helixone	Steam	46.0	261	303	977	74
		80	1.8	Helixone	Steam	59.0	276	326	1,292	95
		100	2.2	Helixone	Steam	73.0	278	331	1,351	116
		5	1.0	Helixone	Steam	8.0	228		614	54
		8	1.4	Helixone	Steam	12.0	254	293	874	74
		10	1.8	Helixone	Steam	14.0	261	303	977	95
	FX CorDiax	60	1.4	Helixone	Steam	47.0	271	319	1,167	74

		80	1.8	Helixone	Steam	64.0	280	336	1,415	95
		100	2.2	Helixone	Steam	74.0	283	341	1,527	116
		600	1.6	Helixone	Steam	47.0	285	354	1,614	95
		800	2.0	Helixone	Steam	64.0	291	365	1,976	115
		1000	2.3	Helixone	Steam	68.0	292	367	2,060	136
	FX Classix	60	1.4	Helixone	Steam	38.0	266	312	1,064	74
		80	1.8	Helixone	Steam	53.0	279	334	1,382	95
		100	2.2	Helixone	Steam	68.0	280	336	1,415	116
Nipro	Elisio HX	13HX	1.3	Polynephron	γ-Irradiation	53.0	268	316	1,103	80
		15HX	1.5	Polynephron	γ-Irradiation	60.0	276	329	1,292	90
		17HX	1.7	Polynephron	γ-Irradiation	67.0	282	341	1,487	102
		19HX	1.9	Polynephron	γ-Irradiation	75.0	288	351	1,771	114
		21HX	2.1	Polynephron	γ-Irradiation	82.0	292	358	2,060	125
	Elisio	13H	1.3	Polynephron	γ-Irradiation	64.0	263	311	1,010	85
		15H	1.5	Polynephron	γ-Irradiation	67.0	270	323	1,145	95
		17H	1.7	Polynephron	γ-Irradiation	74.0	275	332	1,265	105
		19H	1.9	Polynephron	γ-Irradiation	76.0	280	343	1,415	115
		21H	2.1	Polynephron	γ-Irradiation	82.0	284	346	1,569	130
	Elisio M	13M	1.3	Polynephron	γ-Irradiation	17.0	249	288	812	80
		15M	1.5	Polynephron	γ-Irradiation	20.0	257	300	916	91
		17M	1.7	Polynephron	γ-Irradiation	22.0	265	311	1,045	108
		19M	1.9	Polynephron	γ-Irradiation	25.0	268	321	1,103	115
		21M	2.1	Polynephron	γ-Irradiation	27.0	274	331	1,239	128
	Solacea	15H	1.5	ATA (Asym. Cell. Triac.)	γ-Irradiation	61.0	266	312	1,064	86
		17H	1.7	ATA (Asym. Cell. Triac.)	γ-Irradiation	69.0	274	323	1,239	98
		19H	1.9	ATA (Asym. Cell. Triac.)	γ-Irradiation	72.0	278	332	1,351	108
		21H	2.1	ATA (Asym. Cell. Triac.)	γ-Irradiation	76.0	283	340	1,527	118
	Sureflux UX	13UX	1.3	Cellulose Triacetate	γ-Irradiation	30.0	262	304	993	76
		15UX	1.5	Cellulose Triacetate	γ-Irradiation	35.0	270	317	1,145	88
		17UX	1.7	Cellulose Triacetate	γ-Irradiation	38.0	276	328	1,292	98
		19UX	1.9	Cellulose Triacetate	γ-Irradiation	41.0	281	336	1,450	109

		21UX	2.1	Cellulose Triacetate	γ-Irradiation	46.0	285	344	1,614	119
Nikkiso	FDX	120GW	1.2	PEPA	γ-Irradiation	47.0	242	N/A	736	74
		150GW	1.5	PEPA	γ-Irradiation	52.0	251	N/A	836	92
		180GW	1.8	PEPA	γ-Irradiation	57.0	257	N/A	916	111
		210GW	2.1	PEPA	γ-Irradiation	64.0	260	N/A	961	129
	FDY	120GW	1.2	PEPA	γ-Irradiation	48.0	242	N/A	736	74
		150GW	1.5	PEPA	γ-Irradiation	54.0	254	N/A	874	92
		180GW	1.8	PEPA	γ-Irradiation	59.0	260	N/A	961	111
		210GW	2.1	PEPA	γ-Irradiation	64.0	263	N/A	1,010	129
Toray[c]	NF	1.3H	1.3	PMMA	γ-Irradiation	8.8	186	N/A	377	83
		1.6H	1.6	PMMA	γ-Irradiation	8.7	190	N/A	394	103
		1.8H	1.8	PMMA	γ-Irradiation	11.0	192	N/A	403	118
		2.1H	2.1	PMMA	γ-Irradiation	26.0	193	N/A	407	135
		1.3U	1.3	PMMA	γ-Irradiation	33.0	182	N/A	360	83
		1.6U	1.6	PMMA	γ-Irradiation	41.0	188	N/A	385	103
		1.8U	1.8	PMMA	γ-Irradiation	47.0	191	N/A	398	118
		2.1U	2.1	PMMA	γ-Irradiation	50.0	193	N/A	407	135
	Toraylight NS	1.3SL	1.3	Polysulfone	γ-Irradiation	41.0	193	N/A	407	83
		1.5S	1.5	Polysulfone	γ-Irradiation	47.0	194	N/A	412	96
		1.8S	1.8	Polysulfone	γ-Irradiation	50.0	195	N/A	417	111
		2.1S	2.1	Polysulfone	γ-Irradiation	53.0	196	N/A	421	130
	Toraylight NV	1.3U	1.3	Hydrolink (polysulfone)	γ-Irradiation	42.0	192	N/A	403	84
		1.5U	1.5	Hydrolink (polysulfone)	γ-Irradiation	46.0	196	N/A	421	96
		1.8U	1.8	Hydrolink (polysulfone)	γ-Irradiation	51.0	198	N/A	431	111
		21U	2.1	Hydrolink (polysulfone)	γ-Irradiation	52.0	198	N/A	431	130
	Filtryzer NF-H	1.3H	1.3	PMMA	γ-Irradiation	36.0	239	279	707	N/A
		1.6H	1.6	PMMA	γ-Irradiation	43.0	250	293	824	N/A
		1.8H	1.8	PMMA	γ-Irradiation	48.0	257	304	916	N/A
		2.1H	2.1	PMMA	γ-Irradiation	55.0	264	312	1,027	N/A
	Filtryzer BK-F	1.3F	1.3	PMMA	γ-Irradiation	16.0	235	266	671	76
		1.6F	1.6	PMMA	γ-Irradiation	20.0	250	288	824	94
		2.1F	2.1	PMMA	γ-Irradiation	26.0	268	314	1,103	126
	Filtryzer BK-U	1.3U	1.3	PMMA	γ-Irradiation	26.0	228	257	614	76
		1.6U	1.6	PMMA	γ-Irradiation	31.0	245	280	767	94
		2.1U	2.1	PMMA	γ-Irradiation	40.0	263	307	1,010	126
	Filtryzer B1	1.3H	1.3	PMMA	γ-Irradiation	12.0	226[d]	253	599	76
		1.6H	1.6	PMMA	γ-Irradiation	14.0	245[d]	279	767	95
		1.8H	1.8	PMMA	γ-Irradiation	16.0	253[d]	291	861	105

Filtryzer B3	1.0A	1	PMMA	γ-Irradiation	7.0	213	237	512	61
	1.3A	1.3	PMMA	γ-Irradiation	8.8	235	265	671	76
	1.6A	1.6	PMMA	γ-Irradiation	8.7	242	275	736	95
	1.8A	1.8	PMMA	γ-Irradiation	9.9	256	296	902	105
	2.1A	2.1	PMMA	γ-Irradiation	11.0	257	298	916	118

[a]R variant intended for reprocessing

[b]At Q_b = 200 mL/min

[c]Clearances established at an ultrafiltration rate of 10 mL/min

[d]Established at a UF rate of 29 mL/min

Notes:

Polysulfone membranes from different manufacturers differ substantially in their composition, use of additives such as PVP (polyvinylpyrrolidone), and surface geometry as well as their biocompatibility.

Because of space constraints, the dialyzers shown in the table are mostly limited to those between 1.3 and 2.1 m^2 in size. For each line of dialyzers, smaller and often one or more larger (>2.1 m^2) sizes are available. To estimate the K_0A for dialyzers not listed in this table, one can refer to the dialyzer urea clearance specification table from the manufacturer and input the urea clearances at the blood and dialysate flow being used into a K_0A calculator that can be found at www.ureakinetics.org.

AN69-ST Acrylonitrile and sodium methallyl sulfonate copolymer; ATA, asymmetric cellulose triacetate; PAES, polyarylethersulfone; PEPA, polyester polymer alloy; PMMA, polymethylmethacrylate; PVP, polyvinylpyrrolidone; Vit-E, vitamin E.

APPENDIX E

FORMULAS FOR ESTIMATING SOLUTE CLEARANCE WITH HEMODIAFILTRATION

The EUDIAL group (Tattersall, 2013) has proposed the following equations to estimate clearance with hemodiafiltration.

The **diffusive component** (K_D) can be estimated as follows:

$$K_D = \frac{1 - e^{K_0A \times [(Q_b - Q_d)/(Q_b \times Q_d)]}}{(1/Q_b) - (1/Q_d) \times e^{K_0A \times [(Q_b - Q_d)/(Q_b \times Q_d)]}}$$

where Q_b is the blood or plasma water flow rate; Q_d is the dialysis fluid flow rate; and K_0A is the solute-specific dialyzer mass transfer-area coefficient.

The **convective component** (K_C) can be estimated as follows:

$$K_C = \frac{Q_b - K_D}{Q_b} \times Q_f \times S$$

where Q_f is the convective flow rate; and S is the sieving coefficient.

The **total clearance** K_T can be estimated as the sum of the two components as follows:

$$K_T = (K_D + K_C) \times DF$$

where DF stands for dilution factor, depending on how the replacement fluid is infused (postdilution, predilution, or mixed dilution).

Tattersall JE and Ward RA; for the EUDIAL group. Online haemodiafiltration: definition, dose quantification and safety revisited. *Nephrol Dial Transplant*. 2013;28(3):542-50.

APPENDIX F

MOLECULAR WEIGHTS AND CONVERSION TABLES

I. TABLE F.1

TABLE F.1 Molecular Weights and Conversion Tables

Molecular Weights (MW) of Selected Substances

Substance	MW
Acetylsalicylic acid (aspirin)	180
Albumin	68,000
β2-Microglobulin	11,800
Cholesterol	386
Creatinine	113
Dextrose (glucose monohydrate)	198
Ethanol	46
Ethylene glycol	62
Glucose	180
Hemoglobin	68,800
Isopropyl alcohol (isopropanol)	60
Light chains	23,000
Lithium	7
Methanol	32
Myoglobin	17,800
Parathyroid hormone	9,500
Phenobarbital	232
Theophylline	180
Triglycerides	886
Urea	60
“Urea nitrogen” (blood urea nitrogen [BUN] or serum urea nitrogen [SUN])	28
Vancomycin	1,486
Vitamin B_{12}	1,355
Vitamin D_3 (25-D_3)	402

II. CONVERTING BETWEEN WEIGHT, VALENCY, AND MOLARITY

A. Number of milligrams in 1 mEq or 1 mmol of substance

Substance	1 mEq	1 mmol
Na^+	23	23
K^+	39	39
$Ca2^+$	20	40
$Mg2^+$	12	24
Li^+	7	7
HCO_3^-	61	61
Cl^-	35.5	35.5
N (nitrogen)		14
P (phosphorus)		31
C (carbon)		12

B. Changing milligrams to milliequivalents or millimoles

1. Sodium, potassium, chloride, bicarbonate

1 g NaCl	= 1,000 mg/(23 + 35.5) mg
	= 17 mEq or mmol of Na^+
1 g Na^+	= 1,000 mg/23 mg
	= 43 mEq or mmol of Na^+
1 g KCl	= 1,000 mg/74.5 mg
	= 14 mEq or mmol of K^+
1 g K^+	= 1,000 mg/39 mg
	= 26 mEq or mmol of K^+
1 g NaHCO3	= 1,000 mg/84 mg
	= 12 mEq or mmol of Na^+
	= 12 mEq or mmol of HCO_3^-

2. Calcium (mg/dL to mmol/L conversion)

	Example: 10 mg/dL
	= 100 mg/L
	= 100/20 mmol/L, since 20 mg = 1 mEq
	= 5 mEq/L
	= 5/2 mmol/L since 2 mEq = 1 mmol
	= 2.5 mmol/L

3. Magnesium (mg/dL to mmol/L conversion)

	Example: 2.4 mg/dL
	= 24 mg/L
	= 24/12 mEq/L, since 12 mg = 1 mEq
	= 2 mEq/L

= 2/2 mmol/L, since 2 mEq = 1 mmol

= 1 mmol/L

4. **Phosphorus (P) (mg/dL to mmol/L conversion).** Because P values when expressed in mEq/L change with alterations in pH, the mEq/L unit is not ordinarily used in clinical practice.

Example: 2.5-4 mg/dL

= 25-40 mg/L

= (25/31-40/31) mmol/L, since 1 mmol of P = 31 mg

= 0.8-1.3 mmol/L

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