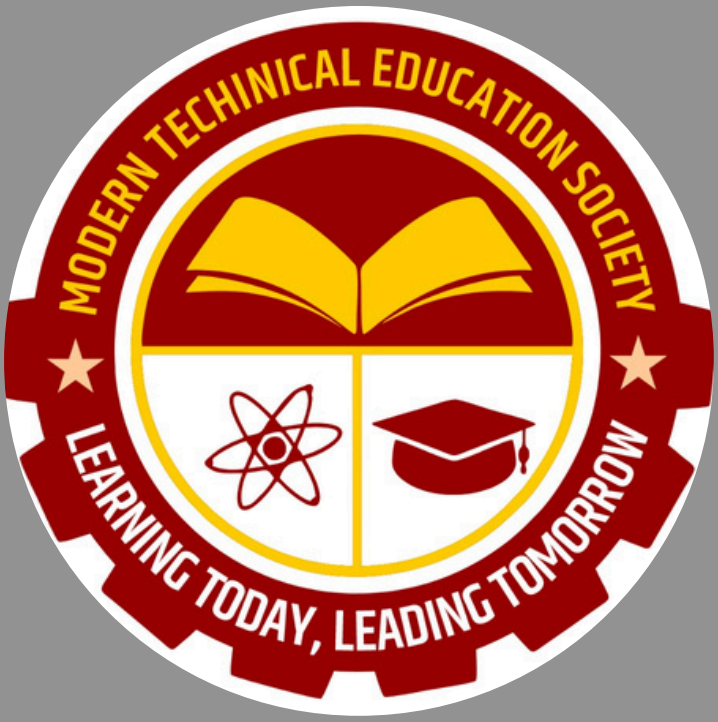
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DIALYSIS



prescription may lead to noncompliance or burnout and consequent technique failure. To increase peritoneal *Kt/V* in CAPD patients, there are three options (Table 25.4): increase the dwell volumes, increase the frequency of daily exchanges, and/or increase dialysis solution tonicity, thereby augmenting ultrafiltration.

a. Increasing the dwell volumes. This increases clearance because the total volume of solution delivered daily rises and the larger dwell volume leads to 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 a 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 greater falloff in equilibration and the percentage of increase in clearance is reduced. To achieve clearance targets in larger (>75 kg) anuric patients, typically at least 2.5-L dwell volumes are required (Virga, 2014). Some programs prefer to initiate such patients on larger dwell volumes to begin with, whereas others use 2-L volumes until residual renal function fades and then make the switch. The main disadvantage of increasing dwell volumes is that some patients may complain of back pain, abdominal distention, and even shortness of breath. This can be minimized if the increased volumes are introduced at the time of initiation of peritoneal dialysis, before the patient becomes accustomed to smaller volumes. 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. Most CAPD patients do four exchanges daily. Increasing the number of exchanges from four to five per day generally does not have a major effect on urea equilibration, which remains at approximately 85% to 90% in patients with average transport characteristics. This will not be the case if patients do not ensure that the five daily exchanges are well spaced, with at least a 4-hour dwell time for each. There will be a noticeable drop in creatinine concentration in the drained effluent because the equilibration curve for creatinine is typically still rising 4 hours after the dwell commences. Thus, increasing the frequency of exchanges is less effective than increasing dwell volumes, especially where CrCl is concerned.

An additional disadvantage of increasing the frequency of exchanges to five daily is that it may interfere with a patient's lifestyle and lead to noncompliance or burnout. Also, 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 tonicity of the dialysis solutions. This strategy increases both ultrafiltration and clearance. It is used in some centers, but there are increasing concerns that it may lead to a higher incidence of hyperglycemia, hyperlipidemia, obesity, and long-term peritoneal membrane damage.

2. APD. The initial APD prescription is quite variable across centers. A typical starting volume is 10 or 12 L daily but some use 15 L, especially in larger patients. Typical cycler time is 8–10 hours, and dwell volumes on the cycler in the daytime are usually 2 L or, in larger patients, 2.5 L. Some start with a day dry prescription if the patient has good residual renal function and/or is small. Others use a day dwell from the start but may shorten the duration of the dwell to avoid fluid resorption, especially in higher transporters, and then either leave the patient "dry" for part of the day or add a second dwell. If icodextrin is available, some centers will use it routinely for the day dwell while others will prescribe it only in high transporters or in patients who have fluid resorption problems and/or in those in whom there are metabolic concerns about excess glucose absorption, for example, diabetic or obese patients.

Peritoneal clearance in APD can be increased using a number of different strategies (Table 25.4) (Durand, 2003). In order of usefulness, these are as follows:

a. Introduction of a day dwell. 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 lon- ger dwell times. Typically, adding a day dwell to a day dry APD patient will increase daily peritoneal *Kt/V* and CrCl by 25% to 50%, and so this is very cost-effective (Blake, 1996). Further increases in clearance can be achieved by adding a second or even a third day dwell, although this is less likely to be required with present more mod- est *Kt/V* urea clearance targets. These added exchanges can be done using the docking-station approach or, if it suits the patient better, using manual CAPD tubing in the conventional way. Day dwell volumes can be titrated to maximize clearance while minimizing mechanical symptoms. This strategy does have the disadvantages of requiring the patient to do more procedures and to have fluid in the peritoneal cavity for at least part of the day.

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 (Perez, 2000; Demetriou, 2006). However, when the number of cycles exceeds 6–9 per 9-hour

treatment, a large proportion of the dialysis session is spent draining and filling, and further increment in clearance becomes minimal. The benefit of more frequent cycles tends to be higher in high transporters and is higher for urea than for creatinine. It may also be influenced by catheter function. Maintaining a small amount of dialysate in the peritoneum constantly (i.e., using tidal PD) can be used to help support clearance during rapid cycling.

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 (i.e., 4 × 2.5 L per session is better than 5 × 2 L per session) though the increase 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.

e. Increasing dialysis solution tonicity. As in CAPD, clearance can be augmented in APD by increasing daytime or nighttime ultrafiltration, but concerns about glucose-related complications limit the usefulness of this approach.

E. Incremental versus maximal prescription. There are two distinct approaches to prescription of peritoneal dialysis when clearance targets are being considered. The incremental approach, which is particularly suitable when dialysis is being initiated early, suggests that peritoneal dialysis should be used to make up the difference between residual renal clearances and targeted clearances (Viglino, 2008). 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 prescrip- tion to meet their targets with peritoneal dialysis alone. This approach considers residual renal function as a temporary bonus that inevitably deteriorates with time.

The advantages of the incremental approach are that it is initially less costly and less onerous for the patient, and it may decrease total glucose exposure and risk of peritonitis, insofar as fewer procedures are required. A disadvantage is that it requires regular monitoring of residual function to ensure that the total clearance achieved does not fall below target levels.

F. Empirical versus modeled approach. Another decision when prescribing peritoneal dialysis 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 peritoneal transport with a PET, and

quantifying residual renal function. It also typically involves 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 there is sometimes a discrepancy between the modeled and actual clearances achieved.

The alternative approach is empirical, in which the physician uses the knowledge of the patient's size, residual renal function, and peritoneal transport status 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 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.

G. Prescription pitfalls in peritoneal dialysis. There are a number of common pitfalls that physicians face in attempting to achieve adequate clearances and fluid removal on peritoneal dialysis.

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 clearance every 2–3 months or by adopting a maximal prescription approach that gives sufficient peritoneal clearance independent of residual function.

2. noncompliance. A chronic peritoneal dialysis patient 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 noncompliance. 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. There is no single test that identifies this particular problem, and a high index of suspicion is required. Serial measurements of 24-hour dialysate plus urinary creatinine excretion may help identify the problem. Patients in whom the total creatinine excretion has increased in comparison with a baseline value should be suspected of noncompliance. The rationale here is that on the day of the collection, creatinine that has

accumulated on previous noncompliant days is being dialyzed out, giving an artificially high value. The alternative explanation for an increase in total creatinine excretion is a gain in lean body mass, but this does not often occur in chronic dialysis patients. There are a number of patterns of noncompliance in peritoneal dialysis patients that should be borne in mind (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 12–16 mg/dL (about 1,000–1,500 mcmol/L). There are a number of possibilities here. One is noncompliance with the prescription. If this is the case, blood urea and potassium may 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 low-transport 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 clear- ance, but rather because of high creatinine generation, in- dicating 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 per week per 1.73 m2 and by show- ing that 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. Iden- tification 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 anuric patients. 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 are high or high-average transporters. This creates a concern because while *Kt/V* is above tar- get, middle-molecule clearance in the absence of residual 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 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 anuric patients.

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 low transporters, 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 have a lower CrCl.
6. Inadequate attention to fluid removal. Fluid removal is frequently neglected in prescriptions for peritoneal dialysis. Prescriptions that yield good clearances may not give sufficient ultrafiltration to control volume status and keep the patient free from hypertension. This is particularly true in high and high-average transporters, especially if long dwells which result in net fluid resorption are used. The use of icodextrin for the long dwell in both CAPD and APD and the prescription of short day dwells in APD are two strategies that may be useful.

III. GlUCOsE-sPArInG strAtEGIEs. In the past decade, there has been increasing concern about the harmful consequences of exposure to the hypertonic glucose in peritoneal dialysis solutions (Holmes, 2006). There is strong evidence that cumulative glucose exposure leads to deterioration in 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 so for 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 increase in body fat mass.

B. non-glucose dialysis solution strategies. These involve the substitution of dialysis solutions containing icodextrin or amino acids for those containing glucose (Paniagua, 2009; Li, 2013).

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. nUtrItIOnAl IssUEs In PErItOnEAl DIAlysIs. Nutritional status in peritoneal dialysis patients 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 as are used to calculate *Kt/V*. The rationale is that, in 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 25.5 for formula and sample calculation). Previously, PNA estimates were normalized to actual body weight, but this can lead to misleadingly high nPNA values in wasted malnourished patients and to inappropriately low values in obese patients (Harty, 1994). Normalization to desirable or ideal weight based on anthropometric tables is now preferred. Recommended target nPNA for peritoneal dialysis patients is 1.2 g/kg per day, but this may be unnecessarily

TABLE 25.5 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 obese patients.

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-hr 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-hr 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

UNA, urea nitrogen appearance; PNA, protein nitrogen appearance.

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 per day should be a cause for concern, especially if accompanied by other evidence of poor nutrition.

2. Caloric intake. This is sometimes neglected in dialysis patients because it cannot be as easily measured as protein intake. In peritoneal dialysis, 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 per day; typically, 10% to 30% of this will come from dialysis solution glucose, with the exact amount absorbed depending on solution tonicity, dwell time, and volume of solution used, as well as on the patient's PET 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 on peritoneal dialysis. Serum albumin in this population is much more than a nutritional marker, as it is influenced by peritoneal transport 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 (Yeun, 1997). 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 done at the bedside, promotes history taking and physical examination, and has been shown to predict patient outcome. The subjective global assessment is de- scribed in detail in Chapter 31.

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 identifiesa patient who is at risk.

B. treatment of malnutrition. This is reviewed in detail in Chapter 31.

1. Amino acid–containing dialysis solution. Intraperitoneal amino acids have longbeen studied and are available in many countries, though not in 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 quality or quantity of life (Li, 2003a).

references and suggested readings

BergströmJ,et al. Calculation of the protein equivalent of total nitrogen appearance from urea appearance: which formulas should be used? Perit Dial Int. 1998;18: 467–473.

Bernardini J, et al. Pattern of noncompliance with dialysis exchanges in peritoneal di alysis patients. Am J Kidney Dis. 2000;35:1104–1110.

Blake PG, et al. Recommended clinical practices for maximizing peritoneal clearance Perit Dial Int. 1996;16:448–456.

Blake PG, et al; CSN Workgroup on Peritoneal Dialysis Adequacy. Clinical practice guidelines and recommendations on peritoneal dialysis adequacy 2011. Perit Dial Int. 2011;31:218–239.

Churchill DN, et al. Adequacy of dialysis and nutrition in continuous peritoneal dialysis [The CANUSA study]. J Am Soc Nephrol. 1995;7:198–207.

De Fijter CW, et al. Clinical efficacy and morbidity associated with CCPD rather than CAPD. Ann Intern Med. 1994;120:264–271.

Demetriou D, et al. Adequacy of automated peritoneal dialysis with and without manual daytime exchange. Kidney Int. 2006;70:1649–1655.

Diaz-Buxo JA. Enhancement of peritoneal dialysis: the “PD Plus” concept. Am J Kidn Dis. 1996;27:92–98.

Dombros N, et al. European Best Practice Guidelines for Peritoneal Dialysis. 7. Ad equacy of peritoneal dialysis. Nephrol Dial Transplant. 2005;20(suppl 9):24–27.

Durand PY. APD schedules and clinical results. Contrib Nephrol. 2003;140:272–277

Fernando SK, et al. Tidal PD: its role in the current practice of peritoneal dialysis. Kid ney Int Suppl. 2006;103:S91–S95.

Guest S. Intermittent peritoneal dialysis: urea kinetic modeling and implications of residual kidney function. Perit Dial Int. 2012;32:142–148.

Harty JC, et al. The normalized protein catabolic rate is a flawed marker of nutrition i CAPD patients. Kidney Int. 1994;45:103–109.

Holmes C, et al. Glucose sparing in peritoneal dialysis: implications and metrics. Kid ney Int Suppl. 2006;103:S104–S109.

Johansen KL, et al. Anabolic effects of nandrolone decanoate in patients receiving d alysis: a randomized controlled trial. JAMA. 1999;281:1275–1281.

Keshaviah PR, et al. The peak concentration hypothesis: a urea kinetic approach t comparing the adequacy of continuous ambulatory peritoneal dialysis and hemodialysis. Perit Dial Int. 1989;9:257–260.

Keshaviah PR, et al. Lean body mass estimation by creatinine kinetics. J Am S Nephrol. 1995;4:1475–1485.

Li FK, et al. A 3 year prospective randomized controlled study on amino acid dialysat in patients on CAPD. Am J Kidney Dis. 2003a;42:173–183.

Li PK, et al. Effects of an ACEI on residual renal function in patients receiving CAPD randomized controlled trial. Ann Intern Med. 2003b;139:105–112.

Li PK, et al. Randomized controlled trial of glucose sparing peritoneal dialysis in dia betic patients. J Am Soc Nephrol. 2013;24:1889–1900.

Lo WK, et al. Effect of Kt/V on survival and clinical outcome in CAPD patients in a randomized prospective study. Kidney Int. 2003;64:649–656.

Paniagua R, et al. Effect of increased peritoneal clearance on mortality rates in per toneal dialysis: ADEMEX, a prospective randomized controlled trial. J Am Soc Nephrol. 2002;13:1307–1320.

Paniagua R, et al. Icodextrin improves fluid and metabolic management in high and high-average transport patients. Perit Dial Int. 2009;29:42–32.

Paniagua R, et al. Ultrafiltration and dialysis adequacy with various daily schedules o dialysis fluids. Perit Dial Int. 2012;32:545–551.

Perez RA, et al. What is the optimal frequency of cycling in APD? Perit Dial Int 2000;20:548–556.

Sarkar S, et al. Tolerance of large exchange volumes by peritoneal dialysis patients. Am J Kidney Dis. 1999;33:1136–1141.
Rodriguez-Carmona A, et al. Compared time profiles of ultrafiltration, sodium removal and renal function in incident CAPD and APD patients. Am J Kidney Dis. 2004;44:132–145.
Viglino G, et al. Incremental peritoneal dialysis: effects on the choice of dialysis modality, residual renal function and adequacy. Kidney Int Suppl. 2008;108:S52–S55.
Virga G, et al. A load volume suitable for reaching dialysis adequacy targets in anuric patients on 4-exchange CAPD. J Nephrol. 2014;27:209–215.
Woodrow G, et al. Comparison of icodextrin and glucose solutions for daytime dwell in APD. Nephrol Dial Transplant. 1999;14:1530–1535.
Yeun JY, et al. Acute phase proteins and peritoneal dialysate albumin loss are the main determinants of serum albumin in peritoneal dialysis patients. Am J Kidney Dis. 1997;30:923–927.

26 Volume Status and Fluid Overload in Peritoneal Dialysis

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Fluid overload in peritoneal dialysis (PD) patients can manifest as generalized edema, pulmonary edema, and hypertension. It contributes to left ventricular hypertrophy and is a major contributor to cardiovascular disease, the leading cause of death in all dialysis patients. It is also associated with hypoalbuminemia, malnutrition, inflammation, and atherosclerosis (Demirci, 2011); and it is a significant cause of technique failure, especially in long-term PD patients (Woodrow, 2011).

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 that weight which gives a well-tolerated normotensive, edema-free state, and, just as in hemodialysis, it is determined by trial and error. Since PD patients 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 cava or of the lungs. Bioimpedance analysis can be done with relatively simple devices and involves 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 (John, 2010). Serum BNP levels are in clinical use and are predictive of patient outcomes, but do not reliably distinguish fluid overload from cardiac injury (Granja, 2007; Wang, 2007).

II. MECHANISMS OF FLUID OVERLOAD. Fluid overload in a PD patient may reflect any combination of inappropriate prescription, noncompliance, loss of residual renal function, mechanical problems, and peritoneal membrane dysfunction. Awareness that any one factor alone may not explain an individual PD patient's volume overload is important and one should avoid thoughtlessly attributing all fluid overload to membrane-related ultrafiltration failure (UFF).

III. DIAGNOSIS OF PERITONEAL MEMBRANE DYSFUNCTION AND ULTRAFILTRATION FAILURE. UFF is definedas fluid overload in association with anultrafiltration volume <equivalent to a 400 mL in a modified PET) (Honeal-Pannakeet, 1997). The modified PET uses a 4.25% dialysate dwell instead of the usual 2.5% bag used in the standard PET (described in Chapter 21). UFF should not be diagnosed if the ultrafiltration volume exceeds 400 mL or if there is no clinical evidence of significant volume overload. *UFF should not be diagnosed until catheter malfunction and leaks have been excluded.* An ultrafiltration volume >400 mL in the modified PET implies normal peritoneal membrane function, and if fluid overload is present, closer attention needs to be paid to nonmem- brane causes as listed in Table 26.1.

If UFF is diagnosed, the next step is to review the solute transport characteristics of the patient using the results of the modified 4.25% PET (or the standard PET as the results are very similar).
A. High transporter with UFF (type I). In this situation, the dialysate dextrose concentration falls quickly after infusion because of rapid absorption, resulting in 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 occurs with time on PD. This occurs to a greater extent in some patients than in others. The contribution of interstitial fibrosis and resultant thickening of the membrane is increasingly recognized (Davies, 2005). Causes of type I UFF include cumulative exposure of the membrane to high glucose loads (Davies, 2001) and perhaps to other bioincompatible features of PD solutions, including low pH, lactate, and toxic glucose degradation products. Other causes may be related to cumulative episodes of peritonitis or to systemic inflammation seen in uremia generally. Type I UFF may also occur transiently in some patients with acute peritonitis who have a temporary increase in transport status during and after the episode owing to acute inflammation of the membrane.

TABLE 26.1 Causes of Fluid Overload in PD Patients

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

B. Low transporter with UFF (type II). This group of patients has reduced small solute clearance and reduced fluid removal. 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 a severe peritonitis or other intra-abdominal complication. It is difficult to maintain these patients on PD unless they have significant residual renal function.

C. UFF with transport in the normal range (usually high-average and low-average transporters). Careful consideration once again should be made to exclude mechanical causes for poor fluid removal in this group.

1. Increased lymphatic absorption of peritoneal fluid is the cause in some patients and this is called **type III UFF**. Lymphatic absorption 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 deficiency. A similar pattern can be seen with the interesting but rarer condition of aquaporin deficiency. This can be diagnosed by measuring the change in dialysate sodium concentration after 30–60 minutes of a 2-L dialysis dwell with 4.25%, dextrose compared with a 2-L dwell using 1.5%, dextrose. 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 5–10 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 (Fig. 21.7). 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 <5 mmol/L difference between the dialysate sodium levels at 30–60 minutes with the 4.25% dwell compared with the 1.5% dwell (Smit, 2004; Ni, 2006).

IV. PREVENTION AND MANAGEMENT OF FLUID OVERLOAD. Often, multiple causes of volume overload coexist in an individual PD patient. 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.

A. General measures

1. Sodium restriction. It is important that patients receive education on sodium and fluid restriction, especially when residual renal function declines. An intake of <100 mmol (2.3 g) of sodium per day is recommended for those with difficult hypertension or volume control problems (Ates, 2001).

2. Patient education on when to use higher-strength glucose solutions.
Patientsare usuallytaught to choose or titrate PD solu-
tion dextrose concentrations in order to achieve target body weight. Underuse of hypertonic solutions may con- tribute to fluid overload. However, regular selection of high-concentration dextrose solutions should not be the preferred method of fluid volume control over sodium re- striction. Overuse of the high-concentration dextrose solu- tions may adversely affect peritoneal membrane function, increasing glucose absorption, worsening blood sugar and lipid control, and promoting obesity. Frequent clinical assessment.
3. Patients need to be assessed regularly and have their target weight reviewed. In PD pa- tients, there is an early tendency to weight gain, likely due to glucose absorption, and so target weight may need to be adjusted to avoid excess use of hypertonic glucose in an at- tempt 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 de- tect this, and clinical examination plus trial and error re- mains the best approach. Good blood sugar control. This will help maintain the glucose
4. concentration gradient across the peritoneal membrane required for fluid removal. Preserving residual renal function. This is important for both clearance and fluid removal. There
5. is clinical trial evidence in PD patients that angiotensin-converting enzyme inhibi- tors and angiotensin receptor blockers preserve residual re- nal function, in terms of both clearance and urine volume. Use of high-dose loop diuretics in patients with residual re- nal function, with or without metolazone, will also increase urine volume and sodium and fluid removal. Avoidance of nephrotoxins and intravascular depletion both serve to protect residual renal function. Biocompatible PD solu- tions based on multipouched bag technology have low glu- cose degradation product content, and some randomized trials suggest that these are associated with better preser- vation of residual renal function (Johnson, 2012); however, there is a concern that this is, at least partly, mediated by less ultrafiltration with these solutions (Blake, 2012). Abdominal leaks. See Chapter 28. Catheter malfunction. See Chapter 23. Preservation of peritoneal membrane function. Reduction in epi- sodes of
6. peritonitis and avoidance of excessive exposure to high-
7. dextrose-concentration PD fluid will help to preserve long-
8. term peritoneal membrane function. Randomized tri- als looking at “biocompatible” PD solutions with low glu- cose degradation product levels have not shown evidence that these solutions preserve membrane function better than when conventional PD solutions are used.

B. Management of UFF

1. High transport status (UFF type I).Short dwell times are required to maintainthe dialysate dextrose concentration gradient and so automated peritoneal dialysis (APD), programmed for short 1–1.5 hour dwells, may be best. Long-duration dextrose-containing dwells in continuous ambulatory peritoneal dialysis (CAPD) and APD must be avoided. In APD, short dextrose 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 dextrose, to produce a concentration gradient for ultrafiltration. It is not absorbed across the membrane, although it does slowly get taken up in the lymphatics. Accordingly, a concentration gradient is maintained throughout a long dwell, allowing ongoing ultrafiltration. Icodextrin is ideal for the 14–16-hour day dwell in APD and for the long nocturnal dwell in CAPD. Use of icodextrin has been shown to improve volume status (Davies, 2003) and to prolong technique survival substantially in patients with UFF and high transport status (Takatori, 2011). Its use has also been shown to reduce the extracellular fluid–to–intracellular fluid ratio as measured by bioimpedance (Woodrow, 2004).
   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 resolution of increased vascularity with time off PD.

2. UFF with low transport status. These patients are unlikely to do much better on APD 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 nonaquaporin channels (La Milia, 2006).

V. 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 now shown that long-term PD patients exposed to more hypertonic glucose are more likely to develop high transport characteristics than those who receive less glucose (Davies, 2001). Systemically, glucose loading may also be harmful as detailed in Chapter 29. 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. Effec- tive 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. 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 can also be substituted for one daily dextrose dwell.

VI. HYPERTENSION AND HYPOTENSION IN PD

A. Hypertension. PDwasinitially advocated as providing bet-terblood pressure control than hemodialysis because of its continuous nature. This was certainly demonstrated in early reports on PD populations. More recently, it has been demonstrated that antihypertensive medication requirements increase with duration on PD, especially when residual renal function is lost (Ortega, 2011).

1. 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).

2. Management. This should focus initially on volume control. Antihypertensives, other than cardioprotective agents, should only be introduced if this approach has been 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.

B. Hypotension. Hypotension is not uncommon in PD populations, 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 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 early mortality rate. Agents such as midodrine and fludrocortisone have been used but with no proven long-term benefit. New onset hypotension may, of course, represent developing sepsis or acute cardiac injury.

References and Suggested Readings

Ates K,et al. Effect of fluidand sodiumremoval on mortality in peritoneal dialysis patients. Kidney Int. 2001;60:767–776.

Blake PG. Balance about balANZ. Perit Dial Int. 2012;32:493–496.

Boudville NC, et al. Blood pressure, volume, and sodium control in an automated peritoneal dialysis population. Perit Dial Int. 2007;27:537–543.

Davies SJ, et al. Peritoneal glucose exposure and changes in membrane solute transport with time on peritoneal dialysis. J Am Soc Nephrol. 2001;12:1046–1051.

Davies SJ, et al. Icodextrin improves the fluid status of peritoneal dialysis patients: results of a double-blind randomized controlled trial. J Am Soc Nephrol 2003;14:2338–2344.

Davies SJ, et al. Longitudinal membrane function in functionally anuric patients treated with APD: data from EAPOS on the effects of glucose and icodextrin prescription. Kidney Int. 2005;67:1609–1615.

Demirci MS, et al. Relation between malnutrition inflammation atherosclerosis and volume status: the usefulness of bioimpedance in peritoneal dialysis patients.
Nephrol Dial Transplant. 2011;26:1708–1716.

Grabia SM, Grabia J. Natriuretic peptide and impedance cardiography to assess volume status in peritoneal dialysis patients. Adv Perit Dial. 2007;23:155–160.

Ho-dac-Pannakeet MM, et al. Analysis of ultrafiltration failure in peritoneal dialysis patients by means of standard peritoneal permeability analysis. Perit Dial Int. 1997;17:144–150.

John B, et al. Plasma volume, albumin and fluid status in peritoneal dialysis patients. Clin J Am Soc Nephrol. 2010;5:1463–1470.

Johnson DW, et al. Effects of biocompatible versus standard fluid on peritoneal dialysis outcomes. J Am Soc Nephrol. 2012;23:1097–1107.

La Milia V. Sodium kinetics in peritoneal dialysis: from theory to clinical practice. G Ital Nefrol. 2006;23:37–48.

Lee JA, et al. Association between serum n-terminal pro-brain natriuretic peptide concentration and left ventricular dysfunction and extracellular water in continuous ambulatory peritoneal dialysis patients. Perit Dial Int. 2006;26:360–365.

Li PK, et al. Effects of an angiotensin-converting enzyme inhibitor on residual renal function in patients receiving peritoneal dialysis: a randomized, controlled study. Ann Int Med. 2003;139:105–112.

Li PK, et al. Randomized controlled trial of glucose-sparing peritoneal dialysis in diabetic patients. J Am Soc Nephrol. 2013;24:1889–1900.

Malliara M, et al. Hypotension in patients on chronic peritoneal dialysis: etiology, management, and outcome. Adv Perit Dial. 2002;18:49–54.

Mujais S, et al. Evaluation and management of ultrafiltration problems in peritoneal dialysis. International Society for Peritoneal Dialysis Ad Hoc Committee on Ultrafiltration Management in Peritoneal Dialysis. Perit Dial Int. 2000;20(suppl 4):S5–S21.

Ni J, et al. Aquaporin-1 plays an essential role in water permeability and ultrafiltration during peritoneal dialysis. Kidney Int. 2006;69:1518–1525.

Ortega LM, Materson BJ. Hypertension in peritoneal dialysis patients: epidemiology, pathogenesis and treatment. J Am Soc Hypertens. 2011;5:128–136.

Paunuccio V, et al. Chest ultrasound and hidden lung congestion in peritoneal dialysis patients. Nephrol Dial Transplant. 2012;27:3601–3605.

Rodriguez-Carmona A, et al. Compared time profiles of ultrafiltration, sodium removal and renal function in CAPD and APD patients. Am J Kidney Dis. 2004;44:132–14

Sharma AP, Blake PG. Should fluid removal be used as an index of adequacy in P Perit Dial Int. 2003;23:107–108.

Smit W, et al. Quantification of free water transport in peritoneal dialysis. Kidney Int. 2004;66:849–854.

Takatori Y, et al. Icodextrin increases technique survival rate in peritoneal dialysis pa- tients with diabetic nephropathy by improving body fluid management: a random- ized controlled trial. Clin J Am Soc Nephrol. 2011;6:1237–1244.

Wang AY, et al. N-terminal pro-brain natriuretic peptide: an independent risk predictor of cardiovascular congestion, mortality, and adverse cardiovascular outcomes in chronic peritoneal dialysis patients. J Am Soc Nephrol. 2007;18:321–320.

Woodrow G. Volume status in peritoneal dialysis patients. Perit Dial Int. 2011;31 (suppl 2):S77–S82.

Woodrow G, et al. Abnormalities of body composition in peritoneal dialysis patients. Perit Dial Int. 2004;24:169–175.

27 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, it is the most common cause of treatment failure, accounting for nearly 30% of the cases. The overall incidence of peritonitis in continuous ambulatory peritoneal dialysis (CAPD) patients during the 1980s and early 1990s averaged 1.1–1.3 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, or 1 episode per 20–60 patient-months of PD (Piraino, 2011). The introduction of Y-set and double-bag disconnect systems has substantially reduced the incidence of peritonitis, particularly episodes caused by gram-positive organisms (Monteon, 1998; Li, 2002). 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 gener- ally different. Patients on APD going "dry" during the day (i.e., no daytime dwell) may have a decreased risk of infection compared with those with a day dwell. The current Interna- tional Society for Peritoneal Dialysis recommendations on PD-related infections (Piraino, 2011) state that every program should monitor infection rates, ideally once a month, but, at a minimum, on a yearly basis.

B. Pathogenesis

1. Pathways of infection

a. Intraluminal. Peritonitis occurs most often because of errors intechnique in making or breaking a transfer set–to-bag or catheter-to–transfer set connection. This allows bacteria to gain access to the peritoneal cavity via the catheter lumen. Typically, the organisms involved are coagulase-negative staphylococci or diphtheroids.

b. Periluminal. Bacteria present on the skin surface can enter the peritoneal cavity via the peritoneal catheter tract.

Typically, the organisms involved are *Staphylococcus aureus* or *Pseudomonas aeruginosa*.

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 diarrheal states and/or instrumentation of the colon, and may also be seen with strangulated hernia. Typical organisms involved are *Escherichia coli* and *Klebsiella* sp.

d. Hematogenous. Less commonly, peritonitis is due to bacteria that have seeded the peritoneum from a distant site by way of the bloodstream. Typical organisms here are streptococci and staphylococci.

e. Transvaginal. This is uncommon, but ascending infection may occur from the vagina via the uterine tubes into the peritoneum. 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 space by any of the routes already mentioned. 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 around 5 and an osmolality ranging from 1.3 to 1.8 times that of normal plasma, depending on the glucose concentration used. These unphysiologic conditions may inhibit the ability of peritoneal leukocytes to phagocytize and kill bacteria. High osmolality, low pH, and the presence of the lactate anion combine to cause inhibition of superoxide. There is now some evidence that newer normal pH, "biocompatible" solutions may reduce the peritonitis rate, but this has not been a consistent finding among published studies (Cho, 2014).

b. Peritoneal dialysis solution calcium levels. The antimicrobial actions of peritoneal macrophages are enhanced by both calcium and cholecalciferol. Use of active vitamin D has been reported to reduce the rate of peritonitis (Kerschbaum, 2013). Use of a 1.25-mM (2.5-mEq/L) calcium concentration in PD solution has gained popularity as it may improve adynamic bone disease and reduce vascular calcification. An increased risk of *Staphylococcus epidermidis* peritonitis has been reported with the use of low-calcium dialysis solutions (Piraino, 1992), but no subsequent confirmatory reports have been published.

C. Etiology. Using appropriate culture techniques, an organism can be isolated from the peritoneal fluid in over 90% of cases in which symptoms and signs of peritonitis and an elevated peritoneal fluid neutrophil count are present. The responsible pathogen is usually a bacterium, but fungal peritonitis occurs occasionally (Table 27.1).

TABLE 27.1 Frequency of Organisms Isolated in Patients with Peritonitis

Organisms Identified	Percentage(%)
Gram-positive organisms	40–50
S. aureus	11–12
Coagulase-negative staphylococcal species	12–30
Gram-negative organisms	20–30
Pseudomonas sp.	12–15
E. coli	6–10
Fungi	2–4
Mycobacterium	~1
Polymicrobial growth	~10
Culture-negative	~15

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 peritoneal fluid cell count (>100/mcL) due predominantly (>50%) to neutrophils, and (c) demonstration of bacteria in the peritoneal effluent by Gram stain or culture.

1. Symptoms and signs. The most common symptom is abdominal pain, but this is sometimes very mild. Others are nausea, vomiting, and diarrhea (Table 27.2). Sometimes, especially in the elderly, the only symptoms are a relatively sudden loss of residual renal function and postural hypotension. On the other hand, abdominal pain can be present in di- alysis patients owing to nonperitonitis-related abdominal causes; in those starting dialysis after a failed transplant in whom steroid treatment has been stopped, abdominal pain due to adrenal insufficiency should be considered.
2. Peritoneal fluid
   a. Cloudiness of the fluid. The peritoneal fluid generally becomes cloudy when the cell count exceeds 50–100/mcL (50–100 × 106/L). In most patients, sudden onset of cloudy fluid with appropriate abdominal symptoms is sufficient evidence of peritonitis to warrant initiation of antimicrobial therapy. However, cloudy peritoneal fluid may be due to other factors (e.g., fibrin, blood, or, rarely, malignancy or chyle) rather than to an increase in the white blood cell (WBC) count. Occasionally, fluid drained after a prolonged dwell period (such as after the daytime dwell in APD patients) appears cloudy in the absence of peritonitis. Conversely, a relatively translucent peritoneal fluid does not completely exclude peritonitis. Cloudy fluid has been reported with the use of calcium channel blockers, presumably because they

TABLE 27.2 Symptoms and Signs of Peritonitis

	Percentage(%)
Symptoms	
Abdominal pain	9
Nausea and vomiting	5
Feverish sensation	3
Chills	0
Constipation or diarrhea	3
	0
Signs	2
Cloudy peritoneal fluid	99
Abdominal tenderness	80
Rebound tenderness	10–50[a]
Increased temperature	33
Blood leukocytosis	25

[a] Highly variable, depending on the severity of infection and the amount of time elapsed between onset and medical evaluation.

increase triglyceride concentration in the peritoneal fluid (Ram, 2012).

b. Importance of performing a differential count of peritoneal fluid cells. Peritonitis is usually associated with an increase in the absolute number and percentage of neutrophils in the peritoneal fluid. On some occasions, a high peritoneal fluid cell count causing cloudy fluid will be present owing to an increase in the number of peritoneal fluid monocytes or eosinophils (see what follows). Most such cases are not associated with peritonitis and do not require antimicrobial treatment. For this reason, one should perform a differential cell count on the peritoneal fluid sample. Prior to counting, the fluid is spun in a special centrifuge (e.g., Cytospin, Shandon, Inc., Pittsburgh, PA) and the sediment colored with Wright stain.

c. Obtaining the specimen

1. CAPD patients. After disconnecting the drain bag full of peritoneal 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. APD patients. A representative cell count can be obtained easily from the daytime dwell by first draining the abdomen and taking 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 peritoneal fluid sample can be obtained directly via the peritoneal catheter. After careful cleaning of the catheter with

povidone–iodine, a syringe is attached using meticulous sterile technique, and 2–3 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 or more of dialysis solution and drain the abdomen, obtain- ing a sample from the effluent. Although the absolute peritoneal fluid 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 become quite difficult in effluent samples stored for more than 3–5 hours prior to injection into the EDTA-containing sample tube.

d. Peritoneal fluid cell counts in peritonitis. The absolute peritoneal fluid cell count in CAPD patients is usually <50 and often <10 cells/mcL. In "day dry" APD patients, the normal cell count may be much higher, especially in specimens taken directly via the catheter when the peritoneal fluid volume is small. Normally, the peritoneal white cells are mainly mononuclear (monocytes, macrophages, and occasional lymphocytes), and the percentage of neutrophils does not exceed 15%. A value >50% suggests peritonitis, while a value >35% should raise suspicion. The percentage of neutrophils is raised in fungal and even tuberculous peritonitis as well as in the more common bacterial peritonitis.

The percentage of neutrophils in the peritoneal fluid is occasionally elevated in the absence of peritonitis—in patients with infectious diarrhea or active colitis (or appendicitis or diverticulitis), in those with pelvic inflammatory disease, and in women who are menstruating or ovulating or who have recently had a pelvic examination.

e. Peritoneal fluid monocytosis. If there is persistent peritoneal fluid monocytosis or lymphocytosis, tuberculous peritonitis should be considered. Peritoneal fluid monocytosis may also occur in conjunction with peritoneal fluid eosinophilia.

f. Peritoneal fluid eosinophilia. The peritoneal fluid eosinophil count may become elevated in PD patients, causing cloudy fluid and leading to a suspicion of peritonitis (Humayun, 1981). Usually, the peritoneal fluid monocyte count is also elevated. Peritoneal fluid eosinophilia occurs most often soon after peritoneal catheter insertion. It may be seen in the sterile peritonitis that can occasionally occur in those patients who have initiated treatment with icodextrin PD solution. The irritant effect of peritoneal air (e.g., introduced at time of laparotomy) and possibly of plasticizers leached into the peritoneum

from PD solution containers and tubings is another suspected cause. In such cases, the eosinophilia most often resolves spontaneously within 2–6 weeks. Peritoneal fluid eosinophilia can also occur uncommonly during the treatment phase of peritonitis. There have been sev- eral case reports of its occurrence in association with fungal and parasitic infections of the peritoneum.

g. Culture of peritoneal fluid. The incidence of positive peritoneal fluid cultures in patients suspected of having peritonitis depends on culture technique. Culture-negative peritonitis should not be >20% of episodes.
   1. Storage. Peritoneal fluid should be cultured promptly; however, infected fluid kept at room temperature or refrigerated for a period often grows pathogenic 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. The volume of peritoneal fluid sent for culture should be at least 50 mL as larger volumes increase the likelihood of a positive culture.
   3. Sample preparation. The aliquot is centrifuged (e.g., at 3,000 g for 15 minutes) to concentrate the organisms. The supernatant is decanted off, and the pellet resuspended in 3–5 mL of sterile saline and inoculated into standard blood culture media (aerobic and anaerobic). Rapid culture techniques (e.g., Septichek, BACTEC) may be utilized.
   4. Yield of positive cultures. Seventy to ninety percent of dialysate samples taken from patients with clinical peritonitis yield positive cultures for a specific organism within 24–48 hours. More time may be needed for more fastidious organisms.
   5. Improving culture yield. This may be done by hypotonic lysis. The centrifuged sediment is resuspended in 100 mL of sterile water to induce lysis of its cellular elements. This may lead to release of bacteria from neutrophils and increase the chance of a positive culture, even in patients who have already received antibiotics.
   6. Incidence of false-positive results. With very sensitive culture techniques, about 7% of cultures may be positive in patients without clinical peritonitis. The significance of this is unclear.

h. Gram stain. Gram stain of the peritoneal fluid sediment is useful but positive in less than half of cases of culture-proven peritonitis. Gram stain is also useful for making the diagnosis of fungal peritonitis. Staining with fluorescent acridine orange dye has been reported to increase the visibility of bacterial organisms.

i. Necessity of performing blood cultures. Routine blood cultures are not necessary unless a patient appears septic or an acute surgical abdominal condition is suspected.

E. Treatment

1. Initial management

a. Choice of antimicrobial therapy. Empiric antibiotics must coverboth gram-positive and gram-negative organisms. Vancomycin or a first-generation cephalosporin such as cefazolin or cephalothin is used in combination with an antibiotic such as ceftazidime or an aminoglycoside. In general, a center-specific selection of empiric therapy, dependent on the local history of sensitivities of organisms causing peritonitis, is recommended.

1. Gram-positive. First-generation cephalosporins (e.g., cefazolin) are often preferred to vancomycin because of the emergence of vancomycin-resistant organisms. Intraperitoneal (IP) cefazolin can be conveniently administered in a single daily dose of 15 mg/kg, although a 25% increase in dose is recommended in patients with substantial residual renal function (Manley, 1999). Alternatives to vancomycin include nafcillin and clindamycin. Vancomycin can be used as first-line treatment or reserved for patients harboring β-lactam–resistant organisms, especially methicillin-resistant *S. aureus* (MRSA), or with penicillin/cephalosporin allergy. Ciprofloxacin alone is not recommended for gram-positive infections.

2. Gram-negative or indeterminate. Gram stain is usually not diagnostic, and so gram-negative organisms need to be covered by a third-generation cephalosporin or aminoglycoside. In theory, aminoglycosides should be avoided if possible in patients with residual renal function because of their nephrotoxicity (Shemin, 1999), although short courses of aminoglycosides probably do not harm residual renal function (Lui, 2005). Aminoglycosides may be used in patients without residual renal function, although one still must be wary of otovestibular toxicity. Table 27.3 lists sample prescriptions based on the use of cefazolin in combination with ceftazidime.

b.Delivery methods and schedules for antimicrobial drugs

1.IP versus oral (PO) or intravenous (IV) antimicrobial therapy. IP administration of antibiotics is preferred toIV or PO dosing for treating peritonitis. IV antibiotics, how- ever, should be used when there is clinical evidence of systemic sepsis. The loading dose. A loading dose of

2. antimicrobials is usually given IP when CAPD is the treatment modality (Table 27.4). If a patient appears toxic, an IV load- ing dose should be used. For aminoglycosides, the IV loading dose is usually gentamicin or tobramycin 1.5 mg/kg or amikacin 5 mg/kg. If a patient is in sub- stantial pain and cannot tolerate the usual exchange

TABLE 27.3 Sample Prescriptions for Initial Treatment of Peritonitis with Unknown Organism Type

CAPD (continuous dosing method)
1. Drain abdomen and obtaincellcount and culture from drainage bag. Change the transferset.
2. Loading dose: Infuse 2-L dialysis solution containing 1,000 mg ceftazidime, 1,000 mg cefazolin, and 1,000 units heparin.
3. Allow to dwell 3–4 hr. In patients who appear septic, administer loading doses IV rather than IP.
4. 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 abdomen and obtain cellcount and culture from drainage bag. Change the transfer set.
2. Loading dose: same 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 in dialysate, add heparin to every exchange.

APD: see text.

volume, the IP loading dose can be administered in a smaller volume of dialysis solution (e.g., 1 L). For APD patients, 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 4–6 hours.

3. Maintenance antimicrobial dose. After the loading dose has been given, a CAPD or APD schedule is continued, with maintenance doses of antimicrobials added to each exchange (Table 27.4). Some centers switch APD patients to CAPD, but this is not routine. Maintenance antibiotics in CAPD patients can be administered as an intermittent dose once daily. For patients on an APD schedule, antibiotics can be administered conveniently in the daytime dwell. For patients on a day dry APD schedule, temporary conversion to a CAPD regimen may be considered because of ease of antibiotic administration, or, alternatively, a low-volume daytime dwell (e.g., 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). (Examples are given in Table 27.5.)

4. Antimicrobial dosing guidelines. Suggested loading and maintenance doses for a number of antimicrobial drugs are listed in Table 27.4. For maintenance doses added to the dialysis solution, continuous and intermittent dosing of antibiotics are equally efficacious. For continuous dosing, the same dose of antibiotic is added to each dialysis solution bag. Alternatively,

TABLE 27.4 Loading and Maintenance Doses of Antimicrobials for Peritonitis (CAPD)a

	Intermittent (per exchange, once daily)	Continuous (mg/L, all exchanges)
Aminoglycosides		
Amikacin	2 mg/kg	LD 25, MD 12
Gentamicin, netilmicin, or tobramycin	0.6 mg/kg	LD 8, MD 4
Cephalosporins		
Cefazolin,cephalothin, or cephradine	15 mg/kg	LD 500, MD 125
Cefepime	1,000 mg	LD 500, MD
Ceftazidime	1,000–1,500 mg	125 LD 500,
Penicillins		MD 125
Ampicillin,oxacillin, or nafcillin	ND	MD 125
Amoxicillin	ND	LD 250–500, MD 50
Penicillin G	ND	LD 50,000 units, MD 25,000 units
Quinolones		
Ciprofloxacin	ND	LD 50, MD 25
Others		
Vancomycin	15–30 mg/kg every 5–7 d	LD 1,000, MD 25
Daptomycin	ND	LD 100, MD 20
Linezolid	Oral 200–300 mg q. d.	
Antifungals		
Fluconazole	200 mg IP every 24–48 hr	
Amphotericin	NA	1.5
Combinations		
Ampicillin–Sulbactam	2 g every 12 hr	LD 1,000, MD 100
Trimethoprim–Sulfamethoxazole	160 mg/800 mg oral twice daily	
Imipenem–Cilastin	1 g b. i. d.	LD 250, MD 50

b. i. d., two times per day; LD, loading dose in mg; MD, maintenance dose in mg; NA, not applicable; ND, no data.

[a] Dosing of drugs with renal clearance in patients with residual renal function (defined as >100 mL per day urine output): dose should be empirically increased by 25%.

Adapted from Li et al. Peritoneal dialysis related infections recommendations: 2010 update. Perit Dial Int. 2010;30:393–423.

TABLE 27.5 Intermittent Dosing of Antibiotics in Automated Peritoneal Dialysis (APD)

Drug	IP dose
Vancomycin	Loading dose 30 mg/kg IP in long dwell, repeat dosing 15 mg/kg IP in long dwell every 3–5 d (aim to keep serum trough levels above 15 mcg/mL)
Cefazolin	20 mg/kg IP every day, in long day dwell
Tobramycin	Loading dose 1.5 mg/kg IP in long dwell, then 0.5 mg/kg IP each day in long dwell
Fluconazole	200 mg IP in one exchange per d every 24–48 hr
Cefepime	1 g IP in one exchange per d

Adapted from Li et al. Peritoneal dialysisrelated infections recommendations: 2010 update (2010).

a larger dose is added to one bag only, every 12 or 24 hours (or, in the case of vancomycin, every 4–5 days). A randomized trial in children showed that intermittent vancomycin was as effective as continuous vancomycin (Schaefer, 1999). Single daily dosing of aminoglycosides has several advantages, including ease of administration, increased efficacy, and potentially less toxicity. Increased bacterial killing rates associated with prolonged postantibiotic effect are obtained using once-daily dosing. However, trough concentrations of antibiotic (i.e., 24 hours after a dose) will be low, and the exact duration of the postantibiotic effect is unknown, which has led to some concern about the advisability of this type of regimen, especially in patients with residual renal function (Low, 1996).

There has been interest in once-daily cephalosporin dosing. Cefazolin at 1–2 g IP daily has been tried (Lai, 1997; Troidle, 1997). However, IP cephalo- sporin levels may fall below the minimum inhibitory concentration (MIC) of most organisms. As there is no postantibiotic effect with cephalosporins, in con- trast to aminoglycosides, there is some concern that once-daily dosing may lead to more treatment failures than intermittent dosing (Fielding, 2002). In general, continuous dosing of cephalosporins is preferred, but intermittent dosing is also widely used.

5. Stability of Antibiotics in Dialysate: Vancomycin, aminoglycosides, and cephalosporins can be mixed in the same dialysis solution bag; however, aminoglycosides are incompatible with penicillins. Vancomycin (25 mg/L) is stable for 28 days in dialysis solution stored at room temperature, although high ambient temper- atures will reduce the duration of stability. Gentamicin

(8 mg/L) is stable for 14 days, but the duration of stability is reduced by the admixture of heparin. Cefazolin (500 mg/L) is stable for at least 8 days at room temperature or for 14 days if refrigerated; addition of heparin does not impair 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.

c. Heparin. Peritonitis is often associated with formation of fibrinous clots in the peritoneal fluid, and the risk of catheter obstruction is high. Most centers add heparin (500–1,000 units/L) to the dialysis solution until peritonitis resolves and fibrinous clots are no longer visible in the effluent.

d. Nystatin. Since the majority of fungal peritonitis episodes are preceded by courses of antibiotics, fungal prophylaxis during antibiotic therapy may prevent some cases of *Candida* peritonitis in programs that have high rates of fungal peritonitis. A number of studies have examined the use of oral nystatin prophylaxis, given during antibi- otic therapy, to prevent fungal peritonitis, and the results are mixed. We believe nystatin prophylaxis should be considered in programs with high baseline rates of fun- gal peritonitis.

e. Alterations in schedule for CAPD and APD. CAPD patients can generally continue their normal schedule of exchanges, unless ultrafiltration becomes inadequate. Some centers prefer to treat moderate-to-severe peritonitis in both CAPD and APD patients for the initial 24–48 hours with a series of 3–4 hour exchanges containing antibi- otics administered via a cycler. In APD patients with mild-to-moderate peritonitis, the usual APD schedule can be continued unchanged with antibiotics admin- istered either continuously (added to all exchanges) or intermittently (added only to the daytime dwell). Some convert the patient to CAPD but this may be a problem for patients, especially if they are being treated at home. Doses of antimicrobials for those who remain on APD are provided in Table 27.5. The decision to hospitalize a patient depends on a variety of factors, including patient reliability, severity of peritonitis, and the treatment schedule chosen. In most centers, the majority of cases are now managed as outpatients.

f. Consideration of secondary peritonitis. In a small but significant proportion of patients with peritonitis, a serious, underlying intra-abdominal disease process (e.g., perforated peptic ulcer, pancreatitis, appendicitis, or diverticulitis) may be present. The presence of peritoneal fluid in the abdomen may mask the local tenderness commonly associated with some of these conditions. If

there is any suspicion of an underlying intra-abdominal disease process, a chest radiograph should be obtained. The presence of free IP air on upright chest radiograph is an unusual finding in CAPD patients, provided recent laparotomy or transfer set change has not been performed, and may suggest the presence of a perforated viscus. However, free IP air may occur more commonly in patients being treated with cyclers.

g. Amylase and lipase. In a dialysis patient suspected of having pancreatitis, the finding of a serum total amylase value in excess of three times the upper limit of normal suggests that pancreatitis is present. Very severe pancre- atitis can be present in dialysis patients with only slight, and therefore nondiagnostic, elevations in the serum total amylase level. The peritoneal fluid amylase concentration, easily obtainable in patients receiving PD, is not a sensitive indicator of pancreatitis because the peritoneal fluid amylase levels can be only slightly elevated in the presence of severe pancreatitis. Nevertheless, an effluent amylase level >100 units/dL is suggestive of pancreatitis or some other intra-abdominal catastrophe.

Serum lipase activity is elevated (as high as twice the upper limit of normal) in about 50% of dialysis patients. In PD patients using icodextrin-based PD solutions, measurement of lipase is superior to amylase for diagnosis of acute pancreatitis.

h. Consequence of 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 result and can be severe in diabetic patients unless glucose values are monitored and insulin doses titrated. Protein losses during peritonitis are temporarily increased.

i. 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 instilled dialysate. If constipation is present, calcium-containing phosphate binders, which can cause or worsen constipation, should be temporarily discontinued.

2. Initial management of peritoneal contamination without peritonitis. After bacterial contamination of the peritoneal cavity, the incubation period for most organisms is about 12–48 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 (e.g., ciprofloxacin) may also be given. However, there is no documentation that these procedures are effective in preventing p eritoniti s.

3. Change in management of peritonitis based on patient course and initial culture results. With effective treatment, the patient should begin to improve clinically within 12–48 hours, and the total cell count and percentage of neutrophils in the peritoneal fluid should begin to decrease. Often visual inspection of the effluent will suffice, but if there is no improvement within 48 hours, repeat cell count and culture are necessary. Isolation of causative bacteria and determination of their antimicrobial sensitivity can generally be obtained within 2–3 days. Longer growth periods may be needed for certain fastidious organisms (e.g., gentamicin- and methicillin-resistant *S. aureus*). A single organism is isolated in 70%–90% of cases (Table 27.1).
   a. Gram-positive organism cultured. If *S. aureus*, *S. epidermidis*, or a *Streptococcus* sp. is identified, then continued therapy with a single antimicrobial agent is recommended. If an aminoglycoside was given initially, it can now be stopped. Many *S. epidermidis*–like organisms reported to be resistant to first-generation cephalosporins are sensitive to the levels achieved in the peritoneal cavity. Thus, if the patient is clinically responding to treatment, there is usually no need to change the antibiotic regimen. If an *Enterococcus* sp. is cultured, ampicillin or vancomycin plus an aminoglycoside is generally employed, unless sensitivity testing indicates vancomycin resistance, in which case linezolid or quinupristin/dalfopristin is needed.
      1. Duration of therapy. For coagulase-negative *Staphylococcus* and *Enterococcus* peritonitis, if patient improvement is prompt, antimicrobial therapy should be continued for a total of 14 days. *S. aureus* peritonitis requires antimicrobials for 3 weeks, and rifampin could be considered an adjunct for the prevention of relapse or repeat *S. aureus* peritonitis. Rifampin induces cytochrome P450 (CYP3A4), which should be kept in mind when the patient is taking other medications metabolized by this pathway. *S. aureus* peritonitis with concurrent exit-site or tunnel infection is unlikely to respond to antibiotic therapy without catheter removal.
      2. Nasal carriage and S. aureus infection. Patients who develop *S. aureus* peritonitis are usually nasal carriers of this organism. Eradication of nasal carriage may help prevent further peritoneal infections by this bacterium. 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). Resistance to mupirocin and rifampin is increasingly common. Eradication of the carrier state should be documented by repeating appropriate cultures after antibacterial treatment.

b. Gram-negative organism cultured. Recovery of a gram-negative organism, even in a patient who is improving clinically, has several important implications: (a) gram-negative infections (especially *Pseudomonas* sp.) are hard to eradicate, and the risk of relapsing peritonitis is high, (b) gram-negative peritonitis may be a sign of unsus- pected intra-abdominal pathology, and (c) prolonged treatment with aminoglycosides carries the risk of oto- vestibular toxicity.

If a single, non-*Pseudomonas* sp. is recovered, the peritonitis can usually be treated by continuation of the initial IP third-generation cephalosporin or aminoglycoside alone, or by another single appropriate antibiotic, although some centers prefer to use two agents. If a *Pseudomonas* sp. is recovered, two antibiotics are mandatory. Usually, the IP aminoglycoside should be continued with the addition of a third-generation cephalosporin administered IP or a semisynthetic penicillin with anti-*Pseudomonas* activity (e.g., piperacillin) administered IV. Semisynthetic penicillins can inactivate aminoglycosides in vitro, and IP coadministration should be avoided. Other alternatives are ciprofloxacin (or another quinolone), aztreonam, imipenem, and trimethoprim– sulfamethoxazole. *Pseudomonas* peritonitis requires catheter removal in up to two-thirds of cases (Bunke, 1995). Fluoroquinolones (such as ciprofloxacin and ofloxacin) have the advantage that effective dialysate levels can usually be achieved after PO dosing; their concurrent administration with phosphate-binding antacids should be avoided to ensure adequate absorption from the gastrointestinal tract.

1. Duration of therapy. In uncomplicated cases, duration of therapy for gram-negative peritonitis is at least 2 and preferably 3 weeks. If the peritoneal catheter is removed, appropriate antibiotics should be continued (either PO or IV) for another 2 weeks, especially with *Pseudomonas*.

2. IP aminoglycoside toxicity. To treat gram-negative peritonitis, a prolonged course (2 weeks) of aminoglycosides may be required. In the usual dosing strategy (after the loading dose), 4–6 mg/L of gentamicin, tobramycin, or netilmicin is added to the PD solution. This results in constant serum drug levels, which may cause otovestibular toxicity. Adding a higher dose to a single bag only every 24 hours (e.g., 20 mg/L of gentamicin or tobramycin) avoids constant serum

levels above 2 mg/L and may reduce the toxicity of IP aminoglycosides.

3. Alternative agents. Many gram-negative organisms are sensitive to aztreonam, newer cephalosporins, quinolones, imipenem, or the semisynthetic penicillins. Use of these alternative agents should be considered both initially and when prolonged therapy of gram-negative peritonitis is required.
4. Infection with Stenotrophomonas (formerly Xanthomonas) sp. The major risk factor for infection with *Stenotrophomonas maltophilia* is the previous use of broad-spectrum antibiotics. These are usually very resistant organisms. Medical therapy requires two antibiotics, usually including cotrimoxazole, and must be extended to a minimum of 3–4 weeks, and catheter removal is usually required (Szeto, 1997).

c. Polymicrobial peritonitis. In general, peritonitis due to multiple gram-positive organisms will respond to antibiotic therapy. About 60% of these infections 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 abscess or a perforated abdominal viscus must be considered. Perforated diverticulum, tubo-ovarian abscess, cholecystitis, appendicitis, perforated ulcer, and pancreatitis must all be included in the differential diagnosis. The risk of mortality is increased (Kern, 2002). Initial management can be accomplished by triple-antibiotic therapy aimed at gram-positive, gram-negative, and anaerobic organisms. Use of an IP aminoglycoside, IP vancomycin, and PO or IV metronidazole is usual. 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. Sometimes, growth appears only after 5–7 days, and cultures should be incubated for this length of time. Management depends on whether the patient is improving clinically. Although the current ISPD recommendation is to continue both of the initial antibiotics for a full 14 days (Li, 2010), many authorities recommend discontinuing the gram-negative coverage (i.e., ceftazidime or aminoglycoside) after 3 days if the patient is improving. Patients with culture-negative peritonitis who do not improve should be recultured using special culture techniques to look for unusual organisms such as yeast, mycobacteria, and fungi. If a dialysis program has a rate of culture-negative peritonitis >20%, the culture methods should be reviewed.

Infection with *Mycobacterium tuberculosis* or with nontuberculous mycobacteria sometimes presents as culture-negative peritonitis. When mycobacterial peritonitis is suspected, special attention must be paid to culture techniques. Diagnostic sensitivity 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.). Catheter removal is often required but is not mandatory provided prompt therapy is given. This consists of a multiple-drug regimen (usually isoniazid, rifampin, ofloxacin, and pyrazinamide). Streptomycin and ethambutol are generally not recommended in dialysis patients.

e. Fungal peritonitis. Fungal peritonitis is a serious complication and should be strongly suspected after recent antibiotic treatment for bacterial peritonitis. Other predisposing factors to fungal peritonitis include diabetes mellitus, immunosuppression (e.g., immunosuppressive therapy, HIV infection), and malnutrition, especially a low serum albumin level. *Candida* is the most prevalent species cultured, 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, 2010), together with treatment for at least 10 days with antifungal agents. The patient is then maintained on hemodialysis. In some patients, a new catheter can be inserted 4–6 weeks later, provided that at least 1 week has elapsed since all clinical evidence of peritonitis has subsided.

In an attempt to limit adhesion formation, in addition to catheter removal, prolonged oral administration of antifungal drugs, such as flucytosine, miconazole, fluconazole, ketoconazole, itraconazole, or voriconazole, has been employed. Voriconazole or posaconazole is an alternative to amphotericin B when filamentous fungi have been cultured, but neither of them can be used alone for *Candida* peritonitis (even with catheter removal). The recommended dosages of these agents are the same as for patients with normal renal function, with the exception of flucytosine, for which the dosage must be reduced (see Chapter 35). The unavailability of oral flu- cytosine in many countries and the high price of many new antifungal agents may affect local practice.

4. Refractory peritonitis and indications for catheter removal. Refractory peritonitis is defined as failure of peritonitis to clear after 5 days of appropriate antibiotics. Catheter removal is indicated in order to reduce patient morbidity and preserve the peritoneal membrane. Ultrasound, computed tomography, or gallium scan is indicated if an intra-abdominal abscess is suspected, since in such cases surgical exploration

and drainage may be needed at the time of or after catheter removal. In general, it is preferable to remove the PD catheter in patients who do not respond to antimicrobials rather than subject the patient to a long period of exposure to antibiotics, with increased risk of superinfection and morbidity, and of damage to the peritoneal membrane. After catheter removal, the safe time interval before a new catheter can be inserted is controversial and probably de- pends on the severity of the peritonitis and whether fungal peritonitis or tunnel infection was present. A conservative approach is to wait 4–6 weeks. Resumption of PD is pos- sible in approximately one-half of patients, but may neces- sitate a change in dialysis prescription to achieve adequate dialysis and ultrafiltration (Szeto, 2002a).

5. Relapsing, recurrent, and repeat peritonitis. Relapsing peritonitis is defined as peritonitis with the same organism within 4 weeks of stopping antimicrobial therapy; *S. epidermidis* or a gram-negative organism is usually involved, but relapsing culture-negative peritonitis is also common. In the case of relapsing gram-negative peritonitis, catheter removal, with or without surgical exploration, should be strongly considered, especially in cases of *Pseudomonas* infection. If it is decided to treat the patient medically, either the aminoglycoside dose should be administered intermittently or an alternative agent should be employed. With less serious infections, it may be possible to insert a new catheter, simultaneous with the removal of the old one, obviating the need for hemodialysis. The new catheter should be inserted well away from the old exit site. This approach has been particularly useful in the management of relapsing peritonitis due to coagulase-negative staphylococci.

Recent 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 had a worse prognosis than relapsing ones. Although repeat peritonitis episodes generally have a satisfactory response to antibiotic, they have a substantial risk of developing further relapsing or repeat peritonitis (Szeto, 2011b) with treatments of relapsing, recurrent, or repeat peritonitis.

a. Fibrinolytic enzymes. 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. Peritonitis with catheter obstruction. Catheter obstruction often accompanies peritonitis. Management is discussed in Chapter 23.

7. Prophylactic antibiotic use. 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.

8. Prevention. The use of prophylactic antibiotic has been discussed above. Spiking of dialysis bags is a high-risk procedure for contamination of the system; the "flush before fill" reduces the risk of contamination. Double-cuffed catheters may provide an added barrier to periluminal movement of *S. aureus* into the peritoneum, and they are clearly superior to single-cuffed catheters in decreasing the risk of peritonitis. No particular catheter has been definitively shown to be better than the standard silicon double-cuff catheter for the prevention of peritonitis.

A number of perioperative measures may help to reduce the incidence of peritonitis (Crabtree, 2005). Skin exit site should be directed downward or laterally. Subcutaneous tunnel incision should not exceed the diameter of the dialysis catheter. The subcutaneous cuff should be positioned 2 to 3 cm from the exit site. Exit site should be the smallest hole possible that provides catheter exit. There should be no sutures anchoring the catheter at the exit site. Hypokalemia is associated with an increased risk of enteric peritonitis, and therefore if present, should be treated. There is an association between both severe constipation and enteritis and peritonitis owing to enteric organisms. It is logical to treat any bacterial enteritis if present. A recent observational study suggests that lactulose treatment may reduce the risk of peritonitis (Afsar, 2010).

Training methods have a substantial influence on the risk of PD infections, and training should follow standard guidelines (Bernardini, 2006); each PD program should consult the standard ISPD guidelines to prepare the trainer and develop a specific curriculum. Each program must also decide when and how often to routinely retrain patients; there is no published study in this area. Retraining should be considered following peritonitis or catheter infection, as well as following change in dexterity, vision, or mental acuity. After each peritonitis episode, it is prudent to perform a root cause analysis to determine etiology so that interventions can be planned to prevent future episodes.

II. EXIT-SITE AND TUNNEL INFECTION. Approximately one-fifth of peri- tonitis episodes are temporally associated with exit-site and tun- nel infections (Piraino, 2005). Purulent drainage from the exit

site generally indicates the presence of infection, while erythema alone may or may not represent infection.

A. Incidence. The incidence of exit-site infections is approximately 1 episode every 24–48 patient-months. Patients with previous infections tend to have a higher frequency of occurrence.

B. Etiology and pathogenesis. Exit-site infections are predominantly due to *S. aureus* and *P. aeruginosa*. *S. epidermidis* is the causative organism in <20% of patients. Approximately 45% of patients are nasal carriers of *S. aureus*, and nasal carriage is associated with exit-site infection and peritonitis (Luzar, 1990a, 1990b). Eradication of the carrier state is helpful in effective management.

C. Therapy. Treatment is dependent on whether there is erythema alone, or erythema along with purulent drainage. For 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 (e.g., 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 efficacy in treating exit- site infection is unknown (Montenegro, 2000).

Treatment is more problematic when there is exit-site infection with purulent drainage; such infection may extend into the subcutaneous tunnel and be evident only on ultrasound examination of the catheter tract (Vychytil, 1999). Therapy should be based on the results of gram stain and culture. The gram stain of exit-site drainage and microbiologic culture findings can guide initial therapy. If gram-positive organisms are found, a cephalosporin or an antistaphylococcal penicillin PO is first-line treatment. If no improvement occurs after 1 week despite appropriate treatment based on culture and sensitivity, rifampin 600 mg per day PO may be added. If the infection has not resolved in 2 weeks, a surgical approach (deroofing, outercuff shaving, or catheter removal) may be required. If tunnel infection is present, early cuff excision in combination with antibiotic administration results in a substantial rate of catheter salvage (Suh, 1997), although catheter removal is sometimes required, especially when there is coexisting peritonitis.

If gram-negative organisms are present, treatment should be based on sensitivity results. Oral quinolones are useful, though care must be taken to avoid ingestion of multivalent cations (calcium, iron, zinc, antacids) within 2 hours of drug ingestion. With more serious pseudomonal infections, IP ceftazidime or aminoglycoside may be necessary. Regardless, antibiotic therapy must be continued until the exit site appears entirely normal. Two weeks is the minimum length of treatment time, and treatment for 3 weeks is probably necessary for exit-site infections caused by *P. aeruginosa*.

Catheter removal should be considered at an early time point for exit-site infections caused by *P. aeruginosa* or if there is tunnel infection; replacement with a new catheter at a different site as a single procedure is often feasible. Table 27.6 lists appropriate oral antimicrobial doses for the treatment of exit-site infections.

D. Prevention. Antibiotic protocols against *S. aureus* nasal carriage are effective in reducing the risk of *S. aureus* catheter infections. Protocols used include rifampin (600 mg PO for 5 days), mupirocin (2% ointment twice daily for 5 days every 4 weeks), and trimethoprim–sulfamethoxazole (one single-strength tablet three times weekly). In a randomized controlled trial, rifampin 600 mg PO for 5 days given every 3 months was effec- tive in decreasing catheter infections (Zimmerman, 1991). In a multicenter randomized trial (Mupirocin Study Group, 1996), use of nasal mupirocin in the regimen stated above in *S. aureus*

TABLE 27.6 Oral Antimicrobial Doses for Exit-Site and Tunnel Infections

Amoxicillin	250–500 mg b.i.d. 500 mg b.i.d. 250–500
Cephalexin	mg b.i.d. 250–500 mg b.i.d. 250–500 mg
Ciprofloxacin	b.i.d. 200 mg once daily 500 mg b.i.d. 2-g
Clarithromycin	load, then 1 g PO, q.day 300 mg once daily
Dicloxacillin	600 mg b.i.d. 400 mg b.i.d. for <50 kg
Fluconazole	400–500 t.i.d. for >50 kg 400 mg first day,
Flucloxacillin	then 200 mg once daily 35 mg/kg per day
Flucytosine	(given as b.i.d. or once daily)
Isoniazid	450 mg once daily for <50 kg
Linezolid	600 mg once daily for >50 kg
Metronidazole	80/400 mg once daily
Ofloxacin	
Pyrazinamide	
Rifampin	
Trimethoprim/sulfamethoxazole	

b.i.d., two times per day; PO, orally; t.i.d., three times per day.
Reproduced from Piraino B, et al. Peritoneal dialysis-related infections recommendations: 2005 update. Perit Dial Int. 2005;25:107–131.

nasal carriers resulted in a significant decline in exit-site infections from this organism; however, the overall incidence of exit-site infections was not decreased because of an increase in gram-negative infections, and rates of tunnel infection and peritonitis were not affected.

Prevention of catheter infections (and thus peritonitis) is the primary goal of exit-site care. There are sufficient data to support the use of exit-site antibiotic cream (either mupirocin or gentamicin) in all patients. In two clinical trials, mupirocin ointment applied daily to the exit site decreased the rate of both exit-site infections and peritonitis in comparison with a historical control group (Bernardini, 1996; Thodis, 1998). In another study (Bernardini, 2005), gentamicin cream was as effective as mupirocin in preventing *S. aureus* infections and reduced *P. aeruginosa* and other gram-negative catheter infections. Peritonitis, particularly that caused by gram-negative organisms, was reduced by 35%. Because of its efficacy against both gram-positive and gram-negative infections, daily gentamicin cream at the exit site has been advocated as the prophylaxis of choice for PD patients. However, the risk of aminoglycoside resistance after prolonged usage has not been assessed.

Whether the incidence of exit-site infections is lower with double-cuff catheters is somewhat controversial (Nessim, 2010; Segal, 2013). The method of catheter placement may be important. Leaving the catheter embedded subcutaneously for several weeks after placement (see Chapter 23) and then exteriorizing it prior to use may reduce the rate of exit-site infection. Use of chlorhexidine versus povidone–iodine solution is associated with a significant decrease in exit-site infections in children (Jones, 1995). Polyhexanide solution also appears to be better than povidone–iodine (Núñez-Moral, 2014).

References and Suggested Readings

AfsarB, et al. Regular lactulose use isassociated with lower peritonitis rates: an observational study. Perit Dial Int. 2010;30:243–246.

Ballinger AE, et al. Treatment for peritoneal dialysis-associated peritonitis. Cochrane Database Syst Rev. 2014;26:CD005284.

Bernardini J, Price V, Figueiredo A; International Society for Peritoneal Dialysis (ISPD) Nursing Liaison Committee. Peritoneal dialysis patient training, 2006. Perit Dial Int. 2006;26:625–632.

Bernardini J, et al. A randomized trial of Staphylococcus aureus prophylaxis in peritoneal dialysis patients: mupirocin calcium ointment 2% applied to the exit site versus cyclic oral rifampin. Am J Kidney Dis. 1996;27:695–700.

Bernardini J, et al. Randomized, double-blind trial of antibiotic exit site cream for prevention of exit site infection in peritoneal dialysis patients. J Am Soc Nephrol. 2005;16:539–545.

Bunke M, et al. Pseudomonas peritonitis in peritoneal dialysis patients: the Network 9 Peritonitis Study. Am J Kidney Dis. 1995;25:769–774.

Cho Y, Johnson DW. Peritoneal dialysis-related peritonitis: towards improving evidence, practices, and outcomes. Am J Kidney Dis. 2014;64:278–289.

Cho Y, et al. Biocompatible dialysis fluids for peritoneal dialysis. Cochrane Database Syst Rev. 2014;27:CD007554.

Choi P, et al. Peritoneal dialysis catheter removal for acute peritonitis: a retrospective analysis of factors associated with catheter removal and prolonged postoperative hospitalization. Am J Kidney Dis. 2004;43:103–111.

Crabtree JH, et al. A laparoscopic method for optimal peritoneal dialysis access. An Surg. 2005;71:135–143.
Daugirdas JT, et al. Induction of peritoneal fluid eosinophilia and/or monocytosis by intraperitoneal air injection. Am J Nephrol. 1987;7:116–120.
Elamin S, et al. Low sensitivity of the exit site scoring system in detecting exit site infections in peritoneal dialysis patients. Clin Nephrol. 2014;81:100–104.
Fielding RE, et al. Treatment and outcome of peritonitis in automated peritoneal dialysis, using a once-daily cefazolin-based regimen. Perit Dial Int. 2002;22:345–349.
Gadallah M, et al. Role of preoperative antibiotic prophylaxis in preventing postoperative peritonitis in newly placed peritoneal dialysis catheters. Am J Kidney Dis 2000;36:1014–1019.
Humayun HM, et al. Peritoneal fluid eosinophilia in patients undergoing maintenance peritoneal dialysis. Arch Intern Med. 1981;141:1172–1173.
Jones LL, et al. The impact of exit-site care and catheter design on the incidence catheter-related infections. Adv Perit Dial. 1995;11:302–305.
Kern EO, et al. Abdominal catastrophe revisited: the risk and outcome of enteric peritoneal contamination. Perit Dial Int. 2002;22:323–324.
Kerschbaum J, et al. Treatment with oral active vitamin D is associated with decreased risk of peritonitis and improved survival in patients on peritoneal dialysis. PLoS One. 2013;8:e67836.
Lai MN, et al. Intraperitoneal once-daily dosing of cefazolin and gentamicin for treating CAPD peritonitis. Perit Dial Int. 1997;17:87–89.
Li PK, et al. Use of intraperitoneal cefepime as monotherapy in treatment of CAPD peritonitis. Perit Dial Int. 2000;20:232–234.
Li PK, et al. Comparison of clinical outcome and ease of handling in two double-bag systems in continuous ambulatory peritoneal dialysis—a prospective randomized controlled multi-center study. Am J Kidney Dis. 2002;40:373–380.
Li PK, et al. Peritoneal dialysis-related infections recommendations: 2010 update. Pe Dial Int. 2010;30:393–423.
Li PK, et al. Infectious complications in dialysis—epidemiology and outcomes. Nat R Nephrol. 2012;8:77–88.
Low CL, et al. Pharmacokinetics on once-daily IP gentamicin in CAPD patients. Peri Dial Int. 1996;16:379–384.
Lui SL, et al. Cefazolin plus netilmicin versus cefazolin plus ceftazidime for treating CAPD peritonitis: effect on residual renal function. Kidney Int. 2005;68:2375–2380.
Luzar MA, et al. Exit-site care and exit-site infection in continuous ambulatory peritoneal dialysis (CAPD): results of a randomized multicenter trial. Perit Dial Int. 1990a ;10:25–29.
Luzar MA, et al. Staphylococcus aureus nasal carriage and infection in patients on c tinuous ambulatory peritoneal dialysis. N Engl J Med. 1990b;322:505–509.
Manley HJ, et al. Pharmacokinetics of intermittent intraperitoneal cefazolin in continuous ambulatory peritoneal dialysis patients. Perit Dial Int. 1999;19: 67–70.
Manley HJ, Bailie GR. Treatment of peritonitis in APD: pharmacokinetic principles. Semin Dial. 2002;15:418–21.
Montenegro J, et al. Exit-site care with ciprofloxacin otologic solution prevents polyurethane catheter infection in peritoneal dialysis patients. Perit Dial Int. 2000;20:209–214.
Monteon F, et al. Prevention of peritonitis with disconnect systems in CAPD: a randomized controlled trial. The Mexican Nephrology Collaborative Study Group. Kidney Int. 1998;54:2123–2138.
Mupirocin Study Group. Nasal mupirocin prevents Staphylococcus aureus exit-site infection during peritoneal dialysis. J Am Soc Nephrol. 1996;7:2403–2408.
Nessim SJ, Bargman JM, Jassal SV. Relationship between double-cuff versus single-cuff peritoneal dialysis catheters and risk of peritonitis. Nephrol Dial Transplant. 2010;25:2310–2314.
Núñez-Moral M, et al. Exit-site infection of peritoneal catheter is reduced by the use of polyhexanide: results of a prospective randomized trial. Perit Dial Int. 2014;34: 271–277.
Piraino B, et al. A five-year study of the microbiologic results of exit site infections and peritonitis in continuous ambulatory peritoneal dialysis. Am J Kidney Dis. 1987;4:281–286.
Piraino B, et al. Increased risk of Staphylococcus epidermidis peritonitis in patient on dialysate containing 1.25 mmol/L calcium. Am J Kidney Dis. 1992;19:371–374

Piraino B, et al. Peritoneal dialysis-related infections recommendations: 2005 update. Perit Dial Int. 2005;25:107–131.
Piraino B, et al. ISPD position statement on reducing the risks of peritoneal dialysis-related infections. Perit Dial Int. 2011;31:614–630.
Ram R, et al. Cloudy peritoneal fluid attributable to non-dihydropyridine calcium channel blocker. Perit Dial Int. 2012;32:110–111.
Schaefer F, et al. Intermittent versus continuous intraperitoneal glycopeptide/ceftazidime treatment in children with peritoneal dialysis-associated peritonitis. The Mid-European Pediatric Peritoneal Dialysis Study Group (MEPPS). J Am Soc Nephrol. 1999;10:136–45.
Segal JH, Messana JM. Prevention of peritonitis in peritoneal dialysis. Semin Dial. 2013;26:494–502.
Shemin D, et al. Effect of aminoglycoside use on residual renal function in peritoneal dialysis patients. Am J Kidney Dis. 1999;34:14–20.
Suh H, et al. Persistent exit-site/tunnel infection and subcutaneous cuff removal in PD patients. Adv Perit Dial. 1997;13:233–236.
Szeto CC, et al. Xanthomonas maltophilia peritonitis in uremic patients receiving continuous ambulatory peritoneal dialysis. Am J Kidney Dis. 1997;29:91–96.
Szeto CC, et al. Feasibility of resuming peritoneal dialysis after severe peritonitis and Tenckhoff catheter removal. J Am Soc Nephrol. 2002a;13:1040–1045.
Szeto CC, et al. Conservative management of polymicrobial peritonitis complicating peritoneal dialysis—a series of 140 consecutive cases. Am J Med. 2002b;113 728–733.
Szeto CC, et al. Recurrent and relapsing peritonitis: causative organisms and response to treatment. Am J Kidney Dis. 2009;54:702–710.
Szeto CC, et al. Persistent symptomatic intra-abdominal collection after catheter removal for PD-related peritonitis. Perit Dial Int. 2011a;31:34–38.
Szeto CC, et al. Repeat peritonitis in peritoneal dialysis: retrospective review of 181 consecutive cases. Clin J Am Soc Nephrol. 2011b;6:827–833.
Thodis E, et al. Decrease in Staphylococcus aureus exit-site infections and peritonitis in CAPD patients by local application of mupirocin ointment at the catheter exit site. Perit Dial Int. 1998;18:261–270.
Troidle L, et al. Two gram intraperitoneal cefazolin for the treatment of peritonitis. Perit Dial Int. 1997;17(suppl 1):S40.
Vychytil A, et al. Ultrasonography of the catheter tunnel in peritoneal dialysis patients: what are the indications? Am J Kidney Dis. 1999;33:722–727.
Williams AJ, et al. Tenckhoff catheter replacement or intraperitoneal urokinase: a randomized trial in the management of recurrent continuous ambulatory peritoneal dialysis (CAPD) peritonitis. Perit Dial Int. 1989;9:65–67.
Yu AW, et al. Neutrophilic intracellular acidosis induced by conventional lactate-containing peritoneal dialysis solutions. Int J Artif Organs. 1992;15:661–665.
Zimmerman SW, et al. Randomized controlled trial of prophylactic rifampin for wwperitoneal dialysis-related infections. Am J Kidney Dis. 1991;18:225–231.

28 Hernias, Leaks, and Encapsulating Peritoneal Sclerosis

Joanne M. Bargman

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 posi- tion 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 in peritoneal dialysis (PD) patients.

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%–20% of patients may develop a hernia at some time on peritoneal dialysis.

Potential risk factors are listed in Table 28.1 and include large dialysate volumes and activities that involve isometric straining or the Valsalva maneuver. Furthermore, deconditioning of the musculature of the abdominal wall increases wall tension and predisposes to hernia formation.

TABLE 28.1 Potential Risk Factors for Hernia Formation

Large dialysate volumes
Sitting position
Isometric exercise
Valsalva maneuver (e.g., coughing, straining at stool)
Recent abdominal surgery
Pericatheter leak or hematoma
Obesity
Deconditioning
Multiparity
Congenital anatomical defects

TABLE 28.2 Types of Hernias Reported in Peritoneal Dialysis Patients

Ventral
Epigastric
Pericatheter
Umbilical
Inguinal (direct and indirect)
Femoral
Foramen of Morgagni
Cystocele
Spigelian
Richter's
Enterocele

B. Types of hernia. Many different types of hernia have been described in the peritoneal dialysis patient. These are listed in Table 28.2.

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. 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 patent also, and repair (see below) should be done bilaterally.

C. Diagnosis. As mentioned above, 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 Omnipaque 300 is added to a 2-L bag of dialysate and 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 entry of dye into the 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 anterior abdominal wall hernia from isolated leaks. In other types of hernia, such as umbilical hernia, CT scanning is not necessary because the diagnosis is usually obvious.

Magnetic resonance imaging may be useful in the diagnosis of abdominal wall and genital leaks, and it may be helpful in patients with allergy to conventional radiologic dye. The dialysate itself looks bright white on the MRI images.

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 renal function (e.g., 10 mL/min or more), it may be possible to stop dialysis altogether for a week and then recommence with small volumes (e.g., 1 L). The patient must be watched for the development of uremic symptoms or hyperkalemia. 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 peritoneal dialysis should be started postoperatively. An alternative is to hemodialyse the patient until wound healing is more complete (2–3 weeks).

Options for the patient with recurrent hernias include a reduction in strenuous physical activity, more frequent dialysis exchanges with lower volumes, or transfer to hemodialysis.

If the patient is too ill or refuses surgery, mechanical support of the hernia can be effected with a corset or truss. The patient should be warned about 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 28.1. 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 when dialysate returns are less than the instilled volume (see Chapter 21). 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, etc.

Pericatheter leak is usually diagnosed by wetness (dialysate) on the exit site dressing. A urine dipstick placed on the wet part will test strongly positive for glucose. Diagnosis can be proven using contrast CT scanning as described under "Hernia formation" (Section I.C).

B. Treatment. Pericatheter leak usually occurs as a postoperative complication of catheter implantation. The patient should be drained and peritoneal dialysis stopped for at least 24–48 hours. The longer the patient can be left off peritoneal dialysis, the greater the chance that the leak will seal itself. If necessary, the patient should receive hemodialysis, and peritoneal dialysis can be recommenced several days later. In most cases, the leak seals spontaneously. If it persists, the catheter should be removed and reinserted at another site, and special care should be taken in catheter implantation. Antibiotic prophylaxis is not usually necessary for pericatheter leak unless there are obvious signs of infection.

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 and continuous ambulatory peritoneal dialysis (CAPD) can then be resumed. 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: Oneis 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 and scrotum, or mons pubi s.

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 distin- guish which route has led to the genital swelling (i.e., anterior abdominal wall or processus vaginalis). Alternatively, 3–5 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. Peritoneal dialysis 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 allows lower IAP and decreases the chances of recurrent leakage.

IV. RESPIRATORY COMPLICATIONS

A. Hydrothorax. Under the influence of raised IAP, dialysate can travel fromthe 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 diag- nostic feature of the pleural fluid is a very high glucose level, although this is often not found. It is otherwise typi- cally 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 dwell- ing 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 gamma camera in earlier shots. CT scanning with intraperitoneal dye can also be used.

3. Treatment. If there are respiratory symptoms, peritoneal dialysis 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

TABLE 28.3 Surgical Options for Treatment of Hydrothorax

Pleurodesis
Talc
Oxytetracycline
Autologous blood
Aprotonin–fibrin glue
Repair of hemidiaphragm
Oversewing defects
Reinforcement with patches

in the pleural cavity and causes pleurodesis, so that peritoneal dialysis can be resumed 1–2 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 treat- ment of hydrothorax are listed in Table 28.3.

B. Altered mechanics of breathing. Pulmonary function is unchanged with peritoneal dialysis, except for a mildly decreased functional residual capacity. Arterial oxygenation has been observed to decrease slightly and transiently with start of C APD.

Peritoneal dialysis 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 cavitybothraises 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 are important when symptoms are acute. Some patients benefit by 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 under- take 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 cath- eter 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 with- out 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

A. Incidence and etiologic factors. Encapsulating Peritoneal Sclerosis (EPS) is a rare butdevastating complication of long-term PD that has been reported to occur in 1%–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 erythropoietin-resistant 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.

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 are still 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 disease 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.

Imaging is helpful in the sclerosing phase, where 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 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 there is already extensive scar formation .

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.

References and Suggested Readings

Balda S, et al. Impactofhernias onperitoneal dialysis technique survival and residual renal function. Perit Dial Int. 2013;33:629–634.

Chow KM, et al. Management options for hydrothorax complicating peritoneal dialysis. Semin Dial. 2003;16:389–394.

Cizman B, et al. The occurrence of increased intraperitoneal volume events in automated peritoneal dialysis in the U.S.: role of programming, patient/user actions and ultrafiltration. Perit Dial Int. 2014;34:434–442.

Davis ID, et al. Relationship between drain volume /fill volume ratio and clinical outcomes associated with overfill complaints in peritoneal dialysis episodes. Perit Dial Int. 2011;31:148–155.

Dimitriadis CA, Bargman JM. Gynecologic issues in peritoneal dialysis. Adv Perit Dial. 2011;27:101–105.

Goldstein M, et al. Continuous ambulatory peritoneal dialysis: a guide to imaging appearances and complications. Insights Imaging. 2013;4:85–92.

Goodlad C, et al. Screening for encapsulating peritoneal sclerosis in patients on peritoneal dialysis: role of CT scanning. Nephrol Dial Transplant. 2011;26: 1374–1379.

Lew SQ. Hydrothorax: pleural effusion associated with peritoneal dialysis. Perit Dial Int. 2010;30:13–18.

Martinez-Mier G, et al. Abdominal wall hernias in end-stage renal disease patients on peritoneal dialysis. Perit Dial Int. 2008;28:391–396.

Prischl F, et al. Magnetic resonance imaging of the peritoneal cavity among peritoneal dialysis patients, using the dialysate as "contrast medium." J Am Soc Nephrol. 2002;13:197–203.

Shah H, Chu M, Bargman JM. Perioperative management of peritoneal dialysis patients undergoing hernia surgery repair without the use of interim hemodialysis. Perit Dial Int. 2006;26:684–687.

29 Metabolic, Acid-Base, and Electrolye Aspects of Peritoneal Dialysis

RajnishMehrotra

While 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 are important for the health of patients with end-stage renal disease.

I. HYPERGLYCEMIA: With PD, ultrafiltration is induced by exerting either crystalloidal osmotic or oncotic pressure across the peritoneal barrier. This is 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 one of these substances is absorbed systemically during the course of the PD dwell leading to systemic metabolic effects. Treatment with glucose- or icodextrin-based PD solutions results in an obligatory daily absorption of 50–150 g of carbohydrates. This obligatory carbohydrate absorption is higher with greater use of more hypertonic solutions, and in individuals with a faster peritoneal solute transfer rate. Absorbed icodextrin is metabolized, not to glucose but to a variety of oligosaccharides and to the disaccharide maltose (Moberley, 2002)

In some individuals with diabetes mellitus, this obligatory absorption results in poorer glycemic control and requires significant adjustments in 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 diabetic patients 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 PD patients, but it is unclear whether this is association or cause and effect (Duong, 2011). There are limited data to determine how much PD increases the incidence of new-onset diabetes, but one Chinese study suggests that about 8% of nondiabetic patients become diabetic (Szeto, 2007). Therefore, blood glucose levels should also be measured every 1–3 months in nondiabetic PD patients.

Just as glucose-based dialysis solutions may worsen glycemic control, glucose-sparing regimens may improve it. These glucose-sparing regimens generally comprise 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 (Paniagua 2008). Substituting a second glucose-based exchange with amino-acid dialysate allows for further reduction in systemic glucose absorption. In IMPENDIA, a recently completed randomized trial, the HbA1c of individuals treated with a regimen in which two bags of glucose-based exchange were substituted with one bag each of icodextrin and amino-acid dialysate was 0.6% lower compared with individuals treated entirely with glucose-based dialysate (Li, 2013). Glucose-sparing regimens should be consid- ered 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 hemodialysis patients, increased body weight is associated with improved survival, but the evidence is conflicting in PD patients, and there is a concern that obesity may predispose to catheter problems and exit site infection (Johnson, 2012). 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 the 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 (Lievense, 2012). 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 greater gain in visceral fat in PD patients; 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 6–8 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 than in individuals undergoing hemodialysis.

This daily peritoneal protein loss is generally not modifiable, and its clinical relevance remains unclear. The 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 hemodi- alysis. All these considerations suggest that PD can be safely continued in patients that 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 (e.g., diabetic nephropathy, other proteinuric renal diseases), and the potential disparate effects of the dialysis modality. The obligatory carbohydrate absorption and peritoneal protein loss with PD can adversely influence the lipid profile of PD patients. The lipid abnormalities described in PD patients include increases in total and low-density cholesterol, triglycerides, lipoprotein(a), and apolipoprotein B (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 9270 enrolled subjects, 496 were undergoing PD at the time of enrollment. While 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, however, to note that severe hypertriglyceridemia is also associated with a higher risk for pancreatitis in PD patients and so may warrant treatment to reduce this risk.

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 acids–based PD solution resulted in a significant decrease in both serum triglycerides and apolipoprotein B (Li, 2013). These modifications to the PD regimen may be considered in selected individuals for the treatment of these lipid abnormalities.

V. HYPokALEMIA/HYPERkALEMIA: Ten to 30 percent of patients treatedwith PD are reportedto 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, renal losses in patients treated with diuretics, and gastrointestinal losses with use of laxatives (Zanger, 2010).

Observational studies have demonstrated that hypokalemia is associated with a higher risk for gram-negative peritonitis and an increase in risk for all-cause, cardiovascular, and infection-related mortality in patients undergoing PD (Torlen, 2012). Whether correction of hypokalemia ameliorates any of these risks is not known. Oral administration of potassium supplements is probably the easiest and safest way to correct hypokalemia. While intraperitoneal administration of injectable potassium chloride can correct hypokalemia, it exposes patients to a higher risk of peritonitis from touch-contamination. Even though it is appealing to consider mineralocorticoid receptor antagonists such as spironolactone, there is no significant effect on serum potassium levels in patients undergoing PD treated with these agents. Significant hyperkalemia is uncommon in PD and is typically related to nonadherence to the PD prescription.

VI. MEtAboLIC ACIdosIs: Progressive loss of excretory function in chronic kidney disease is associated with reduced renal acid excretion. 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 c omplete correction of metabolic acidosis than thrice-weekly in-center hemodialysis. Yet the correction remains incomplete in a significant minority of PD patients. There is evidence that uncorrected metabolic acidosis contributes to protein-energy wasting and osteopenia. Recent observational studies have also demonstrated a higher risk for all-cause or cardiovascular mortality in PD patients with persistently low serum bicarbonate levels (Vasishta, 2013). These data argue for treatment of persistent metabolic acidosis in patients undergoing PD.

A number of clinical trials have tested the clinical benefits with treatment of metabolic acidosis in PD patients (Mehrotra, 2009; Stein, 1997). These studies indicate that 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. HYPo/HYPERnAtREMIA: Hyponatremia is quite common in PD patients, and one center recently reported a prevalence of 15% (Dimitriadis, 2014). 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 2–3 mmol/L fall in serum sodium by the same mechanism. Dilutional hyponatremia in dialysis patients 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 malnutrition. (Cherney, 2001; Dimitriadis, 2014). It 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.

In contrast, treatment with PD has the potential to induce hypernatremia. In patients treated with PD, fluid is removed either through aquaporins or through interendothelial spaces in the peritoneal capillaries (See Chapter 21). 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. While the prevalence of hypernatremia with contemporary PD solutions and regimens is not known, >10% of patients treated with hourly exchanges using hypertonic PD solutions developed hypernatremia. 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 36. Discussion here is limited to issues specific to PD. Studies done almost two 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. There are no contemporary studies that have examined bone histology in patients undergoing PD, and hence the current prevalence of adynamic bone disease is unclear.

References and suggested Readings

Baigent C, etal. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal protection): a randomized placebo-controlled trial. Lancet. 2011;377:2181–2192.

Balafa O, et al. Peritoneal albumin and protein losses do not predict outcomes in peritoneal dialysis patients. Clin J Am Soc Nephrol. 2011;6:561–566.

Cherney DZ, et al. A physiological analysis of hyponatremia: implications for patients on peritoneal dialysis. Perit Dial Int. 2001;21:7–13.

Choi SJ et al. Changes in body fat mass after starting peritoneal dialysis. Perit Dial Int. 2011;31:67–73.

Dimitriadis C, et al. Hyponatremia in peritoneal dialysis: epidemiology in a single center and correlation with clinical and biochemical parameters. Perit Dial Int. 2014;34:260–270.

Duong U, et al. Glycemic control and survival in peritoneal dialysis patients with diabetes mellitus. Clin J Am Soc Nephrol. 2011;6:1041–1048.

Fried L, et al. Recommendations for the treatment of lipid disorders in patients on peritoneal dialysis. ISPD guidelines/recommendations. Perit Dial Int. 1999;19:7–16.

Johnson DW. What is the optimal fat mass in peritoneal dialysis patients? Perit Dial Int. 2007;27(suppl 2):S250–S254.

Li PK, et al Randomized controlled trial of glucose sparing peritoneal dialysis in diabetic patients. J Am Soc Nephrol. 2013;24:1889–1900.

Lievense H, et al. Relationship of body size and initial dialysis modality on subsequent transplantation, mortality and weight gain of ESRD patients. Nephrol Dial Transplant. 2012;27:3631–3638.

Mehrotra R, et al. Effect of high-normal compared with low-normal arterial pH on protein balances in automated peritoneal dialysis patients. Am J Clin Nutr. 2009;90:1532–1540.

Mehrotra R, et al. Adverse effects of systemic glucose absorption with peritoneal dialysis: How good is the evidence? Curr Opin Nephrol Hypertens. 2013;22:663–66

Moberley JB, et al. Pharmacokinetics of icodextrin in peritoneal dialysis patients. Kidney Int Suppl. 2002;81:S23–S33.

National Kidney Foundation. K/DOQI Clinical Practice Guidelines for managing dyslipidemias in chronic kidney disease. http:www.kidney.org/professionals/KDOQI?guidelines_lipids/toc.htm (Last accessed, August 25, 2014).

Paniagua R, et al. Icodextrin improves fluid and metabolic management in high and high-average transport patients. Perit Dial Int. 2009;29:422–432.

Prichard SS. Management of hyperlipidemia in patients on peritoneal dialysis: current approaches. Kidney Int Suppl. 2006;103:S115–S117.

Stein A, et al. Role of an improvement in acid base status and nutrition in CAPD patients. Kidney Int. 1997;52:1089–1095.

Szeto CC, et al. Oral sodium bicarbonate for the treatment of metabolic acidosis in peritoneal dialysis patients: a randomized placebo-control trial. J Am Soc Nephrol. 2003;14:2119–2126.

Szeto CC, et al. New onset hyperglycemia in nondiabetic chinese patients started on peritoneal dialysis. Am J Kidney Dis. 2007;49:524–532.

Torlen K, et al. Serum potassium and cause-specific mortality in a large peritoneal dialysis cohort. Clin J Am Soc Nephrol. 2012;7:1272–1284.

Vashishta T, et al. Dialysis modality and correction of metabolic acidosis: relationship with all-cause and cause-specific mortality. Clin J Am Soc Nephrol. 2013;8:254–264

Zanger R. Hyponatremia and hypokealemia in pateints on peritoneal dialysis. Semin Dial. 2010;23:575–580.

PART IV

CLINICAL PROBLEM AREAS

30 Psychosocial Issues

Scott D. Cohen, Daniel Cukor, and Paul L. Kimmel

Patients with end stage kidney disease (ESKD) are affected by numerous psychosocial stressors. These include 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 costs of treatment and unemployment.

Approximately 10% of ESKD patients who are hospitalized have an underlying psychiatric disorder. Hospitalization rates for psychiatric disorders are high relative to other chronically ill patients. Common problems include depression, dementia and delirium, psychosis, personality and anxiety disorders, and substance abuse.

I. DEPRESSION. Depression is 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. According to the most recent version of the Diagnostic and Statistical Manual for Mental Disorder (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 per se.

Some investigators have estimated that depression occurs in as many as 10%–50% of dialysis patients. Screening tools include the Beck Depression Inventory (BDI) and the Hamilton Rating Scale for Depression. In patients with no underlying medical problems, a BDI score <9 suggests no or minimal depression, 10–18 indicates mild to moderate depression, 19–29 moderate

to severe depression, and ≥30 severe depression. In patients with ESKD, the recommended cutoff scores for depression are higher, with BDI scores ≥14–16 indicating significant disease.

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, to abnormal immunologic function, or to anorexia and poor nutritional status. Depressive affect has also been linked to a higher incidence of peritonitis. Whether depression increases mortality risk is controversial. Some studies have suggested that baseline depressive symptom- atology is associated with increased mortality, even after multiple medical risk factors have been accounted for in analyses.

ESKD patients can display suicidal behavior differently from patients with other chronic illnesses. Their rate of suicide is higher than in the general U.S. population. Important risk factors include a previous history of mental illness, recent hospitalization, age >75, male gender, white or Asian race, and alcohol or drug dependence. ESKD patients 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 manyof the large clinical trials.

1. Pharmacotherapy

a. Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs). Treatment with SSRIs should be continued for at least 4–6 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 dialysis patient population.

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. SSRIs may have an additional benefit of reducing postural and intradialytic

hypotension through effects on vascular tone. Fluoxetine, the first available SSRI, is the best studied drug in this family. A dose of 20 mg of fluoxetine daily is usually well tolerated, although data are limited to the short term. Other medications in this same family include paroxetine, sertraline, and citalopram.

b. Selective norepinephrine reuptake inhibitors (SNRIs). Venla- faxine and bupropion hydrochloride are examples of a different class of antidepressants called SNRIs. The SNRIs should be used with caution in ESKD patients, since these drugs are primarily renally excreted. Bupro- pion has active metabolites that are almost completely removed by the kidney. These metabolites may accumu- late in dialysis patients, predisposing them to developing seizures.

c. Monoamine oxidase inhibitors (MAOIs). MAOIs have numer- ous side effects and should be avoided if possible in ESKD patients, because of their potential to cause hypotension.

2. Nonpharmacologic options. There are several forms of psychotherapy (cognitive behavioral therapy [CBT], 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. Individual psychotherapy (cognitive–behavioral, interpersonal, and supportive) is useful when the patient has identified that there is a problem and has accepted encouragement by the clinician to seek treatment. A recent randomized crossover trial of 65 hemodialysis patients showed significant improvements in depression scores as measured by the Beck Depression Inventory II (BDI II) and the Hamilton Depression Rating Scale in those patients who received CBT. With CBT, 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 improved patient survival. Finally, electroconvulsive therapy may be used for patients with

severe refractory depression, provided that there are no contraindications.

II. DEMENTIA/DELIRIUM. Neurocognitive disorders are common in ESKD patients. Cognitive deficits may be related to underlying uremia or other coexistent underlying medical conditions, as described in more detail in Chapter 40. Physicians should initiate discussions with the family about cessation of dialysis in patients with progressive dementia. Withdrawal from dialysis is relatively common, especially in elderly 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. There was a 45% prevalence of anxiety disorders in a single center study of 70 hemodialysis patients. Disruptive behavior directed toward the dialysis staff occurs in a minority of patients, but nevertheless can be a disturbance to all those 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 an underlying psychiatric symptom, 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 the SSRIs, it is prudent to start with lower doses. The use of diazepam and chlordiazepoxide should be avoided in dialysis patients, owing to their metabolism to pharmacologically active metabolites. Barbiturates should not be used in place of benzodiazepines, since the long-acting ones are removed by hemodialysis. For the acutely agitated patient, 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. ESKD and CKD patients 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.

IV. OTHER PSYCHOSOCIAL ISSUES IN THE ESKD POPULATION

A. Marital issues. There have been only a few studies that assess maritalrelationships in ESKD patients. 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 ESKD patients. Marital conflict may be associated with a patient,s perception of burden of illness and the degree to which a patient does not adhere to the dialysis prescription. Marital satisfaction and conflict may be particu- larly salient for female patients. One study showed that female ESKD patients treated with hemodialysis with higher levels of marital satisfaction had improved survival. Marital satisfac- tion was not associated with differential outcomes in men.

B. Sexual dysfunction. ESKD patients 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 disor- ders, 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 com- mon after the initiation of hemodialysis treatment. The most common menstrual disorder in women with ESKD is anovula- tion. For information about treatment, see Chapter 39.

C. Socioeconomic issues. More than half of ESKD patients 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 psychologic 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 (QOL). It is essential for the medical staff and family to address the patient,s perception of QOL. This is especially important when making decisions regarding the initiation or withdrawal of dialysis. Patients who rate their QOL 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 QOL in ESKD patients, 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 QOL for dialysis patients. ESKD patients with successful renal transplants tend to rate their QOL higher than those with failed transplants or those treated with dialy- sis. There have been several recent clinical trials that evalu- ated the impact of intensification of dialysis prescriptions on patients, perceptions of quality of life. The Frequent Hemodi- alysis Network (FHN) evaluated the effect of intense dialysis six times weekly versus conventional three times weekly treat- ments on quality of life and depression scores. Although there were few changes in many subdomain measures of QOL, there were improvements in both the SF-36 and BDI scores in the six times weekly dialysis arm. Physicians should strongly consider the impact their medical decisions have on a patient's QOL, and discuss these issues in depth with patients and their fami- lies. In addition, patient satisfaction with care is an important aspect of QOL that should be evaluated.

Suggested Readings

American PsychiatricAssociation. Diagnostic and Statistical Manual of Mental Disorders 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.

Atalay H, et al: Sertraline treatment is associated with an improvement in depression and health-related quality of life in chronic peritoneal dialysis patients. Int Urol Nephrol. 2010;42:527–536.

Blumenfield M, et al. Fluoxetine in depressed patients on dialysis. Int J Psychiatry Me 1997;27:71–78.

Castaneda C, et al. Resistance training to reduce the malnutrition-inflammation complex syndrome of chronic kidney disease. Am J Kidney Dis. 2004;43:607–61

Chertow GM, et al. In-center hemodialysis six times per week versus three times pe week. N Engl J Med. 2010;363:2287–2300.

Cohen SD, et al. Screening, diagnosis, and treatment of depression in patients wit end-stage renal disease. Clin J Am Soc Nephrol. 2007;2:1332–1342.

Cukor D, et al. Psychosocial aspects of chronic disease: ESRD as a paradigmatic illn J Am Soc Nephrol. 2007;18:3042–3055.

Cukor D, et al. Anxiety disorders in adults treated by hemodialysis: a single-cente study. Am J Kidney Dis. 2008;52:128–136.

Cukor D, et al. Psychosocial intervention improves depression, quality of life, and flui adherence in hemodialysis. J Am Soc Nephrol. 2014;25:196–206.

Daneker B, et al. Depression and marital dissatisfaction in patients with end-stage renal disease and in their spouses. Am J Kidney Dis. 2001;38:839–846.

Dheenan S, et al. Effect of sertraline hydrochloride on dialysis hypotension. Am Kidney Dis. 1998;31:624–630.

Dogan E, et al. Relation between depression, some laboratory parameters, and quality-of-life in hemodialysis patients. Ren Fail. 2005;27:695–699.

Finkelstein FO, et al. Depression in chronic dialysis patients: assessment and treatment. Nephrol Dial Transplant. 2000;15:1911–1913.
Friend R, et al. Group participation and survival among patients with end-stage renal disease. Am J Public Health. 1986;76:670–672.
Gee CB, et al. Couples coping in response to kidney disease: a developmental perspec tive. Semin Dial. 2005;18:103–108.
Hedayati SS, et al. A practical approach to the treatment of depression in patients with chronic kidney disease and end-stage renal disease. Kidney Int. 2012;81:247–255.
Holley JL. Palliative care in end-stage renal disease: focus on advance care planning, hospice referral, and bereavement [Review]. Semin Dial. 2005;18:154–156.
Kimmel PL. Just whose quality-of-life is it anyway? Controversies and consistencies in measurements of quality-of-life. Kidney Int. 2000;57(suppl 74):113–120.
Kimmel PL, et al. Marital conflict, gender and survival in urban hemodialysis patients. J Am Soc Nephrol. 2000;11:1518–1525.
Kimmel PL, et al. Multiple measurements of depression predict mortality in a longitudinal study of chronic hemodialysis patients. Kidney Int. 2000;57:2093–2098.
Kimmel PL, et al. Depression in end-stage renal disease patients treated with hemodi- alysis: tools, correlates, outcomes, and needs. Semin Dial. 2005;18:73–79.
King K, et al. The frequency and significance of the “difficult” patient: the nephrology community,s perceptions. Adv Chronic Kidney Dis. 2004;11:234–239.
Kolewaski CD, et al. Quality-of-life and exercise rehabilitation in end stage renal disease. CANNT J. 2005;15:22–29.
Kouidi E, et al. Exercise renal rehabilitation program: psychosocial effects. Nephron. 1997;77:152–158.
Kurella M, et al. Chronic kidney disease and cognitive impairment in the elderly: the Health, Aging and Body Composition Study. J Am Soc Nephrol. 2005;16:2127–213
Kurella M, et al. Suicide in the end-stage renal disease program. J Am Soc Nephrol 2005;16:774–781.
Lopes AA, et al. Depression as a predictor of mortality and hospitalization among hemodialysis patients in the United States and Europe. Kidney Int. 2002;62:199–20
Moss AH, et al. Palliative care [Review]. Am J Kidney Dis. 2004;43:172–173.
Painter P. Physical functioning in end-stage renal disease patients: update 2005 [Review]. Hemodial Int. 2005;9:218–235.
Patel SS, et al. Psychosocial variables, quality of life and religious beliefs in end-stage r disease patients treated with hemodialysis. Am J Kidney Dis. 2002;40:1013–1022.
Patel S, et al. The impact of social support on end-stage renal disease. Semin Dial. 2005;18:89–93.
Renal Physicians Association. Shared decision making (guideline regarding withdrawal from dialysis and palliative care). Available at http://www.renalmd.org/. Accessed September 12, 2006.
Shidler NR, et al. Quality-of-life and psychosocial relationships in patients with chronic renal insufficiency. Am J Kidney Dis. 1998;32:557–566.
Snow V, et al. Pharmacologic treatment of acute major depression and dysthymia. American College of Physicians-American Society of Internal Medicine. Ann Intern Med. 2000;132:738–742.
Tawney K. Developing a dialysis rehabilitation program. Nephrol Nurs J. 2000;27: 524–539.
Turk S, et al. Treatment with antidepressive drugs improved quality-of-life in chronic hemodialysis patients. Clin Nephrol. 2006;65:113–118.
Unruh ML, et al. Health-related quality-of-life in nephrology research and clinical practice. Semin Dial. 2005;18:82–90.
Watnick S, et al. The prevalence and treatment of depression among patients starting dialysis. Am J Kidney Dis. 2003;41:105–110.
Wilson B, et al. Screening for depression in chronic hemodialysis patients: comparison of the Beck Depression Inventory, primary nurse, and nephrology team. Hemodial Int. 2006;10:35–41.
Wu AW, et al. Changes in quality-of-life during hemodialysis and peritoneal dialysis trea ment: generic and disease specific measures. J Am Soc Nephrol. 2004;15:743–753
Wuerth D, et al. Chronic peritoneal dialysis patients diagnosed with clinical depres- sion: results of pharmacologic therapy. Semin Dial. 2003;16:424–427.
Wuerth D, et al. The identification and treatment of depression in patients maintained on dialysis. Semin Dial. 2005;18:142–146.

31 Nutrition

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I. CAUSES OF PROTEIN ENERGY WASTING (PEW) IN CKD PATIENTS.

Metabolic and nutritional derangements are common in patients with chronic kidney disease (CKD), especially in patients on maintenance dialysis therapy (Ikizler, 2013). These derangements are called protein energy wasting (PEW) of CKD. Patients with this syndrome have increased rates of hospitalization and mortality (Kalantar-Zadeh, 2004). There are multiple etiologies of PEW (Table 31.1), 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). PEW affects approximately one-third of hemodialysis and peritoneal dialysis patients (Pupim, 2006). The sequelae of PEW 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 (Kaysen, 2001). Proinflammatory cytokines can cause anorexia with suppression of nutrient intake (Kaizu, 2003). 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 (GH) and insulin-like growth factor-1 (IGF-1) axis leads to decreased protein synthesis. Increased leptin concentrations may worsen anorexia due to central effects.

A. Obesity. Concern has always focused on wasting in CKD patients, because the death rate increases steeply with evidence of skeletal muscle loss, weight that is below peer weight, or body mass index. There is, however, an increasing incidence of obesity among patients initiating maintenance dialysis therapy (Kramer, 2006). Although obesity has traditionally been defined in terms of body mass index, some dialysis patients who are normal or overweight by BMI have been found to be obese as defined by percent body fat (Gracia-Iguacel, 2013). Studies of the effect of obesity on survival in dialysis patients

TABLE 31.1 Causes of Kidney Disease Wasting

Decreased nutritional intake
Overzealous dietaryrestrictions
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
Gastrointestinalblood 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 per 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)

are difficult to interpret because of the observational nature of the studies, differences in analysis techniques and definitions of obesity, and confounding (Stenvinkel, 2013).

II. NUTRITIONAL ASSESSMENT

A. Patient interview and physical examination. Symptoms of nausea, vomiting,and anorexia, as wellas recent changes in body weight, should be carefully evaluated to ascertain cause. Non- uremic causes of changes in weight and/or food intake must be kept in mind, including severe congestive heart failure, dia- betes, various gastrointestinal diseases, and depression. Phos- phate binders or oral iron preparations can cause dyspepsia and other gastrointestinal symptoms.

B. Assessment of food intake. Patient recall of food intake should be determined on both dialysis and nondialysis days, performed biannually (Kopple, 2001); intake on dialysis days typically is about 20% lower (Burrowes, 2003). Food frequency questionnaires may also provide useful information (Kalantar-Zadeh, 2002).

C. Nutritional screening tools: A variety of screening tools are avail- able, such as the Malnutrition Universal Screening Tool (MUST), Mini Nutritional Assessment (MNA), and others. All these tools require a brief patient interview. Questions that are common to all screening tools include information about body weight changes within a given time frame, amount of oral intake, or lack of appetite. Because of its simplicity and reliability, the Malnutrition Screening Tool (MST), which is simpler to apply than the more comprehensive MUST, is suggested as the first option. The MST includes two questions about weight loss and one question about appetite. When scores for answers to these questions are added together and the result is greater than 2, the patient is at risk for malnutrition/PEW, and a nutritional assessment is recommended.

D. Nutritional assessment tools

1. Body composition

a. Body weight and body mass index. One should compare ideal or medianstandard weight (see Appendix B) with actual body weight. Comparison with prior values is important as both body weight and lean body mass decrease over time in hemodialysis patients (Di Filippo, 2006; Rocco, 2004). Although BMI is easy to calculate and is used in many nutritional guidelines, it should be emphasized that this metric is a poor estimate of fat mass and its distribu- tion within the body, especially in patients with CKD.

b. Anthropometry. The waist–hip ratio (WHR) and skinfold thickness are superior to BMI for the correct classification of obesity in CKD in cross-sectional studies. Skinfold thickness measured at the biceps or triceps provides an estimate of body fat, whereas midarm circumference can be used to estimate muscle mass. These measures can be compared with reference ranges established in well-nourished dialysis patients (Chumlea, 2003). Patients with values below the 25th percentile for either middle upper arm circumference or triceps skinfold thickness are likely to be malnourished. Bioimpedance. Bioimpedance

c. analysis is based on the measurement of resistance and reactance when a con- stant alternating electrical current is applied to a patient. Empirical equations are used to predict total-body water from resistance and total-body mass from the ratio of resistance to reactance or from its geometrical deriva- tive, the phase angle. Phase angle correlates strongly with anthropometric measures of nutritional status and with serum albumin levels. For reproducibility, bioimpedance measurements should be performed within 120 min- utes of the end of a dialysis treatment (Di Iorio, 2004). Low phase angle measurements are associated with an increased risk of mortality (Mushnick, 2003). An interna- tional study using bioimpedance spectroscopy has noted an impairment in the lean tissue index in all dialysis

patients, with better preservation in peritoneal dialysis patients versus hemodialysis patients (van Biesen, 2013). d. Dual energy x-ray absorptiometry (DEXA). This test was devel- oped to measure bone density, but was later adapted to quantify soft tissue composition, including fat and fat- free mass. A DEXA scan takes only 6–15 minutes, involves minimal radiation exposure, and hence can be used seri- ally to follow changes over time. At present, DEXA is used mostly for research purposes; it is more costly, and there are no data relating DEXA results to outcome in patients with advanced kidney disease. DEXA findings must be evaluated with hydration status in mind as well. Composite indices.

2. 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) dietary nutrient intake; (c) the presence of anorexia, nausea, vomiting, diarrhea, or abdominal pain; (d) functional capacity; and (e) metabolic demands in view of underlying disease state. Physical parameters focus on 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 in end stage kidney disease (ESKD) patients (Duerksen, 2000). Other scoring systems that have been proposed include the modified SGA (Churchill, 1996), the Dialysis Malnutrition Score, and the Malnutrition Inflammation Score (Kalantar-Zadeh, 2001), all of which use a combination of objective and subjective factors. The Geriatric Nutritional Risk Index (GNRI) consists of only three objective parameters—body weight, height, and serum albumin level; the score is predictive of mortality (Kobayashi, 2010).

E. Laboratory 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 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 or some combination of these mechanisms. Additional assessment including, but not limited to, physical exam, dietary recalls and measurement of acute phase reactants (e.g., plasma C-reactive protein level) is necessary for appropriate management of the patient.

2. 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.

3. Urea nitrogen appearance (g). This measurement can be used to estimate protein intake. This is because, in the absence of marked catabolism or anabolism, the urea nitrogen appearance rate reflects protein intake. In catabolic or anabolic patients, protein intake will be over- or underestimated, respectively. As discussed in Chapter 3, in hemodialysis patients, the **g** can be computed using a pre- and postdialysis SUN. In patients with AKI, g can be estimated by measuring SUN at two time points, usually 24 hours apart, after making an estimate of total body water. Another method used in computing **g** for both hemodialysis and peritoneal dialysis patients is to collect aliquots of the spent dialysate as well as urine, and to measure the amount of urea nitrogen in each.

4. Protein equivalent of total nitrogen appearance (PNA). Several formulas are available for the calculation of PNA from **g**, given that, on average, the percentage of nitrogen from protein that winds up as urea is known. Dialysis modeling programs usually normalize the PNA to the "kinetic" body weight; the latter is estimated as urea distribution volume divided by 0.58. The kinetic weight (which usually is an internal number and is not reported) is usually, but not always, close to the actual body weight. Dividing PNA by the kinetic weight gives a "normalized" PNA, or nPNA in units of g/kg per day.

5. Clinical utility of the nPNA. The utility of the PNA in terms of predicting outcomes has been questioned. In the HEMO trial, as well as in observational data sets, once serum albu- min and creatinine were controlled for, the PNA had little, if any, additional predictive power in terms of outcome. In the HEMO trial, PNA was a very poor predictor of dietary pro- tein intake. It was assumed that the dietary recall method used was not sufficiently sensitive to show a relationship, but alternative explanations are possible as well.

6. Other laboratory measures. Serum transferrin is low in almost all dialysis patients and is influenced by changes in iron stores, presence of inflammation, and changes in volume status; it is not a good indicator of nutritional status. **Serum prealbumin** levels may be elevated because of interaction of prealbumin with retinol-binding protein and decreased renal clearance. **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 in ESKD patients, reducing their practical utility, but serial CRP measurements may provide valuable information.

III. DIETARY REQUIREMENTS. The recommended average levels of nutritional intake are listed in Table 31.2, and include recommendations that are generally consistent with the National Kidney Foundation's (NKF) Kidney Disease Outcome Quality

TABLE 31.2 Daily Dietary Recommendations For Dialysis Patients[a]

Nutrient or Substance	Hemodialysis	Peritoneal Dialysis
Protein (g/kg)	>1.2	>1.2; >1.5 with peritonitis
Calories (sedentary, kcal/kg)	30–35[b]	30–35[b, c]
Protein (%)	15–25	
Carbohydrate (%)	50–60[d]	50–60[c, d]
Fat (%)	25–35	
Cholesterol	<200 mg (0.52 mmol)	
Saturated fat (%)	< 7	
Crude fiber (g)	20–30	
Sodium	80–100 mmole	
Potassium	< 1 mmol/kg if elevated	Usually not an issue
Calcium	2.0 g (50 mmol)[f]	
Phosphorus	0.8–1.0 g (26–32 mmol)[g]	
Magnesium	0.2–0.3 g (8–12 mmol)	
Iron	See Chapter 34	
Vitamin A	None	
β-carotene	None	
Retinol	None	
Thiamine (mg)	1.5	
Riboflavin (mg)	1.7	
Vitamin B6 (mg)	10	
Vitamin B12 (mg)	0.006	
Niacin (mg)	20	
Folic acid (mg)	>1.0	
Pantothenic acid (mg)	10	
Biotin (mg)	0.3	
Vitamin C (mg)	60–100	
Vitamin E	None	
Vitamin D	See Chapter 36	
Vitamin K	See text	

[a]All intakes calculated on the basis of normalized body weight (i.e., the average body weight of normal persons of the same age, height, and sex as the patient).
[b]35 kcal/kg body weight per day if <60 years of age; 30–35 kcal/body weight per day if >60 years of age.
[c]Includes glucose absorbed from dialysis solutions.
[d]Carbohydrate intake should be decreased in patients with hypertriglyceridemia.
[e]Lower sodium intakes, in the range of 1.0–1.5 g (43–65 mmol), may result in better control of blood pressure in peritoneal dialysis patients and a lower dialysis solution glucose load, and are recommended if this can be done while maintaining energy intake.
[f]The total dose of elemental calcium provided by the calcium-based phosphate binders should not exceed 1,500 mg (37 mmol) per day, and the total intake of elemental calcium (including dietary calcium) should not exceed 2,000 mg (50 mmol) per day.
[g]For patients with serum phosphorus level >5.5 mg/dL (1.8 mmol/L); use phosphate binders if elevated.

Initiative (KDOQI) 2001 guidelines on nutrition (NKF, 2001) and the European best practice guidelines for nutrition (Dombros, 2005). A. Need for individualization. A "renal" diet has numerous restric-

tions, 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. Specific nutritional issues in the diabetic dialy- sis patient are discussed in Chapter 32. Too many restrictions should be avoided as they may lead to poor intake. The nutri- tional 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. Peer rather than actual body weight. One problem with dietary intake recommendations for dialysis patients, who often have PEW, is the choice of weight to use in the denominator. For example, if a patient has lost body mass such that his or her weight is now 50 kg versus a premorbid weight of 90 kg, ingestion of an "adequate" amount of protein or calories based on actual weight may maintain the patient at that lower body weight, but may not be optimal for regaining lost weight, assuming that this is desired. Protein and caloric recommendations should be based on the median standard (or "peer") body weight (see Tables B.1 and B.2 in Appendix B) for healthy subjects of the same sex, height, age, and body frame size as the patient. On the other hand, in obese patients, adjusted body weight should be used (Adjusted BW = Peer Body Weight + 0.25 × (actual Body Weight – Peer Body Weight).

Example: A severely malnourished 35-year-old male hemodialysis patient weighs 60 kg. Using the Tables in Appendix B for peer weight, we find that the peer weight for this medium-frame patient (were he healthy) given a height of 183 cm (72 in.) would be about 84 kg. Our urea kinetic modeling program had reported that his nPNA was 1.2 g/kg per day. As discussed above, this nPNA is based on the patient's "kinetic" weight. Is this patient ingesting an adequate amount of protein?

We can recover the value for modeled *V* from the program and divide this by 0.58 to find the "kinetic" weight that was used by the program. Assume that this turns out to be 60 kg. Then 1.2 g/kg per day = 1.2 × 60 = 72 g per day for his PNA, which means that estimated protein intake is also 72 g per day. To compute PNA normalized to this patient's peer weight, we divide 72 by 84 kg. Now his PNA/peer weight is only 72/84 = 0.86 g/kg per day, which may be suboptimal.

C. 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. Hav- ing said this, in the HEMO study, there was no improvement in either protein or energy intake in patients randomized to high-dose (single-pool *Kt/V*~1.65) compared with patients randomized to standard-dose (single-pool *Kt/V* ~1.25) 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 changing hemodialy- sis patients from a three per week to 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 (Kaysen, 2012). Claims have also been made of nutritional improvement in patients receiving intermittent hemofiltration or hemodiafiltration, but the sup- portive evidence is also relatively weak.

D. Protein. KDOQI guidelines recommend that both hemodialysis and peritoneal dialysis patients should ingest 1.2 g of protein/kg (using peer body weight) per day. At least 50% of the protein ingested should be of high biologic value. This level of protein intake is often difficult to achieve in practice, however, and 30%–50% of hemodialysis patients report intakes of <1.0 g of protein/kg per day (Rocco, 2004).

E. Energy. KDOQI guidelines recommend that all dialysis patients younger than 61 years ingest 35 kcal/kg per day. For patients older than 60 years, the recommended intake is 30–35 kcal/kg per day, with the lower value used for sedentary patients. Note that this level of intake includes any calories provided from the dialysis procedure. Higher levels of caloric intake may be required for patients who perform strenuous labor, for patients who are well below their desired weight, and for patients who are hospitalized, have peritonitis, or have other causes of catabolic stress. This recommended level of caloric intake is difficult to achieve in practice; as an example, in the HEMO study, intake based on dietary recall averaged 23–27 kcal/kg. The data correlate with an observed mean resting energy expenditure of 24.6 kcal/kg per day in Japanese hemodialysis patients (Kogirima, 2006). This may be related to the usual underreporting observed in dietary recalls. The KDOQI recommended levels of dietary protein and energy intake have been achieved in some patients receiving more frequent hemodialysis (Rocco, 2013).

In peritoneal dialysis patients, a substantial amount of glucose absorbed from the dialysate contributes to total energy intake (Table 31.3), which occurs daily; the amount depends on the percent dextrose used for each dwell, the length of each exchange, the volume of each dwell, the number of exchanges, and peritoneal membrane transport properties.

TABLE 31.3 Estimated Kilocalories of Glucose Absorbed as Instilled Volume Varies in CAPD and APD Patients

Instilled Volume	%D Daytime	%D Overnight	kcal Absorbed
CAPD 4 × 2.0 L			
4 × 2.5 L	1.5% D	2.5% D 7.5% Icodextrin	33
4 × 2.5 L	1.5% D	2.5% D	2
4 × 3.0 L			18
APD (day dwell)[a]			7
3 × 2.0 & 2.0	1.5% D	1.5% D	38
3 × 2.5 & 2.5	2.5% D	1.5% D	99
3 × 3.0 & 3.0	1.5% D	1.5% D	43
3 × 2.5 & 2.5 + 2.5	2.5% D	1.5% D	396
3 × 2.5 & Ico	Both 1.5% D	1.5% D	342
	7.5% Icodextrin	1.5% D	144

D, % dextrose of instilled solution; APD, automated peritoneal dialysis.
[a]APD using 9 hours overnight and three exchanges per night and a last-bag-fill for APD regimens 1, 2, 3, and 5. APD 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.

1. Percent carbohydrates. Table 31.2 reflects the conventional wisdom that 50%–60% of dietary intake (including glucose absorbed from dialysate) should be carbohydrates. This would represent 1,000 kcal, or 250 g of carbohydrates, for a 2,000-kcal diet. Given that 300–400 kcal of glucose is normally absorbed with most peritoneal dialysis regimens, in peritoneal dialysis patients the percent carbohydrates ingested as food needs to be reduced by a similar amount. Hypertriglyceridemia and impaired glucose tolerance are common in peritoneal dialysis patients and are not rare in those being treated with hemodialysis. For such patients, the percent carbohydrates may need to be further reduced, with the caloric deficit being made up primarily by increased intake of both protein and monounsaturated fats (Arora, 2005).

F. Lipids. The classic therapeutic goal for hemodialysis patients has been to achieve a low-density lipoprotein (LDL) cholesterol of <100 mg/dL (2.6 mmol/L) and a fasting triglyceride level of <500 mg/dL (5.7 mmol/L). Therapeutic lifestyle changes include diet, weight reduction, increased physical activity, abstinence from alcohol, and treatment of hyperglycemia, if present. However, in dialysis patients, low LDL cholesterol levels are not associated with improved cardiovascular health or survival. Thus, these recommendations are not evidence- based but rather are ported from patients with normal kidney function. With regard to diet composition, the usual recom- mendation has been a diet containing <7% saturated fat, with

polyunsaturated fat <10% of total calories and monounsaturated fat <20% of total calories, and with total fat at 25%–35% of total calories. However, the conventional wisdom regarding the adverse cardiovascular effects of saturated fat is currently the subject of a large amount of controversy (Chowdhury, 2014). Carbohydrates should not exceed 50%–60% of total calo- ries in hemodialysis patients, and dietary carbohydrate intake should likely be even less in peritoneal dialysis patients. In all dialysis patients, 20–30 g of fiber per day should be consumed to help reduce dyslipidemia and to reduce gastrointestinal transit time, as high-fiber diets have in general been associ- ated with lower cardiovascular mortality. Many uremic toxins such as indoxyl sulfate and p-cresol sulfate may be generated by bacteria in the gut, and reducing gastrointestinal transit time may limit the time during which gut bacteria can gener- ate these toxins. Lipid management is discussed in more detail in Chapter 38.

G. 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. Regulatory bodies in the past suggested that healthy (non-CKD) persons limit dietary sodium intake to 2.3 g (100 mmol) per day, and for older persons, African Americans, or patients with kidney disease, a restriction to 1.5 g (65 mmol) per day, (Institute of Medicine, 2004); however, the extent to which sodium reduction leads to cardiovascular benefits is currently a source of controversy (Insti- tute of Medicine, 2013). In peritoneal dialysis, although one can remove sodium-stimulated fluid ingestion using higher glucose dwells, this comes at the cost of glucose loading, with potential adverse effects on the peritoneal membrane as well as on lipids and triglyceride levels, so a lower sodium intake is desirable. In ESKD patients who are anuric, fluid intake gener- ally should be limited to about 1.0–1.5 L per day. Additional fluid can be consumed in patients with residual renal func- tion, with the amount based on the daily urine volume.

H. Potassium. Mild potassium restriction (4 g or 100 mmol per day) is usually all that is needed in patients with a moderate degree of residual renal function. Hyperkalemia sometimes becomes an issue in the presence of acidemia or hypoaldosteronism, or with the administration of nonsteroidal anti-inflammatory drugs (NSAIDs), potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, angiotensin blockers, aldosterone receptor antagonists, or β-receptor blockers.

Hyperkalemia in anuric peritoneal dialysis patients is unusual because the dialysate contains no potassium. Peritoneal dialysis patients typically require only modest potassium restriction (4 g or 100 mmol per day) or no restriction at all. In hemodialysis patients with limited residual renal function,

a lower intake of potassium (2 g or 50 mmol per day) is often required to prevent predialysis hyperkalemia. An important issue that needs attention is to limit exposure to very low potassium (0 K or 1 K) hemodialysis solutions, as the latter have been associated with arrhythmias and an increased risk of sudden death. Calcium and phosphorus. The dietary intake

I. of calcium and phosphorus and management of hyperphosphatemia are dis- cussed in Chapter 36. An important issue that needs to be kept in mind is that dietary protein recommendations should con- sider not only the phosphorus content from protein sources but also the phosphorus content in additives and preserva- tives in processed foods, which can be substantial (Kalantar- Zadeh, 2010)

J. Vitamins

1. Water-soluble vitamins. Dialysis patients may develop deficiencies of water-soluble vitamins unless supplements are given. Vitamin deficiencies are caused by poor intake, interference with absorption by drugs or uremia, altered metabolism, and losses to the dialysate. All dialysis patients should receive supplementary folic acid and B vitamins in the doses listed in Table 31.2. B-vitamin replacement may need to be more intensive in patients undergoing high-flux dialysis owing to increased losses (Kasama, 1996). High levels of folate supplementation, however, do not result in a significant decrease in homocysteine levels (Ghandour, 2002). Ascorbic acid supplementation should be limited to 60–100 mg per day as higher doses can result in the accumulation of its metabolite, oxalate. The use of injectable vitamin B12 in patients with lower-range serum cobalamin levels to reduce erythropoietin stimulating agent requirements is discussed in Chapter 34.

2. Fat-soluble vitamins. Fat-soluble vitamins cannot be removed by either hemodialysis or peritoneal dialysis. Multivitamin supplementation in maintenance dialysis patients should not include fat-soluble vitamins. The dosing of vitamin D is discussed in Chapter 36. Vitamin E has been promoted as an antioxidant in maintenance dialysis patients, although supplemental therapy has not led to any changes in markers of inflammation or oxidative stress (Himmelfarb, 2014) despite encouraging earlier studies. One should carefully check any vitamin given to ESKD patients to make sure that it does not contain vitamin A. High levels of vitamin A can result in multiple, serious adverse effects in nonuremic individuals. Hypervitaminosis A in dialysis patients can also cause anemia and abnormalities of lipid and calcium metabolism. Recently there has been a focus on low vitamin K levels and impaired vitamin K recycling in ESKD patients as a potential cause for accelerated vascular calcification. Vitamin K comes in 2 avaiable forms, phylloquinone (K1), found in green leafy vegetables, and menaquinone (K2),

found in fermented dairy products. Phylloquinone can be converted to menaquinone. Dietary menaquinone intake correlates inversely with levels of an inactivated form of calcification inhibitor, dephosphorylated, uncarboxylated matrix Gla protein (dp-uc-MGP; Calluwe, 2014). Currently there are two randomized trials in progress (Calluwe, 2014; Krueger, 2014) that will give either menaquinone (K2) or phylloquinone (K1) supplements, respectively, to dialy- sis patients, to see if this retards progression of vascular calcification.

IV. NUTRIENT REQUIREMENTS IN HOSPITALIZED PATIENTS WITH KIDNEY DISEASE

A. Energy requirements in hospitalized dialysis patients. In general, mostpatients withacute kidney injury (AKI) requiring dialy- sis have energy needs between 30 and 40 kcal/kg. 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. A simple method is to assume a baseline requirement of 30 or 35 kcal/kg per day, and then multiply by one or more adjustment factors, which range from 1.1 to 1.7, and are used when hypermetabolism is likely to be pres- ent (Table 31.4). Apart from these adjustment factors, energy expenditure in acutely ill patients with AKI has not been

TABLE 31.4 Adjustment factors for determination of energy requirements

Clinical Condition	Adjustment Factor
Mechanical ventilation Without sepsis With sepsis Peritonitis Infections Mild Moderate Sepsis Soft tissue trauma Bone fractures Burns (% of body surface area) 0%–20% 20%–40% 40%–100%	1.10–1.20 1.25–1.35 1.15 1.00–1.10 1.10–1.20 1.20–1.30 1.10 1.15 1.15 1.50 1.70

Recommendations adapted from Blackburn GL, et al. Nutritional and metabolic assessment of the hospitalized patient. J Parenter Enteral Nutr. 1977;1:11–22; Bouffard Y, et al. Energy expenditure in the acute renal failure patient mechanically ventilated. Intens Care Med. 1987;13:401–404; Schneeweiss B, et al. Energy metabolism in acute and chronic renal failure. Am J Clin Nutr. 1990;52:596–601; Soop M, et al. Energy expenditure in postoperative multiple organ failure with acute renal failure. Clin Nephrol. 1989;31:139–145.

shown to be higher than in acutely ill patients with normal kidney function (Soop, 1989).

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 a hospitalization should be in the range of 1.1–2.0 g/kg per day. There appears to be no benefit in using higher levels of pro- tein 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. 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 lip- ids. 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 PEW of CKD should be diligently pursued and corrected (see Fig. 31.1 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 PEW of CKD (Wang, 2003) and is often secondary to anorexia. Anorexia has many etiolo- gies. The provision of adequate dialysis is a crucial first step in improving nutritional status; however, data on more frequent hemodialysis is mixed regarding the benefit of an increased dose of dialysis on nutritional parameters (Rocco, 2013). Other medical conditions, especially infection and inflamma- tion, acidemia, intercurrent illness, and cardiovascular dis- ease, should be identified and treated if possible. Metabolic acidosis promotes PEW by increasing muscle protein catab- olism and by stimulating the oxidation of essential amino acids. Thus, a predialysis goal of 22–24 mmol/L in hemodialy- sis patients and >22 mmol/L in peritoneal dialysis patients is suggested for patients with PEW (Stein, 1997). Causes of inflammation, including the use of central venous catheters in hemodialysis, should be treated or eliminated if possible. Cor- rection of GI disturbances, including diabetic gastroparesis, colitis, and pancreatic insufficiency, may also improve nutri- tional status. Other considerations include access to, and abil- itity to prepare, food, ethnic and personal food preferences,

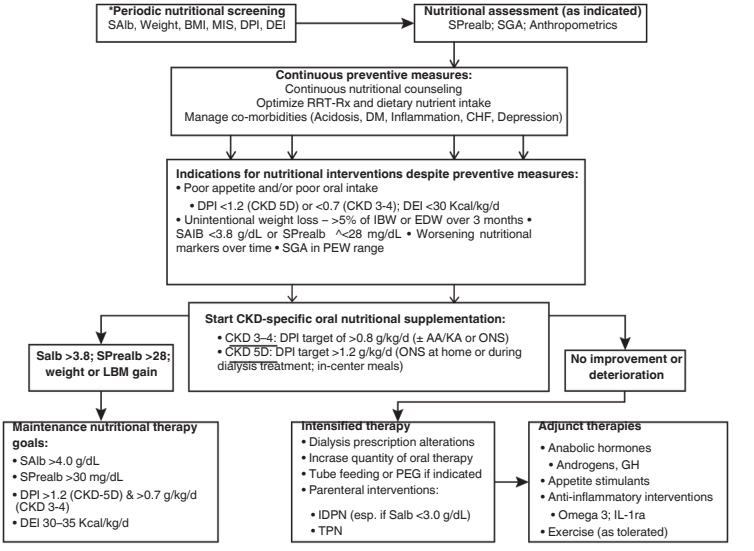


FIGURE 31.1 Algorithm for nutritional management and support in patients with chronic kidney disease. (Reproduced with permission from MacMillan Publishers Ltd: Ikizler TA, Cano NJ, Franch H, et al. Prevention and treatment of protein energy wasting in chronic kidney disease patients: a consensus statement by the International Society of Renal Nutrition and Metabolism. Kidney Int. 2013;84:1096–1107.) BMI, body mass index; CHF, congestive heart failure; 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; PEW, protein energy wasting; RRT, renal replacement therapy; Salb, serum albumin; SPrealb, serum prealbumin; SGA, subjective global assessment; TPN, total parenteral nutrition.

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.

B. When to initiate nutritional supplements. The International Society of Renal Nutrition and Metabolism has recently published recommendations for the nutritional management and sup- port of patients with CKD (Ikizler, 2013). Once preventive and preliminary corrective approaches have failed, indications for prescription of nutritional supplements include the following (Fig 31.1):

1. Poor appetite and/or poor oral intake
2. Dietary protein intake (DPI) <1.2 g/kg per day, Dietary energy intake (DEI) <30 kcal/kg per day
3. Serum albumin level <3.8 g/dL or (if patient anuric) serum prealbumin level <28 mg/dL
4. Unintentional weight loss >5% of ideal body weight (IBW) or end-dialysis weight (EDW) over 3 months

5. Worsening nutritional markers over time
6. SGA in PEW range

The initial nutritional supplementation should be CKD specific with a target dietary protein intake of >1.2 g/kg per day for ESKD and >0.8 g/kg per day for nondialysis CKD patients, a target dietary energy intake of 30–35 kcal/kg per day, a goal serum albumin level of 3.8 g/dL (38 g/L) initially, with a long-term goal of >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 (Cano, 2009), and parenteral interventions. Intradialytic parenteral nutrition (IDPN) should be reserved for patients who cannot tolerate or do not respond to oral intake or use of a feeding tube. (Cano, 2006). Adjuvant therapies that can be considered include anabolic hormones, appetite stimulants, anti-inflammatory interventions, and exercise.

C. Oral supplements. Oral amino acid supplementation, given either during hemodialysis (Kalantar-Zadah, 2013) or two to three times a day (preferably 1 hour after main meals), has been shown to improve whole-body protein metabolism in the short term and SGA, serum albumin, and serum prealbumin in the long term (Stratton, 2005) as well as patient outcomes (Weiner, 2014).

A number of different enteral formulas specifically formulated for maintenance dialysis patients are available. Other considerations in the choice of oral nutritional supplements include cost, palatability, and lactose tolerance.

D. Intradialytic total parenteral nutrition (IDPN) in hemodialysis patients

1. Indications and benefits. IDPN is indicated in the adequately dialyzed hemodialysis patient with PEW who is unable to ingest or absorb sufficient food via the gastrointestinal tract. IDPN promotes protein anabolism in the acute setting. There are conflicting reports of the benefits of IDPN; it appears that there is a correlation between the response to nutritional supplementation and the severity of PEW and the amount of nutrients received. (Cano, 2007).

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 also 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 31.5.

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

TABLE 31.5 Composition of a "typical" solution for intradialytic parenteral nutrition

Component	Amount
50% dextrose (D-glucose)	125 g (250 mL) 42.5 g (500 mL) 50 g (250 mL)
8.5% crystalline amino acids (essential and nonessential)	Sodium, phosphate, potassium sulfate, chloride, and magnesium with amount per IDPN bag adjusted for serum electrolyte levels See text and Table 31.2 Adjusted/blood glucose levels 425 kcal/treatment 500 kcal/treatment 925 kcal/treatment
20% lipids	
Electrolytes:	
Vitamins	
Insulin, regular	
Caloric content	
50% dextrose	
20% lipid emulsion	
Total	

IDPN, intradialytic parenteral nutrition.

suddenly discontinued. Patients should consume some carbohydrate 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 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 serum urea nitrogen level.

E. Total parenteral nutrition (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 31.6.

1. Carbohydrates. Approximately 50%–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

TABLE 31.6 Composition of "typical" total parenteral nutrition 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 Chloride Potassium Acetate Calcium Phosphorus Magnesium Iron Vitamins	See text See text <35 mmol/d 35–40 mmol/d 5 mmol/d 5–10 mmol/d 2–4 mmol/d 2 mg/d See text and Table 31.2
Caloric content	
Solution	
Administration Rate:	40 mL/hr or 960 mL/d 762 kcal/d 640 kcal/d 1,402 kcal/d
70% dextrose	762 kcal/d
20% lipid emulsion (LE)	352 kcal/d
Total with 20% LE	1,114 kcal/d
70% dextrose	60 mL/hr or 1,440 mL/d 1,142 kcal/d 960 kcal/d 2,102 kcal/d 1,142 kcal/d
10% lipidemulsion(LE)	528 kcal/d
Total with 10% LE	1,670 kcal/d

[a]The specific amount of electrolytes given should be modified on the basis of 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 total parenteral nutrition sodium level of about 140 mmol/L will prevent hyponatremia, but requires either daily dialysis or continuous renal replacement therapy for adequate volume control.

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 dialysis patients, 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 renal replacement therapy (CRRT) or intermittent hemodialysis (IHD) is being done. With CRRT, the TPN solutions, as well as most other infusates, should have a sodium level close to 140 mM. With IHD, 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 maintenance dialysis patients (Table 31.2).

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.

F. Intraperitoneal infusion of amino acids in peritoneal dialysis patients

1. Indications and benefits. Amino acid dialysate should be considered in peritoneal dialysis patients with PEW who are unable to tolerate or are not suitable for oral nutritional supplements. The evidence of benefit of amino acid dialysate is conflicting; benefit is more likely when significant hypoalbuminemia is present. (Jones 1998)

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 continuous ambulatory peritoneal dialysis (CAPD) patients or as the long daytime dwell in continuous cycling peritoneal dialysis patients 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.

G. Adjuvant therapies and exercise. Other therapies that can be considered include growth hormone, anabolic steroids, exercise, appetite stimulants, and anti-inflammatory interventions. Evidence of the effectiveness of these interventions is weak.

In maintenance dialysis patients, endurance exercise has been associated with an improvement in the rate of glucose disappearance and a reduction in fasting plasma insulin levels; in addition, with exercise, plasma triglyceride values decrease, and high-density lipoprotein (HDL) cholesterol concentra- tions increase. Other benefits of exercise include an increase in muscle size and strength, and improvement in endurance.

References and Suggested Readings

AroraSK, McFarlane SI. The case for lowcarbohydrate diets in diabetes managemen
Nutr Metab. (Lond). 2005;2:16.

Burrowes JD, et al. Effects of dietary intake, appetite, and eating habits on dialysis and non-dialysis treatment days in hemodialysis patients: cross-sectional results from the HEMO study. J Ren Nutr. 2003;13:191–198.

Caluwé R, et al. Vitamin K2 supplementation in haemodialysis patients: a randomize
dose-finding study. Nephrol Dial Transplant. 2014;29:1385-90.

Cano N, et al. ESPEN guidelines on enteral nutrition: adult renal failure. Clin Nutr
2006;25:295–310.

Cano NJ, et al. Intradialytic parenteral nutrition does not improve survival in malnour-
ished hemodialysis patients: a 2-year multicenter, prospective, randomized study
J Am Soc Nephrol 2007;18:2583–2591.

Cano NJ, et al. ESPEN Guidelines on Parenteral Nutrition: adult renal failure. Clin Nu
2009;28:401–414.

Carrero JJ, et al. Etiology of the protein-energy wasting syndrome in chronic kidney disease: a consensus statement From the International Society of Renal Nutrition and Metabolism (ISRNM). J Ren Nutr. 2013;23:77–90.

Chowdhury R, et al. Association of dietary, circulating, and supplement fatty acids wi
onary risk: a systematic review and meta-analysis. Ann Intern Med. 2014;160:39

Chumlea WC, et al; Nutritional status assessed from anthropometric measures in the
HEMO study. J Ren Nutr. 2003;13:31–38.

Churchill DN, Taylor W, Keshaviah PR. Adequacy of dialysis and nutrition in con-
tinuous peritoneal dialysis: association with clinical outcomes. Canada-USA (CANUSA) Peritoneal Dialysis Study Group. J Am Soc Nephrol. 1996;7:198–207

Di Filippo S, et al. Reduction in urea distribution volume over time in clinically st
dialysis patients. Kidney Int. 2006;69:754–759.

Di Iorio BR, et al. A systematic evaluation of bioelectrical impedance measurement
after hemodialysis session. Kidney Int. 2004;65:2435–2440.

Dombros N, et al. for the EBPG Expert Group on Peritoneal Dialysis. European best practice guidelines for peritoneal dialysis. 8 Nutrition in peritoneal dialysis. Nephrol Dial Transplant. 2005;20(suppl 9):ix28–ix33.

Duerksen DR, et al. The validity and reproducibility of clinical assessment of nutri-
tional status in the elderly. Nutrition. 2000;16:740–744.

Ghandour H, et al. Distribution of plasma folate forms in hemodialysis patients receiv
ing high daily doses of L-folinic or folic acid. Kidney Int. 2002;62:2246–2249.

Gracia-Iguacel C, et al. Subclinical versus overt obesity in dialysis patients: more tha
meets the eye. Nephrol Dial Transplant. 2013;28(suppl 4):iv175–iv181.

Himmelfarb J, et al. Provision of antioxidant therapy in hemodialysis (PATH): a
randomized clinical trial. J Am Soc Nephrol. 2014;25:623–633.

Ikizler TA, Cano NJ, Franch H et al. Prevention and treatment of protein energy wast
ing in chronic kidney disease patients: a consensus statement by the Internationa
Society of Renal Nutrition and Metabolism. Kidney Int. 2013;84:1096–1107.

Institute of Medicine. Dietary reference intakes: water, potassium, sodium, chloride, and
sulfate. Washington, DC, National Academy Press, 2004.

Jones M, et al. Treatment of malnutrition with 1.1% amino acid peritoneal dialysis so
tion: results of a multicenter outpatient study. Am J Kidney Dis. 1998;32:761–769

Kaizu Y, et al. Association between inflammatory mediators and muscle mass in long
term hemodialysis patients. Am J Kidney Dis. 2003;42:295–302.

Kalantar-Zadeh K, et al. A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance hemodialysis patients. Am J Kidney Dis. 2001;38:1251–1263.

Kalantar-Zadeh K, et al. Food intake characteristics of hemodialysis patients as obtained by food frequency questionnaire. J Ren Nutr. 2002;12:17–31.
Kalantar-Zadeh K, et al. Appetite and inflammation, nutrition, anemia, and clinical outcome in hemodialysis patients. Am J Clin Nutr. 2004;80:299–307.
Kalantar-Zadeh K, et al. Understanding sources of dietary phosphorus in the treatment of patients with chronic kidney disease. Clin J Am Soc Nephrol. 2010;5: 519–530.
Kalantar-Zadeh K, Ikizler TA. Let them eat during dialysis: an overlooked opportunity to improve outcomes in maintenance hemodialysis patients. J Ren Nutr. 2013;23:157–163.
Kasama R, et al. Vitamin B6 and hemodialysis: the impact of high flux/high-efficiency dialysis and review of the literature. Am J Kidney Dis. 1996;8:680–686.
Kaysen GA. The microinflammatory state in uremia: causes and potential consequences. J Am Soc Nephrol. 2001;12:1549–1557.
Kaysen GA, et al; and the FHN Trial Group. The effect of frequent hemodialysis on nutrition and body composition: frequent Hemodialysis Network Trial. Kidney Int. 2012;82:90–99.
Kobayashi I, et al. Geriatric Nutritional Risk Index, a simplified nutritional screening index, is a significant predictor of mortality in chronic dialysis patients. Nephrol Dial Transplant. 2010;25:3361–3365.
Kogirima M, et al. Low resting energy expenditure in middle-aged and elderly hemodialysis patients with poor nutritional status. J Med Invest. 2006;53:34–41.
Kopple JD. National kidney foundation K/DOQI clinical practice guidelines for nutrition in chronic renal failure. Am J Kidney Dis. 2001; 37(suppl 2):S66–S70.
Kramer HJ, et al. Increasing body mass index and obesity in the incident ESRD population. J Am Soc Nephrol. 2006;17:1453–1459.
Krueger T, et al. Vitamin K1 to slow vascular calcification in haemodialysis patients (VitaVasK trial): a rationale and study protocol. Nephrol Dial Transplant. 2014;29:1633-1638.
McCann L, et al. Effect of intradialytic parenteral nutrition on delivered Kt/V. Am J Kidney Dis. 1999;33:1131–1135.
Mushnick R, et al. Relationship of bioelectrical impedance parameters to nutrition and survival in peritoneal dialysis patients. Kidney Int. 2003;87(suppl):S53–S56.
National Kidney Foundation. K/DOQI clinical practice guidelines for nutrition in chronic renal failure. New York, NY: National Kidney Foundation, 2001.
Pupim LB, Cuppari L, Ikizler TA. Nutrition and metabolism in kidney disease. Semin Nephrol. 2006;26:134–157.
Rocco MV, et al; for the HEMO Study Group. The effect of dialysis dose and membrane flux on nutritional parameters in hemodialysis patients: results of the HEMO study. Kidney Int. 2004;65:2321–2334.
Rocco MV. Does more frequent hemodialysis provide dietary freedom? J Ren Nutr. 2013;23:259–262.
Siew ED, Ikizler TA. Insulin resistance and protein energy metabolism in patients with advanced chronic kidney disease. Semin Dial. 2010;23:378–382.
Soop M, et al. Energy expenditure in postoperative multiple organ failure with acute renal failure. Clin Nephrol. 1989;31:139–145.
Stein A, et al. Role of an improvement in acid-base status and nutrition in CAPD patients. Kidney Int. 1997;52:1089–1095.
Stenvinkel P, Zoccali C, Ikizler TA. Obesity in CKD—What Should Nephrologists Know? J Am Soc Nephrol. 2013;24:1727–1736.
Stratton RJ, et al. Multinutrient oral supplements and tube feeding in maintenance dialysis: a systematic review and meta-analysis. Am J Kidney Dis. 2005;46:387–405
van Biesen W, et al. A multicentric, international matched pair analysis of body composition in peritoneal dialysis versus haemodialysis patients. Nephrol Dial Transplant. 2013;28:2620–2628.
Wang AY, et al. Important factors other than dialysis adequacy associated with inadequate dietary protein and energy intakes in patients receiving maintenance peritoneal dialysis. Am J Clin Nutr. 2003;77:834–841.
Wang W, et al. Outcomes associated with intradialytic oral nutritional supplements in patients undergoing maintenance hemodialysis: a quality improvement report. Am J Kidney Dis. 2012;60:591–600.
Weiner DE. Oral intradialytic nutritional supplement use and mortality in hemodialysis patients. Am J Kidney Dis. 2014;63:276–285.

32 Diabetes

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More than 40% of all new patients starting dialysis in the United States are diabetic. Provision of maintenance dialysis for this group can be a challenging task. Morbidity and mortality are substantially higher in diabetic patients maintained on dialysis than in their non- diabetic counterparts, with cardiovascular disease and infection being the leading causes of death. In the United States, the 3-year survival rate of diabetic patients maintained on dialysis is only about 50% (USRDS, 2013).

I. WHEN TO INITIATE DIALYSIS. Early referral to nephrologists of diabetic patients with renal failure reportedly improves outcomes. Previous guidelines emphasized initiation of dialysis prior to the appearance of frank uremic manifestations (at an estimated glomerular filtration rate [eGFR] of ≤15 mL/min per 1.73 m2). However, a recent randomized controlled trial that examined mortality versus time of dialysis initiation, the IDEAL study, found no difference in survival between early or late initiation of dialysis, and in that study, approximately one-third of the participants were diabetic (Cooper, 2010).

II. HEMODIALYSIS VERSUS PERITONEAL DIALYSIS. The potential problems with each form of dialysis are listed in Table 32.1. Long-term peritoneal dialysis (PD) in diabetic patients may complicate control of blood sugar 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 PD patients have difficulty ingesting the higher recommended amount of protein for PD patients (1.2 g/kg daily). On the other hand, the incidence and severity of hypoglycemic episodes is reduced in continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD) compared with hemodialysis (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 diabetic and nondiabetic patients on PD. Administration of insulin intraperitoneally appears to increase slightly the risk of peritonitis in PD

TABLE 32.1 Dialysis Modalities for Diabetics

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 session Predialysis hyperkalemia Prone to hypoglycemia
CAPD	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 similar to those in nondiabetic dialysis patients) Protein loss to dialysate Increased intra-abdominal pressure effects (hernias, fluid leaks, etc.) Often needs helper (e.g., some blind patients) Protein loss to dialysate
APD	Good cardiovascular tolerance No need for arteriovenous access Good control of serum potassium Lower risk of hypoglycemia Good for blind diabetics Peritonitis risk slightly less than for CAPD	

CAPD, continuous ambulatory peritoneal dialysis; APD, automated peritoneal dialysis.

patients and, though appealing on physiologic grounds, is now less commonly employed. With HD, coexisting blood vessel disease often hinders creation of an adequate, long-lasting vascular access. The survival rates of both arteriovenous (AV) fistulas and grafts are substantially reduced in diabetic compared with nondiabetic patients. A small fraction of diabetic patients develop severe hand ischemia after creation of an ipsilateral AV fistula, which can lead to gangrene and need for amputation; prompt ligation of the fistula is indicated in such instances. Because of autonomic nervous system dysfunction or cardiac diastolic dysfunction, diabetic patients are at increased risk for hypotension during HD. Problems with vascular access and increased risk of hypotension may cause diabetic patients to receive a lesser amount of dialysis (in terms of fractional urea clearance [Kt/V]) than their nondiabetic counterparts.

Lower extremity amputations are frequent in diabetic patients 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 diabetic patients 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 diabetics. A number of devices are available to help visually impaired patients connect the dialysis solution container to the peritoneal transfer set (see Chapter 22). APD is a better therapeutic choice for blind diabetic patients because many APD schedules require the performance of only one "on" and one "off" procedure daily.

Earlier reports from the U.S. Renal Data System suggested that mortality is higher in diabetic patients, and especially diabetic 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 was actually higher with HD than PD among younger diabetics with no comorbidity but lower with HD in older diabetics, especially if they had comorbidities (Vonesh, 2004). These results are undoubtedly also 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, diabetic patients 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, diabetic dialysis patients often require early and intensive nutritional support.

A. Routine dietary prescription. The diets advocated for nondiabetic HD and PD patients in Chapter 31 also apply to patients with diabetes. In an anuric diabetic patient being treated with HD, the stringent sodium, potassium, and fluid restrictions described in Chapter 31 should be applied. Special effort should be made to limit intake of simple sugars and saturated fats.

1. Carbohydrates percentage. The general recommendation for a diabetic diet is for 50%–60% of intake to be carbohydrates, with some interest in using an even lower carbohydrate diet in diabetic patients (Arora, 2005). In patients undergoing PD, the glucose calories supplied from the PD regimen (usually around 400 kcal) 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). Levelsof AGEsare increasedin food that has been cooked at high temperature,especiallyif food contains a high proportion of fat. Dietary AGE ingestion has been linked to adverse lipid profiles and inflammatory mark- ers in diabetic patients (Uribarri, 2005) and to increased serum levels of AGEs in end-stage kidney disease (ESKD) patients, with perhaps increased risk of access thrombosis. Any reason to additionally restrict food in ESKD patients should be done with caution, given the high prevalence of malnutrition; however, some attention to food prepa- ration with a focus on minimizing formation of AGEs (avoidance of deep frying, extensive heating) might be a consideration.

B. Diabetic gastroparesis and enteropathy. The diagnosis of diabetic gastroparesis is often made on the basis of symptoms of nau- sea, vomiting, early satiety, and postprandial fullness. Since other treatable conditions can have similar symptoms, an esophagogastroduodenoscopy should be performed before symptoms are ascribed to gastroparesis alone. The traditional "gold standard" to establish the diagnosis of gastroparesis is scintigraphic measurement of gastric emptying. However, a drawback is that 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 13C-labeled acetate and octanoic acid breath tests. 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 six times per day) feedings may improve symptoms. The pharmacologic treatment of gastroparesis in diabetic persons on dialysis is unsatisfactory. Metoclopramide given in a small starting dose (5 mg before meals) with small increments until results are seen is usually the first drug prescribed. This drug is associated with a high incidence of extrapyramidal complications in dialysis patients, 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 (e.g., 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 CKD. In uremic patients (both diabetic and nondiabetic), insulin secretion by the β cells of the pancreas is reduced, and the responsiveness of peripheral tissues (e.g., muscle) to insulin is depressed; that is, there is increased insulin resistance. Insulin resistance occurs in almost all uremic patients and results in hyperglycemia. The literature suggests that hepatic glucose production and uptake are normal in uremia and that 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 6–8 units of insulin are degraded by the kidney each day, roughly 25% of the daily production of insulin by the pancreas. Renal metabo- lism is enhanced in diabetic subjects receiving exogenous in- sulin, 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 de- cline in hepatic metabolism. All of these abnormalities are only partially corrected after institution of maintenance dialysis therapy.

1. Abnormal glucose tolerance tests in all dialysis patients. The glucose tolerance test cannot be used to diagnose diabetes in dialysis patients because the rise in serum glucose concentration will be greater and more prolonged than normal in all dialysis patients as a result of uremia-induced insulin resistance. However, fasting serum glucose concentrations are normal in nondiabetic HD patients; a high level suggests the presence of diabetes. In PD patients, a true fasting state is never achieved owing to 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 CAPD patients using icodextrin, serum glucose values may be spuriously overestimated by auto-analyzers that use the glucose dehydrogenase method of sample analysis (Tsai, 2010).
2. Increased sensitivity to insulin. In diabetic dialysis patients being treated with exogenous insulin, the importance of reduced insulin catabolism overrides the impact of insulin resistance; when exogenous insulin is adminis- tered, its effect may be intensified and prolonged. Thus,

smaller-than-usual doses should be given. Bolus administration of moderately large intravenous doses (e.g., 15 units of regular insulin), even when ketosis is present, can result in severe hypoglycemia. Hypoglycemia can occur also after administration of the longer-acting insulins, such as isophane insulin (NPH) and insulin glargine.

3. Hyperglycemia. The clinical presentation of hyperglycemia is modified when renal function is absent. The absence of the "safety valve" effect of glycosuria may result in the development of severe hyperglycemia (serum glucose level >1,000 mg/dL [56 mmol/L]). 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 dialysis patients (Al-Kudsi, 1982). However, manifestations can include thirst, weight gain, and, on occasion, pulmonary edema or coma (Tzamaloukas, 2004). Diabetic ketoacidosis, frequently accompanied by severe hyperkalemia and coma, can develop in insulin-dependent dialysis patients. 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 of the 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 2 units/hr) with close clinical monitoring and measurement of serum glucose and po- tassium concentrations at 2- to 3-hour intervals. 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.

4. Hypoglycemia. Avoidance of hypoglycemia is often the rate-limiting step in obtaining good glucose control. Treat- ment 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 diabetic patients, HD solution should always contain about 90 mg/dL (5 mM) glucose; if glucose is not added,

severe hypoglycemia during or soon after the HD session can result (Burmeister, 2012). Higher (200 mg/dL, 11 mM) dialysate glucose levels may increase the frequency of hyperglycemia (Raimann, 2012), and may not protect against hypoglycemic episodes better than the 90 mg/dL option.

B. Insulin therapy. Achieving and maintaining reasonable glucose control while avoiding hypoglycemia is the challenge in managing patients with diabetes on dialysis. Reasonable glycemic control in diabetic patients 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 HbA1c between 7% and 8%. Several large studies have found no significant correlation between glycemic control and survival, yet a much higher risk of hypoglycemia with stricter glycemic control (Williams, 2010). The HbA1c target that is associated with the best outcome in dialysis patients has not been established (KDOQI clinical practice guidelines, 2005). It has been suggested that measurement of glycated albumin more accurately assesses glycemic control in this population as it is not affected by the Hb level, but this test is not readily available. Another issue with HbA1c is that it can be affected (reduced) by administration of ESAs and iron (Ng, 2010).

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 PD patients, AGE deposition in the peritoneal membrane is associated with an increase in permeability and excessive protein losses in the dialysate (Nakamoto, 2002).

1. Insulin regimens. The following dose recommendations have been made for insulin dosage in the setting of kidney disease (Snyder, 2004):
   a. No dose adjustment is required if the GFR is above 50 mL/min .
   b. Reduce the insulin dose by 25% when the GFR is 10–50 mL/min .
   c. Reduce the dose by 50% when the GFR is less than 10 mL/min .
2. 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 3 daily meals, or 3–4 units rapid-acting insulin per meal.

3. 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.

4. Other insulin combinations. New basal and rapid-acting insulin analogs are expected to be available for clinical use in 2015, but have not been studied in patients with ESKD (Danne, 2011).

5. 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 his or her glucose values before each meal).

6. 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. With both of the above regimens, a reasonable "correction dose" of insulin would be 1 extra unit of daily insulin for every 50 mg/dL glucose above target (for example the target level might be 150 mg/dL) for that patient.

7. Effect of hemodialysis 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 insu- lin requirement in any given patient may change, depend- ing 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 HD patients, several different insulin regimens can be used to achieve glycemic control. The glargine- and NPH-based regimens described above 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 dialysis patients.

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. 8. Effect of peritoneal dialysis 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-percent dextrose (glu- cose monohydrate, 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 PD patients less insulin can be re- quired than anticipated owing to decreased carbohydrate in- take 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 sugar 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 (Tsai, 2010; Firanek, 2013). 9. Use of an insulin infusion pump. In fragile type 1 diabetic pa- tients where frequent hypoglycemia is a problem, continu- ous subcutaneous insulin injection can be of benefit. In such cases, 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).

C. Oral hypoglycemic agents and noninsulin injectable agents. These agents are useful adjuncts in the treatment of diabetic pa- tients and are used by many nephrologists. Suggested agents and appropriate doses are listed in Table 32.2. In a 2010 survey of U.S. dialysis patients with diabetes, 80% were recorded as receiving some form of glycemic therapy, and of these, 49/80 were being managed with insulin alone, 8/80 with insulin plus some form of oral medication, and 23/80 with an oral agent only. Of the oral agents being used in 2010, the great major- ity were either sulfonylureas or thiazolidinediones, although this may change as more information and experience with the newer agents become available.

1. Sulfonylureas. Sulfonylureas are insulin secretagogues that bind to the sulfonylurea receptor, a part of the potassium channel, on pancreatic β cells. They cause potassium chan- nel closure with subsequent membrane depolarization, which, in turn, causes opening of voltage-gated calcium channels. This allows for a sudden increase in intracellu- lar calcium, which causes preformed insulin to be released from intracellular secretory granules. First generation sulfonylureas (acetohexamide, chlorpropamide, tolaza- mide, and tolbutamide) are almost never used anymore. The second generation drugs (glipizide, glyburide, and glimepiride) are still fairly widely employed. All the sec- ond generation sulfonylureas undergo hepatic metabolism with a variable percentage of renal excretion (Spiller, 2006). Glyburide and glimepiride have active metabolites with relatively long half-lives that are renally excreted and so are not recommended for end-stage kidney disease (ESKD) pa- tients. The metabolite of **glipizide** has little or no hypoglyc- emic activity and a short half-life of 2–4 hours. Therefore, even though its renal excretion is high (80%–85%), glipizide is the sulfonylurea of choice in dialysis patients. However, sulfonylureas as a class show a relatively high incidence of hypoglycemia, plus many drugs frequently used in di- alysis patients can either antagonize (phenytoin, nicotinic acid, diuretics) or enhance (salicylates, warfarin, ethanol) the hypoglycemic action of sulfonylureas. Another reason that sulfonylureas are not optimal in the ESKD population is that their mechanism of action (facilitating insulin re- lease) presupposes that the individual being treated is still producing some endogenous insulin. In people with type 2 diabetes, endogenous insulin, assessed by C-peptide mea- surements, was highest in people with recently diagnosed disease and progressively decreased in people as the dura- tion 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 insu- lin and so will be unable to respond to sulfonylureas.

2. Metformin. Metformin, a member of the biguanide class, is perhaps the most widely used oral agent to treat type 2

TABLE 32.2 Agents for Diabetes Mellitus in Chronic Kidney Disease

Drug	Usual Nonuremic Dose	Dialysis Patient Dose (% of Nonuremic Dose)
Insulins		
Short-acting		
Regular	0.2–1 units/kg/d SC b.i.d.–q.i.d.	Decrease dose (25%–50%)
Lispro	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 (not defined)
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)
Sulfonylureas		
Glipizide	2.5–20 mg PO q24h–b.i.d.	2.5–10 mg PO q24h–b.i.d. (50%)
Glimeperide	1–8 mg PO q24h	1–4 mg PO q24h (50%)
Tolbutamide	250–3,000 mg PO q24h	Same (100%)
Glyburide	1.25–10 mg PO q24h	Avoid in renal failure
Thiazolidinedionesa		
Rosiglitazone	4–8 mg PO q24h–b.i.d.	Same (100%)
Pioglitazone	15–30 mg PO q24h	Same (100%)
a-Glucosidase inhibitors		
Acarbose	50–100 mg PO t.i.d.	Not recommended in renal failure
Miglitol	50–100 mg PO t.i.d.	Not recommended 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	850–2,550 mg PO q24h–b.i.d.	Avoid in renal failure
Amylin analogs		
Pramlintide	30–120 mcg SC q.a.c.	Same (100%). No data on dialysis patients
SGLT-2 inhibitor		
Canagliflozin	100 mg–300 mg q24h	If eGFR 45 to <60 mL/min/1.73 m2, 100 mg Avoid if eGFR <45 mL/min/1.73 m2

(continued)

TABLE 32.2 Agents for Diabetes Mellitus in Chronic Kidney Disease (continued)

Drug	Usual Nonuremic Dose	Dialysis Patient Dose (% of Nonuremic Dose)
DPP-4 inhibitors		
Sitagliptin	100 mg q24h	If eGFR ≥30 mL/min/1.73 m2 and <50 mL/min/1.73 m2, 50 mg (50%) If eGFR <30 mL/min/1.73 m2, 25 mg (25%)
Saxagliptin	2.5–5 mg q24h	If eGFR <50 L/min/1.73 m2, 2.5 mg (50%)
Linagliptin	5 mg q24h	Same
Alogliptin	25 mg q24h	If eGFR ≥30 mL/min/1.73 m2 and <50 mL/min/1.73 m2, 12.5 mg (50%) If eGFR <30 mL/min/1.73 m2, 6.25 mg (25%)
GLP-1 receptor agonists		
Exenatide	2 mg weekly SC Up to 10 mcg b.i.d. SC	Avoid if eGFR <30 mL/min/1.73 m2
Liraglutide	Up to 1.8 mg q24h SC	Limited experience with advanced renal disease; caution advised

[a]May cause fluid retention in chronic kidney disease patients not on dialysis.
SC, subcutaneously; b.i.d., two times per day; q.i.d., four times per day; q24h, daily; PO, by mouth; t.i.d., three times per day; q.a.c., before meals.

diabetes in patients with normal renal function and has several distinct advantages. Metformin use is associated with a very low incidence of hypoglycemia, weight loss instead of weight gain, and 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, but patients with markedly reduced renal function are at increased risk. Metformin is not metabolized, and 90% is excreted as the active drug by the kidneys (Spiller, 2006). Plasma metformin levels are thus substantially higher in patients with reduced creatinine clearance (Lipska, 2011). There is controversy r egarding the safety of use in patients with nondialysis CKD; in the United

States, the drug label warns against use of metformin when serum creatinine is greater than 1.5 mg/dL (130 mcmol/L) in males or 1.4 mg/dL (124 mcmol/L) in females, whereas there are studies suggesting that metformin can be used with relative safety down to a GFR of 45 mL/min. Metfor- min should not be used in dialysis patients.

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 (Spiller, 2006; Reilly, 2010). 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 (Spiller, 2006; Reilly, 2010). Neither acarbose nor miglitol has been well studied in patients in whom eGFR is less than 25 mL/min per 1.73 m2, and, in general, their use is not recommended in dialysis patients.

4. Peroxisome proliferator-activated receptor (PPAR) agonists. 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 glu- cose production. They may also have beneficial anti-inflam- matory, vascular, and metabolic (hypolipidemic) effects.

   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 in 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, 2007). This restriction was partially lifted by the U.S. Food and Drug Administration (FDA) in November of 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, 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 glitazones 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 sulfonylurea receptor and functions in a manner similar to the sulfonylureas, but it has an additional β cell binding site and thus a different binding profile (Hatorp, 2002). It differs from the sulfonylureas in several ways. First, it has a much shorter duration of action with a half-life of 1–1.5 hours with somewhat less hypoglycemic risk than SUs. Second, it is eliminated almost entirely by he- patic 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 pharmacokinet- ics (Marbury, 2000; Schumacher, 2001; Hatorp, 2002). 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 hypo- glycemia, and repaglinide is not contraindicated in people with renal disease but should be used with caution, starting at a low dose (0.5 mg) and titrating upward slowly. Stud- ies were not conducted in patients with eGFR <20 mL/min per 1.73 m2 or in patients with renal failure requiring di- alysis. Like the SUs, it 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 (Spiller, 2006; Reilly, 2010). Use of nateglinide in patients on dialysis should thus be avoided or done with the greatest caution.

6. Glucagon-like peptide-1(GLP-1) receptor agonists. There are two glucagon-like peptide-1 (GLP-1) receptor agonists available, exenatide (which comes in both twice-per-day and once-per-week formulations) and liraglutide. **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. GLP-1 is rapidly degraded by dipeptidyl peptidase 4 (DPP-4). However, both exenatide and liraglutide are degradation-resistant and undergo little systemic metabolism.

Exenatide is excreted mainly by the kidneys. The half-life increases with decreasing renal function. Exenatide was generally well tolerated in the mild and moderate renal insufficiency without dose adjustment, but not in subjects with ESKD due to nausea and vomiting (Linnebjerg, 2007). Its use is not recommended for those with eGFR <30 mL/min per 1.73 m2. Caution is also advised for people who have received kidney transplants. Exenatide caused an increased incidence in thyroid C-cell tumors at clinically relevant exposures in rats compared with controls. It is unknown whether it causes thyroid C-cell tumors in humans, including medullary thyroid carcinoma; nonetheless, it is contraindicated in patients with a personal or family his- tory of medullary thyroid carcinoma and in patients with multiple endocrine neoplasia syndrome type 2. Pancreati- tis has been identified in postmarketing studies as a pos- sible adverse consequence of exenatide use.

In contrast to exenatide, only about 6% of **liraglutide** (as metabolites) is excreted by the kidneys; the pharmacokinetics of the drug is little altered by kidney disease (Jacobsen, 2009). However, there is increased incidence of nausea in those with eGFR <60 mL/min per 1.73 m2, though the number of people studied was small (Davidson, 2011). No dose adjustment is required in US labeling, but it should be used with caution in people with advanced kidney impairment because of limited experience. Liraglutide carries the same warnings as exenatide with regard to medullary thyroid cancer, multiple endocrine neoplasia syndrome type 2, and pancreatitis.

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 glucagon-like peptide 1 (GLP-1), a gut hormone that stimu- lates insulin, suppresses glucagon, delays gastric emptying, and decreases appetite.

Approximately 75%–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 >50 mL/min per 1.73 m2. This dose should

be reduced to 50 mg if eGFR falls below 50 mL/min per 1.73 m2, and to 25 mg daily if eGFR is below 30 mL/min per 1.73 m2 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 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 per 1.73 m,2 but 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 concentra- tions. Its 5-mg daily dose does not need to be adjusted in renal disease (Graefe-Mody, 2011). However, experience in people with advanced renal disease is limited.

About 10%–20% of **alogliptin** is metabolized by the liver to compounds with little pharmacological 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/day) for patients with eGFR between 30 and 50 mL/min per 1.73 m2, and by three-quarters (to 6.25 mg/day) in those with eGFR < 30 mL/min per 1.73 m2 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. The U.S. FDA and the European Medicines Agency (EMA) working in parallel reviewed nonclinical toxicology studies, clinical trial data, and epidemiologic data relating to these medications. Both agencies agreed and published that assertions concerning a causal association between incretin-based medications and pancreatitis or pancreatic cancer were inconsistent with their review (Egan, 2014).

8. Sodium glucose co-transporter 2 inhibitor. Canagliflozin and dapaglifozin are sodium glucose co-transporter 2 inhibitors. These medications lower the renal threshold for glucose, cause an osmotic diuresis by increasing urinary glucose excretion, and thereby decrease plasma glucose in hyperglycemic patients. Because of their urine-dependent mechanism of action, these medications are not effective in patients with severe renal impairment.
9. Pramlintide. Pramlintide is a synthetic analog of human amylin. Amylin is a naturally occurring hormone synthesized by pancreatic β cells that is co-secreted 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 per 1.73 m2. There are few or no data on its use in patients on dialysis.

V. HYPERKALEMIA. Hyperkalemia occurs commonly in diabetic patients 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 diabetic patients on maintenance PD. Treatment in diabetic patients 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 incidenceof hypertension is high in diabeticdialysis patients. Control ofhigh blood pressure is very important for the prevention of cardiovascular sequelae and deterioration of vision. Most diabetics 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 diabetic dialysis patients is similar to that for all such patients, and is discussed in detail in Chapter 33.

B. Coronary artery disease. Despite the increased prevalence of diabetic patients, outcomes of coronary artery bypass grafting have continuously improved in dialysis patients. Nonetheless, mortality rates remain almost threefold higher compared with non-ESKD patients (Parikh, 2010). See Chapter 38.

C. Peripheral vascular disease. Diabetic patients 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 diabetic dialysis patients than in 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 diabetic dialysis patients is unknown, and the use of aspirin theoretically increases the risk of intraocular hemorrhage. Coumarin anticoagulants also increase bleeding risk in this population more than in nonuremic diabetic patients and are associated with additional risks of vascular calcification and calciphylaxis.

VIII. EYE PROBLEMS IN DIABETICS ON DIALYSIS

A. Diabetic retinopathy. Retinopathy is present in almost all type 1 diabetic patients with ESKD. In such patients, another cause of kidney disease should be sought if the retinal examination (including fluorescein angiography) is normal. The situation in type 2 diabetic patients 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 Kimmelsteil–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).

Hypertension, which is also present in the majority of dialysis patients, accelerates 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 is an indication for laser treatment, which decreases the risk of detachment and the need for oxygen (by destroying nonessential parts of the retina). Vitreous hemorrhages from proliferative retinopathy obstruct the path of light and may lead to retinal detachment and blindness. Vitrectomy and other microsurgi- cal techniques (removal of retinal membranes, reattachment of retina) can improve vision in one-third to one-half of patients. Evidence is accumulating for a role for inhibitors of vascular endothelial growth factor (VEGF) in this condition (Osaadon, 2014). Active collaboration with an ophthalmologist skilled in laser photocoagulation is necessary. Most diabetic patients with ESKD have retinopathy by the time dialysis is initiated. Additional laser therapy and regular screening for glaucoma are vital components of comprehensive care for diabetic dialysis patients.

B. Other eye problems. Diabetic patients on dialysis are subject to other eye complications common to all patients on dialysis. **Conjunctivitis and keratitis** are treated with ophthal- mic preparations of antibiotic, antifungal, or antiviral agents in the usual doses. The dose of antibiotics given system- atically should be adjusted for dialysis. **Band keratopathy** (corneal–conjunctival calcification) may afflict both diabetic and nondiabetic dialysis patients 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 dialysis patients are treated in the same way as in the general population. Proactive eye sur- veillance and intervention have been effective in sustaining at least ambulatory vision in nearly all diabetic dialysis patients.

IX. IMPOTENCE. Impotence is common in diabetic dialysis patients. Autonomic neuropathy and peripheral vascular disease associated with diabetes are operative, as are the usual uremic causes.

X. REFERRAL FOR TRANSPLANTATION. In diabetic patients in whom no contraindication to transplantation exists, renal transplantation is the preferred method of managing ESKD because of improved survival with transplantation (approximately 80% 3-year survival vs. 50% 3-year survival in patients maintained on dialysis). Among predialysis diabetic patients with chronic kidney disease 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 diabetic dialysis patients 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).

XI. BONE DISEASE. Adynamic bone disease is common among diabetic patients with ESKD (see Chapter 36).

XII. ANEMIA. The response to erythropoietin is satisfactory for anemic diabetics treated with either HD or PD (see Chapter 34).

XIII. CONCLUSION. The care of diabetic patients with ESKD is a demanding task. In addition to members of the dialysis team, representatives of other specialties (e.g., vascular surgery, podiatry, ophthalmology, neurology, transplantation surgery) are needed. The existence of a diabetic team, with all of 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.

References and Suggested Readings

AbeM,et al. Clinical effectiveness and safety evaluation of long-term pioglitazone treatment for erythropoietin responsiveness and insulin resistance in type 2 diabetic patients on hemodialysis. Expert Opin Pharmacother. 2010;11:1611–1620.

Adamis AP, et al. Changes in retinal neovascularization after pegaptanib (Macugen) therapy in diabetic individuals. Ophthalmology. 2006;113:23–28.

Agrawal A, Sautter M, Jones N. Effects of rosiglitazone maleate when added to a sulfonylurea regimen in patients with type 2 diabetes mellitus and mild to moderate renal impairment: a post hoc analysis. Clin Therap. 2003;25:2754–2764.

Al-Kudsi RR, et al. Extreme hyperglycemia in dialysis patients. Clin Nephrol. 1982;17:228–231.

Aramwit P, Supasyndh O, Sriboonruang T. Pharmacokinetics of single-dose rosiglitazone in chronic ambulatory peritoneal dialysis patients. J Clin Pharm Therap. 2008;33:685–690.

Arjona Ferreira JC, et al. Efficacy and safety of sitagliptin in patients with type 2 diabetes and ESRD receiving dialysis: a 54-week randomized trial. Am J Kidney Dis. 2013;61:579–587.

Arora SK, McFarlane SI. The case for low carbohydrate diets in diabetes management. Nutr Metab (Lond). 2005;2:16.

Atherton G. Renal replacement and diabetes care: the role of a specialist nurse. J Diab Nursing 2004;8:70–72.

Baldwin D, et al. A randomized trial of two weight-based doses of insulin glargine and glulisine in hospitalized subjects with type 2 diabetes and renal insufficiency Diabetes Care. 2012;35:1970–1974.

Beardsworth SF, et al. Intraperitoneal insulin: a protocol for administration during CAPD and review of published protocols. Perit Dial Int. 1988;8:145

Bergman AJ, et al. Effect of renal insufficiency on the pharmacokinetics of sitagliptin, a dipeptidyl peptidase-4 inhibitor. Diabetes Care. 2007;30:1862–1864.

Boulton DW, et al. Influence of renal or hepatic impairment on the pharmacokinetics of saxagliptin. Clin Pharmacokinet. 2011;50: 253–265.

Burmeister JE, Campos JF, Miltersteiner DR. Effect of different levels of glucose in the dialysate on the risk of hypoglycaemia during hemodialysis in diabetic patients. J Bras Nefrol. 2012;34:323–327.

Castellino P, et al. Glucose and amino acid metabolism in chronic renal failure: effect of insulin and amino acids. Am J Physiol. 1992;262:F168–F176.

Chan JCN, et al. Safety and efficacy of sitagliptin in patients with type 2 diabetes and chronic renal insufficiency. Diabetes Obes Metab. 2008;10:545–555.

Chapelsky M, et al. Pharmacokinetics of rosiglitazone in patients with varying degrees of renal insufficiency. J Clin Pharmacol. 2003;43:252–259.

Charpentier G, Riveline JP, Varroud-Vial M. Management of drugs affecting blood glucose in diabetic patients with renal failure. Diabet Metab. 2000;26(suppl 4):73–85.

Chiang C, et al. Rosiglitazone in diabetes control in hemodialysis patients with and without viral hepatitis infection effectiveness and side effects. Diabetes Care. 2007;30:3–7.
Cooper BA, et al. The IDEAL Study: a randomized, controlled trial of early versus lat initiation of dialysis. N Engl J Med. 2010;363:609–619.
Czock D, et al. Pharmacokinetics and pharmacodynamics of lispro-insulin in hemodi alysis patients with diabetes mellitus. Int J Clin Pharmacol Ther. 2003;41:492–49
Daniels ID, Markell MS. Blood glucose control in diabetics: II. Semin Dial. 1993;6:394
Danne T, Bolinder J. New insulins and insulin therapy. Diabetes Care. 2011;34:661–
Dasgupta MK. Management of patients with type 2 diabetes on peritoneal dialysis. A Perit Dial. 2005;21:120–122.
Davidson J, et al. Mild renal impairment has no effect on the efficacy and safety o liraglutide. Endocr Pract. 2011;17:345–355.
DeFronzo RA, et al. Glucose intolerance in uremia. Quantification of pancreatic beta cell sensitivity to glucose and tissue sensitivity to insulin. J Clin Invest. 1978;62:4 435.
Duckworth W, et al; for the VADT Investigators. The duration of diabetes affects the response to intensive glucose control in type 2 subjects: the VA Diabetes Trial.
J Diabetes Complications. 2011;25:355–361.
Egan AG, et al. Pancreatitis and safety of incretin-based drugs—FDA and EMA assessme N Engl J Med. 2014;370:794–797.
Firanek CA, Jacob DT, Sloand JA. Avoidable iatrogenic hypoglycemia in patients o peritoneal dialysis: the risks of nonspecific glucose monitoring devices and drug-device interaction. J Patient Saf. 2013 Sep 27.
Flynn CT. The Iowa Lutheran protocol. Perit Dial Bull. 1981;1:100.
Goldberg T, et al. Advanced glycoxidation end products in commonly consumed food J Am Diet Assoc. 2004;104:1287–1291.
Golightly LK, Drayna CC, McDermott MT. Comparative clinical pharmacokinetics of dipeptidyl peptidase-4 inhibitors. Clin Pharmacokinet. 2012;5:501–514.
Graefe-Mody U, et al. Effect of renal impairment on the pharmacokinetics of the di- peptidyl peptidase-4 inhibitor linagliptin. Diabetes Obes Metab. 2011;13:939–946
Graham GG, et al. Clinical pharmacokinetics of metformin. Clin Pharmacokinet. 2011;50:81–98.
Hatorp V. Clinical pharmacokinetics and pharmacodynamics of repaglinide [Review]. Clin Pharmacokinet. 2002;41:471–483.
Iglesias P, Diez JJ. Peroxisome proliferator-activated receptor gamma agonists in re disease. Eur J Endocrinol. 2006;154:613–621.
Jackson MA, et al. Hemodialysis-induced hypoglycemia in diabetic patients. Clin Nephrol. 2000;54:30–34.
Jacobsen L, et al. Effect of renal impairment on the pharmacokinetics of the GLP- analogue liraglutide. Br J Clin Pharm. 2009;68:898–905.
K/DOQI Workgroup. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis 2005;45(suppl 3):S1.
Khanna R, et al. The Toronto Western Hospital protocol. Perit Dial Bull. 1981;1:101.
Legrain M, Rottembourg J. The “Pitie-Salpetriere” protocol. Perit Dial Bull. 1981;1:10
Lin CL, et al. Improvement of clinical outcomes by early nephrology referral in type II diabetics on hemodialysis. Ren Fail. 2003;25:455–464.
Linnebjerg H, et al. Effect of renal impairment on the pharmacokinetics of exenatide. Br J Clin Pharm. 2007;64:317–327.
Lipska KJ, Bailey CJ, Inzucchi SE. Use of metformin in the setting of mild-to-modera renal insufficiency. Diabetes Care. 2011;34:1431–1437.
List JF, et al. Sodium-glucose co-transport inhibition with dapagliflozin in type 2 dia- betes mellitus. Diabetes Care. 2009;32:650–657.
Little R, et al. Can glycohemoglobin be used to assess glycemic control in patients w chronic renal failure? Clin Chem. 2002;48:784–785.
Locatelli F, Pozzoni P, Del Vecchio L. Renal replacement therapy in patients with dia tes and end-stage renal disease. J Am Soc Nephrol. 2004;(suppl 1):S25–S29.
Marbury T, Ruckle J, Hatorp V. Pharmacokinetics of repaglinide in subjects with rena impairment. Clin Pharmacol Therap. 2000;67:7–15.
Maxwell R, et al. Insulin influence on the mitogenic-induced effect of the peritoneal effluent in CAPD patients. In: Khanna R, et al., eds. Advances in Peritoneal Dialysis. Toronto, Canada: University of Toronto Press; 1991:161–164.
McCormack J, Johns K, Tildesley H. Metformin’s contraindications should be contrai dicated. CMAJ. 2005;173:502–504.

Murphy DM, et al. Reducing hyperglycemia hospitalwide: the basal-bolus concept. Jt Comm J Qual Patient Saf. 2009;35:216–23.
Nakamoto H, et al. Effect of diabetes on peritoneal function assessed by peritoneal dialysis capacity test in patients undergoing CAPD. Am J Kidney Dis. 2002;40:1045–1054.
Ng JM, et al. The effect of iron and erythropoietin treatment on the A1C of patients with diabetes and chronic kidney disease. Diabetes Care. 2010;33:2310–2313.
Nissen S, Wolsky K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Eng J Med. 2007;356:2457–2471.
Nowicki M, et al. Long-term treatment with the dipeptidyl peptidase-4 inhibitor saxagliptin in patients with type 2 diabetes mellitus and renal impairment: a randomised controlled 52-week efficacy and safety study. Int J Clin Pract. 2011;65:1232–1239.
O'Hare AM, et al. Factors associated with future amputation among patients undergoing hemodialysis: results from the Dialysis Morbidity and Mortality Study Waves 3 and 4. Am J Kidney Dis. 2003;41:162–170.
Oomichi T, et al. Impact of glycemic control on survival of diabetic patients on chronic regular hemodialysis: a 7-year observational study. Diabetes Care. 2006;29:1496–1500.
Osaadon P, et al. A review of anti-VEGF agents forproliferative diabetic retinopathy. Eye (Lond) 2014;28:510–520.
Parikh DS, et al. Perioperative outcomes among patients with end-stage renal disease following coronary artery bypass surgery in the USA. Nephrol Dial Transplant. 2010;25:2275–2283.
Parving HH, et al. Prevalence and causes of albuminuria in non-insulin-dependent diabetic patients. Kidney Int. 1992;41:758–762.
Phakdeekitcharoen B, Leelasa-nguan P. Effects of an ACE inhibitor or angiotensin receptor blocker on potassium in CAPD patients. Am J Kidney Dis. 2004;44:738–746.
Quellhorst E. Insulin therapy during peritoneal dialysis: pros and cons of various forms of administration. J Am Soc Nephrol. 2002;13(suppl 1):S92–S96.
Raimann JG, et al. Metabolic effects of dialyzate glucose in chronic hemodialysis: results from a prospective, randomized crossover trial. Nephrol Dial Transplant. 2012;27:1559–1568.
Reilly JB, Berns JS. Selection and dosing of medications for management of diabetes in patients with advanced kidney disease. Semin Dial. 2010;23:163–168.
Schomig M, et al. The diabetic foot in the dialyzed patient. J Am Soc Nephrol. 2000;11:1153–1159.
Schumacher S, et al. Single- and multiple-dose pharmacokinetics of repaglinide in patients with type 2 diabetes and renal impairment. Eur J Clin Pharmacol. 2001;52:147–152.
Schwartz MM, et al. Renal pathology patterns in type II diabetes mellitus: relationship with retinopathy. The Collaborative Study Group. Nephrol Dial Transplant. 1998;13:2547–52.
Shurraw S, et al. Glycemic control and the risk of death in 1,484 patients receiving maintenance hemodialysis. Am J Kidney Dis. 2010;55:875–884.
Sloan L, et al. Efficacy and safety of sitagliptin in patients with type 2 diabetes and ESRD receiving dialysis: a 54-week randomized trial. Am J Kidney Dis. 2013;61: 579–587.
Snyder RW, Berns JS. Use of insulin and oral hypoglycemic medications in patients with diabetes mellitus and advanced kidney disease. Semin Dial. 2004;17:365–370.
Spiller HA, Sawyer TS. Toxicology of oral antidiabetic medications. Am J Health-Syst Pharm. 2006;63:929–938.
St Peter W, Weinhandl ED, Flessner MF. Sitagliptin—another option for managing type 2 diabetes in dialysis patients? Am J Kidney Dis. 2013;61:532–535.
Thompson-Culkin K, et al. Pharmacokinetics of rosiglitazone in patients with end-stage renal disease. J Int Med Res. 2002;30:391–399.
Tsai CY, et al. False elevation of blood glucose levels measured by GDH-PQQ-based glucometers occurs during all daily dwells in peritoneal dialysis patients using icodextrin. Perit Dial Int. 2010;30:329–335.
Tzamaloukas AH, Oreopoulos DG. Subcutaneous versus intraperitoneal insulin in the management of diabetics on CAPD: a review. Adv Perit Dial. 1991;7:81–85.

Tzamaloukas AH, et al. Serum tonicity, extracellular volume and clinical manifestations in symptomatic dialysis-associated hyperglycemia treated only with insulin. Int J Artif Organs. 2004;27:751–758.

Uribarri J, et al. Diet-derived advanced glycation end products are major contributors to the body's AGE pool and induce inflammation in healthy subjects [Review]. Ann N Y Acad Sci. 2005;1043:461–466.

U.S. Renal Data System. USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2013.

Vonesh EF, et al. The differential impact of risk factors on mortality in hemodialysis and peritoneal dialysis. Kidney Int. 2004;66:2389–2401.

Williams ME, et al. Glycemic control and extended hemodialysis survival in patients with diabetes mellitus: comparative results of traditional and time-dependent Cox model analyses. Clin J Am Soc Nephrol. 2010;5:1595–1601.

Windus DW, et al. Prosthetic fistula survival and complications in hemodialysis patients: effects of diabetes and age. Am J Kidney Dis. 1992;19:448–452.

Yale JF. Oral antihyperglycemic agents and renal disease: new agents, new concepts [Review]. J Am Soc Nephrol. 2005;16(suppl 1):S7–S10.

Yale JF, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab. 2013;15:463–473.

33 Hypertension

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Treatmentofhypertensionrepresents a major area of intervention forcardiovascularriskreduction in dialysis patients.

I. DEFINITIONANDMEASUREMENT. Blood pressure (BP) is commonly measured across hemodialysis, but 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. Thus out-of-office BP monitoring is the preferable method for diagnosing and monitoring BP in hemodialysis patients. Both home and 24-hour ambulatory BP monitoring (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 are more reproducible than pre- and postdialysis BP, and associate with ABPM better than peridialytic measurements (Agarwal, 2012). Furthermore, home measurements reflect target organ (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 (i.e., 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 dialysis patients, but effective means of correcting lack of nocturnal BP dipping in this population have not been determined.

The definition of hypertension (Table 33.1) depends on the method of measurement (average home BP: >135/85 mm

TABLE 33.1 Definition of Hypertension Indications for Drug Therapy of Hypertension in Dialysis Patients

Definition
Hypertension in dialysis patients should be preferentially defined on the basis of home or 24h-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 24h-ABPM measurements (midweek dialysis interval): systolic BP >130 mm Hg and/or diastolic pressure >80 mm Hg
Ifhome or24h-ABPM cannot be applied, hypertension can be diagnosed as midweek median intradialysis systolic pressure >140 and/or diastolic pressure > 90mm Hgwhenthe 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 24h-ABPM <130/80 or median intradialysis BP <140/90 mm Hg.

BP, blood pressure.

Hg; ABPM: >130/80 mm Hg; midweek median intradialysis BP: >140/90 mm Hg). Average home BP >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.

II. PATHOPHYSIOLOGY

A. Extracellular volume expansion and sodium retention remains themaincause of hypertension. A relationship between chronic volume expansion and mortality is well estab- lished (Wizemann, 2009). There is an association between ECF volume expansion and diastolic dysfunction in dialysis patients (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 hyperten- sion (Kopp, 2013), and a similar finding was documented over 30 years ago in dialysis patients (Montanari, 1978). The consequences of nonosmotic sodium accumulation in vari- ous tissues are not fully known, but elevated sodium stores may impact inflammatory and cardiac fibrotic processes

via vascular endothelial growth factor C (Mallamaci, 2008; Machnik, 2010) and other mechanisms.

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 dialysis patients, and associates 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 dialysis patients, and radiofrequency abla- tion of renal sympathetic nerve fibers produces similar effects (Schlaich, 2013). Asymmetric dimethyl-arginine (ADMA), an endogenous inhibitor of nitric oxide synthase, is elevated in dialysis patients, and high levels associate with elevated sym- pathetic nervous system activity (Mallamaci, 2004).

C. Hypertension and left ventricular hypertrophy. 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 left ventricular hypertrophy, and many studies looking at reduction of fluid overload and/or antihypertensive treatment of dialysis patients have focused on change in left ventricular mass. It is important to realize that substantial left ventricular hypertrophy can be present in dialysis patients 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.

III. TREATMENT

A. Prevention

1. Sodium and fluid restriction. Most fluid intake is driven by salt ingestion, and nutritional recommendations are discussed in Chapter 31. Patients should be encouraged to restrict sodium chloride ingestion to 5 g per day (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 dialysis patients, 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. Some nephrologists favor 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 dialy- sate sodium during the treatment, so that dialysis ends it 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 ses- sion does not exceed the initial plasma level.

Preliminary data suggest that lowering dialysate sodium unitwide (from 140 to 137 mM) may reduce interdialytic weight gain as well as fluid-related hospitalization rate (Lacson, 2011).

2. Longer and/or more frequent dialysis sessions. These are discussed in Chapter 16. Frequent dialysis schedules and long, nocturnal dialysis may substantially improve BP control in hypertensive dialysis patients 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.

B. Correction of salt and fluid overload

1. Clinical assessment of dry weight

Ideally, a dialysis treatment should bringthe patientback to a normal extracellular 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 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 dialysis patients. 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 longstanding fluid excess is due to vascular remodeling.

b. Need for frequent reassessment. Dry weight and the 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 râles) may be difficult. Furthermore, edema may not be detectable until the interstitial volume has risen by about one-third above normal (e.g., 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, Germany) is one such device that has been well validated in dialysis patients (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, no evidence has been produced so far that use of BCM-guided "dry weight" increases survival or reduces fluid-related hospitalization.

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). Use of lung ultrasonography to help establish dry weight in dialysis patients with heart disease is attractive in theory, but its ability to improve hard outcomes such as hospitalization or mortality has not been tested.

C. Common clinical problems

1. Excessive ultrafiltration. Overzealous ultrafiltration may precipitatesevere 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 cogni- tion (Selby, 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 in one observational study, ultrafiltration rates greater than 12.4 mL/kg per hour were associated with increased mortality (Movilli, 2007). Methods of minimizing the risk of intradialytic hypotension are discussed in Chapter 12. Another issue with reduction of extracellular fluid volume in both hemo- and peritoneal dialysis patients is an associated fall in residual urine volume. This urine volume is important in avoiding spikes in extracellular fluid volume, as well as for associated removal of phosphorus, 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. Intradialysis and end-dialysis hypertension can occur in about 15% of dialysis patients and have been associated

2. with a higher death risk (Inrig, 2009). This disturbance is mul- tifactorial and may reflect subclinical volume overload. Sympathetic and renin–angiotensin overactivity as well as endothelial dysfunction also have been linked to this condition. At the present time, it is not clear how to treat this; anecdotally, lowering the target dry weight has worked in some patients, but it is by no means clear that such patients are uniformly fluid-overloaded. Recurrent hypertension. If hypertension recurs in a patient after being well controlled by volume subtraction, the most likely explanation is that the

3. 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 dialysis patients 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 beta-blockers. The mean number of antihypertensive drugs prescribed for incident hemodialysis and peritoneal dialysis patients is 2.5 at the sixth month of dialysis treatment. Prescription patterns of these drugs vary by dialysis modal- ity, and substantial changes in prescription patterns of beta-blockers, renin–angiotensin system antagonists, and calcium channel blockers occur from the sixth month on. Further- more, prescription classes vary by comorbidity, race/ethnicity, and age, but little by sex (St Peter, 2013).

1. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs). These drugs are generally well tolerated. The fact that serum plasma renin activity is overtly high in some dialysis patients 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 dialysis patients, as so many have LVH to begin with. However, randomized, placebo-controlled trials using ramipril in normotensive dialysis patients (Yu, 2006) and in patients with LVH and normal or high BP (Zannad, 2006) failed to show LVH regression. In hypertensive dialysis patients, open–label randomized trials with candesartan (Takahashi, 2006) or with various angiotensin receptor blockers (candesartan, losartan, or valsartan; Suzuki, 2008) versus placebo showed a significant risk reduction with ARBs (about 30%) for death and cardiovascular events, even though BP control in the ARB-treated patients was almost identical to that in the corresponding control arms. One large open-labeled trial with olmesartan in hypertensive dialysis patients without previous cardiovascular complications, failed to show a benefit on mortality and cardiovascular events (Iseki, 2013).

   a. Side effects and dosing adjustments. ACE inhibitors, by interfering with bradykinin breakdown, may be associated with an increased incidence of anaphylactoid reactions during dialysis. ACE inhibitors have been associated with hyperkalemia in patients with renal insufficiency, but can often be used in dialysis patients 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 inhibitors, an effect that depends on the accumulation of N-acetyl-seryl-aspartyl-lysyl-proline, a physiologic inhibitor of hematopoiesis whose degradation depends on ACE. Because plasma half-life of many ACE inhibitors (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. Beta-, alpha/beta-, and alpha-adrenergic blockers. Beta- blockers counteract the cardiovascular effects of high sympa- thetic activity and lower plasma renin activity (PRA) and angiotensin II, which may all participate in causing high BP in dialysis patients. Many show a documented cardioprotective effect in the setting of myocardial ischemia or infarction. High plasma noradrenaline associates with cardiovascular mortality in ESKD (Zoccali, 2002). Carvedilol, an alpha/beta-blocker, reduces morbidity and mortality in dialysis patients with systolic dysfunction (Cice, 2003). A superior cardioprotective effect of beta-blockade by atenolol over ACE inhibition by lisinopril has been recently documented in the HDPAL trial (Agarwal, 2014). In this trial of 200 dialysis patients 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 lisonopril-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 recom- mended early termination of the trial. a. Side effects and dosing adjustments. Alpha-blockers may

   cause postural hypotension. Prazosin has been associated with first-dose syncope, so the first dose must be administered at bedtime. Beta-adrenergic blockers have a high incidence of side effects, such as drowsiness, lethargy, and depression. Non-selective beta-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. Beta-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 aug- ment insulin-induced hypoglycemia. All may cause bra- dycardia and interfere with reflex tachycardia following volume depletion.

   Water-soluble beta-blockers atenolol, nadolol, and bisprolol are removed substantially by hemodialysis and should be preferentially administered postdialysis.

3. Calcium channel blockers. These drugs are frequently used for the treatment of volume-resistant hypertension in dialysis patients. 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

beta-blockers, ACE inhibitors, and angiotensin II recep- tor blockers in reducing the risk of stroke, and similarly effective in preventing coronary heart disease events (Law, 2009). In a randomized, double blind trial in hypertensive dialysis patients, 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 sec- ondary end point (mortality from any cause or cardiovas- cular event), while the risk reduction (35%) for mortality (primary end point) failed to achieve statistical signifi- cance (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 beta-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 33.2), and their dosage does not require any adjustment.

4. Sympatholytic drugs (e.g., methyldopa, clonidine, guanabenz). As noted above, there appears to be increased tonic sympathetic activity in dialysis patients, so use of central sympatholytic drugs, which inhibit sympathetic outflow by stimulating alpha-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 dialysis patients (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 diabetic patients. 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. A large clinical trial of moxonidine in heart failure, MOXCON, was stopped because of excessive deaths in the moxonidine group (Cohn, 2003), which contrasts with the beneficial effect

TABLE 33.2 Antihypertensive Drugs in Dialysis Patients: Dosages and Removal during Dialysis

Drug Ca	Tablet Size (mg)	Initial Dose in Dialysis Patients (mg)	Maintenance Dose Dialysis Patients (mg)	Removal During Hemodialysis
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	30–60	No
Nifedipine XL		b.i.d.	b.i.d.	
Verapamil	30, 60	30 q24h	30–60 q24h	No
	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
Benazepril	5, 10, 20, 40	5 q24h	5–20 q24h	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	Yesa
Lisinopril	5, 10, 20, 40	2.5 q24h or q48h	2.5–10 q24h or q48h	Yesa
Perindopril	4	2 q48h	2 q48h	Yesa
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	Yesa
Beta-blockers				
Acebutolol	200, 400	200	200–300	Yes
Atenolol	50, 100	q24h 25	q24h 25–50	a
Bisoprolol	2.5	q48h 2.5	q48h 2.5	Yes
Carvedilol	5	q24h 5	q24h 5 q24h	a
Metoprolol	50, 100	q24h 50	50–100 b.i.d.	Yes
Nadolol	20, 40, 80, 120, 160	b.i.d. 40	40–120 q48h	a
		q48h		Yes
Pindolol	5, 10	5 b.i.d.	5–30 b.i.d.	Yesa
Propranolol	10, 40, 80	40 b.i.d.	40–80 b.i.d.	Yesa
Adrenergic modulators				a
				Yes
Clonidine	0.1, 0.2, 0.3, TTS 0.2	0.1 b.i.d.	0.1–0.3 b.i.d., TTS weekly	Noa

(continued)

TABLE 33.2 Antihypertensive Drugs in Dialysis Patients: Dosages and Removal During Dialysis (continued)

Drug	Tablet Size (mg)	Initial Dose in Dialysis Patients (mg)	Maintenance Dose Dialysis Patients (mg)	Removal During Hemodialysis
Guanabenz	4, 8 1, 2	4 b.i.d. 1	4–8 b.i.d.	No No No No
Guanfacine	100, 200,	q48h 200	1–2 q24h	No
Labetalol	300 1, 2, 5	b.i.d. 1 b.i.d. 1	200–400 b.i.d.	
Prazosin	1, 2, 5	b.i.d.	1–10 b.i.d.	
Terazosin			1–10 b.i.d.	
Vasodilators				
Hydralazine				
Minoxidil	10, 25, 50, 100	25 b.i.d.	50 b.i.d.	No
Angiotensin II receptor blockers	2.5, 10	2.5 b.i.d.	2.5–10 b.i.d.	Yesa
Candesartan				
Eprosartan	4, 8, 16, 32	4 q24h 400	8–32 q24h	No
Irbesartan	400, 600	q24h 75–	400–600	No
Losartan	75, 150, 300	150 q24h	q24h 150–	No
Telmisartan	50	50 q24h 40	300 q24h	No
Valsartan	40, 80	q24h 80	50–100 q24h	No
Olmesartan	80, 160	q24h 10	20–80 q24h	No
[a]	10-40	q24h	80–160 q24h	No
			10-40 q24h	

The dose of drugs that are removed by hemodialysis should be scheduled so that it is administered after dialysis.
None of the drugs in the table undergoes substantial removal during continuous ambulatory peritoneal dialysis.
q24h, daily; b.i.d., two times per day; q48h, every other day; ACE, angiotensin-converting enzyme; TTS, transdermal therapeutic system.

of beta-blockers in the same condition. The use of this drug in dialysis patients with heart failure 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. Guana- benz is metabolized by the liver and requires no dosage adjustment in renal failure.

5. Vasodilators (e.g., hydralazine, minoxidil). These are third-line drugs. They usually require addition of a sympatholytic or beta-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 per day. Because of diminished renal excretion of its active metabolite(s), the maximum allowable dosage should be reduced in dialysis patients. Minoxidil has been associated with pericardi- tis and is generally avoided in women because of hyper- trichosis. Minoxidil is usually reserved to treat resistant hypertension.

IV. HYPERTENSIVE URGENCIES AND EMERGENCIES

A. Hypertensive urgency. The term hypertensive urgency is reserved forpatients 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 beta-blocker, an ACE inhibitor, 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 IV infusion (0.3–0.8 mcg/kg per minute ini- tially to a maximum of 8 mcg/kg per minute) is particularly useful in heart failure and dissecting aneurysm but requires careful monitoring because its toxic metabolite (thiocya- nate) 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 10–20 mg given slowly intravenously is a well-tried alternative, but this drug should be avoided in ischemic heart disease.

References and Suggested Readings

Agarwal R. The controversies of diagnosing and treating hypertension among hemodialysis patients. Semin Dial. 2012;25:370–376.

Agarwal R. B-type natriuretic peptide is not a volume marker among patients on hemodialysis. Nephrol Dial Transplant. 2013;28:3082–3089.

Agarwal R, Light RP. Median intradialytic blood pressure can track changes evoked by probing dry-weight. Clin J Am Soc Nephrol. 2010;5:897–904.

Agarwal R, et al. Home blood pressure measurements for managing hypertension in hemodialysis patients. Am J Nephrol. 2009;30:126–134.

Agarwal R, et al. Inferior vena cava diameter and left atrial diameter measure volume but not dry weight. Clin J Am Soc Nephrol. 2011;6:1066–1072.

Agarwal R, et al. Hypertension in hemodialysis patients treated with atenolol or lisino- pril (HDPAL): a randomized controlled trial. Nephrol Dial Transplant. 2014;29:672– 681.

Charra B, Bergstrom J, Scribner BH. Blood pressure control in dialysis patients: importance of the lag phenomenon. Am J Kidney Dis. 1998;32:720–724.

Cice G, et al. Carvedilol increases two-year survivalin dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. J Am Coll Cardiol. 2003;41:1438–1444.

Cohn JN, et al. Adverse mortality effect of central sympathetic inhibition with sustained-release moxonidine in patients with heart failure (MOXCON). Eur J Heart Fail. 2003;5:659–667.

Converse RL Jr, et al. Sympathetic overactivity in patients with chronic renal failure. N Engl J Med. 1992;327:1912–1918.

Curatola G, et al. Ultrafiltration intensification in hemodialysis patients improves hypertension but increases AV fistula complications and cardiovascular events. J Nephrol. 2011;24:465–473.

Grassi G, et al. Sympathetic nerve traffic and asymmetric dimethylarginine in chronic kidney disease. Clin J Am Soc Nephrol. 2011;6:2620–2627.

Hausberg M, et al. Effects of moxonidine on sympathetic nerve activity in patients with end-stage renal disease. J Hypertens. 2010;28:1920–1927.

Hur E, et al. Effect of fluid management guided by bioimpedance spectroscopy on cardiovascular parameters in hemodialysis patients: a randomized controlled trial. Am J Kidney Dis. 2013;61:957–965.

Inrig JK, et al. Association of blood pressure increases during hemodialysis with 2-year mortality in incident hemodialysis patients: a secondary analysis of the Dialysis Morbidity and Mortality Wave 2 Study. Am J Kidney Dis. 2009;54:881–890.

Iseki K, et al. Effects of angiotensin receptor blockade (ARB) on mortality and cardio- vascular outcomes in patients with long-term haemodialysis: a randomized con- trolled trial. Nephrol Dial Transplant. 2013;28:1579–1589.

Joseph G, et al. Extravascular lung water and peripheral volume status in hemodialysis patients with and without a history of heart failure. ASAIO J. 2006;52:423–429.

Klassen PS, et al. Association between pulse pressure and mortality in patients undergoing maintenance hemodialysis. JAMA. 2002;287:1548–1555.

Kopp C, et al. Na magnetic resonance imaging-determined tissue sodium in healthy subjects and hypertensive patients. Hypertension. 2013;61:635–640.

Lacson EK, et al. Lower dialysate sodium impacts weight gain and fluid overload hospitalizations [abstract]. J Am Soc Nephrol. 2011;22:93A.

Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009;338:b1665.

Machnik A, et al. Mononuclear phagocyte system depletion blocks interstitial tonicity-responsive enhancer binding protein/vascular endothelial growth factor C expression and induces salt-sensitive hypertension in rats. Hypertension. 2010;55:755–761.

Mallamaci F, et al. Analysis of the relationship between norepinephrine and asymmetric dimethyl arginine levels among patients with end-stage renal disease. J Am Soc Nephrol. 2004;15:435–441.

Mallamaci F, et al. Vascular endothelial growth factor, left ventricular dysfunction and mortality in hemodialysis patients. J Hypertens. 2008;26:1875–1882.

Mallamaci F, et al. Detection of pulmonary congestion by chest ultrasound in dialysis patients. JACC Cardiovasc Imaging. 2010;3:586–594.

Mancia G, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2013;31:1281–1357.

Moissl U, et al. Bioimpedance-guided fluid management in hemodialysis patients. Cl J Am Soc Nephrol. 2013;8:1575–1582.

Moissl UM, et al. Body fluid volume determination via body composition spectroscopy in health and disease. Physiol Meas. 2006;27:921–933.

Mominadam S, et al. Interdialytic blood pressure obtained by ambulatory blood pressure measurement and left ventricular structure in hypertensive hemodialysis patients. Hemodial Int. 2008;12:322–327.

Montanari A, et al. Studies on cell water and electrolytes in chronic renal failure. Clin Nephrol. 1978;9:200–204.

Movilli E, et al. Association between high ultrafiltration rates and mortality in uraemic patients on regular haemodialysis: a 5-year prospective observational multicenter study. Nephrol Dial Transplant. 2007;22:3547–3552.

Özkahya M, et al. Long-term survival rates in haemodialysis patients treated with strict volume control. Nephrol Dial Transplant. 2006;21:3506–3513.

Reddan DN, et al. Intradialytic blood volume monitoring in ambulatory hemodialysis patients: a randomized trial. J Am Soc Nephrol. 2005;16:2162–2169.

Rossignol P, et al. Visit-to-visit blood pressure variability is a strong predictor of cardiovascular events in hemodialysis: insights from FOSIDIAL. Hypertension. 2012;60:339–346.

Schlaich MP, et al. Feasibility of catheter-based renal nerve ablation and effects on sympathetic nerve activity and blood pressure in patients with end-stage renal disease. Int J Cardiol. 2013;168:2214–2220.

Selby NM, McIntyre CW. How is the heart best protected in chronic dialysis patients? Protecting the heart in dialysis patients—intradialytic issues. Semin Dial. 2014;27:332–335.

Shoji T, et al. Hemodialysis-associated hypotension as an independent risk factor for two-year mortality in hemodialysis patients. Kidney Int. 2004;66:1212–1220.

St Peter WL, et al. Patterns in blood pressure medication use in US incident dialysis patients over the first 6 months. BMC Nephrol. 2013;14:249.

Suzuki H, et al. Effect of angiotensin receptor blockers on cardiovascular events in patients undergoing hemodialysis: an open-label randomized controlled trial. Am J Kidney Dis. 2008;52:501–506.

Takahashi A, et al. Candesartan, an angiotensin II type-1 receptor blocker, reduces cardiovascular events in patients on chronic haemodialysis—a randomized study.
Nephrol Dial Transplant. 2006;21:2507–2512.

Tepel M, et al. Effect of amlodipine on cardiovascular events in hypertensive haemodialysis patients. Nephrol Dial Transplant. 2008;23:3605–3612.

Vonend O, et al. Moxonidine treatment of hypertensive patients with advanced renal failure. J Hypertens. 2003;21:1709–1717.

Wizemann V, et al. The mortality risk of overhydration in haemodialysis patients. Nephrol Dial Transplant. 2009;24:1574–1579.

Yu WC, et al. Effect of ramipril on left ventricular mass in normotensive hemodialysis patients. Am J Kidney Dis. 2006;47:478–484.

Zannad F, et al. Prevention of cardiovascular events in end-stage renal disease: results of a randomized trial of fosinopril and implications for future studies. Kidney Int. 2006;70:1318–1324.

Zoccali C, et al. Cardiac natriuretic peptides are related to left ventricular mass and function and predict mortality in dialysis patients. J Am Soc Nephrol. 2001;12: 1508–1515.

Zoccali C, et al. Plasma norepinephrine predicts survival and incident cardiovascular events in patients with end-stage renal disease. Circulation. 2002;105 1354–1359.

Zoccali C, et al. Pulmonary congestion predicts cardiac events and mortality in ESRD J Am Soc Nephrol. 2013;24:639–646.

34 Hematologic Abnormalities

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I. ANEMIA

A. Etiology. Theanemia of chronic kidney disease (CKD) is p rimarily due toinsufficient production of the glycoprotein hormone erythropoietin(EPO). Although EPO can be produced in many of the body's tissues, EPO required for erythropoiesis generally is produced by endothelial cells in proximity to the renal tubules. As renal excretory function is lost, there is a relative decline in the production of EPO that correlates with the declining glomerular filtration rate. The severity of the resulting anemia varies, but if untreated, then hematocrit values in end-stage kidney disease (ESKD) of 18%–24% are typical. While the primacy of EPO deficiency is indisputable, other factors may play important contributory roles. Also, patients with ESKD may develop any of the other causes of anemia common in nonuremic subjects.

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 heart's compensatory changes. The most prominent symptoms of anemia are fatigue and dyspnea. Symptoms develop slowly, and the patient may gradually constrict his or her 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 diminished oxygen-carrying capacity of blood by attempting to maintain systemic oxygen delivery with increased cardiac output and left ventricular hypertrophy. Patients may notice worsening dyspnea and palpitations at this stage. Other problems include deranged hemostatic function, impaired immune function, and diminished cognitive and sexual function. Exacerbations of angina, claudication, and transient ischemic attacks may also 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. Because EPO deficiency is the primary cause of anemia in patients with CKD, agents that replace erythropoietin have a primary role in treatment. Since the last edition of this handbook, the preferred term for these agents has changed to erythropoiesis-stimulating agents (ESA). Drugs may be erythropoietin analogs or may stimulate erythropoiesis in other ways. There are many different erythropoietin analogs commercially available in the United States and elsewhere: Epoetin alfa (Epogen, Procrit) and darbepoetin alfa (Aranesp) are currently available in the United States, and methoxy-polyethyleneglycol-epoetin beta (Mircera) is widely used in Europe and probably will be available shortly in the United States. Peginesatide (Omontys) currently is not being marketed in the United States, after a substantial number of allergic reactions occurred with its use. The cause is currently being investigated. **Epoetin alfa** is a glycoprotein that is indistinguishable from native erythropoietin. It is manufactured by recombinant DNA technology and has a molecular weight of 30,400 Da and a circulating half-life after intravenous administration of approximately 8 hours. **Dar- bepoetin alfa** is a synthetic analog of erythropoietin with increased carbohydrate content that increases the molecular weight by approximately 20% compared with native erythro- poietin. As a result of the altered structure, the drug's phar- macokinetics are changed and the serum half-life is increased to approximately three times longer, 24 hours, compared with epoetin alfa. **Mircera** has an unusually long serum half-life of approximately 5.5 days. **Peginesatide** is a synthetic peptide attached to polyethylene glycol that mimics the structure of erythropoietin, but that has no amino acid sequence homol- ogy to EPO. Biological analogs of ESAs, so-called biosimilars, have been manufactured and are in use outside of the United States. The safety of these agents has been variable, but under careful FDA scrutiny, it is likely that biosimilar forms of EPO will become available in the United States.

One new class of ESAs currently under development acts to stabilize hypoxia inducible factor-1 (HIF). Synthesis of HIF is increased in the presence of hypoxia, and HIF acts to increase the transcription of EPO. HIF is rapidly degraded when normoxic conditions are present, and drugs that stabilize HIF result in increased endogenous erythropoietin production, even in anephric individuals. These drugs will be an important new class of ESAs if they are demonstrated to be safe and effective.

2. Benefits of anemia treatment with ESA.

a. Effect on outcomes. Cross-sectional and retrospective studies have suggested that anemia in patients undergoing hemodialysis is associated with increased mortality, particularly when the hemoglobin concentration is <10 g/dL (100 g/L). Analyses of large administrative

and clinical databases have shown that risk for mortality, hospitalization rate, and hospitalization days continue to decrease even at hemoglobin levels >11 g/dL (110 g/L). In contrast to these observational studies, interventional studies have not demonstrated improved outcomes following normalization of hemoglobin with ESA treatment. In fact, cardiovascular outcomes in these studies generally have been worse (see below).

b. Reduction in transfusion-related complications. Prior to ESA therapy, up to 20% of patients on dialysis required frequent transfusions with attendant risk of immediate transfusion reactions, viral infection, iron overload, and immune sensitization. The rate of blood transfusion has been greatly reduced by the use of ESA therapy.

c. Improved quality of life and overall sense of well-being. Various assessment tools have documented an improved quality of life and functional status in ESKD patients treated with ESA. Patients feel less fatigued and their exercise capacity increases. Symptoms that had been disabling in the pre-ESA era are now easily managed. However, the target level of hemoglobin for optimized quality of life is not completely known. Whether higher hemoglobin targets further improve quality of life is unclear. Some studies suggest that improvements may continue as hemoglobin is raised toward the normal range, while others have found no improvement in quality of life despite higher hemoglobin targets.

3. Risks of ESA Therapy. Several well-powered randomized controlled trials have tested the safety of ESA treatment aiming at relatively high hemoglobin targets (13–15 g/ dL, or 130–150 g/L) in patients with CKD. In these stud- ies, the comparison groups (controls) were either given ESA treatment to a lower Hgb target or, in one study, the control group received mostly placebo. Four such trials are particularly noteworthy: the Normal Hematocrit Trial (Besarab, 1998), CREATE (Drueke, 2006), CHOIR (Singh, 2006), and TREAT (Pfeffer, 2009). Only one of these four studies (Besarab, 1998) was done in dialysis patients, while the other three recruited nondialysis CKD subjects with eGFR or CrCl normalized to 1.73 m2 in the range of 15–35 mL/min (CREATE), 15–50 (CHOIR), or 20–60 (TREAT). While results were somewhat inconsistent, there was a strong general trend toward increased cardiovascular risk, including risk of death, with ESA treatment to such high Hgb targets.

The mechanism of harm for an ESA treatment with a Hgb target >13 g/dL is unknown. The benefit versus risk of ESA treatment aiming at a lower Hgb target has not been formally studied in a randomized fashion. Post hoc analysis of these high Hgb target studies suggests that a higher achieved Hgb level per se may not be the source of

increased risk. In these trials, mortality was higher in those patients receiving high doses of ESAs; however, it is not at all clear whether this association was causal. Patients requiring high doses of ESAs, or so-called ESA-resistant patients, show many markers of increased illness severity such as cachexia and increased levels of serum inflam- matory markers, and ESA resistance is associated with a poor prognosis for survival. In one of the randomized trials noted above (TREAT), the risk of stroke was doubled, and the risk of cancer was also increased in the group given an ESA targeting a high Hgb level. The results of these studies prompted the FDA to include "black box" warnings in the product inserts for ESAs, and for various guideline committees to revise target Hgb levels downward, with the idea that one should use ESAs sparingly, and attempt only partial correction of anemia.

4. Indications for ESA therapy and target hemoglobin. ESA therapy should generally be initiated in CKD patients when the Hgb falls below 10 g/dL (100 g/L). The optimal Hgb level for a patient with ESKD is not known. The Kidney Disease: Improving Global Outcomes (KDIGO) anemia guidelines (2012) simply recommend that Hgb for dialysis patients should not exceed >11.5 g/dL (115 g/L). This recommendation is in some conflict with current FDA prescribing instructions, which recommend holding ESA dosing when the hemoglobin is >11.0 g/dL (110 g/L). A reasonable hemoglobin target for patients on dialysis would be 9.5–11.5 g/dL (95–115 g/L).
   a. Effect of volume status on target hemoglobin. When Hgb is assessed prior to a hemodialysis session, extracellular volume tends to be high, and so due to dilution, the Hgb level is at a relatively low value for the week. Monday/Tuesday predialysis Hgb levels are at their low point for the week and are about 0.3 g/dL (3 g/L) lower than midweek predialysis levels. Immediate postdialysis Hgb levels can be very substantially higher than predialysis values. So the time-averaged weekly Hgb value can be substantially underestimated by predialysis numbers. In patients with markedly fluctuating degrees of fluid overload, a change in predialysis Hgb may reflect a change in fluid status more than a change in red cell mass. This potential dilution issue must be kept in mind when monitoring Hgb levels and using this information to adjust ESA dose. For the same reason, a change from a 3 per week to a more frequent dialysis schedule can result in a modest increase in Hgb that is more a reflection of reduced extracellular fluid volume and sampling after a 1-day interdialytic interval rather than to an increase in red cell mass. Lastly, if one is trying to parse Hgb targets from nondialysis CKD patients to patients receiving dialysis, a Hgb target of 11 g/dL (110 g/L) in CKD may

correspond to a somewhat lower predialysis target value indialysispatientsdueto thedilution effect.

5. Route of administration

a. Subcutaneous versus intravenous ESAs. The subcutaneous route improves the efficiency of therapy, resulting in a reduced dosing requirement (of about 25%) for short-acting ESAs, specifically epoetin alfa. (Kaufman, 1998). When epoetin is given intravenously, its short half-life probably results in some drug never binding to erythropoietin receptors prior to clearance of epoetin from the circulation. When given subcutaneously, the serum half-life of epoetin is extended, allowing for more efficient receptor binding and a greater erythropoietic effect. Despite the dose reduction advantage of subcutaneous administration, the majority of patients undergoing hemodialysis in the United States continue to be treated via the intravenous route. The primary reason is probably discomfort with subcutaneous injections, whereas reduced dosing requirements are a benefit that does not directly accrue to the patient. ESAs with a longer serum half-life provide extended time in circulation to allow for greater opportunity for the drug to bind to erythropoietin receptors. There is probably no advantage or need for subcutaneous dosing for methoxypolyethylene glycol-epoetin beta, peginesatide or possibly even darbe- poetin alfa. Intravenous administration of any of these agents would appear to be a better choice than subcuta- neous injection of epoetin alfa in hemodialysis patients, to reduce patient discomfort. For patients on peritoneal dialysis, subcutaneous injections remain the dominant
routeof administration.

6. Dosing

a. Initial dose. Treatment with ESA should ideally be initiated, if required, in the pre-ESKD period. If treatment needs to be initiated for a patient already on dialysis, reasonable starting doses of epoetin alfa for a hemodialysis patient would be 2,000–3,000 units three times per week, and for a peritoneal dialysis patient 6,000 units once per week. A typical dose of darbepoetin alfa would be approximately 25 mcg once weekly for a hemo- dialysis patient or 60 mcg every 2 weeks for a patient on peritoneal dialysis. A typical dose of Mircera would be 150 mcg given once monthly. Selection of a specific dose requires clinical judgment as to how symptomatic the patient is and the starting level of hemoglobin. An excessively rapid rise in the hemoglobin level should be avoided, as this may lead to an increased risk of worsen- ing hypertension.

b. Initial response and plateau effect. During the initiation phase of therapy, hemoglobin should be checked every 1–2 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 hemoglobin 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 defi- ciency. Once the target level of hemoglobin has been reached, the hemoglobin should be checked every 2–4 weeks. During this maintenance phase of therapy, the dose of ESA should be adjusted on the basis of subse- quent changes in hemoglobin (Fig. 34.1). The patient's responsiveness to ESA should be re-assessed on a continuing basis. Most patients will be responsive, with hemoglobin values consistently >10 g/ dL (100 g/L), and an epoetin dose of <5,000 units three times per week. In contrast, some patients will have or develop relative resistance to therapy. These patients need to be fully evaluated for causes of ESA hypore- sponse. The responsiveness to ESA in all patients should be evaluated on an ongoing basis because the degree of responsiveness changes over time. In our experience, the development of resistance often signals the presence of iron deficiency or infection.

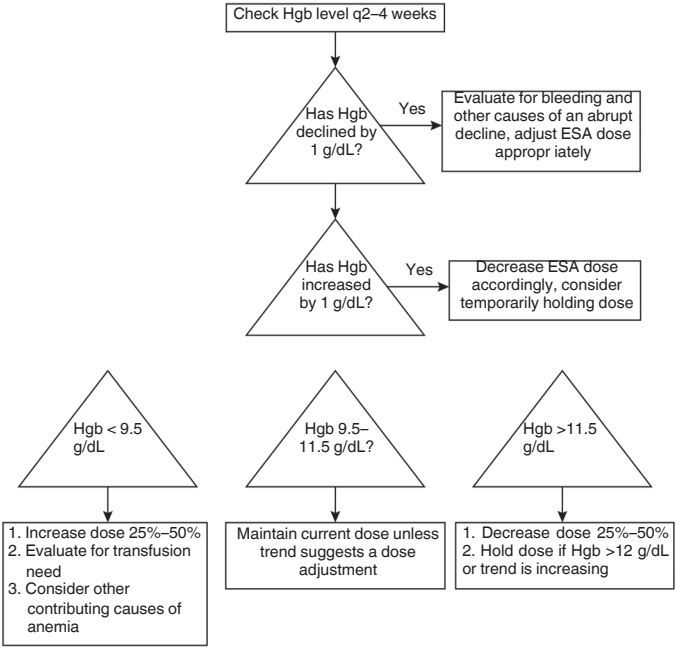


FIGURE 34.1 Flow chart for adjusting the ESA dose based on hemoglobin (Hgb) results for dialysis patients.

Data from ESA practice patterns in the United States suggest that the median weekly dose of intravenous EPO is about 7,000 units per week, and for darbepoetin this is 25 mcg per week (Coritsidis, 2014). Side effects of ESA therapy have been reported in patients getting the high doses. ESA-resistant patients are a selected group with poor outcome; however, it is possible that use of high doses of ESAs *per se* may be associated with increased side effects. Response to ESAs tends to plateau at high doses, and use of very high doses is uneconomical. For these reasons, the 2012 KDIGO guidelines recommend not generally exceeding four times the usual baseline weight-adjusted dose of EPO when managing EPO- resistant patients (KDIGO Anemia, 2012).

c. Individualized anemia management. The pharmacodynamics of ESA use are complicated, as the achieved Hgb levels depend not only on ESA sensitivity, but on the average lifespan of red blood cells (RBCs) in a given patient. A number of algorithms have been developed with the goal of maximizing the time that Hgb remains in a desired range. Algorithms in development may be enhanced by estimates of Hgb measured during each dialysis session by use of optical or ultrasound blood line sensors. The use of such algorithms has been reported to reduce Hgb variability as well as overall ESA dose (Lines, 2012; Gaweda, 2014).

D. Side effects of ESA therapy. See Section 3, above, for a discussion of cardiovascular risks of ESA therapy.

1. Worsening of hypertension. This is a common problem during the partial correction 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. Risk factors include preexisting hypertension, a rapid increase in hemoglobin, the presence of dysfunctional native kidneys, and severe anemia prior to treatment. The cause of the hypertensive effect is incompletely understood. Factors that may contribute include the partial reversal of hypoxic vasodilation as the hemoglobin rises, reduced nitric ox- ide, increased cytosolic calcium levels, increased plasma endothelin levels, activation of the renin–angiotensin– aldosterone system and others. Various antihypertensives, including long-acting calcium channel blockers, are effec- tive for treating hypertension associated with ESA.
2. Seizures. These may occur in a small number of patients during periods of rapidly increasing hemoglobin in association with hypertension. The risk of seizures is small using current ESA dosing protocols.
3. Graft clotting. The increase in blood viscosity with higher hemoglobin values from either ESA therapy or other causes could theoretically cause increased dialyzer and arteriovenous

graft clotting. Studies to date have not consistently demonstrated an increased risk of thrombosis when the hemoglobin is raised to the 11–12 g/dL (110–120 g/L) range. The impact of higher hemoglobin levels is controversial. It should be clear that some patients may experience substantial hemoconcentration during or after the hemodialysis treatment, and effects on blood viscosity and risk for access thrombosis may be a particular concern in this setting.

4. Stroke. The risk of stroke has been increased in some of the randomized trials of ESAs where a relatively high Hgb level has been targeted, but this was not noted in all such studies.

5. Effect on ***Kt/V.*** During dialysis, urea is removed from both red cells and plasma, and so urea clearance and Kt/V-urea are not affected by an increase in the Hgb. Creatinine and phosphorus are removed from the plasma only during passage of blood through the dialyzer, and as the Hgb is increased, at any given blood flow rate, the plasma flow rate and creatinine and phosphorus clearances will be proportionately reduced.

E. ESA Treatment and Cancer. In studies of ESA treatment for anemia related to chemotherapy or cancer, there has been some evidence to suggest that ESA treatment could reduce overall and progression-free survival. 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 treatment decisions (Hazzan, 2014).

The data, however, are not entirely consistent. For example, five published meta-analyses of published trials have not found ESA treatment to adversely impact complete responses, disease progression, or progression-free survival. However, spe- cific studies of certain types of cancer do indicate an adverse effect, for example, in patients with head and neck cancer receiving radiotherapy. It should be noted that in studies dem- onstrating potential harm, ESA treatment was used to target relatively high hemoglobin levels (up to 16 g/dL in men). While the meta-analyses provide some reassurance, the adverse effects of ESAs in some studies should drive a conservative approach to treatment until the question is fully resolved.

We would suggest that for ESKD patients with a history of past malignancy, ESA therapy can be cautiously employed with hemoglobin targets as noted above for general treatment of ESKD patients. In patients with active malignancy, whether or not the patient is currently receiving chemotherapy, we would recommend a more conservative approach to treatment. This is based on an uncertainty in current knowledge on progression-free survival and increased thromboembolic risk in cancer patients. We would suggest lowering the target hemoglobin to 9–10 g/dL (90–100 g/L). For symptomatic, urgent anemia correction, blood transfusion should be employed.

F. Causes of decreased response to ESA therapy

1. Iron deficiency. The most importantcause of a suboptimal responseto ESA therapy is iron deficiency. Iron deficiency can be present at the outset of therapy, but more commonly, it develops during therapy, either due to rapid utilization of iron to support erythropoiesis or as the result of blood loss (Table 34.1). a. Blood loss. Hemodialysis patients 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 bleeding, iron losses may be substantial. Because of the overall burden of blood loss, it is very difficult to maintain iron stores in hemodialysis patients using oral iron supplements only. Losses in peritoneal dialysis patients are substantially less, and these patients can often be maintained on oral iron therapy.

b. 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 intravenous injection of ESA, there is an increase in the rate of erythropoiesis that leads to a greater immediate need for iron. In this setting, iron deficiency may occur even in the face of normal body iron stores. This phenomenon has been termed "functional iron deficiency."

c. Inflammation (reticuloendothelial blockade). Occult inflammation is often present in ESKD patients. It causes an increase in serum hepcidin concentrations, which

TABLE 34.1 Causes of Iron Deficiency in Hemodialysis Patients

- Depletion of iron stores
- Chronic 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 increased rate of erythropoiesis induced by erythropoiesis-stimulating agents
  2. Impaired release of iron from storage tissues (reticuloendothelial blockade)

causes reduced intestinal iron absorption and diminished availability of iron in storage tissues.

d. Poor absorption of dietary iron. Iron deficiency among patients on dialysis may be exacerbated by poor absorption of dietary or medicinal iron. However, the subject is controversial, and results from studies have been conflicting.

2. Diagnosis

a. Serum ferritin. Ferritin is a protein used to store iron inside cells in a nontoxic form. Free iron is toxic to cells because it can generate free radicals. Although most ferritin is intracellular, some appears in the circulation and reflects iron stores, although the function of ferritin is to store iron and not to transport it in the circulation. Because serum ferritin is cleared by the liver, in hepatic insufficiency, serum levels may be markedly increased. A more common cause of increased serum ferritin is any sort of inflammation, as ferritin is an acute phase reactant. Serum ferritin levels can also be high in certain cancers and with malnutrition. If the serum ferritin level is <200 mcg/L, the likelihood of iron deficiency is quite high. However, absolute iron deficiency can be present with much higher serum ferritin levels in the presence of inflammation.

b. Transferrin saturation. 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 a 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 240–450 mcg/dL (43–81 mcmol/L). The percent transferrin saturation (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%–50%.

c. Use of serum ferritin and TSAT to diagnose cause of anemia and ESA resistance. The serum ferritin concentration and transferrin saturation percentage (TSAT) have been the two most widely used tests of iron status for dialysis patients. However, neither test is very accurate for the assessment of iron deficiency in this patient population; the tests provide only a rough estimate of iron status. Thus, patients should not be treated intensively with intravenous iron based only on the results of these indices. The NKF's KDOQI anemia guidelines state that iron tests should be interpreted in the context of patients' clinical status, Hgb 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; however, these guidelines recommend monitoring these levels more frequently

when initiating or increasing ESA dose, when there is blood loss, when monitoring response after a course of IV iron, and in other circumstances where iron stores may become depleted.

In our opinion, intensification of iron therapy for hemodialysis patients should be considered at a serum ferritin of <200 ng/mL or TSAT of <20%. We would recommend maintaining TSAT >20% and serum ferritin > 100 ng/mL in peritoneal dialysis patients. Iron testing should usually be delayed for 1 week after treatment with intravenous iron. **Functional iron deficiency** can manifest as a low TSAT with normal or elevated ferritin levels. With inflammation and **reticuloendothelial blockade**, ferritin levels are typically increased, but TSAT may be normal, as serum iron may be low, but inflammation also lowers serum transferrin, and so the TSAT is often not reduced.

d. Reticulocyte hemoglobin content (CHr). This test is another test 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). When the CHr value is <29–32 pg/cell, patients are usually iron deficient and benefit from intravenous iron treatment.

3. Iron treatment

a. General principles. Iron therapy is an integral component ofanemia treatment in ESKD. Intravenous 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.

b. Oral iron. Oral iron preparations are safe and relatively inexpensive. However, these supplements are associated with poor efficacy and troublesome side effects, such as constipation, dyspepsia, bloating, or diarrhea. Three randomized trials have compared oral iron with either placebo or no iron treatment in hemodialysis patients; none of the three was able to demonstrate any efficacy for oral iron. Therefore, oral iron should not be used for most hemodialysis patients.

For patients on peritoneal dialysis, oral iron is much more convenient than intravenous iron. Since these patients experience less chronic blood loss, oral iron may be sufficient to maintain iron stores. Intravenous iron therapy should be used in peritoneal dialysis patients when resistance to ESA is present and the serum ferritin is <100 ng/mL and the TSAT is <20%. 1) Dosage and administration. Oral iron usually is given as ferrous sulfate, fumarate, or gluconate, in a dosage of 200 mg of elemental iron per day. The timing of the

iron dose is important; ideally, iron should be taken on an empty stomach to optimize efficacy. The primary sites of iron absorption are the duodenum and proximal jejunum, and gastrointestinal symptoms are proportional to the amount of elemental iron presented to the duodenum at a single time; reduction of symptomatology may require changing the oral preparation, using pediatric dosages at more frequent intervals, or even taking the iron dosage with food. Others have suggested giving the medication during dialysis sessions (e.g., at the beginning and the end of the session) to help ensure patient compliance. Yet another strategy is to give oral iron only at bedtime. A common problem with oral iron is constipation, which can be partially managed, if necessary, with stool softeners or laxatives. Some iron preparations contain small doses of ascorbic acid to enhance iron absorption, but the advantage of the added vitamin is not estab- lished. Phosphorus binders, antacids, histamine-2 antagonists, and proton-pump inhibitors may all inhibit the absorption of oral iron supplements. On the other hand, some novel phosphorus binders such as ferric citrate contain iron, and their use serves not only to reduce serum phosphorus in dialysis patients, but also to supply measurable amounts of iron via the gastrointestinal tract with lower requirements for IV iron and ESA (Umanath, 2013).

c. Intravenous iron. Four preparations are available in the United States: Iron dextran, ferric gluconate, ferumoxytol, and iron sucrose. Intravenous iron therapy has superior availability and efficacy when compared with oral iron therapy. In hemodialysis patients, the target hemoglo- bin level is difficult to achieve without intravenous iron treatment. As a result, most hemodialysis patients will require intravenous iron on a regular basis. In contrast, intravenous therapy costs more, and its safety profile is less clear than that of oral iron. There are two commonly used intravenous iron dosing strategies. One is to treat established iron deficiency with a repletive 1,000-mg dose administered over 8–10 consecutive hemodialysis treatments. Alternatively, since iron deficiency occurs so frequently in hemodialysis patients, a weekly maintenance dose of 25–100 mg may be used. A recent observational study found the repletion method to have greater efficacy compared with maintenance dosing (Kshirsagar, 2013a), while not obviously 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 intravenous iron is required for peritoneal dialysis patients, infusions of 250 mg of iron may be administered over 1–2 hours.

1) Intravenous iron safety: General considerations. The most important issue to understand about the safety of intravenous iron is that it has not been well studied. There have been no studies of sufficient size and duration. Because of iron's oxidizing properties, direct injection of iron into the circulation has important potential safety implications. Without adequate study data, it is difficult to balance the benefits or risks of intravenous iron.

2) Intravenous iron safety: Anaphylaxis. The best understood complication of intravenous 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. Such reactions are less frequently observed, and tend to be of milder intensity with the nondextran forms of iron.

3) Intravenous iron safety: Infection. Iron is a vital growth factor for microorganisms, and intravenous iron treatment has the potential to make iron more readily available to these pathogens. In addition, in vitro studies suggest that iron treatment may interfere with phagocytic function of white blood cells. Early retrospective studies found higher serum ferritin levels in hemodialysis patients to be associated with increased risk of infection. In contrast, a large, prospective, multicenter study (Hoen, 2002) found no relation between serum ferritin or treatment with intravenous iron and risk of bacteremia. The current literature on this subject remains inconclusive (Brookhart, 2013), but a prudent approach would be to avoid intravenous iron treatment during acute infectious episodes.

4) Intravenous iron safety: Oxidation. Iron is a highly oxidative substance, and treatment with intravenous iron has the potential to overburden the body's native antioxidant systems. Oxidative damage to tissue and molecules has been clearly demonstrated experimentally, although the clinical significance of such findings is not clear (Fishbane, 2014). A potential harmful effect of vascular oxidation would be an acceleration of atherosclerotic processes.

d. Intravenous iron drugs.

1) Intravenous iron dextran. Because of the higher expected risk of anaphylaxis, iron dextran use should generally be reserved for patients who have a long history of prior safe use of the drug. This is probably true for all current forms of iron dextran, but particularly the high molecular weight variety (Chertow, 2006). In nonuremic patients, immediate allergic reactions to intravenous iron dextran have been reported. These

usually occur within 5 minutes of injection but may be delayed by 45 minutes or more. For this reason, epinephrine and other means to treat anaphylaxis must be at hand when intravenous iron dextran is administered. Importantly, Walters and Van Wyck (2005) reported that almost all severe reactions occur with the test dose or first therapeutic dose. Milder immediate hypersensitivity reactions to iron dextran infusion include itching and urticaria. Delayed reac- tions can manifest as lymphadenopathy, myalgia, arthralgia, fever, and headache.

2) Sodium ferric gluconate. Intravenous sodium ferric gluconate is a nondextran form of iron used in the United States since 1999 and in Europe for several decades. As discussed above, adverse reactions are probably less frequent and less severe than those seen with iron dextran. 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; Michael, 2004). Intravenous sodium ferric gluconate may be administered to hemodialysis patients in the amount of 1,000 mg given in divided doses over eight consecutive treatments (i.e., 125 mg/dose).

3) Iron sucrose. Intravenous iron sucrose was approved for use in the United States in 2000 and has been in use in Europe for many years. Like sodium ferric gluconate, the other widely used nondextran form of iron, reports generally indicate a good safety and efficacy profile. No serious adverse reactions occurred in 665 hemodialysis patients 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 25–100 mg.

4) 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 adding a small amount of iron to the patient during each dialysis treatment. Preliminary phase 3 results of this compound have been encouraging (Lin, 2013), especially in reducing ESA dosage. A new drug application for Triferic was filed in the United States in 2014 for use of this compound, but it is not yet available for clinical use.

e) Other causes of ESA resistance.

1) Bleeding. Animportant cause of an apparent hyporesponsiveness to ESA is bleeding. Sometimes, the bleeding may be occult, as in gastrointestinal blood loss. Often, the bleeding may be obvious, as in patients undergoing surgery, menstruating women, or those with accidents involving the vascular access. It is

vitally important to limit blood loss by any means possible. In addition, fecal occult blood testing should be performed when unexplained ESA resistance is present.

2) Red blood cell life span. It is well known that RBC lifespan is 20%–30% shorter on average in hemodialysis or peritoneal dialysis patients than normal subjects. Recently, a correlation was found between the degree of shortening of RBC lifespan and ESA resistance, but no treatment has been devised to prolong RBC lifes- pan in those patients in whom lifespan is shortest (Dou, 2012).

3) Inflammation and infection. As with infection, inflammatory states lead to resistance to ESA therapy. In patients on dialysis, the underlying cause of inflammation may not be readily apparent. Cytokine release results in downregulation of expression of erythropoietin receptors on erythrocyte precursors. In addition, chronic inflammation and infection increases hepcidin production, which disrupts iron availability by diminishing intestinal iron absorption and release from reticuloendothelial cells (D'Angelo, 2013). There is no perfect marker for occult inflam- mation, but C-reactive protein (CRP) is a helpful test for predicting ESA hyporesponsiveness caused by inflammation (Kalantar-Zadeh, 2003). A retained, nonfunctioning renal allograft can increase CRP levels and be a source of EPO resistance (Lopez- Gomez, 2004). ESA resistance is increased in patients with evidence of cytomegalovirus (CMV) infection (Betjest, 2009), but, paradoxically, may be reduced in patients infected with hepatitis C (Seong, 2013). Also, in African American patients with sickle cell trait or hemoglobin C, a moderately higher aver- age ESA dose is required (about 12%, Derebail, 2014).

A search for occult infection should be undertaken in patients with unexplained ESA resistance. If infection is present, higher doses of ESA may be effective by partially overcoming the temporary resistance. One occult site of infection is in old, nonfunctioning, arteriovenous grafts, where treatment of the infection may reverse ESA resistance (Nassar, 2002).

4) Hyperparathyroidism. Hyperparathyroidism may be a cause of ESA resistance. There is a clear relationship between elevated iPTH levels and diminished ESA response. In addition, after parathyroidectomy, responsiveness improves (Al-Hilali, 2007). It does not appear that parathyroid hormone itself inhibits erythropoiesis. The pathogenesis is incompletely understood, but appears to represent a complex interplay of a variety of pathogenic factors. In the

ESA-resistant patient who is found to have elevated iPTH levels, an intensification of the treatment of hyperparathyroidism is indicated.

5) Vitamin D. Data suggest that Hgb levels are lower in dialysis patients with low serum levels of 25-hydroxyvitamin D, and vitamin D is a potent suppressor of hepcidin in humans, suggesting that treatment with vitamin D may improve anemia management. Although some preliminary data suggest that vitamin D treatment may be of some use, at present, results are preliminary and require confirmation by larger randomized trials (see Icardi, 2013)

6) Relative vitamin B12 deficiency. Vitamin B12 and folic acid levels should be checked when unexplained ESA resistance is present; a case can be made for more routine evaluation of this parameter. Many dialysis patients are taking proton-pump inhibitors, known to be associated with subnormal B12 levels, and intensive, high-flux hemodialysis and hemodiafiltration treatments have been shown to lower vitamin B12 levels. In one study from Australia (Killen, 2014), 91/142 hemodialysis patients had serum vitamin B12 levels of less than 300 pmol/L, a level suggesting deficiency. Only five patients had levels of less than 150 pmol/L, which represents clear-cut deficiency. A short course of three treatments of hydroxycobalamin 1,000 mcg per week was given. Treatment was repeated if B12 levels remained below 300 pmol/L. Hydroxycobalamin treatment resulted in a more than 50% reduction in median EPO requirement, from 11 to 5 thousand units per week. IV iron requirements were also reduced by half. The authors also suggest that cyanocobalamin (a form of B12 commonly used in oral supplements) should not be given to ESKD patients because of cyanide accumulation, but that hydroxycobalamin be used. In this study, B12 was given intramuscularly. It is not clear whether subcutaneous administration would lead to similar results.

7) Inadequate dialysis. In the urea reduction ratio (*URR*) range of 60 to 75%, there appears to be a weak association with increased hematocrit and higher levels of *URR* (Ifudu, 2000). Beyond that, careful, randomized studies of more frequent dialysis (i.e., the FHN Trials), either in-center or nocturnal, have shown no benefit in terms of increasing ESA responsiveness.

8) Aluminum intoxication. Although problems with aluminum have become less common among dialysis patients, 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.

9) Angiotensin-converting enzyme (ACE) inhibitors. ACE inhibitors may reduce EPO production in patients with chronic renal failure or following renal transplant. Among patients on dialysis, a reduction in ESA responsiveness has not been uniformly demonstrated in association with these agents.

10) Pure red cell aplasia. An outbreak of immune-mediated pure red cell aplasia has been 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, Hgb declines rapidly as does the reticulocyte count. Patients become transfusion-dependent, and the bone marrow demonstrates absence of erythroid precursors. The cause is the development of antierythropoietin antibodies that neutralize both therapeutic and endogenous erythropoietin. The majority of cases occurred in Europe, with epoetin alfa sold under the brand name of Eprex. After a peak in cases in 2002, the number declined substantially, but sporadic cases continued to develop. The cause of the syndrome (why do antierythrpoietin antibodies develop) was never fully elucidated. Certain biosimilar forms of ESAs have been associated with a greater risk for antierythropoietin antibodies, so vigilance is required as use of biosimilar ESAs increases.

11) Other hematologic disease. 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 the potential causes 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 as a last step in the process to rule out unexpected hematologic disease.

G. Red blood cell transfusions. Transfusion of packed red cells should be used in severely anemic patients who are experiencing symptoms. Transfusion should never be utilized without a concurrent evaluation for causes of bleeding.

H. Carnitine. It has been suggested that carnitine may enhance responsiveness to ESA. A recent 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. Ascorbic acid. Although the
I. literature is mixed, several studies have found that intravenous ascorbic acid may improve epo- etin responsiveness for patients on hemodialysis. A typical regimen is intravenous vitamin C given three times weekly with the hemodialysis treatment. Deved (2009) conducted a meta-analysis. While concerned about small sample sizes and deficits in study quality, the authors found ascorbic acid to generally result in increased Hgb 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.

II. HEMOlySIS

A. General comments. Destruction of RBCs, either intravascularly or extravascularly, may occasionally contribute to anemia in dialysis patients. Generally speaking, red cell survival appears to be shortened with chronic renal failure (approximately 30% compared with healthy subjects [Ly, 2004]). It is likely that this is due not to an inherent abnormality of the red cell, but to an effect of the uremic environment. Diagnosis. Chronic
B. hemolysis should be suspected when the patient develops high-grade ESA resistance in the presence of increased serum lactic dehydrogenase (LDH), unconjugated bilirubin, or a decrease in serum haptoglobin. The differen- tial diagnosis of chronic hemolysis is broad, and includes all causes of hemolysis seen in nonuremic patients (Table 34.2) and several causes specific to patients treated with hemodi- alysis. Occasionally, hemolysis can be 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). Etiology. The most
C. common correctible cause of hemolysis is due to some problem with the hemodialysis system. Faulty or kinked blood line 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 and 5. Treatment. If acute, severe hemolysis is suspected, the
D. dialysis treatment should be terminated immediately. Circulatory sup- port should be provided as needed, and an electrocardiogram

TABLE 34.2 Causes of Hemolysis in Dialysis Patients

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
Subclavian catheter (helmet cells, schistocytes)
Malfunctioning cardiac valve prosthesis
Insufficient dialysis
Hypersplenism
Associated diseases
Sickle cell anemia
Other hemoglobinopathies
Connective tissue diseases with vasculitis
Drug-induced
Hypophosphatemia

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 determination of hemoglobin, 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 muscle and joints. Prior to the introduction of dialysis, bleeding tendencies were long recognized among uremic subjects. 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 most important. Platelet counts may be slightly reduced, but commonly are normal in well-dialyzed patients, and severe thrombocytopenia is uncommon. Platelet aggregation is abnormal, probably because of reduced plate- let granule adenosine phosphate and serotonin levels, and defective thromboxane A2 production. Platelet function may also be hindered in uremic patients by increased endothelial

nitric oxide production (Remuzzi, 1990). An adhesion receptor, the glycoprotein (GP) IIb–IIIa complex, plays an important role in controlling the formation of platelet thrombi. In uremic patients, 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; abnormally prolonged bleeding time is significantly improved when the hematocrit is increased to >30%. The hemodialysis procedure itself may impact on 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 find- ing. Antiplatelet drugs may further impair platelet function in ESKD. Hemodialysis patients 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 and by testing of skin bleeding time. Patients with ecchymoses, excessive access bleeding, or any clinically significant bleeding episodes (including hemorrhagic pericarditis) should have platelet count, prothrombin time, partial thromboplastin time, and bleeding time tested. The bleeding time becomes abnormal when the platelet count is markedly decreased, when platelet function is impaired, or if the vascular wall is damaged. The risk of hemorrhage increases when the bleeding time is elevated to more than 10 minutes.

D. Treatment. The management of dialysis patients 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 previously underdialyzed patients often results in some improvement in bleeding tendency. The administration of cryoprecipitate (a plasma extract with high concentrations of von Willebrand factor) does not consistently result in improved platelet function. In one study, only two of five treated patients had normalized bleeding time and a favorable outcome (Triulzi, 1990). Desmopressin (a synthetic analog of antidiuretic hormone) leads to increased release of von Willebrand factor multim- ers. A dose of 0.3 mcg/kg body weight may be administered diluted in 50 mL of saline intravenously over 30 minutes. In a well-designed study, this regimen led to a reduction in bleeding time in 1 hour, which lasted for 8 hours. The drug has little vasoconstrictive effect and should not cause hyponatremia in ESKD patients. Finally, repetitive intravenous infusions of conjugated

estrogens may reduce bleeding time significantly. More practically, one oral dose of 25 mg conjugated estrogen (Premarin) normalizes bleeding time for up to 10 days. This effect is in contrast to the relatively short period of action of cryoprecipitate or desmopressin. We recommend the use of desmopressin empirically for dialysis patients with severe acute bleeding. In contrast, conjugated estrogens may be helpful in correcting an abnormal bleeding time prior to planned surgery or to treat chronic gastrointestinal bleeding in patients with telangiectasia. Estrogens alone, PO, IV, or transdermally (Sloand & Schiff, 1995), or estrogen– progesterone combinations have all been used (Boccardo, 2004).

References and Selected Readings

Alarcon MC, et al. Hormone therapy with estrogen patches for the treatment of recurrent digestive hemorrhages in uremic patients. Nefrologia. 2002;22:208–209.

Al-Hilali N, et al. Does parathyroid hormone affect erythropoietin therapy in dialysis patients? Med Princ Pract. 2007;16:63–67.

Aronoff G, et al. Iron sucrose in hemodialysis patients: safety of replacement and maintenance regimens. Kidney Int. 2004;66:1193–1198.

Besarab A, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med. 1998;339:584–590.

Betjest MGH, Weimar W, Litjens NHR. CMV seropositivity determines epoetin dose and hemoglobin levels in patients with CKD. J Am Soc Nephrol. 2009;20:2661–266

Boven K, et al. Epoetin-associated pure red cell aplasia in patients with chronic kidney disease: solving the mystery. Nephrol Dial Transplant. 2005;20(suppl 3):iii33–iii40.

Brookhart MA, et al. Infection risk with bolus versus maintenance iron supplementation in hemodialysis patients. J Am Soc Nephrol. 2013;24:1151–1158.

Brugnara C. Iron deficiency and erythropoiesis: new diagnostic approaches. Clin Chem 2003;49:1573–1578.

Chertow GM, et al. Update on adverse effects associated with parenteral iron. Nephrol Dial Transplant. 2006;21:378–382.

Coritsidis GN, et al. Anemia management trends in hospital-based dialysis centers (HBDCs), 2010 to 2013. Clin Therap. 2014;36:408–418.

D'Angelo G. Role of hepcidin in the pathophysiology and diagnosis of anemia. Blood Res. 2013;48:10–15.

Daugirdas JT, Bernardo AA. Hemodialysis effect on platelet count and function and hemodialysis-associated thrombocytopenia. Kidney Int. 2012;82:147–157.

Derebail VK, et al. Sickle trait in African-American hemodialysis patients and higher erythropoiesis-stimulating agent dose. J Am Soc Nephrol. 2014;25:819–826.

Deved V, et al; Alberta Kidney Disease Network. Ascorbic acid for anemia management in hemodialysis patients: a systematic review and meta-analysis. Am J Kidney Dis. 2009;54:1089–1097.

Drüeke TB, et al, and the CREATE Investigators. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med. 2006;355: 2071–2084.

Dou Y, et al. Red blood cell life span and 'erythropoietin resistance'. Kidney Int. 2012;81:1275–1276.

Duffy R, et al. Multistate outbreak of hemolysis in hemodialysis patients traced to faulty blood tubing sets. Kidney Int. 2000;57:1668–1674.

Escolar G, Diaz-Ricart M, Cases A. Uremic platelet dysfunction: past and present [Review]. Curr Hematol Rep. 2005;4:359–367.

Fishbane S, et al. A randomized trial of iron deficiency testing strategies in hemodialysis patients. Kidney Int. 2001;60:2406–2411.

Fishbane S, Mathew A, Vaziri ND. Iron toxicity: relevance for dialysis patients. Nephrol Dial Transplant. 2014;29:255–259.

Foley RN, et al. Effect of hemoglobin levels in hemodialysis patients with asymptomatic cardiomyopathy. Kidney Int. 2000;58:1325–1335.

Furuland H, et al. A randomized controlled trial of haemoglobin normalization with epoetin alfa in pre-dialysis and dialysis patients. Nephrol Dial Transplant. 2003;18:353–361.

Gaweda AE, et al. Determining optimum hemoglobin sampling for anemia management from every-treatment data. Clin J Am Soc Nephrol. 2010;5:1939–1945.

Gaweda AE, et al. Individualized anemia management reduces hemoglobin variabilit in hemodialysis patients. J Am Soc Nephrol. 2014;25:159–166.

Gunnell J, et al. Acute-phase response predicts erythropoietin resistance in hemodia sis and peritoneal dialysis patients. Am J Kidney Dis. 1999;33:63–72.

Hazzan AD, et al. ESA treatment and cancer. Kidney Int. 2014;86:34-39.

Hiremath S, et al. Antiplatelet medications in hemodialysis patients: a systematic review of bleeding rates. Clin J Am Soc Nephrol. 2009;4:1347–1355.

Hoen B, et al. Intravenous iron administration does not significantly increase the risk of bacteremia in chronic hemodialysis patients. Clin Nephrol. 2002;57:457–461.

Icardi A, et al. Renal anaemia and EPO hyporesponsiveness associated with vitamin D deficiency: the potential role of inflammation. Nephrol Dial Transplant. 2013;28:1672–1679.

Ifudu O, et al. Adequacy of dialysis and differences in hematocrit among dialysis facilities. Am J Kidney Dis. 2000;36:1166-74.

Kalantar-Zadeh K, et al. Effect of malnutrition-inflammation complex syndrome on EPO hyporesponsiveness in maintenance hemodialysis patients. Am J Kidney Dis. 2003;42:761–773.

Kaufman JS, et al. Subcutaneous compared with intravenous epoetin in patients receiving hemodialysis. Department of Veterans Affairs Cooperative Study Group on Erythropoietin in Hemodialysis Patients. N Engl J Med. 1998;339:578–583.

Kaw D, Malhotra D. Platelet dysfunction and end-stage renal disease. Semin Dia 2006;19:317–22.

Killen JP, Brenninger VL. Hydroxycobalamin supplementation and erythropoiesis stimulating agent hyporesponsiveness in haemodialysis patients. Nephrology. 2014;19:164–171.

Kshirsagar AV, et al. The comparative short-term effectiveness of iron dosing and for mulations in us hemodialysis patients. Am J Med. 2013a;126:541.

Kshirsagar AV, et al. Intravenous iron supplementation practices and short-term risk cardiovascular events in hemodialysis patients. PLoS One. 2013b;8:e78930.

Levin A, et al. Canadian randomized trial of hemoglobin maintenance to prevent or delay left ventricular mass growth in patients with CKD. Am J Kidney Dis. 2005;46:799–811.

Lines SW, et al. A predictive algorithm for the management of anaemia in haemodial sis patients based on ESA pharmacodynamics: better results for less work. Neph Dial Transplant. 2012;27:2425–2429.

Lin VH, et al. Soluble ferric pyrophosphate (SFP) administered via dialysate reduces ESA requirements in CKD-HD patients with ESA hypo-response, SA-OR082 [abstract]. J Am Soc Nephrol. 2013;24:90A.

Lopez-Gomez JM, et al. Presence of a failed kidney transplant in patients who are on hemodialysis is associated with chronic inflammatory state and erythropoietin resistance. J Am Soc Nephrol. 2004;15:2494–2501.

Ly J, et al. Red blood cell survival in chronic renal failure. Am J Kidney Dis. 2004; 715–719.

Macdougall IC, et al. Pharmacokinetics of novel erythropoiesis stimulating protein (NESP) compared with epoietin alfa in dialysis patients. J Am Soc Nephro 1999;10:2392–2395.

Mercadal L, et al. L-carnitine treatment in incident hemodialysis patients: the multicenter, randomized, double-blinded, placebo-controlled CARNIDIAL trial. Clin J Am Soc Nephrol. 2012;7:1836–1842.

Michael B, et al. Sodium ferric gluconate complex in hemodialysis patients: adverse reactions compared to placebo and iron dextran. Kidney Int. 2002;61:1830–1839

Michael B, et al. Sodium ferric gluconate complex in haemodialysis patients: a prosp tive evaluation of long-term safety. Nephrol Dial Transplant. 2004;19:1576–1580.

Nassar GM, et al. Occult infection of old nonfunctioning arteriovenous grafts: a novel cause of erythropoietin resistance and chronic inflammation in hemodialysis patients. Kidney Int Suppl. 2002;(80):49–54.

Noris M, Remuzzi G. Uremic bleeding: closing the circle after 30 years of controversi Blood. 1999;94:2569–2574.

Ofsthun N, et al. The effects of higher hemoglobin levels on mortality and hospitalization in hemodialysis patients. Kidney Int. 2003;63:1908–1914.
Parfrey PS, et al. Double-blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. J Am Soc Nephrol. 2005;16:2180–2189.
Pfeffer MA, et al, and the TREAT Investigators. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med. 2009;361:2019-2032.
Pillon L, Manzone T. Accuracy of anemia evaluation is improved in a wide variety of acute and chronically ill patients by accounting for volume status. J Am Soc Nephrol. 2008;19:164A.
Pollak VE, Lorch JA. Macrocytosis in chronic hemodialysis (HD) patients [abstract]. J Am Soc Nephrol. 2005;16:477A.
Remuzzi G, et al. Role of endothelium derived nitric oxide in the bleeding tendency of uremia. J Clin Invest. 1990;86:1768–1771.
Rodrigue MF, et al. Relationship between eicosanoids and endothelin-1 in the pathogenesis of erythropoietin-induced hypertension in uremic rats. J Cardiovasc Pharmacol. 2003;41:388–395.
Roob JM, et al. Vitamin E attenuates oxidative stress induced by intravenous iron in patients on hemodialysis. J Am Soc Nephrol. 2000;11:539–549.
Singh AK, et al and the CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med. 2006;355:2085-2098.
Sloand JA, Schiff MJ. Beneficial effect of low-dose transdermal estrogen on bleeding time and clinical bleeding in uremia. Am J Kidney Dis. 1995;26:22–26.
Spinowitz BS, et al. The safety and efficacy of ferumoxytol therapy in anemic chronic kidney disease patients. Kidney Int. 2005;68:1801–1806.
Triulzi DJ, Blumberg N. Variability in response to cryoprecipitate treatment for hemostatic defects in uremia. Yale J Biol Med. 1990;63:1–7.
Umanath K, et al. Ferric citrate as a phosphate binder reduces IV iron and erythropoietin stimulating agent (ESA) use, SA-PO-521 [abstract]. J Am Soc Nephrol. 2013;24:221A.
Van Wyck DB, et al. Safety and efficacy of iron sucrose in patients sensitive to iron dextran: North American Clinical Trial. Am J Kidney Dis. 2000;36:88–97.
Walters BA, Van Wyck DB. Benchmarking iron dextran sensitivity: reactions requiring resuscitative medication in incident and prevalent patients. Nephrol Dial Transplant. 2005;20:1438–1442.
Xia H, et al. Hematocrit levels and hospitalization risks in hemodialysis patients. J Am Soc Nephrol. 1999;10:1309–1316.

35 Infections

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I. DERANGEMENT OF IMMUNE FUNCTION IN UREMIA

A. Etiology. In dialysispatients, thereisimpairment of several aspects of lymphocyteand granulocyte function. Unidentified uremic toxinsarethought to be responsible; malnutrition or vitamin D deficiencycansometimes be contributory factors.

B. Clinical implications

1. Increased susceptibility to infection

a. Frequency of bacterial infections. Bacterial infections occur moreoftenin dialysis patients than in their nonuremic counterparts; the increase is probably related more to frequent violation of normal skin and mucosal barriers than to immune system dysfunction. Severity of

b. bacterial infections. Owing to the presence of a vascular access, infections in hemodialysis patients are often associated with bacteremia, and there is a substan- tial risk of serious complications such as endocarditis, osteomyelitis, and epidural abscess. Use of a hemodialysis catheter is associated with a threefold increase in hospitalization and death from septic complications as compared with use of a native or graft fistula. In peritoneal dialysis patients, peritonitis is rarely associated with systemic infection.

c. Role of hemodialysis membrane or peritoneal dialysis solution. Some of the immune defects previously attributed to uremia may be due, in part, to periodic exposure of the blood to certain dialysis membranes or to lack of removal of putative inhibitors of immune function by low-flux membranes. However, in the HEMO study, infection-related deaths were not reduced by utilization of biocompatible, high-flux dialyzers (Allon, 2004). In peritoneal dialysis patients, peritoneal neutrophil function is depressed owing to removal of opsonins (immunoglobulin and complement) in the dialysate and to regular exposure to low pH, high osmolality, and glucose degradation products present in some dialysis solutions.

II. DERANGEMENT OF TEMPERATURE CONTROL IN UREMIA

A. Baseline hypothermia in uremic patients. Inabout50% of hemodialysis patients, the predialysisbody temperature is subnormal. The reason for this is unknown. Reduced pyrexic response

B. associated with infections. Uremia per se does not appear to affect the temperature response to pyrogens. In addition, the degree of interleukin-1 (IL-1) production by stimulated uremic monocytes is normal. However, because of baseline hypothermia, and possibly because of frequently coex- isting malnutrition, severe infections in some dialysis patients may be associated with an attenuated or absent fever response.

III. BACTERIAL INFECTIONS IN DIALYSIS PATIENTS

A. Related to the access site

1. Hemodialysis patients. Prevention, diagnosis, and treatment ofvascularaccess infections are described in Chapters 9 (venous catheters) and 8 (fistulas and grafts). Several additional clinical points are emphasized here.

a. Bacteremia versus pyrogen reaction. The dialysis patient 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. Delayed treatment of sepsis in dialysis patients is an important cause of morbidity and mortality. In general, patients with venous hemodialysis catheters and fever should be assumed to have catheter-related bacteremia and treated with broad-spectrum antibiotics pending results of blood cultures.

1. Pyrogen reaction. Low-grade fever during hemodialysis 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 the rule: Fever and chills that occur shortly after catheter manipulation (for instance, commencement or cessation of dialysis) suggests catheter-associated bacteremia. Use of high-flux dialysis (especially in conjunction with bicarbonate dialysate) and dialyzer reuse are associated with an increased incidence of pyrogenic reactions. Blood cultures should always be obtained in any febrile hemodialysis patient, 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 hemodialysis machines or solutions. Occasionally, bacteremia may result from contamina- tion of hemodialysis machines. These are generally gram-negative and occasionally fungal infections. Outbreaks of such infections have been caused by inadequate disinfection of water treatment or distri- bution systems or reprocessed dialyzers (Rao, 2009). Contamination of the waste drain ports of the hemodialysis machine has alsobeen described.

b. Prophylactic antimicrobial administration 1. Prophylaxis prior to an invasive procedure likely to result in

Although there is no definite evidence in the literature, it is our policy to administer antimicrobial prophylaxis to hemodialysis patients prior to invasive procedures associated with a substantial risk of bacteremia because of the abnormal vascular communication present. 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 IM or IV given 30 minutes before the procedure). In penicillin-allergic patients, either clindamycin 600 mg by mouth or IV (dental or esophageal procedures) or vancomycin 1.0 g IV (other GI and genitourinary procedures) can be substituted.

2. Long-term, continuous prophylaxis. The skin and nasal carriage rate of *Staphylococcus aureus* in hemodi- alysis patients is about 50%. Intranasal mupirocin ointment is effective in eradicating the carrier state and in uncontrolled studies has decreased the inci- dence of staphylococcal infection. 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 con- cern is the development of mupirocin resistance with chronic use. In general, there is insufficient evidence to support routine *Staphylococcus aureus*, including methicillin-resistant *Staphylococcus aureus* (MRSA) decolonization.

On the other hand, a reduction in catheter-related bacteremia has been demonstrated by 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 (Lok and Mokrzycki, 2011). Their use is par- ticularly beneficial in patients who have nasal carriage of *Staphylococcus aureus*. Dry gauze dressings rather than transparent film dressings are recommended be- cause 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.

c. Vancomycin-resistant gram-positive infections. Concern about an increasing prevalence of vancomycin-resis- tant enterococci (VRE) in hospitalized patients has resulted in recommendations that vancomycin use be restricted in dialysis patients. Because of the relatively high incidence of staphylococcal organisms resistant to antistaphylococcal penicillins and cephalosporins, it is currently our policy to utilize vancomycin as initial therapy of life-threatening suspected *S. aureus* infections (e.g., catheter-related bacteremia). If sensitivity results warrant, vancomycin can be discontinued in several days, and prolonged treatment with an alternative anti- biotic can then be employed. Certain cephalosporins (e.g., cefazolin) have a very prolonged half-life in end- stage kidney disease (ESKD) patients and can be dosed conveniently postdialysis.

2. Peritoneal dialysis patients.
   a. Antimicrobial prophylaxis. In the absence of other indications for prophylaxis, we do not routinely administer antibiotics prior to invasive procedures unless a vascular access is present. Long-term, continuous prophylaxis is discussed in Chapter 27.

B. Unrelated to the access site
   1. Urinary tract infection (UTI). In dialysis patients, the incidence of UTI is high, especially in patients with polycystic kidney disease.
      a. Clinical presentation. In oliguric patients, the symptoms of cystitis are similar to those in nonuremic individuals, although gross hematuria is unusually common and occurs in up to one-third of cases. Anuric patients may present with suprapubic discomfort or foul-smelling urethral discharge and progress to pyocystis (see below).
      b. Diagnosis. Voided urine samples from oliguric patients, 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 symptomatic anuric patient. 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. As in nonuremic patients, a colony count greater than 103 in a properly collected urine specimen is considered to be suggestive of infection, but there are no good studies in dialysis patients.

c. Treatment. Optimally, antimicrobial therapy should be based on sensitivity testing of the organism involved. If empirical therapy is warranted, penicillin, ampicillin, cephalexin, a fluoroquinolone, or trimethoprim should be used because they are safe and may attain adequate urine levels in ESKD patients. Male patients from susceptible populations (Asian and Mediterranean) should be tested for glucose-6-phosphatase deficiency before receiving trimethoprim–sulfamethoxazole. In female dialysis patients, trimethoprim–sulfamethoxazole is generally chosen over ampicillin for 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 dialysis patients with cystitis has not been well studied. A urine culture should be repeated on the third or fourth day of treatment documenting that the urine shows no growth, and therapy should be continued for a total of 5–7 days. Ten days of antimicrobial therapy is warranted in patients with adult polycystic kidney disease because of their increased susceptibility to pyogenic complica- tions of UTIs. A follow-up urine culture should be ob- tained 7–10 days after completing therapy.

It is difficult to achieve adequate urinary drug levels of ticarcillin, doxycycline, sulfisoxazole, and the aminoglycosides in dialysis patients; hence, these agents are not recommended for treatment of cystitis. However, when the responsible urinary pathogen is resistant to trimethoprim–sulfamethoxazole, cephalexin, fluoroquinolones, and the penicillins, one of these alterna- tive 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 anuric patients due to the prolonged half-lives of these agents and the accumulation of toxic metabolites.

If repeated culture and sensitivity testing show bacterial resistance, the antimicrobial therapy should be adjusted. If the original infecting organism is still sensi- tive to the initial therapy, the dosage should be increased if possible or intravesical antimicrobial therapy should be administered. If a source of bacteria, such as a stag- horn calculus, is identified, it must be removed to cure the UTI permanently. Bacterial persistence is a recurrent

infection from a source within the urinary tract. It is suspected if infections with the same bacteria return immediately after treatment is completed. Causes include infected cysts, infection stones (e.g., staghorn calculus), and bacterial prostatitis. Reinfection is a recurrent infection caused by the same or different species of bacteria entering the urinary tract at varied intervals. Reinfection 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 reinfe ction .

All patients with recurrent infection 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 dialysis patients 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 removed surgically. The safety of long-term antimicrobial prophylaxis in dialysis patients with frequent urinary bladder reinfections is not known. Low-dose trimethoprim– sulfamethoxazole and cephalexin would probably be the safest drugs to use.

d. Upper urinary tract infections and pyogenic complications.

Upper tract infections in dialysis patients occur most commonly as a result of retrograde ascent of urinary pathogens in the urinary tract. Rarely, acute pyelonephritis occurs in dialysis patients from a hematogenic 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 (111In) leukocyte imaging and gallium-67 (67Ga) 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 immediate 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 (e.g., diabetic patients), pyocystis (pus in the defunctionalized bladder) may be an unsuspected source of infection. Pyocystis should always be suspected in an anuric dialysis patient 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 careful examina- tion. A complete peripheral blood count often shows leukocytosis. Blood cultures may or may not be positive. Bladder catheterization reveals pus, culture of which usually grows a 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 sensitivity reports, should be administered if sys- temic 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. Dialysis patients 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 inflam- mation, even in the absence of infection.
3. Intra-abdominal infections. Diverticulosis and diverticulitis occur commonly in dialysis patients, and especially in those with polycystic kidney disease. Strangulated hernia is also frequently encountered. In peritoneal dialysis patients, the differentiation between dialysis-associated peritoni- tis and peritonitis due to a disease process involving the abdominal viscera can be difficult (see Chapter 27). Acalcu- lous cholecystitis has been reported. Intestinal infarction can occur as a complication of hypotension occurring dur- ing a dialysis session or between dialyses; bowel infarction should always be suspected in a dialysis patient with unex- plained, refractory septic shock.
4. Tuberculosis. The incidence of tuberculosis has been estimated to be as much as tenfold higher among hemodialysis patients than among the general population. Tuberculosis in hemodialysis patients 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. New immunologic tests using interferon-gamma release assays have shown promise in ESKD patients

(Segall and Kovic, 2010; Grant, 2012). 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 culture of biopsy material. When the index of suspicion for tuberculosis is high, presump- tive therapy with antitubercular agents is sometimes warranted. Mortality in dialysis patients with tuberculosis has been reported to be as high as 40%.

5. Listeriosis. Listeriosis, an unusual infection in the nonimmunocompromised host, has been reported to occur in hemodialysis patients suffering from iron overload.
6. Salmonella septicemia. In dialysis patients, severe *Salmonella* septicemia has been noted to occur; in nonuremic patients, *Salmonella* enteritis rarely progresses to sepsis.
7. Yersinia septicemia. This infection has been reported in iron-loaded dialysis patients 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 ESKD patients as in patients with normal renal function. Therapy is similar to that for nonuremic patients.

IV. VIRAL INFECTIONS

A. Hepatitis A. The incidence of hepatitis A in dialysis patients is nogreater than in the general population, given that transmission is usually by the fecal–oral route. The disease pursues the usual clinical course in dialysis patients. Chronic hepatitis after hepatitis A infection is believed to occur rarely.

B. Hepatitis B

1. Epidemiology

a. The incidence of infection with hepatitis B virus (HBV) is now quite low in the United States. (Finelli, 2005). The low incidence is due to screening of the blood supply for evidence of this infection and to low transfusion requirements due to the availability of erythropoietin. However, outbreaks of hepatitis B in several hemodialysis units have occurred. Hepatitis B vaccine should be administered to all susceptible hemodialysis patients. Of note, only 50%–60% of vaccinated hemodialysis patients develop a protective antibody response; optimal vaccination techniques are discussed below.

b. Peritoneal dialysis patients. This group is at very low risk of acquiring hepatitis B infection. Nevertheless, hepatitis B can be transmitted through exposure to peritoneal ef f lu ent.

2. Clinical presentation. Hepatitis B infection is largely asymp- tomatic in dialysis patients. Commonly, malaise is the only complaint. The occurrence of visible jaundice is rare. The only manifestation of infection may be an unexplained, mild (two- to threefold) 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 con- centrations may remain normal or be
3. elevated only slightly. Chronic hepatitis B infection. Hepatitis B infection in dialysis patients 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 nondialysis patients. Patients with high serum ferritin levels appear to be at increased risk for developing persistent hepatitis. Treatment is indi- cated in HBsAg-positive patients with evidence of viral replication and abnormal transaminase levels, preferably
in conjunction with liver histology. A level of 4 to 5 log10 copies/mL 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, lamivudine, adefovir, or entecavir can be utilized for the treatment of chronic hepatitis B. Entecavir is the recommended first-line therapy in dialysis patients. The doses of all antiviral medications must be adjusted appropriately according to renal function. The dosing for lamivudine, adefovir, and entecavir are 100 mg by mouth daily, 10 mg by mouth daily, and 0.05 mg by mouth daily, respectively. In view of the side effects of interferon in patients on dialysis, nucleotide or nucleoside analogs are better choices.

4. Routine screening. Hemodialysis patients 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 then be tested monthly in 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
5. positive for anti-HBc but negative for HBsAg and anti-HBs as such patients can occasionally be infectious.

Prevention
Epidemiologic principles can be utilized to decrease the risk of hepatitis B infection, both among patients and among dialysis staff. Table 35.1 lists some helpful precautions.

a. Restricting the possibility of exposure to the virus.

Some centers recommend that patients with hepatitis B antigenemia be treated with either home hemodialysis or home peritoneal dialysis in order to decrease the chance of transmission to other patients and staff.

b. Vaccination. See Section V below.

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 dialysis patients is higher than in healthy populations. Recent data indicate that 8%–10% of dialysis patients in the United States have anti-HCV. Worldwide, there is considerable variability in the prevalence of anti-HCV, ranging from 1% to 63%. However, there is also great variability in HCV testing practices in dialysis centers (Meyers, 2003). The high incidence and prevalence of HCV infection among dialy- sis patients can be attributed to several risk factors, includ- ing number of blood transfusions, duration of dialysis, mode of dialysis (lower risk in peritoneal dialysis patients), and a

TABLE 35.1 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 HBsAg-positive patients (not necessary for human immunodeficiency virus [HIV]- and hepatitis C virus [HCV]-infected patients)
   c. Cleansing of dialysis machines and blood/body fluid contaminated areas with 1% sodium hypochlorite (bleach) solution
   d. Dialyzer reuse prohibited for HBV-positive patients (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 (e.g., 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 weeks later
   b. Testing for HIV (employee consent required) at time of incident and 6 weeks and 6 months 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)

history of previous organ transplantation or intravenous drug abuse. Infection rates among dialysis patients in the United States have not changed appreciably since tests for anti-HCV were first developed in the early 1990s. At the present time, there is no evidence that sharing of dialysis machines, type of dialysis membrane used, or dialyzer reprocessing are risk factors. Therefore, the Centers for Disease Control and Prevention (CDC) does not recommend dedicated machines, isolation of patients, or prohibition of reuse in hemodialysis patients with anti-HCV. However, observations suggest both a higher incidence of new cases of hepatitis C 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 HCV-positive patients, use of dedicated machines, and restriction on dialyzer reuse for patients infected with HCV may be warranted (Agarwal, 2011). The CDC recom- mends that all hemodialysis patients should be tested for anti-HCV antibodies on admission, and anti-HCV-negative patients should be tested for anti-HCV antibodies semiannu- ally thereafter.

The prevalence of anti-HCV among dialysis staff is similar to that of the general population (0%–6%). Immune globulin and/or α-interferon for postexposure prophylaxis against hepatitis C in health care workers are not recommended.

The natural history of hepatitis C in dialysis patients is difficult to ascertain since there have been no large studies in which liver biopsy was performed. The association between liver enzymes (e.g., ALT) and histologic severity is poor. Multivariate analyses have shown an increased risk of death in hepatitis C–infected patients, with excess mortality predominantly due to cirrhosis and liver cancer.

Until very recently (Gentile, 2014), treatment options were suboptimal. α-Interferon results in decreased transaminase levels and improved liver histology in most patients, with a sustained response in about 40% of patients, a response rate at least comparable to that seen in patients without renal disease. However, the incidence of side effects is substantial. Common side effects are myalgias, headache, fatigue, and depression, but more serious adverse effects, including bone marrow suppression, pancreatitis, cardiac failure, and lymphoma, have been reported. Therefore, the benefit-to-risk ratio in the dialysis population is unclear. Treatments with interferon (IFN-α2a) and pegylated IFN achieve a cure rate of 30%–45% in this population. Addition of ribavirin may increase the cure rate, but is tolerated poorly in ESKD patients (Esforzado and Campistol, 2012). Ribavirin is normally renally excreted and causes dose-related hemolysis; therefore, it must be used with extreme caution and at a reduced dose in dialysis patients.

Treatment for hepatitis C should at present be considered only for patients with significant liver disease with a r easonable

likelihood of prolonged survival, especially in patients in whom transplantation is planned. A recent meta-analysis found that dose of IFN (≥3 × 106 thrice weekly), treatment for ≥6 months, treatment completion, lower baseline HCV RNA, female gender, and early virologic response were predictive of sustained virologic response (Gordon, 2009). 2008 KDIGO guidelines recommend monotherapy with standard IFN that is dose adjusted for a glomerular filtration rate (GFR) <15 mL/min per 1.73 m*2*. A possible regimen is 3 million units of IFNα-2b administered subcutaneously three times per week for 6 to 12 months (if tolerated). Close observation for significant side effects is mandatory.

The recent high cure rates achieved with new interferon-free drug regimens using combinations of direct-acting antiviral agents such as daclatasvir, asunaprevir, dasabuvir, sofosbuvir, and ABT-450/r-ombitasvir with or without ribavirin has markedly enhanced the chances for cure of hepatitis C infection in nondialysis patients (Chung and Baumert, 2014; Gentile, 2014). There is very limited experience with any of these new drug combinations in dialysis patients, although many of these drugs are primarily excreted by the liver. Some time will be needed to see how and to what extent these very new major advances against hepatitis C infection can be applied to the ESKD population.

D. Cytomegalovirus (CMV) and mononucleosis. These viral infections can mimic hepatitis due to B or C virus but occur uncommonly in dialysis patients.

E. Influenza. Dialysis patients 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 below.

F. Human immunodeficiency virus (HIV)

1. Incidence and prevalence. The rate of HIV infection in hemodialysis patients is elevated, but only slightly above that in the general population. The incidence of HIV infection in the U.S. ESKD program is stable. Both incidence and prevalence are much higher in large urban areas serving minorities.

2. Clinical manifestations. Dialysis patients 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 HIV-infected patients has markedly improved, and many patients who are HIV positive without other clinical manifestations can live for many years on dialysis.

3. Routine screening. There exists some controversy as to whether hemodialysis patients without clinical evidence of AIDS should be routinely screened for HIV positivity. The recommendation from the CDC is that routine screening

not be performed. However, some dialysis units (especially those serving high-risk populations) are screening for HIV. Issues of confidentiality must be balanced against the risk to other patients and dialysis staff.

4. Dialysis in patients who are HIV positive. The CDC recommendation is that the choice between hemodialysis and peritoneal dialysis should not be affected by the finding of HIV positivity. However, home dialysis will lessen any possible risk to other patients and to dialysis staff. The peritoneal effluent of HIV-positive patients should be considered infectious and handled appropriately. If hemodialysis is elected, the CDC guidelines maintain that only the usual body fluid precautions attendant to routine dialysis need be followed. The CDC does not recommend that a special dialysis machine be set aside for HIV-positive patients, and dialyzer reuse in HIV-positive patients is not forbidden.

A number of dialysis units see the CDC recommendations as too liberal and are treating HIV-positive patients in the same manner as patients who are HbsAg positive (see Table 35.1). 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.

V. VACCINATION. In dialysis patients, 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 dialysis patients. Table 35.2 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.

A. Vaccination against hepatitis B. All dialysis patients except those who are HbsAg or HbsAb (antibody) positive should receive the hepatitis B vaccine. To increase the chances of successful

TABLE 35.2 Immunizations Recommended for Dialysis Patients

Vaccine	Frequency of Administration
Influenza A and B	Annually
Tetanus, diphtheria	Booster every 10 years
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)

vaccination, the dosage of hepatitis B vaccine in dialysis patients should be twice the normal amount. Giving an additional dose, especially if there is a fall in antibody titer below 10 mIU/mL, is recommended. A series of four IM injections of 40 mcg HbsAg should be given into the deltoid muscles at intervals of 0, 1, 2, and 6 months to complete the primary immunization series. 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 nonuremic as well as in uremic patients).

Overall, the percentage of successful vaccination against hepatitis B in dialysis patients is less than in the general population, and rates as low as 50%–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 DIALYSIS PATIENTS. Table 35.3 lists dosing guidelines for most commonly used antimicrobial, antifungal, and antiviral agents in patients treated with intermittent hemodialysis and peritoneal dialysis. Due to increased efficiency of drug removal in continuous renal replacement therapy (CRRT), optimal dosing strategies for antimicrobials in CRRT differ from traditional dialysis dosing. Additional dosing recommendations for drugs studied in CRRT are provided in Chapter 15.

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 hemodialysis and peritoneal dialysis. Therefore, both dosage reduction and posthemodialysis 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.

Amoxicillin-clavulanate, ticarcillin-clavulanate, piperacillin-tazobactam, and ampicillin-sulbactam are examples of pencillins combined with β-lactamase inhibitors. β-lactamase inhibitors slow the breakdown of β-lactams by bacteria exhibiting resistance to pencillins. The β-lactamase inhibitor of these combination drugs may exhibit longer half-lives in ESKD. Clavulanate is a β-lactamase inhibitor that is frequently com-

TABLE 35.3 Systemic Antibiotic, Antiviral, and Antifungal Drug Dosages for an Adult Dialysis Patient

Drug	Usual Nonuremic Dosea	Half-life: Nonuremic Patient (hr)	Half-life: Dialysis Patient	Dialysis Patient Dosage (% of Nonuremic Dose)	Usual Dialysis Patient Dosage	Post-HD Supplement	Dosage for CAPDb
Antibiotics							
Penicillins							
Amoxicillin PO	250–500 mg q8h	0.7–1.4	7–21	50–80	250–500 mg q24h	DAD	250–500 mg q12h
Ampicillin IV	1–2 g q4–6h	1–1.8	7–20	50–80	1–2 g q12–24h	DAD	250 mg
Ampicillin/sulbactam IV	1.5–3 g q6h	See ampicillin			1.5–3 g q12–24h	DAD	q12h
Dicloxacillin PO	125–500 mg q6h	0.6–0.8	1.3 1.2	95–100	250 mg q6h	No	3 g q24h
Nafcillin IV	1–2 g q4h	0.5–1	0.3–	100	1–2 g q4h	No	Same
Oxacillin IV	0.5–1 g q4–6h	0.3–1	1.0	95–100	0.5–1.0 g q4–6h	No	Same
Penicillin G IV/IMc	0.5–4 mU q4h	0.5–0.84	3.3–	25–50	0.5–1 mU q4–6h or 1–2 mU q8–12h	DAD	Same
			5.1				Same
Penicillin V PO	250 mg q6h	0.5	4.0	50	250 mg q12h	No	Same

TABLE 35.3 Systemic Antibiotic, Antiviral, and Antifungal Drug Dosages for an Adult Dialysis Patient (continued)

Drug	Usual Nonuremic Dosea	Half-life: Nonuremic Patient (hr)	Half-life: Dialysis Patient (hr)	Dialysis Patient Dosage (% of Nonuremic Dose)	Usual Dialysis Patient Dosage	Post-HD Supplement	Dosage for CAPDb
Piperacillin IV	3–4 g q4–6h	1.0	3.3–5.1	50–70	2 g q8h	1g	3–4g q8h
Piperacillin/tazobactam IV	3.375–4.5 g q6–8h	See piperacillin			2.25 g q12h, for HAP 2.25 g q8h	0.75 g	Same
Ticarcillin/ clavulanate IV	3.1 g q4–6h	1.1	12	50–80	2 g (ticarcillin) q12h or 2 g q8h without supplemental dose	3.1 g	3.1 g q12h
Cephalosporins							
Cefaclor PO	0.25–0.5 g q8h	0.5–1	2.8	50–	250 mg q12h	250	Same Same
Cefadroxil PO	0.5–1 g q12h	1.4	22	80	1–2 g q36h	mg	0.5 mg
Cefazolin IV/IM	1–2 g q8h	2	40–70	25– 50	0.5–1 g q24 or 1–2 g q48–72h	0.5–1 g	q12h
Cefdinir PO	600 mg q.d. or 300 mg q12h	1.7	?	50– 80	300 mg q48h	300 mg 1g	?

(Continued)

TABLE 35.3 Systemic Antibiotic, Antiviral, and Antifungal Drug Dosages for an Adult Dialysis Patient (continued)

Drug	Usual Nonuremic Dosea	Half-life: Nonuremic Patient (hr)	Half-life: Dialysis Patient	Dialysis Patient: Dosage (% of Nonuremic Dose)	Usual Dialysis Patient Dosage	Post-HD Supplement	Dosage for CAPDb
Cefepime IV	1–2 g q8–12h	2	13.5	25	1 g q24h × 1 then 1–2 g q48–72h or 2 g t.i.w.	DAD	1–2 g q48h
Cefotaxime IV	1–2 g q4–12h	1–1.5	15–	50	1–2g q24h	DAD	1g q24h
Cefotetan IV/IM	1–2 g q12h	3–5	35	80–95	0.25–0.5 g q24h on non-dialysis days	1g	1 g q24h
Cefoxitin IV/IM	1–2 g q6–8h	0.6–1	13–23	15	0.5–1 g q12–48h	1–2 g	1g q24h
Cefpodoxime PO	100–400 mg q12h	2.2	9.8	25	100–400 mg t.i.w.	DAD	100–400 mg q24h
Cefprozil PO	500 mg q24h or 250–500 mg q12h, or 250 mg t.i.d.	1.3	6.0	45	250 mg q24h	DAD	?
Ceftaroline IV	600 mg q12h	2.7	?	33	200 mg q12h	DAD	?
Ceftazidime IV/IM	2 g q8h	1–2	13–25	0–50	0.5–1 g q24h or 1–2 g q48–72h	1 gd	1 g load then 500 mg q24h

TABLE 35.3 Systemic Antibiotic, Antiviral, and Antifungal Drug Dosages for an Adult Dialysis Patient (continued)

Drug	Usual Nonuremic Dosea	Half-life: Nonuremic Patient (hr)	Half-life: Dialysis Patient	Dialysis Patient: Dosage (% of Nonuremic Dose)	Usual Dialysis Patient Dosage	Post-HD Supplement	Dosage for CAPDb
Ceftibuten PO	400 mg q24h	2	13–22	25–50	400 mg or 9 mg/kg (after each dialysis session)	DAD	?
Ceftriaxone IV	1–2 g q12–24h	5–9	12–16	100	1–2 g q12–24h	None	Same
Cefuroxime IV	0.75–1.5 g q8h	1–2	17	75	0.75–1.5 g q24h	DAD	Same
Cefuroxime PO	250–500 mg q12h	1–2	17	33	?	?	?
Cephalexin PO	0.25–1.0 g q6h	0.5–1.2	30	50–80	250 mg q12-24h	DAD	Same
Carbapenems/ monobactams							
Aztreonam IV	1-2 g q6-8h	1.7–2.9	6–8	50–80	LD of 0.5, 1, or 2 g then 0.25-0.5 g q6-8h; or 500 mg q12h	for severe infections 125–250 mg after dialysis	Same

(Continued)

TABLE 35.3 Systemic Antibiotic, Antiviral, and Antifungal Drug Dosages for an Adult Dialysis Patient (continued)

Drug	Usual Nonuremic Dosea	Half-life: Nonuremic Patient (hr)	Half-life: Dialysis Patient	Dialysis Patient Dosage (% of Nonuremic Dose)	Usual Dialysis Patient Dosage	Post-HD Supplement	Dosage for CAPDb
Doripenem IV	500 mg q8h	1.0	18	48	250 mg q24h, for PSA 500 mg q12h (on day 1) then 500 mg q24h	?	?
Ertapenem IV/IM	1 g q24h	4.	>4.0	5	500 mg q24h	150 mgj	500 mg q24h
Imipenem/cilastin IV/IM	0.5 q6h	0	4	0	250–500 mg q12h	DAD	Dosed by weight
Meropenem IV	0.5-2 g q8h	1. 1–1.5	6–8	5 25	500 mg q24h	DAD	0.5-2 g q24h
Fluoroquinolones							
Ciprofloxacin IV	400 mg q12h IR 500–	3–	6–	90–	200–400 mg q24h	?	?
Ciprofloxacin PO	750 mg q12h; ER 500–1,000 mg q24h	5 3–	9 6–	100 90–	IR 250–500 mg q24h; ER 500 mg q 24h	DAD	Same
Gemifloxacin PO	320 mg q24h	7 7–12	9	100	160 mg q24h	DAD	Same
Levofloxacin IV/PO	750 mg q24h	6–8	76	25	750 mg once then 500 mg q48h	DAD	Same

TABLE 35.3 Systemic Antibiotic, Antiviral, and Antifungal Drug Dosages for an Adult Dialysis Patient (continued)

Drug	Usual Nonuremic Dosea	Half-life: Nonuremic Patient (hr)	Half-life: Dialysis Patient	Dialysis Patient: Dosage (% of Nonuremic Dose)	Usual Dialysis Patient Dosage	Post-HD Supplement	Dosage for CAPDb
Moxifloxacin IV/PO	400 mg q24h	8–15 (IV) 12–16 (PO)	9–16	100	400 mg q24h	No	Same
Ofloxacin IV/PO	200–400 mg q12h	4–5, then 20–25	28–37	25	100–200 mg q24h	DAD	300 mg q24h
Aminoglycosides							
Amikacin IV	5–7.5 mg/kg q12h	1.4–2.3	28–	8	See text	See text	See text
Gentamicin IV	1–2.5 mg/kg q8–12h	1.5–3	86	0	See text	See text	See text
Neomycin PO	0.5–2 g q6–8h	Avoid in renal failure	36–	5			
Streptomycin IM	15–30 mg/kg q24h	5	70 30–80	0 15	7.5–15 mg/kg t.i.w. on dialysis days	DAD	See text
Tobramycin IV	1–2.5 mg/kg q8–12h	2–3	5–70	30–75	1–2 mg/kg q48–72h	See text	See text
Macrolides and ketolides							
Azithromycin IV/PO	500 mg q24h × 1d, 250 mg q24h × 4 d	68–72	?	100	500 mg q24h × 1 d, 250 mg q24h × 4 d	No	Same

(Continued)

TABLE 35.3 Systemic Antibiotic, Antiviral, and Antifungal Drug Dosages for an Adult Dialysis Patient (continued)

Drug	Usual Nonuremic Dosea	Half-life: Nonuremic Patient (hr)	Half-life: Dialysis Patient	Dialysis Patient: Dosage (% of Nonuremic Dose)	Usual Dialysis Patient Dosage	Post-HD Supplement	Dosage for CAPDb
Clarithromycin PO	250–500 mg q12h	3–7	?	50	250 mg q12h	DAD	?
Erythromycin IV/PO	250–500 mg q6–12h	1.5-2	5–6	80–95	250–500 mg q6-12h	No	Same
Telithromycin PO	800 mg PO q24h	10	15		600 mg q24h	DAD	?
Glycopeptides							
Telavancin IV	10 mg/kg q24h	6.6–9.6	?	?	?	?	?
Vancomycin IV	15–20 mg/kg q12h	5–11	200–250	<10	1 g q4–7 d	See text	See text
Tetracyclines							
Demeclocycline PO	150 mg q6h or 300 mg q12h	Avoid in renal failure					
Doxycycline IV/PO	100–200 mg q12–24h	12–15	18–25	10	100–200 mg q12–24h	No	Same
Minocycline IV/PO	200 mg LD, 100 mg q12h	11–22	?	0 10 0	100 mg PO q12h	No	Same

TABLE 35.3 Systemic Antibiotic, Antiviral, and Antifungal Drug Dosages for an Adult Dialysis Patient (continued)

Drug	Usual Nonuremic Dosea	Half-life: Nonuremic Patient (hr)	Half-life: Dialysis Patient	Dialysis Patient: Dosage (% of Nonuremic Dose)	Usual Dialysis Patient Dosage	Post-HD Supplement	Dosage for CAPDb
Tetracycline PO	250–500 mg q6h	8–11	57–108	80–95	?	No	?
Nitroimidazoles							
Metronidazole IV/PO	500 mg q6–8h	8	18–32	0–50	500 mg q8–12h	DAD	250 mg q6–8h or 500 mg q12h
Tinidazole PO	2g q24h	13	11.1–14.7	100	2 g q24h	1g	?
Diaminopyrimidines							
Pyrimethamine PO	25–50 mg q24h	80–95		100	25–50 mg q24h	No	?
Trimethoprim (T)/ sulfameth-oxazole(S) IV/PO	See text	8–10 (T) 35 (S)	26 (T) 50 (S)	50	See text	See text	See text

(Continued)

TABLE 35.3 Systemic Antibiotic, Antiviral, and Antifungal Drug Dosages for an Adult Dialysis Patient (continued)

Drug	Usual Nonuremic Dosea	Half-life: Nonuremic Patient (hr)	Half-life: Dialysis Patient	Dialysis Patient Dosage (% of Nonuremic Dose)	Usual Dialysis Patient Dosage	Post-HD Supplement	Dosage for CAPDb
Antituberculars							
Ethambutol PO	15 mg/kg q24h	2.5–3.6	7–15	50	15 mg/kg q48h or 15 mg/kg t.i.w.	DAD	Same
Isoniazid IV/PO	300 mg q24h	0.5–1.5 (fast acetylators)	2.3	100f	300 mg q24h	DAD	Same
		2.5–3.6 (slow acetylators)	7–15				
Pyrazinamide PO	15–30	9–10	?	50	25–35 mg/kg	DAD	? ?
Rifabutin PO	mg/kg/d 300	45	ND	50	t.i.w. 150 mg	?	Same
Rifampin IV/PO	mg q24h 600	3.5	4.0	10	q24h 600 mg	No	
Miscellaneous antibiotics	mg q24h			0	q24h		
Colistin	1.25–2.5 mg/kg q12h	2–3	48–72		1.5 mg/kg q24–48h	DAD	?
Clindamycin PO	150–450 mg q6h	2–3, 3.4–5.1 (elderly)	4.0	100	Same	No	Same

TABLE 35.3 Systemic Antibiotic, Antiviral, and Antifungal Drug Dosages for an Adult Dialysis Patient (continued)

Drug	Usual Nonuremic Dosea	Half-life: Nonuremic Patient (hr)	Half-life: Dialysis Patient	Dialysis Patient Dosage (% of Nonuremic Dose)	Usual Dialysis Patient Dosage	Post-HD Supplement	Dosage for CAPDb
Clindamycin IV	600–900 mg q8h	2.3, 3.4–5.1 (elderly)	4.0	10	400–900 mg q8h	No	Same
Dapsone PO	50–100 mg q24h	10–50		0 10	Pneumocystis pneumonia prophylaxis 50 mg q12h	DAD	?
Daptomycin IV	4–6 mg/kg q24h	8–9	30	0 50	4–6 mg/kg q48hi or 6 mg/kg t.i.w. after dialysis	DAD	Same
Linezolid IV/PO	600 mg q12h	4–5	6–8	70	600 mg q12h	DADe	Same
Methenamine PO	1 g q6h (mandelate) 1 g q12h (hippurate)	Avoid in renal failure					
Nitrofurantoin PO	50–100 mg q6h	Avoid in renal failure					
Quinupristin/ Dalfopristin IV	7.5 mg/kg q8–12h	1.3–1.5	?	100	7.5 mg/kg q8–12h	No	Same
Spectinomycin IM	2–4 g once	1.2–2.8	4.7–29.3	50	2–4 g once	No	Same

(Continued)

TABLE 35.3 Systemic Antibiotic, Antiviral, and Antifungal Drug Dosages for an Adult Dialysis Patient (continued)

Drug	Usual Nonuremic Dosea	Half-life: Nonuremic Patient (hr)	Half-life: Dialysis Patient	Dialysis Patient Dosage (% of Nonuremic Dose)	Usual Dialysis Patient Dosage	Post-HD Supplement	Dosage for CAPDb
Antivirals							
Acyclovir IV	5–10 mg/kg q8h	3.	19.5	15–	2.5–5 mg/kg q24h	DAD	Same
Acyclovir PO	200–800 mg 5x/day	0	19.5	20	200 mg q12h	DAD	Same
Amantadine PO	100 mg q12h	3.	168–	15–	200 mg q wkg	No	Same
Boceprevir	300 mg t.i.d.	0	240	20	300 mg t.i.d.	No	Same
Cidofovir IV	5 mg/kg weekly to every other week	24	3	<10	Contraindicated with creatinine clearance ≤55 mL/min or serum creatinine >1.5 mg/dL		
Famciclovir PO	125–500 mg q8–12h	3 2–4	3–24	100 25	125–250 mg t.i.w.	DAD	?
Foscarnet IV	60 mg/kg q8h × 3 wk, then 90–120 mg/kg q24h	3.0	?	50–100	45–90 mg/kg t.i.w.	DAD	?
Ganciclovir IV	5 mg/kg/d q12–24h	1.7–5.8	5–28	25	0.625–1.25 mg/kg/dose t.i.w.	DAD	Same

TABLE 35.3 Systemic Antibiotic, Antiviral, and Antifungal Drug Dosages for an Adult Dialysis Patient (continued)

Drug	Usual Nonuremic Dosea	Half-life: Nonuremic Patient (hr)	Half-life: Dialysis Patient	Dialysis Patient Dosage (% of Nonuremic Dose)	Usual Dialysis Patient Dosage	Post-HD Supplement	Dosage for CAPDb
Oseltamivir PO	75 mg b.i.d.	6–10	No data	<20	75 mg t.i.w.	DAD	30 mg q7d
Ribavirin PO	800–1,200 mg in two divided doses daily	24 (capsule), 120–170 (tablet)	?	50	200 mg q24h	No	Same
Rimantidine PO	100 mg q12h	25	40	50	100 mg q24h	No	Same
Valacyclovir PO	1–2 g q 8–12h	3.0	14	16	500 mg q24h	DAD	Same
Valganciclovir PO	900 mg q12–24h	Avoid in patients receiving hemodialysis					
Zanamivir PO	10 mg b.i.d.	2.5–5	18.5	100	10 mg b.i.d.	No	Same
Antiretrovirals							
Abacavir PO	300 mg q12h or 600mg q24h	1–1.5	?	100	300 mg q12h	No	?
Adefovir PO	10 mg q24h	7.5	15	10–30	10 mg q7d	DAD	?
Atazanavir PO	300–400 mg q24h	7.0	?	97.9	300 q24hh	?	?

(Continued)

TABLE 35.3 Systemic Antibiotic, Antiviral, and Antifungal Drug Dosages for an Adult Dialysis Patient (continued)

Drug	Usual Nonuremic Dosea	Half-life: Nonuremic Patient (hr)	Half-life: Dialysis Patient	Dialysis Patient Dosage (% of Nonuremic Dose)	Usual Dialysis Patient Dosage	Post-HD Supplement	Dosage for CAPDb
Darunavir	800 mg q24h	15	? ?	43	? ? <60 kg: capsule	? ?	? ?
Delavirdine PO	400 mg q8h	5.8	2.5–	100	not	No	Same
Didanosine PO	25–60 kg: 200 mg q24h > 60 kg: 400 mg q24h	1.3–1.5	5	65–80	recommended >60 kg: 25 mg q24h 0.05–0.1 mg q24h		
Entecavir PO	0.5–1 mg q24h	128–149	?	87	?	DAD	Same
Efavirenz PO	600 mg q24h	40–55	?	100	Avoid in patients receiving dialysis	?	?
Elvitegravir/cobicstat/emtricitabine/tenofovir PO	1 tab q24h	4–13	?	?			
Enfuvirtide SC	90 mg q12h	3.8		100	90 mg q12h	No	?
Emtricitabine PO	Capsule 200 mg q24h; Solution 240 mg q24h	10	>10	70	Capsule 200 mg q96h; Solution 60 mg q24h	DAD	?
Fosamprenavir PO	1400 mg q24h	7.7	?	?	1400 mg q24h		?

TABLE 35.3 Systemic Antibiotic, Antiviral, and Antifungal Drug Dosages for an Adult Dialysis Patient (continued)

Drug	Usual Nonuremic Dosea	Half-life: Nonuremic Patient (hr)	Half-life: Dialysis Patient (hr)	Dialysis Patient Dosage (% of Nonuremic Dose)	Usual Dialysis Patient Dosage	Post-HD Supplement	Dosage for CAPDb
Indinavir PO	800 mg q8h	1.4–2.2	?	100	?	?	?
Lamivudine PO	150 mg q12h or 300 mg q24h	3–7	15–35	76	50 mg LD, then 25 mg q24h	No	Same
Lopinavir/ritonavir PO (1 tablet = 200 mg lopinavir and 50 mg ritonavir)	2 tablets q12h	3.67		100	2 tablets q12h	No	?
Maraviroc PO	300 mg q12h	14–18	?	10	300 mg q12h	?	?
Nelfinavir PO	1250 mg q12h or 750 mg q8h	3.5–5	?	0 10	1250 mg q12h	?	Same
Nevirapine PO	200 mg q12h	25–30	?	56	?	200 mg	?
Raltegravir PO	400 mg q12h	9	?	100	400 mg q12h	DAD	?
Rilpivirine PO	25 mg q24h	50	?	100	25 mg q24h	No	Same
Ritonavir PO	600 mg q12h	3–5	?	100	?	?	?

(Continued)

TABLE 35.3 Systemic Antibiotic, Antiviral, and Antifungal Drug Dosages for an Adult Dialysis Patient (continued)

Drug	Usual Nonuremic Dosea	Half-life: Nonuremic Patient (hr)	Half-life: Dialysis Patient	Dialysis Patient: Dosage (% of Nonuremic Dose)	Usual Dialysis Patient Dosage	Post-HD Supplement	Dosage for CAPDb
Saquinavir	1000 mg b.i.d. with 100 mg ritonavir b.i.d.	13	?	100	?	?	?
Stavudine PO	≥60 kg:40 mg q12h <60 kg:30 mg q12h	1.6	1.55–5.4	69	≥60 kg: 20 mg q24h < 60 kg: 15 mg q24h	DAD	?
Telaprevir PO	1125 mg q12h	4–11			?	?	? ? ? ?
Telbivudine PO	600mg q24h	40–49	? ?		600 mg q96h	DAD	Same
Tenofovir PO	300 mg q24h	17	?	90? 100	300 mg q7d	DAD	
Tipranavir PO	500 mg q12h	5.5–6	1.	See text	500mg q12h	?	
Zidovudine PO	300 mg q12h	1.0	4		100 mg q6–8h		
Antifungals							
Amphotericin B cholesteryl sulfate complex (Amphotec)	3–4 mg/kg/d	28	?	100	?	?	?
Amphotericin B lipid complex (Abelcet IV	5 mg/kg q24h	173 (after multiple doses)	?	100	5 mg/kg q24h	No	Same

TABLE 35.3 Systemic Antibiotic, Antiviral, and Antifungal Drug Dosages for an Adult Dialysis Patient (continued)

Drug	Usual Nonuremic Dosea	Half-life: Nonuremic Patient (hr)	Half-life: Dialysis Patient	Dialysis Patient: Dosage (% of Nonuremic Dose)	Usual Dialysis Patient Dosage	Post-HD Supplement	Dosage for CAPDb
Amphotericin B liposome (AmBisome IV	3–6 mg/kg q24h	7–10 (after a single 24h dosing interval)	?	100	3–6 mg/kg q24h	No	Same
Anidulafungin IV	100–200 mg day 1, then 50–100 mg q24h	40–50	?	100	100–200 mg day 1, then 50–100 mg q24h	No	?
Caspofungin IV	70 mg LD, 50 mg q24h	9–11	?	100	70 mg LD, 50 mg q24h	No	Same
Fluconazole IV/PO	150–800 mg q24h	30	?	100	200–800 q24h	DAD	?
Flucytosine PO	50–150 mg/kg/d in divided doses q6h	2–5	75–200	10–25	37.5 mg/kg q24–48h	DAD	0.5–1.0 g q24h
Griseofulvin PO (microsize)	500 mg q24h	9–24	?	100	?	?	?
Griseofulvin PO (ultramicrosize)	375–750 mg q24h	9–24	?	100	?	?	?
Itraconazole PO capsule	200–600 mg in divided doses daily	21	?	100	200–400 mg in divided doses daily	No	?

(Continued)

TABLE 35.3 Systemic Antibiotic, Antiviral, and Antifungal Drug Dosages for an Adult Dialysis Patient (continued)

Drug	Usual Nonuremic Dosea	Half-life: Nonuremic Patient (hr)	Half-life: Dialysis Patient	Dialysis Patient Dosage (% of Nonuremic Dose)	Usual Dialysis Patient Dosage	Post-HD Supplement	Dosage for CAPDb
Itraconazole PO suspension	100–200 mg q24h	21	?	100	?	?	?
Ketoconazole PO	200–400 mg q24h	8.0	8.0	100	200–400 mg q24h	No	?
Micafungin IV	50–150 mg q24h	11–21	?	100	50–150 mg q24h	No	?
Posaconazole PO Delayed-release tablet	300 mg q12h or q24h	26–31	?	100	300 mg q12h or q24h	No	?
Posaconazole PO Oral Suspension	100 – 400 q12h or q24h or 200 mg q8h Depends on indication	20–66	?	100	100–400 q12h or q24h or 200 mg q8h	No	?
Posaconazole IV	300 mg q 12–24h	Not recommended in patients with creatinine clearance No			≤ 50 mL/min or <18YOA		
Terbinafine PO	250 mg q24h	recommended in patients with creatinine clearance No			≤ 50 mL/min		
Voriconazole IV	6 mg/kg q12h LD, 4 mg/kg q12h	recommended in patients with creatinine clearance			≤ 50 mL/min		
Voriconazole PO	≥40 kg: 200 mg q12h	Variable and dose dependent		100	≥ 40 kg: 200 mg q12h	No	Same

TABLE 35.3 Systemic Antibiotic, Antiviral, and Antifungal Drug Dosages for an Adult Dialysis Patient (continued)

Drug	Usual Nonuremic Dosea	Half-life			Usual Dialysis Patient Dosage	Post-HD Supplement	Dosage for CAPDb
		Nonuremic Patient (hr)	Dialysis Patient (hr)	Dialysis Patient Dosage (% of Nonuremic Dose)			
	< 40 kg: 100 mg q12h				< 40 kg: 100 mg q12h	No	Same

DAD, no post-HD supplement required, but on hemodialysis days schedule the usual dialysis patient dose after the dialysis session; HD, hemodialysis; CAPD, continuous ambulatory peritoneal dialysis; IM, intramuscular; IV, intravenous; LD, loading dose; PD, peritoneal dialysis (primarily CAPD); PO, oral; SC, subcutaneous; q24hr, daily; q.h.s., at bedtime; t.i.d., three time/d; b.i.d., two times/d; t.i.w., three times per week.

[a] Usual doses recommended for treatment of moderate-to-severe infections.

[b] Same as usual dialysis patient dosage.

[c] Prolonged half-life allows dosing thrice weekly post-HD.

[d]

[e] Supplemental dose may be considered early in treatment course.

[f] No dosage reduction needed in patients known to be fast acetylators.

[g] Long-term administration best avoided unless blood levels are followed.

[h] Recommended only in antiretroviral treatment-naive patients as boosted therapy with ritonavir 100 mg once daily.

[i] If next planned dialysis is >72 hr away, give 9mg/kg.

[j] If dosed < 6 hr prior to HD give 150mg AD.

Sources: Lexi-Drug, Lexi-Comp ® [Internet database]. Hudson, OH: Lexi-Comp, Inc. Available at http://www.crlonline.com. Accessed April 10, 2014. Data from Facts and Comparisons. Available from http://online.factsandcomparisons.com. Accessed April 23, 2013; Up to date. Available from http://www.uptodate.com/contents/search. Accessed April 23, 2013; Micromedex. Available from http://www.micromedex.com/index.html. Accessed April 23, 2013; The Sanford guide to antimicrobial therapy 2012, 42nd ed. Antimicrobial Therapy Inc., Sperryville, VA, 2012; McNicholl IR, Rodriguez RA. Dosing of Antiretroviral Drugs in Adults with Chronic Kidney Disease and Hemodialysis. HIVinsite. Available at. http://hivinsite.ucsf.edu/insite?page=md-rr-18 Accessed May 10, 2013; Heintz BH, Matzke GR, Dager WE. Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. Pharmacotherapy. 2009;29:562–577; Stathoulopoulou F, et al. Clinical pharmacokinetics of oral acyclovir in patients on continuous ambulatory peritoneal dialysis. Nephron. 1996;74:337. Stanford Hospital and Clinics Antimicorobial Dosing Reference Guide 2013. Available at http://bugsanddrugs.stanford.edu/documents/2013SHCABXDosingGuide.pdf. Accessed April 10, 2014.

bined with amoxicillin or ticarcillin. 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 35.3 will usually apply as well to the antimicrobial–clavulanate combination.

Ticarcillin is no longer available without clavulanate in the United States or the United Kingdom. The recommended dose for ticarcillin-clavulanate in patients on hemodialysis is 2 g of ticarcillin component every 12 hours; supplemented with 3.1 g (ticarcillin/clavulanate) after each dialysis session. Alternatively, 2 g every 8 hours can be given without a supplemental dose for severe infections (Heintz, 2009). In CRRT, ticarcillin-clavulanate should not be administered in intervals exceeding every 8 hours. The clavulanate component is hepatically eliminated, and extending the dosing interval beyond 8 hours may result in loss of beta-lactamase inhibition (Trotman, 2005). In patients weighing less than 60 kg, ticarcillin-clavulanate dosing is weight based.

In renal failure, tazobactam accumulates proportionally to piperacillin, and dosing is based on the optimal piperacillin dose. Piperacillin-tazobactam should be dosed more frequently (2.25 g every 8 hours) for nosocomial pneumonia in patients on hemodialysis. Piperacillin- tazobactam is cleared by all forms of CRRT. In CH (continuous hemofiltration) the recommended dose is 2.25–3.375 g every 6–8 hours and in CHD (continuous hemodialysis) the dose is slightly higher: 2.25–3.375 g every 6 hours. Treatment of resistant pathogens, such as *Pseudomonas*, requires higher doses, and an alternate dosing of 4.5 g every 8 hours has been recommended. In CRRT, there is some concern of tazobactam accumulation, given its lower clearance relative to piperacillin, and using piperacillin alone to alternate with piperacillin-tazobactam, particularly in CH-dependent patients, may minimize this concern. Ampi- cillin-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 dosing adjustment is required in dialysis patients. The remaining cephalosporins are excreted by the kidney to a large extent (e.g., 30%–96%), and most are removed to some extent by dialysis; therefore, dosage reduction is almost always necessary for dialysis patients. Some of the long-acting cephalosporins (e.g., cefazolin, ceftazidime) can be administered thrice weekly (e.g., after each hemodialysis session in patients being dialyzed three times a week). In patients on intermittent hemodialysis, 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 at a higher dose of 4 g per day can be considered to treat *Pseudomonas* or life-threatening infections in order to maximize time above the minimum inhibitory concentration

(MIC) (Trotman, 2005). Cefepime doses of 1 g every 8 hours achieve similar steady-state concentrations as 2 g every 12 hours at lower costs (Heintz, 2009). Doses of 2 g every 8 hours may be needed to treat infection with gram-negative rods showing an MIC ≥4 mg/L (Heintz, 2009). Ceftaroline is the newest fifth generation cephalosporin and is the only cepha- losporin with some activity against MRSA. It is approved for treatment of skin and soft tissue infections as well as commu- nity-acquired pneumonia. Like others in its class, it is renally cleared and requires a significant dose reduction in ESKD.

Cephalosporins in CHD or CHDF (continuous hemodiafiltration) should be dosed according to the dosing recommendations for patients with a CrCl of 30–50 mL/min. Studies with ceftazadime appear to suggest CH does not remove cephalosporins as efficiently as CHD (Trotman, 2005). In CHDF, ceftazadime may be given with a 2-g loading dose followed by 3 g over 24 hours as a continuous IV infusion to maintain concentrations ≥ four times the MIC for susceptible pathogens (Heintz, 2009). Not all cephalosporins have been studied in CRRT; however, extrapolations on dosing can be made based on antibiotics of similar pharmacokinetic and molecular properties.

C. Carbapenem/monobactams. Imipenem is available with cilastatin as 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 CRRT, imipenem/cilastin doses of 250 mg every 6 hours or 500 mg every 8 hours are rec- ommended, while higher doses of 500 mg every 6 hours may be required for more resistant infections (Trotman, 2005).

Ertapenem, meropenem, and doripenem 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*. Ertapenem has the advantage of once-daily dosing. The dose should be reduced by 50% in patients with renal dysfunction. Meropenem has similar coverage to imipenem/cilastin, and doses of 500–1,000 mg every 12 hours are recommended in CRRT. Doripenem is the newest carbapenem, and 52% is removed during a 4-hour hemodialysis session in ESKD patients. The recommended dose with intermittent hemodialysis is 250 mg every 24 hours; however, when treating *Pseudomonas,* the recommended dose is 500 mg every 12 hours on day 1, followed by 500 mg every 24 hours.

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 rash to both penicillins and cephalosporins, or patients who have an immediate-type allergy (i.e., 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 di- alysis session (given in addition to the maintenance doses). Alternatively, aztreonam can be dosed 500 mg every 12 hours in patients on hemodialysis (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 orally and intravenously. Moxifloxacin is the only antibiotic in this class that does not require dosage adjustment with intermittent hemodialysis or CRRT. Levofloxacin is removed by CH and CHDF but not intermittent hemodialysis. Higher doses of ciprofloxa- cin may be required for CRRT. 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 for UTI. Oral and IV formulations of gatifloxacin were discontinued in 2006 owing to the risk of profound hypoglycemia.

E. Colistimethate. Colistimethate (Colistin) 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, colistin is one of the few drugs that can still have activity against multidrug-resistant gram-negative organisms such as *Pseudomonas* and *Acinetobacter*. It is a large, highly tissue-bound molecule, and dialytic removal is small. Doses should be based on ideal body weight in obese patients, and recommended doses are expressed in terms of colistin base. In CRRT, colistin can be dosed at 2.5 mg/kg every 48 hours; however, a single case report has demonstrated that the use of 2.5 mg/kg every 48 hours with a dialysate flow rate of 1 L/hour may be inadequate and that dosing every 24 hours was well-tolerated. Based on pharmacokinetic analysis, dosing as frequent as every 12 hours can be recommended in patients receiving CHDF (Li, 2005). Colistin also comes in nebulized inhalation form that can be used for bronchiectasis and pulmonary colonization/ infection in patients with cystic fibrosis.

F. Aminoglycosides. Renal excretion of aminoglycosides is normally > 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 dialysis patients) 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 obese patients.

1. Gentamicin and tobramycin
   a. Hemodialysis patients**.** In patients receiving hemodialysis three times a week, a loading dose of 2–3 mg/kg is recommended followed by maintenance doses according to indication as follows: For mild UTI or synergy (making use of a synergystic effect of aminoglycoside with other concomitantly administered antibiotics), 1 mg/kg every 48–72 hours is recommended and redosing for prehemodialysis or posthemodialysis concentrations <1 mg/L should be considered. For moderate-to-severe UTI, 1–1.5 mg/kg every 48–72 hours is recommended, and redosing for prehemodialysis concentrations <1.5–2 mg/L or posthemodialysis concentrations <1 mg/L should be considered. For systemic gram-negative rod infection, 1.5–2 mg/kg every 48–72 hours and redosing for prehemodialysis concentrations <3–5 mg/L or posthemodialysis concentrations <2 mg/L is recommended. Although removal of gentamicin and tobramycin is primarily renal, extrarenal excretion of up to 20–30 mg per day has been reported in dialysis patients. Furthermore, many dialysis patients have some residual renal function, accounting for some renal drug removal. The postdialysis dose will replace drug lost during hemodialysis and 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 below).

   b. Peritoneal dialysis patients. The easiest strategy for treating nonperitoneal infections in continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD) patients is to give the usual loading dose IV and then to add 4–6 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. CRRT. CRRT effectively removes aminoglycosides. The half-life of aminoglycosides in patients on CRRT is around 18–60 hours. In CRRT, a loading dose of 2–3 mg/kg should be followed by: 1 mg/kg every 24–36 hours (redose when concentration <1 mg/L) for

mild UTI or synergy, 1–1.5 mg/kg every 24–36 hours (redose when concentration <1.5–2 mg/L) for moderate-to-severe UTI, or 1.5–2.5 mg/kg every 24–48 hours (redose when concentration <3–5 mg/L) for systemic gram-negative infection. As with any aminoglyco- side 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 5.0–7.5 mg/kg. Redosing is recommended when prehemodialysis concentration is <10 mg/L or when posthemodialysis concentration is <6–8 mg/L (Heintz, 2009). In peritoneal dialysis patients, the recommended amount of amikacin to add to the peritoneal dialysis solution was formerly 18–25 mg/L. Now there has been a trend to use lower doses of amikacin (e.g., for peritonitis; see Chapter 27). The recommended CRRT dose for amikacin is a 10-mg/kg load with a maintenance dose of 7.5 mg/kg every 24–48 hours, with further adjustment based on serum drug levels. For severe gram-negative rod infections, the target peak concentration is 15–30 mg/L, and redosing is recommended when the concentration is <10 mg/L (Heintz, 2009).

H. Streptomycin. One-half of the normal (nonuremic) dosage should be administered after hemodialysis. In CAPD patients, 20 mg/L should be added to the dialysis solution. In CRRT, administer doses every 24–72 hours and monitor levels.

I. Monitoring of serum aminoglycoside levels. Serum drug levels should be monitored in all dialysis patients 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 c ommon .

1. Peak aminoglycoside levels. The volume of distribution for aminoglycosides in dialysis patients is similar to that for nonuremic patients; therefore, peak serum levels should be similar to those in nonuremic patients 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 nonuremic patients, the dosing interval of the aminoglycosides is adjusted based on the trough (predose) level, as trough levels >2 mg/L (gentamicin, tobramycin) or 10 mg/L (amikacin) are associated with toxicity. In dialysis patients, the altered pharmacokinetics of aminoglycosides may lead to difficulties in dosing. For example, when gentamicin is given posthemodialysis, 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 4.0–6.0 mg/L may be associated with predialysis levels of >2.0 mg/L. Thus, predialysis levels >2.0 mg/L may need to be accepted if therapeutic peak levels are desired. Whether predialysis levels of >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 peritoneal dialysis patients using IP maintenance dosages will result in random serum aminoglycoside levels of >2 mg/L (for gentamicin or tobramycin) or >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 3–6 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 four 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 and ketolides. Erythromycin undergoes 5%–20% renal excretion in nonuremic patients 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 <30mL/min and given after dialysis. Additional dose adjust- ments are necessary if coadministered with the protease inhibitors atazanvir and ritonavir, which may increase the serum concentration of clarithromycin. As with erythromycin, azithromycin does not require dosage adjustment for inter- mittent hemodialysis, peritoneal dialysis, or CRRT (Heintz, 2009).

The ketolides are a new class of antibiotics, similar to the macrolides. To date, telithromycin is the first and only agent on the market in the United States. Compared with the macrolides, the ketolides have additional activity against multiresistant *Streptococcus pneumoniae*, *S. aureus* (methicillin- and erythromycin-susceptible isolates only), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydia pneumoniae,* and

Mycoplasma pneumoniae. Telithromycin is currently approved only for mild to moderate community-acquired pneumonia; safety issues regarding hepatoxicity and fatal cases of myasthenia gravis alerted the Food and Drug Administration (FDA) and led them to remove prior approved indications for acute bacterial sinusitis and acute bacterial exacerbations of chronic bronchitis. In hemodialysis, the recommended dose is 600 mg once daily, and when renal impairment is accompanied by hepatic impairment, the dose should be further reduced to 400 mg once daily.

K. Glycopeptides. Vancomycin is useful for the treatment of severe gram-positive infections in dialysis patients. 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 7–10 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. In the past, target peak and trough plasma concentrations were typically 30–40 and 5–10 mg/L, respectively, and a usual regimen was to give a 1-g loading dose followed by 500 mg after each hemodialysis session. However, these doses are frequently inadequate, especially in patients with high body mass index. Moreover, the development of antibiotic resistance resulting in the need for higher vancomycin trough levels (15–20 mg/L) has been noted (Vandecasteele and De Vriese, 2010). It is now recommended that hospitalized patients with life-threatening infection should receive a 25–30 mg/kg (max 2 g) loading dose followed by posthemodialysis supplements guided by trough levels. Posthemodialysis doses of 500–1,000 mg or 5–10 mg/kg are recommended when trough levels are <10–15 mg/L (Heintz, 2009). An alternate strategy of redosing based on prehemodialysis concentrations is as follows: if <10 mg/L, administer 1,000 mg after hemodialysis; if 10–25 mg/L, administer 500–750 mg after hemodialysis; and if >25 mg/L, hold vancomycin.

Vancomycin is removed to only a minimal extent by peritoneal dialysis, and dosing is similar to that for hemodialysis patients. Vancomycin administration via peritoneal dialysis fluid should be 15–30 mg/L of peritoneal dialysis fluid, and systemic administration for peritoneal dialysis patients is with a loading dose of 1,000 mg, followed by 500–1000 mg every 48–72 hours with close monitoring of levels. In less ill patients who are managed in the outpatient hemodialysis center, once an administered posthemodialysis supplement has been shown to result in a desired trough concentration (i.e., prior to the next hemodialysis session), continued drug monitoring may not be necessary (Pai and Pai, 2004).

Suggested dosing for vancomycin in CRRT is as follows: CH, loading dose of 15–25 mg/kg, followed by either 1,000 mg every 48 hours or 10–15 mg/kg every 24–48 hours; CHD, loading dose of 15–25 mg/kg, followed by either 1,000 mg every 24 hours or 10–15 mg/kg every 24 hours; and CHDF, loading dose of 15–25 mg/kg, followed by either 1,000 mg every 24 hours or 7.5–10 mg/kg every 12 hours. For all forms of CRRT, redosing should be considered for vancomycin concentrations <10–15 mg/L. Vancomycin dosing is based on actual body weight.

In 2009, telavancin, an IV glycopeptide with activity against MRSA became available for the treatment for 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 *Staphylococcus 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 in patients with CrCl <50 mL/min; however, no adjustments are provided by the manufacturer for patients with CrCl <10 mL/min or on hemodialysis 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 (e.g., anemia, leukopenia, thrombocytopenia) and neuropathic (e.g., peripheral neuropathy) adverse events when administer- ing for extended periods is recommended. If linezolid is not given immediately after a dialysis session, then a supplemen- tal dose, especially early in the treatment course, may be considered. However, no supplemental dose or dosage adjustment for patients on intermittent hemodialysis, peritoneal dialysis, or CRRT has been suggested (Heintz, 2009; Trotman, 2005).

M. Daptomycin. Daptomcyin is a large molecule that does not appear to be readily removed by dialysis or CRRT. Higher doses of 6 mg/kg every 24 hours are recommended for *Staphylococcal* bacteremia. In obese patients, doses should be based on adjusted body weight. Dose adjustments in hemodialysis and CRRT used to coincide with the dose recommended for patients with CrCl <30 mL/min (Trotman, 2005); however, for CRRT, this dosing strategy appears to result in a low Cmax. Thus, patients on CRRT may require 4–6 mg/kg every 24 hours (or 8 mg/kg every 48 hours), depending on site or severity of

infection, and whether or not the patient is responding to standard dosing (Heintz, 2009). Alternatively, in intermit- tent hemodialysis and peritoneal dialysis, daptomycin can be dosed at 6 mg/kg after hemodialysis 3 times weekly (Salama, 2010). Baseline and weekly creatine phosphokinase monitor- ing 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 plasma 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 hemodialysis, peritoneal dialysis, or CRRT. Minocycline is minimally excreted by the kidney and can be given in the usual dosages, but should not exceed 200 mg per day.

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 show- ing an increased risk of death with tigecycline for approved uses as well as unnapproved 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-neg- ative activity as well as activity against methicillin-resistant *S. aureus*. Tigecycline is cleared by the liver and requires no renal dose adjustments in hemodialysis, peritoneal dialysis, or CRRT.

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%–90% excreted by the kidney. Renal excretion of sulfamethoxazole is normally 20%–30%. Trimethoprim and sulfamethoxazole are removed well by hemodialysis but poorly by peritoneal dialysis. For 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 (e.g., for treatment of *Pneumocystis carinii* pneumonia) in dialysis patients, 50% of the usual dose (the latter being 15–20 mg/kg per day based on the trimethoprim component) is given as divided doses every 6 to 12 hours; the incidence of leukopenia may be increased when treating dialysis patients, and careful

monitoring is essential. In CRRT, doses of 2.5–7.5 mg/kg of trimethoprim every 12 hours are recommended and are highly dependent on indication. Critically ill patients with *Pneumocystis carinii* pneumonia receiving CHDF 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 dialysis patients as the half-life does not differ if dosing is less than 600 mg daily. IP dosing of rifampin for treatment of peritonitis should be consid- ered, given the low dialysate concentration of the by mouth formulation, according to the International Society for Peritoneal Dialysis guidelines. 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 dialysis patients because decreased renal excretion is balanced by removal during dialysis. However, some authors recommend a small dosage reduction (e.g., 200 mg per day rather than 300 mg per day), because accumulation of isoniazid may occur in patients who are "slow acetylators" receiving 300 mg per day.

Ethambutol is largely excreted by the kidney in nonuremic patients. In dialyzed patients, an increase in the dosing interval is required (see Table 35.3). Patients on dialysis should receive the same pyrazinamide dose as patients with a CrCl <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 hemodialysis patients as excretion of amantadine is almost exclusively renal. Because of its large volume of distribution, amantadine is removed very slowly by either hemodialysis or peritoneal dialysis. Rimantadine is primarily metabolized by the liver, with <25% typically excreted unchanged by the kidney and is not removed by hemodialysis. Oseltamivir requires dose adjustment for CrCl <60 mL/min and requires weight-based dosing in children with renal impairment. 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 CAPD patients (Stathoulopoulou, 1996). In patients with residual renal function, IV acyclovir can lead to the formation of insoluble crys- tals in the renal tubules, which can lead to acute kidney injury (Perazella, 2003). Risk is decreased with administration of IV acyclovir over 1–2 hours (Laskin, 1983). Valacyclovir is the prodrug to acyclovir and offers about 55% more bioavailability (Perry and Faulds, 1996). Oral famciclovir is a prodrug to penciclovir, and the latter is available only as a topical formula- tion. 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 ≤55 mL/min (Lea and Brysom, 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 1–2 hours directly before cidofovir adminis- tration and giving probenecid 2 g by mouth 3 hours beforehand and 1 g 2 and 8 hours following cidofovir.

Foscarnet is primarily used in CMV-infected patients that have resistance to ganciclovir. It is only available as an IV drug owing to poor bioavailability of the oral formulation. Foscarnet is associated with a >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 60–90 mg/kg post dialysis followed by maintenance doses of 45–60 mg/kg, aiming at peak plasma concentrations of 400–800 mcmol/L has been suggested. In CRRT, dosing should be the same as for patients with CrCl of 10–50 mL/min. Valganciclovir is a prodrug of ganciclovir with higher oral bioavailability than oral ganciclovir. Owing to ganciclovir's poor bioavailability, the IV formulation is more commonly used. The manufacturer recommends that valganciclovir be avoided in patients receiving hemodialysis and to consider ganciclovir, instead. 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 ESKD patients with 100 mg t.i.d. dosing has been observed. There is no significant removal of the drug or its metabolite by either hemodialysis or peritoneal dialysis. Other NRTIs (e.g., didanosine, emtricitabine, lamivudine, tenofovir, stavudine) also require dosage adjustments in renal failure (see Table 35.3). 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 hemodialysis. Pharmacokinetic evaluations of most protease inhibitors in hemodialysis patients have not been conducted. Studies have been performed with atazanavir, lopinavir, and ritonavir that exhibit significantly lower concentrations in hemodialysis patients 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 atazanvir clearance and decreased exposure levels in patients managed with hemodialysis. Lopinavir/ritonavir should not be given less than twice daily with hemodialysis. Caution should be exercised with patients whose HIV virus has protease inhibitor resistance mutations as lopinavir and ritonavir levels may not be adequate for viral suppression in dialysis patients. 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, and rilpivirine are a heterogenous group with respect to limited renal clearance (see Table 35.3). 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 hemodialysis or peritoneal dialysis unlikely.

Enfuvirtide belongs to a new class of antiretrovirals (i.e., 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 <30 mL/min should not receive maraviroc. Hemodialysis 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 and elvitegravir/cobicistat both work through 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/cobicstat used in combination with emtricitabine/tenofovir should not be initiated in patients with CrCl <70 mL/min, and should be discontinued in patients with CrCl <50 mL/min.

To reduce the increasing pill burden of antiretroviral regimens, several fixed-dose combinations are currently available: efavirenz/emtricitabine/tenofovir, zidovudine/lamivudine, rilpivirine/emtricitabine/tenofovir, abacavir/lamivudine, zidovudine/lamivudine/abacavir, and emtricitabine/tenofovir. The general rule in hemodialysis is to substitute with the component drugs and adjust the dose of each drug separately.

T. Antifungals. The use of amphotericin B deoxycholate (conventional amphotericin B), the standard for treatment of fungal infections for decades, is limited because of its nephrotoxicity potential. Three lipid-based amphotericin B formulations are FDA approved (Amphotec, Abelcet, and AmBisome) with the intention of less toxicity compared with amphotericin B deoxycholate. Nephrotoxicity may 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.

The systemic azole antifungals include two groups: the triazoles, which encompass fluconazole, itraconazole, voriconazole, and posaconazole, 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.

Posaconazole affords the broadest spectrum of activity and interacts less with other drugs; however, the oral suspension formulation has an erratic bioavailability owing to its dependence on a high-fat meal. It is also available as delayed-release tablets, which provides an option in fasting patients.

An IV formulation has recently become available in April 2014, but is not recommended for use in patients with CrCl <50 mL/min. Itraconazole and voriconazole have erratic bioavailabil- ity, which is improved somewhat with use of the suspension formulation as opposed to the capsule. Voriconazole can also exhibit decreased bioavailability when taken with high-fat meals, and bioavailability is subject to variability on account of genetic factors, also. Voriconazole is the gold standard for the treatment of invasive aspergillosis. While oral voriconazole is not dose adjusted with renal dysfunction, the IV form cannot be given if a patient's CrCl is <50 mL/min owing to the accumulation of the vehicle cyclodextrin. The Infectious Diseases Society of America Guidelines recommend drug level monitoring for itraconazole when it is being used to treat aspergillosis, histoplasmosis, or blastomycosis. It is also becoming more common to see the monitoring of voriconazole and posaconazole drug levels, with trough recommendations between >1 mg/L and <5.5 mg/L, and ≥ 0.7 mg/L, respectively.

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 (e.g., 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).

Caspofungin, micafungin, and anidulafungin are antifungal agents belonging to a class of drugs called echinocandins. This class of antifungals works on the fungal cell wall compared with the 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 the echinocandins is comparable, and all have FDA indications for esophageal candidiasis and invasive candidiasis. Moreover, all agents are administered in IV form and do not need to be adjusted for renal dysfunction, although the dose of caspofungin should be reduced in moderate hepatic insufficiency. Unlike the azoles, echinocandins do not interact significantly with the cytochrome P450 enzyme class, resulting in fewer drug interactions, though monitoring of calcineurin inhibitor levels is recommended when being given with caspofungin and micafungin.

U. Postdialysis supplements. Recommended posthemodialysis supplements are listed in Table 35.3. These should be given in addition to the maintenance dosages listed. The

posthemodialysis supplements recommended here are geared for a conventional, 4-hour hemodialysis treatment only. With very short dialysis treatments, the amount of drug removed by hemodialysis may not be substantial enough to necessitate a posthemodialysis supplement, but timing of dosing so that a dose is given after dialysis is recommended. In general, peritoneal dialysis patients can be treated with usual hemodialysis patient doses. Drug dosing during CRRT has recently been reviewed elsewhere (Heintz, 2009).

References and Suggested Readings

Agarwal SK.Hemodialysis ofpatientswithHCV infection: isolation has a definite role. Nephron Clin Pract. 2011;117:c328–c332.

Allon M. Dialysis-catheter related bacteremia: treatment and prophylaxis. Am J Kidney Dis. 2004;44:779–791.

Andes D, et al. Antifungal therapeutic drug monitoring: established and emerging indications. Antimicrob Agents Chemother. 2009;53:24.

Aoki FY, et al. AMMI Canada Guidelines, "The use of antiviral drugs for influenza: guidance for practitioners 2012/2013". Can J Infect Dis Med Microbiol. 2012;23: e79–e92.

Ballantine L. Tuberculosis screening in a dialysis program. Nephrol Nurs J. 2000;27: 489–499; quiz 500–501.

Bloom S, et al. Clinical and economic effects of mupirocin calcium on preventing Staphylococcus aureus infection in hemodialysis patients. Am J Kidney Dis. 1996;27:687–694.

Bruchfeld A, et al. Pegylated interferon and ribavirin treatment for hepatitis C in haemodialysis patients. J Viral Hepat. 2006;13:316–321.

Chapman SW, et al. Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. Clin Infect Dis. 2008;46:1801.

Conly JM, Grieves K, Peters B. A prospective, randomized study comparing transparent and dry gauze dressings for central venous catheters. J Infect Dis. 1989;159: 310–319.

Degos F, et al. The tolerance and efficacy of interferon-alpha in haemodialysis patients with HCV infection: a multicentre, prospective study. Nephrol Dial Transplant. 2001;16:1017–1023.

Deray G, et al. Pharmacokinetics of 3'-azide-3 deoxy-thymidine (AZT) in a patient undergoing hemodialysis. Therapie. 1989;44:405.

Dinits-Pensy M, et al. The use of vaccines in adult patients with renal disease. Am J Kidney Dis. 2005;46:997–1011.

Esforzado N, Campistol JM. Treatment of hepatitis C in dialysis patients. Contrib Nephrol. 2012;176:54–65.

Fabrizi F, et al. Intradermal vs intramuscular vaccine against hepatitis B infection in dialysis patients: a meta-analysis of randomized trials. J Viral Hepat. 2011;18: 730–737.

Finelli L, et al. National surveillance of dialysis-associated diseases in the United States, 2002. Semin Dial. 2005;18:52–61.

Fiore AE, et al, Centers for Disease Control and Prevention (CDC). Antiviral agents for the treatment and chemoprophylaxis of influenza—recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2011;60:1.

Gentile I, et al. Interferon-free therapies for chronic hepatitis C: toward a hepatitis C virus-free world? Expert Rev Anti Infect Ther. 2014;12:763–773.

Gordon CE, et al. Interferon for hepatitis C virus in hemodialysis—an individual patient meat-analysis of factors associated with sustained virologic response. Clin J Am Soc Nephrol. 2009;4:1449–1458.

Grant J, et al. Interferon-gamma release assays are a better tuberculosis screening test for hemodialysis patients: a study and review of the literature. Can J Infect Dis Med Microbiol. 2012;23:114–116.

Heintz BH, Matzke GR, Dager WE. Antimicrobial dosing concepts and recommendations for critically ill adult patients receiving continuous renal replacement therapy or intermittent hemodialysis. Pharmacotherapy. 2009;29:562–577.
Jaber BL. Bacterial infections in hemodialysis patients: pathogenesis and prevention Kidney Int. 2005;67:2508–2519.
Kallen AJ, Jernigan JA, Patel PR. Decolonization to prevent infections with Staphylococcus aureus in patients undergoing hemodialysis: a review of current evidence Semin Dial. 2011;24:533–539.
Kubin CJ, et al. Incidence and predictors of acute kidney injury associated with intravenous polymyxin B therapy. J Infect. 2012;65:80–87.
Laskin OL. Clinical pharmacokinetics of acyclovir. Clin Pharmacokinet. 1983;8:187.
Lea AP, Bryson HM. Cidofovir. Drugs. 1996;52:225.
Li J, et al. Pharmacokinetics of colistin methanesulfonate and colistin in a critically ill patient receiving continuous venovenous hemodiafiltration. Antimicrob Agents Chemother. 2005;49:4814–4815.
Li, PK, et al. Peritoneal dialysis-related infections recommendations: 2010 update. P Dial Int. 2010;30:393–423.
Lok CE, Mokrzycki MH. Prevention and management of catheter-related infection in hemodialysis patients. Kidney Int. 2011;79:587–598.
Marr KA, et al. Catheter-related bacteremia and outcome of attempted catheter salvage in patients undergoing hemodialysis. Ann Intern Med. 1997;127 275–280.
Masuko K, et al. Infection with hepatitis GB virus C in patients on maintenance hemodialysis. N Engl J Med. 1996;334:1485–1490.
Messing B, et al. Antibiotic-lock technique: a new approach to optimal therapy for catheter-related sepsis in home-parenteral nutrition patients. J Parenter Enteral Nutr. 1988;12:185–189.
Meyers CM, et al. Hepatitis C and renal disease: an update. Am J Kidney Dis. 2003;42:631–657.
Novak JE, Szczech LA. Management of HIV-infected patients with ESRD. Adv Chron Kidney Dis. 2010;17:102–110.
Pai AB, Pai MP. Vancomycin dosing in high flux hemodialysis: a limited-sampling algorithm. Am J Health Syst Pharm. 2004;61:1812–1816.
Patel PR, et al. Epidemiology, surveillance, and prevention of hepatitis C virus infections in hemodialysis patients. Am J Kidney Dis. 2010;56:371–378.
Perazella MA. Drug-induced renal failure: update on new medications and unique mechanisms of nephrotoxicity. Am J Med Sci. 2003;325:349–362.
Perry CM, Faulds D. Valaciclovir: a review of its antiviral activity, pharmacokinetic properties and therapeutic efficacy in herpesvirus infections. Drugs. 1996;52:754
Rubinstein E, et al. Telavancin versus vancomycin for hospital-acquired pneumonia due to gram-positive pathogens. Clin Infect Dis. 2011;52:31–40.
Rao CY, et al. Contaminated product water as the source of Phialemonium curvatum bloodstream infection among patients undergoing hemodialysis. Infect Control Hosp Epidemiol. 2009;30:840–847.
Salama NN, et al. Single-dose daptomycin pharmacokinetics in chronic haemodialysis patients. Nephrol Dial Transplant. 2010;25:1279–1284.
Segall L, Covic A. Diagnosis of tuberculosis in dialysis patients: current strategies. C J Am Soc Nephrol. 2010;5:1114–1122.
Stathoulopoulou F, et al. Clinical pharmacokinetics of oral acyclovir in patients on continuous ambulatory peritoneal dialysis. Nephron. 1996;74:337.
Tokars JI, et al. National surveillance of hemodialysis associated diseases in the United States, 2000. Semin Dial. 2002;15:162–171.
Tong NKC, et al. Immunogenicity and safety of an adjuvanted hepatitis B vaccine in pre-hemodialysis and hemodialysis patients. Kidney Int. 2005;68:2298–2303.
Trifillis AL, et al. Use of human renal proximal tubule cell cultures for studying foscarnet-induced nephrotoxicity in vitro. Antimicrob Agents Chemother. 1993;37:2496.
Trotman RL, et al. Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy. Clin Infect Dis. 2005;41:1159–1166.
Van Geelen JA, et al. Immune response to hepatitis B vaccine in hemodialysis patien Nephron. 1987;45:216.
Vera EM, et al. Urinalysis in the diagnosis of urinary tract infections in hemodialysis patients. J Am Soc Nephrol. 2002;21:639A.

Vidal L, et al. Systematic comparison of four sources of drug information regarding adjustment of dose for renal function. Br J Med. 2005;331:263.
Vistide prescribing information. Gilead Sciences, Inc., Foster City, CA, USA; 1996.
Walsh TJ, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis. 2008;46:327.
Wheat LJ, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis. 2007;45:807.
Zampieron A, et al. European study on epidemiology and management of hepatitis C virus (HCV) infection in the haemodialysis population. Part 3: prevalence and incidence. EDTNA ERCA J. 2006;32:42–44.

36 Bone Disease

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Indialysispatients,themineralbone axis is deranged. In attempts tooptimize this,anumberofdrugs are usually given, including phosphorus binders,activevitamin D derivatives, and calcium-receptor-sensitizers.Dietaryrestrictions are often required to limit the amount ofphosphorusabsorbed. To understand how to manage the mineral bonedisorder(MBD)of chronic kidney disease (CKD), a basic understanding ofitspathophysiology is helpful.

I. PATHOPHYSIOLOGY. Three hormones are involved primarily in maintaining mineral bone homeostasis in early CKD: FGF23, calcitriol (also known as 1,25D or 1,25 dihydroxycholecalciferol), and parathyroid hormone (PTH). These hormones interact with the minerals calcium, phosphorus, and, to a lesser extent, magnesium to ensure adequate mineral absorption from the gut, appropriate mineral excretion by the kidney, and optimal conditions in the bone to permit ongoing mineralization and remodeling.
As kidney function declines, there is a progressive loss of the ability to maintain mineral homeostasis and normal bone turnover. The first problem that arises is the need to maintain excretion of phosphorus being ingested from food. The reduced number of functioning nephrons results in an increased phosphorus load being filtered by each nephron. In an attempt to help increase excretion of this added phosphorus load, the levels of the hormone **FGF23** (fibroblast growth factor 23) are increased. FGF23, produced by osteocytes, affects the function of renal tubular cells by acting on a Klotho-FGF receptor complex. FGF23 stimulates phosphaturia by decreasing the expression and activity of sodium-phosphate cotransporters in the renal tubules. These transporters normally function to reabsorb filtered phosphorus, and downregulating them increases the per nephron excretion of phosphorus, limiting phosphorus overload.

A second hormone involved in mineral bone homeostasis is **calcitriol**. Calcitriol is synthesized by the body in a 3-stage process. The first stage occurs in the skin, which, when exposed to ultraviolet light, converts 7-hydroxycholesterol into cholecalciferol (vitamin D3). Cholecalciferol is an inactive steroid prohormone; it becomes slightly active after the steroid ring is

hydroxylated in the 25-position by the liver. This so-called "25-D" can then be fully activated by a third step: hydroxylation of the steroid ring at the 1-position. This final hydroxylation step can occur in a variety of tissues locally, but the most important site where 1,25-D is synthesized is in the renal tubules, by an enzyme called 1-α hydroxylase. Another name for 1,25-D is calcitriol. Calcitriol has many actions pertaining to mineral balance. It increases gut calcium and phosphorus absorption, increases calcium reabsorption in the kidney, and suppresses the parathyroid gland from making PTH. Calcitriol also helps mineralize bone.

In early CKD, the levels of calcitriol are reduced. This is thought to occur by two mechanisms: (1) the increased levels of FGF23 induced by the need to increase *per nephron* phosphorus excretion suppress the 1-α hydroxylase enzyme in the renal tubules, blocking conversion of 25-D to 1,25-D, and (2) there is less conversion of 25-D to 1,25D because of reduced functioning renal mass. The decrease in 1,25D in early CKD may be somewhat compensatory, as slowing calcitriol synthesis results in reduced phosphorus absorption from the gut, and this in turn reduces the phosphorus excretion burden on the dwindling number of nephrons. The reduced serum 1,25-D levels also result in reduction of gut calcium absorption, and higher serum phosphorus levels can result in lower serum calcium levels directly. Thus, some degree of mild hypocalcemia is not uncommonly seen in moderate to advanced CKD.

The third hormone involved in mineral balance is parathyroid hormone. This is a peptide hormone composed of 84 amino acids, with the primary binding to its receptor requiring the presence of the first two amino acids on the N-terminal of the molecule. The main stimulus to PTH secretion is hypocalcemia, which acts on calcium-sensing receptors on the parathyroid gland. One of the main functions of this hormone is to maintain the serum calcium level. PTH does this in a number of ways: (1) PTH decreases the reabsorption of phosphorus in the kidney, increasing urinary phosphorus excretion. This lowers serum phosphorus, which tends to raise the serum calcium; (2) PTH stimulates the activity of the 1-α hydroxylase enzyme in the kidney that converts 25-D to 1,25-D; normally, this results in more calcitriol, and more calcium being absorbed via the gut; and (3) PTH increases the rate of bone turnover, freeing up calcium from bone. Note that PTH and FGF23 both act to increase renal phosphorus excretion, but they have the opposite effects on the kidney enzyme that makes 1,25D. In a feedback loop, secretion of PTH is inhibited by 1,25D acting on calcitriol receptors in the parathyroid gland. This feedback loop can be exploited physiologically and pharmacologically using calcitriol and various analogs of calcitriol to suppress PTH secretion. Finally, PTH secretion is stimulated by high serum phosphorus levels.

As the glomerular filtration rate (GFR) declines and as circulating 1,25-D levels decrease, intestinal calcium and phosphorus absorption are reduced, thus helping to maintain mineral homeostasis. The net effect of the changes in FGF23, calcitriol,

and PTH during progressive CKD is maintenance of serum calcium and phosphorus within the normal range until stage 4 or 5 CKD. The low 1,25 D level, the low serum calcium level, and the high serum phosphorus level, however, all act to stimulate PTH secretion and contribute to worsening hyperparathyroidism. With onset of stage 5 CKD and initiation of dialysis, this elegant homeostasis system breaks down, leading to very high FGF23 and PTH levels, uniformly low calcitriol levels, hyperphosphatemia, and low or low normal serum calcium.

These hormonal changes have adverse effects on bone physiology, as described below. Hyperphosphatemia, common in dialysis patients, contributes to the development of hyperparathyroidism and bone disease, and may play a pathological role in the development and progression of cardiovascular disease. High serum phosphorus levels may contribute to impaired bone mineralization and enhance vascular and other tissue calcification. High FGF23 levels, induced by hyperphosphatemia and other factors, have been shown to induce left ventricular hypertrophy in animal models.

II. CONTROL OF HYPERPHOSPHATEMIA. The normal range for serum phosphorus is 2.7 to 4.6 mg/dL (0.9–1.5 mmol/L). In dialysis patients, the KDIGO bone guidelines recommend attempting to maintain predialysis phosphorus in the normal range, based on observational data that better phosphorus control is associated with better outcomes. Also, there are data from animal studies showing that hyperphosphatemia stimulates hyperparathyroidism and promotes vascular calcification. In clinical practice, most physicians and dietitians strive to maintain predialysis phosphorus between 3.0 and 5.5 mg/dL (1.0–1.8 mmol/L).

Hyperphosphatemia occurs in anuric dialysis patients because the amount of phosphorus removed during three dialysis sessions per week is only a fraction of the phosphorus absorbed from the diet. For this reason almost all dialysis patients being dialyzed three times per week and eating a normal diet are required to ingest some form of phosphorus binder along with their food to limit the amount of phosphorus absorbed.

Hypophosphatemia in dialysis patients following a conventional 3-per-week schedule is not the norm and usually is the result of markedly reduced food intake unless there was some error in drawing the blood (e.g., from the dialyzer outlet instead of inlet at the start of dialysis) or unless there was excessive use of binders. Patients with persistent predialysis hypophosphatemia while off binders usually also have low protein intake, and should be counseled to increase dietary protein and phosphorus intake. Use of phosphorus supplements (K Phos Neutral, consisting of 8 mmol (250 mg) phosphorus, 13 mmol sodium, and 1.1 mmol potassium, starting at one tab daily) is indicated if the serum phosphorus remains below 3.0 mg/dL (1.0 mmol/L).

A. Dietary restriction. Restricting phosphorus in the diet to 800 to 1,200 mg per day is the key to controlling serum phosphorus.

Inorganic phosphates, added as preservatives and flavor enhancers to processed foods, are absorbed much more readily than phosphorus in natural food (Gutekunst, 2011). Continuing patient education by a knowledgeable dietitian is the best method to establish and maintain proper dietary habits. See Table 36.1 and Appendix B for foods high in phosphorus (Moe, 2011; Gutekunst, 2011). Although the phosphorus content of foods is related to their protein content, phosphorus is more readily absorbed from sources of animal protein than from those of plant protein (Moe, 2011).

B. Removal of phosphorus by dialysis. Hemodialysis typically removes about 800 mg of phosphorus per treatment regardless of predialysis serum levels. High flux dialyzers and dialyzers with larger surface areas, as well as use of hemodiafiltration, can increase phosphorus clearance to a modest degree (Penne, 2010). For hemodialysis, the total weekly time on dialysis is the most important factor affecting phosphorus removal. After the first hour of dialysis, the intradialysis serum phos- phorus level tends to stabilize at a low level. This is different than what happens with urea, the levels of which continue to fall as dialysis is prolonged. The maintained intradialysis serum levels of phosphorus cause it to behave somewhat like a middle molecule, where even prolonged dialysis sessions con- tinue to improve phosphorus removal. Dialysis frequency has an additional impact on phosphorus removal because during the initial hour of dialysis, intradialysis serum phosphorus is at a higher level than during the remainder of the treatment. The average patient needs 24–28 hours per week of dialysis to allow a predialysis serum phosphorus level <4.5 mg (1.45 mmol/L) without use of phosphorus binders. Patients undergoing frequent and long nocturnal dialysis with weekly dialysis times greater than 24–28 hours per week typically require addition of phosphorus to the dialysis solution to prevent hypophosphatemia.

Peritoneal dialysis removes approximately 300 mg per day of phosphorus when being treated with a CAPD regimen of four 2 L exchanges per day. This also is far less than the amount of phosphorus absorbed from the diet, and as a result, most peritoneal dialysis patients require the use of binders to control serum phosphorus levels.

TABLE 36.1 Foods Especially High in Phosphorus[a]

Dairy products (milk, yogurt, cheese)
Organ and processed meat
Beans/peas
Nuts/seeds
Whole-grain breads, bran, and cereals
Many soft drinks (particularly colas)

[a]See also Appendix B.

C. Residual kidney function. Residual kidney function contributes substantially to phosphorus removal from the body, and patients with urine volumes >500 mL per day typically require substantially lower amounts of phosphorus binders and have lower predialysis serum phosphorus levels than anuric patients (Penne, 2011). Phosphorus binders.

D. Phosphorus binders play an important role in phosphorus control in conjunction with dietary restriction. These agents work by binding phosphorus in the gastrointestinal tract, either by forming an insoluble com- plex or by binding it into a resin. Despite phosphorus dietary restriction and adequate hemodialysis, approximately 90% of dialysis patients continue to need oral phosphorous bind- ers in an effort to control their phosphorus levels. Other than simply lowering phosphorus, recent observational data have suggested that the use of phosphorus binders may also correlate with longer survival and better nutritional status for patients on maintenance hemodialysis (Lopes, 2012; Cannata-Andia, 2013).

See Table 36.2 for a summary of commonly used phosphorus binding agents. One can think of phosphorus binders in two broad categories, those that contain calcium (calcium car- bonate and calcium acetate) and those that do not (sevelamer, lanthanum, magnesium carbonate, sucroferric oxyhydroxide, ferric citrate, and aluminum-containing compounds). 1. Phosphorus binder equivalent dose: Using data from various comparative studies, one can roughly establish an equivalent dose for various binders relative to the phosphorus binding capacity of calcium carbonate (Daugirdas, 2011). This so-called phosphorus binding equivalent dose (PBED) allows one to compare dosages in patients taking multiple binders or different binders. In U.S. patients with minimal residual kidney function being dialyzed according to typical U.S. practices, PBED averages around 6 g per day (Daugirdas, 2012). This means that such patients would need 6 g per day of calcium carbonate to control their serum phosphorus (Table 36.3). The average required PBED is somewhat less, around 4–5 g per day, in smaller patients, those with substantial residual renal function, and is also lower in women versus men, as women tend to eat less phosphorus-rich foods such as meats than men.

2. Calcium load associated with some phosphorus binders. Calcium acetate, on a gram-per-gram basis, is about as effective as calcium carbonate as a phosphorus binder, but calcium acetate contains only 25% calcium by weight, whereas calcium carbonate contains 40% calcium by weight. Thus, attempting to manage a relatively large, anuric patient solely with calcium carbonate would require giving that patient 6.0 g of calcium carbonate per day, and 0.4 × 6.0 = 2.4 g of elemental calcium per day. This is far in excess of the maximum total calcium ingestion recommended

TABLE 36.4 Selected Phosphorus 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 binder; on empty stomach as 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 MgCO3 and 235 mg of Ca acetate	60 mg/tab		Reduction of calcium load; Mg may have anticalcification properties; not available in the US
Lanthanum carbonate	Fosrenal	250-mg 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-mg and 800-mg tablets and powder	0	Has been tested to 14 g/d in normal individuals. Dose may be limited by side effect 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 significant increase in serum iron markers

by guidelines issued by Kidney Disease Outcomes Quality Initiative (KDOQI) and Kidney Disease: Improving Global Outcomes (KDIGO). Using calcium acetate would be associated with a somewhat smaller calcium load of 0.25 × 6.0 = 1.5 g per day. This value is at the upper limit of daily calcium ingestion from both food and binders recommended by KDOQI. For this reason, many patients being managed with calcium-containing phosphorus binders are treated with additional, noncalcium binders.

Another strategy is to combine magnesium and calcium compounds to bind phosphorus. In the United States, MagneBind, a mixture of magnesium and calcium carbonate is sold as a dietary supplement and is sometimes used off-label as a phosphorus binder. In Europe, a magnesium/calcium binder made up of magnesium carbonate and calcium acetate (Osvaren) is approved for use as a phosphorus binder based on successful clinical trials (de Francisco, 2010). As shown in Table 36.3, a 6 g per day PBED of Osvaren would be associated with a daily calcium load of only 0.5 g per day. In addition to limiting the amount of calcium absorbed, magnesium-containing binders have at least two potential beneficial effects: (1) magnesium is an anticalcification factor, and it might retard vascular calcification in dialysis patients, although the evidence for this is limited (Spiegel, 2009); (2) mortality tends to be reduced in dialysis patients with higher serum magnesium levels, although it is not clear that magnesium supplementation beyond achievement of physiological serum levels is beneficial. Magnesium overload is something that one needs to watch for in any dialysis patient ingesting sources of magnesium.

A more effective strategy to eliminate the problem of calcium absorption from phosphorus binders is to use one of the newer binders that contain no calcium. Guideline groups recommend avoiding calcium-containing phosphorus binders in patients prone to vascular calcification, or with evidence of vascular calcification; this is hard to do, as the great majority of dialysis patients, especially patients with diabetes, will have evidence of calcification on abdominal X-ray or on visualization of the heart valves.

3. Dosing relative to meals. Phosphorus binders are much more effective when they are ingested with meals, and where the amount of binder given corresponds to the phosphorus load of each meal (Schiller, 1989). Some of the binders require ingestion of multiple pills, while reducing the number of pills by making them larger can make swallowing them more difficult. This has been addressed partially with some binders by making them chewable, or else supplying them as a powder that can be sprinkled over food.

TABLE 36.3 Dosages of Selected Phosphorus Binders Required to Reach a Phosphorus Binder Equivalent Dose (PBED) of 6.0 g per day

Phosphorus Binder	Unit dose size (mg)	Phosphate Binder Equivalent Dose of One Tablet to 1 g Ca Carbonate	Dose of Binder Needed to Reach a PBED of 6 g/d	Approximate Number of Tablets to Reach PBED of 6 g/d	Gram of Calcium in a 6-g PBED dose
Calcium carbonate	750 667 435/235a	0.75 0.67 0.75	6.0 6.0 —	8 9 8	2.4 1.5 0.5
Calcium acetate					
Osvaren (Mg carbonate + Ca acetate)					
Lanthanum	500b	1.0	3.0	6	0
Sevelamer carbonate	800	0.60	8.0	10	0
Sucroferric Oxyhydroxide (Velphoro)	500	1.6	1.5	3.75	0
Ferric citrate	210	0.64	2.0	9	0

The equivalent dose of PA21 is based on a single randomized controlled trial versus sevelamer (Floege, 2014), and thus the equivalent dose is not as precise as for some of the other binders, where multiple studies were considered.
Ferric citrate numbers were obtained from a single clinical randomized controlled trial vs sevelamer and calcium acetate (Lewis, 2014); Osvaren is not available in the United States.
[a] Each tablet contains 435-mg Mg carbonate and 235-mg Ca acetate.
[b] Tablets are sold by weight of lanthanum and not of lanthanum carbonate.

III. SELECTED PHOSPHORUS BINDING DRUGS

A. Calcium-containing compounds. These agents are often used in the initialmanagement of hyperphosphatemia based on a profile of effective phosphorus binding and low cost. They may also be useful when some degree of calcium supplementation is desired. However, dose titration is limited by KDIGO recommendations that elemental calcium ingestion should generally not exceed 1.5 g per day. In addition, dialysis solution calcium concentration should be limited to 2.25 to 2.5 mEq/L (1.12 to 1.25 mM) to avoid positive calcium balance during dialysis. The coadministration of calcium and active vitamin D preparations predisposes up to 50% of patients to hypercalcemia, and this practice warrants close monitoring (Schaefer, 1992).

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 with the regular tablet formulation), Caltrate (240 mg of elemental calcium/tab), and OsCal 500 (500 mg of elemental calcium/tab). A reasonable starting dose is 1–2 tablets with each meal. However, the use of more than 1.5 g of elemental calcium per day exposes patients to excessive calcium loading and the risk of hypercalcemia, and so it is usually impossible to control phosphorus with calcium carbonate alone without very substantially exceeding the maximum recommended targets for calcium ingestion.

   Calcium carbonate is available typically as a swallowed tablet, although TUMS does come in chewable formulations. It should be noted that calcium carbonate dissociates best in an acidic environment, and consequently its solubility can be inhibited by medications such as proton pump inhibitors. This agent 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 2–3 weeks to establish adequate phosphorus control to a maximum daily dose of 1.5 g of elemental calcium. On a mg calcium carbonate versus mg calcium acetate basis, effi- cacy of the two drugs as phosphorus binders appears to be similar. However, because calcium acetate is 25% calcium while calcium carbonate is 40% calcium, calcium acetate use is associated with less calcium loading. Still, to achieve a PBED of 6 g per day, use of calcium acetate alone engen- ders the administration of 1.5 g per day of elemental cal- cium. Administration is a swallowed tablet, and side effects include hypercalcemia, nausea, and constipation.

B. Sevelamer carbonate (Renvela) is a nonaluminum-, noncalcium-based phosphorus binder that traps phosphorus in the bowel through ion exchange and hydrogen binding. The drug is

available in 400- and 800-mg tablets, and granule packets, and should be started at 800–1,600 mg three times per day with meals. It can be titrated upward to a maximum of 13g per day to attain necessary phosphorus control, though this may require a significant pill load and financial burden for the patient. It is recommended to give other drugs 1 hour before or 3 hours after sevelamer administration. The absence of calcium makes sevelamer useful for those predisposed to hypercalcemia and those already at the limit of calcium sup- plementation. Sevelamer may also have pleiotropic, beneficial anti-inflammatory effects in dialysis patients that are not completely mediated by LDL cholesterol reduction (Rastogi, 2013).

The main side effects of sevelamer are nausea, diarrhea, dyspepsia, and constipation. Sevelamer use may lead to hypocalcemia, which should be treated with supplemental calcium.

C. Lanthanum Carbonate (Fosrenol) became available in the United States in 2005. As a trivalent cation, lanthanum binds phosphorus ionically. It is a noncalcium, nonaluminum-based binder. It is available in 250-, 500-, 750-, and 1,000-mg chew- able tablets that may also be crushed. A reasonable starting dose is 500 mg three times per day with upward titration as needed, but not to exceed 1,250 mg three times per day. Very little lanthanum is absorbed, and to date there has been no evidence of toxic accumulation or adverse effects on bone metabolism (Hutchison, 2009). Its main side effects are similar to the other phosphorus binders and are related to GI discom- fort. The chewable preparation may be convenient for patients with a large swallowed pill load, but difficult for patients with poor dentition. In a large prospective randomized European multicenter comparator trial, the efficacy of lanthanum car- bonate was compared with that of calcium carbonate. Phos- phorus control was similar in both groups; however, there was a significantly lower incidence of hypercalcemia in the lantha- num carbonate group, which makes it particularly useful in individuals at risk for hypercalcemia (Hutchison, 2005).

Both lanthanum and sevelamer are notably more expensive than other available phosphorus binders. Although the long-term safety of lanthanum carbonate has been called into question, subsequent reports over 1, 3, and 6 years have demon- strated a satisfactory long-term safety profile (Hutchison, 2009).

D. 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 dialysis patients in Europe. The potential benefits, as well as minor risks, of giving magnesium in this context have been discussed above.

E. Sucroferric oxyhydroxide (PA21 or Velphoro). PA21 is an iron-containing phosphorus binder that contains no calcium or aluminum. PA21 completed Phase 3 clinical trials in hemodialysis patients and was approved for use as a phosphorus

binder in the United States in 2013 (Floege, 2014). It comes as a 500-mg chewable tablet; the starting dose is 1.5 g per day (3 tablets per day with meals) with a suggested maximum dose of 3 g per day. In contrast to ferric citrate, which is another iron-based phosphorus binder described below, Velphoro is associated with only minimal oral iron absorption. Ferric citrate.

F. Ferric citrate is an iron-based phosphate binder that contains no calcium or aluminum. Ferric citrate has been approved for both CKD and ESKD patients in Japan (Yokoyama, 2014a, 2014b) and was approved in the United States in 2014 based on the results of a Phase 3 52-week clinical trial (Lewis, 2014). Ferric citrate comes as a tablet containing 210 mg ferric iron as 1 g ferric citrate and can be titrated to its maximum dose of 12 tablets/day (2.5 g ferric iron/day). Patients treated with ferric citrate demonstrated significant improvement in serum iron measures (TSAT, ferritin) in addition to a reduced need for IV iron (50% less IV iron requirement than in control patients treated with non-iron phosphorus binders) and reduced need for eryth- ropoiesis stimulating agents (24% less than control patients treated with non-iron phosphorus binders) while still maintain- ing hemoglobin. The tablet size and relative phosphorus binding ability are shown in Tables 36-2 and 36-3. Ferric citrate may prove highly effective as dual therapy in hyperphosphatemic patients that require iron repletion. However, in patients where iron load- ing is a concern, ferric citrate may not be an optimal choice.

G. Aluminum carbonate and aluminum hydroxide. Aluminum-based binders were the primary therapy for hyperphosphatemia until the mid-1980's, when the accumulation of aluminum to toxic levels was found to result in hematologic, neurologic, and bone complications. Consequently, these agents should no longer be used chronically. Usage of aluminum-based therapies for short periods may be necessary to reduce severely elevated phosphorus and calcium × phosphorus products in patients with severe hyperparathyroidism and/or concurrent hypercalcemia. They are also still an important tool for hyperphosphatemia control in developing countries (Mudge, 2011). Co-ingestion of citrate (Shohl's solution, calcium citrate, fruit juices, Alka-Selzer) greatly enhances aluminum absorption and can lead to acute aluminum neurotoxicity.

H. Use of more than one phosphorus binder. Combined treatment with different types of phosphorus binders may be advantageous and cost effective. Regimens should be individually tailored to each patient. Combinations should take into account the patient's medication preferences, side effect tolerance, and financial considerations. Total daily exposure to elemental calcium and magnesium should also factor into the choice of agents used. The combination of calcium- and non–calcium-based agents may provide target phosphorus control and calcium supplementation without risking excess exposure to calcium.

IV. OPTIMIZING SERUM CALCIUM. The normal range for serum calcium is 8.4 to 10.2 mg/dL (2.10–2.55 mmol/L), and the KDIGO guidelines

recommend maintaining predialysis total calcium within this range. There is great patient variability in the calcium set point (the calcium level at which PTH secretion is 50% of maximum).

Serum calcium circulates in a free (ionized) and a protein-bound state. Total calcium reported on standard lab tests reflects both of these circulating forms. Protein-bound calcium is proportional to the concentration of albumin, which accounts for most of the protein binding. On average, total calcium falls by 0.8 mg / dL for every 1.0 g/dL (0.20 mmol/L for every 1.0 g/L) decrease in albumin. Consequently, in hypoalbuminemia, the total calcium reported from the laboratory can be corrected by using the equation :

$$\text{Corrected calcium (in mg/dL)} = \text{total calcium} + (0.8 \times (4.0 - \text{albumin [in g/dL]}))$$

$$\text{Corrected calcium (in mmol/L)} = \text{total calcium} + (0.20 \times (40 - \text{albumin [in g/L]}))$$

In most new dialysis patients, corrected and ionized calcium concentrations are usually slightly low or in the low normal range. Calculation of corrected calcium can be used to estimate whether a hypoalbuminemic patient's serum calcium is high, normal, or low. Unfortunately, corrected calcium is dependent on which albumin assay is employed, and has been shown to be no more accurate than total calcium in predicting whether ionized calcium is high, normal, or low (Gauci, 2008). Therefore, in dialysis practice, use of total calcium is recommended, and determination of ionized calcium is indicated when the result could change management. Differing from the older KDOQI bone guidelines, KDIGO does not recommend the routine use of albumin-corrected calcium.

A. Hypercalcemia. Hypercalcemia is usually due to excessive use of calcium-based binders and/or to use of vitamin D receptor agonists that increase gut calcium absorption. Patients with low PTH appear to have the highest range of serum calcium, which may reflect adynamic bone disease (see below) and poor ability of bone to buffer calcium. Advanced hyperparathyroidism associated with a large mass of autonomous parathyroid tissue can rarely result in hypercalcemia in the absence of oral calcium administration or the use of active vitamin D. This is referred to as tertiary hyperparathyroidism.

B. Hypocalcemia. Low levels of total uncorrected calcium are often due to a low serum albumin. A low corrected calcium may be due to poor gastrointestinal absorption of calcium due to vitamin D deficiency, severe hyperphosphatemia, or use of the calcimimetic agent, cinacalcet.

C. Dialysis solution calcium concentration. Dialysis solution calcium should generally be 2.5 mEq/L (1.25 mM) in most patients on chronic hemodialysis. This will usually maintain a neutral calcium balance. Cautious use of a 2.25 mEq/L (1.12 mM) calcium bath or lower 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, however, and lead to bone demineralization. Use of very low calcium dialysis solutions also has been linked to an increased risk of QTc dispersion and sudden death (see Chapter 11).

Peritoneal dialysis fluid calcium concentration should be 2.5 mEq/L (1.25 mM) in most patients. A 3.5 mEq/L (1.75 mM) dialysate is available, but should be reserved for patients with a chronically low calcium that the clinician has determined warrants therapy. Higher dialysate calcium concentration, especially when used in conjunction with calcium-based phosphorus binders, creates a chronically positive calcium balance, suppresses PTH, and may contribute to vascular and tissue calcification.

V. OPTIMIZING SERUM LEVELS OF 25-D (25-HYDROxYCHOLECALCIFEROL).

25-D (25-hydroxycholecalciferol) is synthesized by the liver from cholecalciferol and reflects vitamin stores. These are frequently low in dialysis patients. Several factors likely account for the high incidence of deficiency, including poor sun exposure in ill patients, restriction of vitamin D–fortified dairy products for purposes of phosphorus control, and the high prevalence of Black patients who are frequently lactose intolerant and whose dark pigmentation reduces effective vitamin D formation upon ultraviolet light exposure. However, Black patients also appear to have lower D-binding protein levels in the blood, leading to a higher ratio of bioactive (free) hormone to bound hormone. Therefore, Blacks may not have the frequency and severity of vitamin D deficiency that standard testing suggests.

Treatment of vitamin D deficiency is appropriate despite the loss of adequate 1-alpha-hydroxylase activity in the kidney, as other tissues possess this enzyme and produce calcitriol for autocrine and paracrine actions. Treatment has also been shown to increase endogenous calcitriol levels, though not usually to normal (Jen, 2010). Treatment should replete, then maintain adequate stores. Vitamin D stores are assessed by measuring 25-OH vitamin D in the blood. Levels >30 ng/mL (>75 nmol/L) are considered normal, while levels <30 ng/mL (<75 nmol/L) warrant treatment with ergocalciferol or cholecalciferol.

Treatment of low serum 25-D levels differs between the United States and other countries. The most logical treatment is to give the natural precursor to 25-D, which is cholecalciferol, a compound derived from animal sources. Cholecalciferol is widely available in the United States as a food supplement, but not as an FDA-approved pharmaceutical that is reimbursable. While there is no recommended daily intake for cholecalciferol to maintain stores, 800 to 2,000 IU per day is likely sufficient and safe. In the United States, ergocalciferol is available as a prescription drug. Ergocalciferol, a plant-based sterol, differs from cholecalciferol slightly in terms of structure, but it is hydroxylated by the liver at the 25 position and then dihydroxylated at the 1-α position to

yield a biologically active compound similar in action to calcitriol. Ergocalciferol is commonly called vitamin D2, while cholecalciferol is called vitamin D3. Most (but not all) assays of serum 25-D levels detect both the 25-D2 and 25-D3 compounds. Ergocalciferol can be given as large weekly or monthly doses, or smaller daily doses, and the dose administered should be proportional to the severity of the deficiency, and the size and adiposity of the patient. We commonly prescribe 50,000 IU/ month for 6 months when levels are 15–29 ng/mL (37–72 nmol/L), and 50,000 IU weekly for 2 to 3 months, then 50,000 IU monthly when levels are <15 ng/mL (<37 nmol/L). Obese patients will generally require larger doses or longer repletion due to the fat soluble nature of the vitamin.

VI. BONE DISEASE IN CKD. Bone normally undergoes a coordinated turnover, with osteoblast cells producing new bone matrix proteins (osteoid) that undergo mineralization, coupled with the activity of osteoclasts that causes bone resorption. The pathological classification of renal osteodystrophy is based on both the static and the dynamic histological parameters obtained by transiliac bone biopsy. Evaluation of the biopsy for **T**urnover rate, **M**ineralization, and **V**olume, the so-called TMV system, has been proposed as the best method for classifying renal bone disease. Fluorescent labels, tetracycline and demeclocycline, are deposited along the lines of mineralization. Administration of such labels for one to three days followed two to three weeks later by the repeat administration of label allows for the determination of the rate of bone formation. With high bone turnover, for example, the distance between the two labels would be increased. Mineralization is evaluated by examining the osteoid volume, increased osteoid maturation time, or increased mineralization lag time. Bone volume is prone to greatest error because with bone biopsy only a single location is sampled. Any aluminum deposition is tested for by staining the biopsy sample with acid solochrome azurine.

A. Osteitis fibrosa. This form of renal osteodystrophy occurs when PTH is persistently high. It is characterized by accelerated formation and resorption of bone due to an increased number and activity of osteoblasts and osteoclasts, and increased marrow fibrosis. The severity of osteitis fibrosa is roughly proportional to the degree and duration of PTH elevation. Mild osteitis fibrosa is probably preferable to adynamic bone (see below) in that bone strength is greater and there is less alteration in mineral metabolism. When osteitis fibrosa is severe, bone is laid down so rapidly that it is not properly mineralized or structured. In such cases, the amount of unmineralized bone (osteoid) is increased. The alignment of the collagen is irregular instead of in the usual lamellar pattern. This “woven” bone may become mineralized as amorphous calcium phosphorus rather than hydroxyapatite. The resulting bone is more prone to fracture.

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 or pain and stiffness.

Radiological findings are usually absent in mild disease but are always present in severe hyperparathyroidism. As such, bone films are not generally recommended for the assessment of bone disease in dialysis patients. Hand films most reliably demonstrate changes of hyperparathyroidism. The characteristic finding is bone loss (resorption) in the subperiosteal area, best seen on the radial side of the second and third phalanges. Associated erosion of the tuft of the distal phalanx also may be visible and, when severe, may lead to blunting of the fingertip. The latter changes are pathognomonic of present or past osteitis fibrosa. Evidence of bone resorption also may be seen elsewhere in the skeleton, including the skull, giving it a "salt-and-pepper" appearance, and in the long bones, particularly the lesser trochanter of the femur.

Disorganized, accelerated bone formation is associated with osteitis fibrosa and may be visible radiologically as osteosclerosis. Bone scanning using technetium radiopharmaceuticals will show increased skeletal uptake of isotope. The bone/soft tissue ratio of isotope uptake will be increased; however, bone scans generally add little to the diagnostic evaluation of osteitis fibrosa.

B. Adynamic bone. Adynamic bone disease is characterized by reduced osteoblast and osteoclast number and low or absent bone formation rate as measured by tetracycline labeling. The osteoid thickness is normal or reduced, distinguishing it from osteomalacia. Associated laboratory findings may include an iPTH less than 100 pg/mL (11 pmol/L), low serum bone-specific alkaline phosphatase, and, occasionally, a slightly elevated serum ionized calcium level. Vertebral and peripheral bone densities tend to be normal or low.

The causes of adynamic bone histology are unknown, but persistently low (for dialysis patients) PTH levels play a major etiologic role. Predisposed are the elderly, women, those with diabetes, and subjects of the Caucasian race. Adynamic bone is more common in peritoneal dialysis patients, as is a low PTH. Use of dialysis solution calcium concentration of 2.5 mEq/L (1.25 mM) may reduce the prevalence of adynamic bone and PTH oversuppression. Aluminum is now a rare cause of adynamic bone disease.

Initially thought to be asymptomatic and not requiring treatment, adynamic bone is now known to be associated with a higher fracture rate than osteitis fibrosa. Adynamic bone is also associated with hypercalcemia (likely due to impaired ability of the bone to buffer serum calcium), and vascular and other soft tissue calcification. Symptoms, such as pain from nontraumatic fractures, are usually absent until the disease is advanced.

C. Osteomalacia. Like adynamic bone disease, osteomalacia represents a state of low bone turnover. It differs, however, because

of the presence of large amounts of unmineralized osteoid. In the absence of renal failure, vitamin D deficiency is the most common cause of osteomalacia and should be considered in dialysis patients with low bone mass and frequent fractures. This lesion was first described in patients with aluminum overload, wherein bone aluminum accumulation prevented bone mineralization and also suppressed PTH secretion. With recognition of its toxicity, aluminum is now rarely used as a long-term phosphorus binder, and properly treated dialysis solution is free of aluminum. Consequently, the incidence of aluminum-induced osteomalacia has decreased substantially. Rarely, osteomalacia has been ascribed to iron overload.

D. Mixed Lesions. Some patients display histologic evidence of both osteitis fibrosa and osteomalacia on bone biopsy. Such patients frequently have high PTH levels and impaired bone formation and mineralization. In the past, this condition was often found in patients with concomitant aluminum poisoning.

E. Osteoporosis. 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, selective or nonselective estrogens, teriparatide (Forteo) if the PTH is persistently low, and vitamin D. None of these treatments have been tested for efficacy and safety in the hemodialysis population. Caution should be used before prescribing these medications to dialysis patients with osteoporosis.

VII. PARATHYROID HORMONE LEVELS

A. PTH assays. Parathyroid hormone is an 84 amino acid peptide (PTH(1-84)) that activatesa 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 midregion 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. Initially, it was thought that such dual antibody assays bound to PTH(1-84) only . However, several incomplete PTH fragments, including the fragment PTH (7-84), are also bound by this assay, and these incomplete fragments account for as much as half of the PTH measured in dialysis patients by the first generation “intact” PTH group of assays.

There are numerous commercial iPTH assays available, and the contribution of inactive PTH fragments to the total PTH measurement varies greatly. Consequently, in dialysis patients, different assays can lead to very different iPTH results (Souberbielle, 2006; Cavalier, 2012), and at higher iPTH values, the discrepancy in results becomes even greater. This large interassay variability means no specific PTH target can apply to all assays, and use of different assays in the same patient (such as a hospital test versus a dialysis center test) can lead to different interpretations.

Some assays employ a detection antibody that binds at or very near the first amino acid, and are referred to as "biPTH", "bio-intact PTH", or "whole PTH". As these assays are thought to bind exclusively to PTH(1-84), measured levels are approximately 55% of the corresponding iPTH values. In theory such "bio-intact" assays should be superior to the "intact" PTH assays. Clinical practice, however, has not demonstrated that these assays are superior. Most laboratories continue to employ the iPTH assay, and the 2009 KDIGO bone guidelines recommend continued use of the "intact" iPTH assay rather than the theoretically more precise "bio-intact" 1-84 versions.

B. PTH target values. The purpose of treating hyperparathyroidism in dialysis patients is to prevent the development of severe hyperparathyroidism that can cause severe bone disease and fractures, and contribute to tissue calcification. Medical man- agement of hyperparathyroidism is also intended to reduce the need for surgical parathyroidectomy.

The treatment goals should be balanced against the risks of medical interventions. Overtreatment of hyperparathyroidism can induce adynamic bone disease, which predisposes patients to hypercalcemia and vascular calcification.

The 2009 KDIGO bone guidelines recognized the lack of sufficient outcomes trials to make firm recommendations on the management of hyperparathyroidism in dialysis patients. They recommend balancing the potential benefits of treatments against the known and potential risks. In dialysis patients, they recommend maintaining a stable PTH level over time, generally in a range of two to nine times the upper limit of normal (for most assays this is approximately 150 to 600 pg/mL [16–64 pmol/L]), while avoiding hypercalcemia and hypocalcemia. This range is broader than the older KDOQI guideline recommendation of 150–300 pg/mL (16–32 pmol/L; about two to four times the upper limit of normal). The higher target range was recommended because the narrower KDOQI target appeared to lead to oversuppression of bone turnover and hypercalcemia in many patients.

Dialysis patients should not have 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, cinacalcet, and calcium-based phosphorus binders, as well as with use of high calcium dialysis solutions, (e.g., >3.0 mEq/L [1.5 mM]).

Clinicians should remember that in an individual patient, PTH in a given range does not always correlate with the 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 (e.g., fractures, hypercalcemia) that do not correlate with the results of repeated PTH measures warrant further evaluation.

C. Serum bone and total alkaline phosphatase. The KDIGO guidelines also suggest monitoring another marker of high bone turnover, such as bone alkaline phosphatase. In clinical practice, this is an expensive test to obtain, and few centers routinely measure it. Normalization of serum alkaline phosphatase, of which bone alkaline phosphatase is a component, may serve as a secondary indicator that the patient does not have high bone turnover, though it is not predictive of whether adynamic bone disease is present.

Serum total alkaline phosphatase is frequently elevated in dialysis patients, usually due to elevation of bone-specific alkaline phosphatase due to osteitis fibrosa from hyperparathyroidism. However, alkaline phosphatase originates from other tissues, the most important being liver, intestine, and kidney. Bone alkaline phosphatase can be measured when the source of a high serum alkaline phosphatase is in doubt. Alternatively, an elevation of gamma glutamyl transferase (GGT) suggests the increase in alkaline phosphatase may be due to liver dis- ease, and evaluation of the liver and gall bladder is indicated. If GGT is normal, hyperparathyroid bone disease is likely the cause of the elevated alkaline phosphatase, and more inten- sive treatment may be indicated. In dialysis patients, both total alkaline phosphatase and bone-specific alkaline phosphatase levels are usually elevated in severe hyperparathyroidism and improve during successful treatment. In clinical practice, a PTH value that is two to nine times the upper limit of normal and a normal serum total alkaline phosphatase suggests that hyperparathyroid bone disease is either mild or absent, and therefore intensification of present therapy to suppress PTH may not be indicated.

D. Methods of lowering or raising serum PTH. As discussed in the opening pages of this chapter, the reasons for hyperparathyroidism in CKD are a low level of 1,25-D (1,25-D suppresses the parathyroid gland), low levels of serum calcium (hypocalcemia stimulates the parathyroid gland to produce PTH), and high levels of serum phosphorus (phosphorus stimulates the parathyroid gland). Accordingly, stimulating the vitamin D recep- tor, raising the serum calcium or activating the parathyroid gland calcium-sensing receptor by other means, or reducing serum phosphorus, could all be expected to lower serum PTH. 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 cinacalcet) or lowering the serum calcium slightly (e.g., by lowering dialysis solution calcium or avoiding calcium-containing phosphorus binders) can be expected to increase PTH levels.

E. Vitamin D receptor activators. Active vitamin D (calcitriol) and vitamin D receptor agonists (see Table 36.4) 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. The medications are usually given intravenously during each dialysis, but can be given orally, usually two to three times a week. Because these drugs can increase gut absorption of phosphorus, they should be given cautiously to patients with hyperphosphatemia, and preferably only after elevated serum phosphorus levels have been somewhat controlled. A number of observational studies have suggested that use of calcitriol or vitamin D receptor agonist is associated with increased survival (Duranton, 2013), but randomized outcome trials to confirm this observation have not yet been don e. 1. Calcitriol (Calcijex; Rocaltrol) or 1,25(OH)

2D3 is a synthetic form of the natural compound, and is usually started at 1–2 mcg IV with each hemodialysis or orally two to three times per week in patients treated with peritoneal dialysis. 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 analog that has less hypercalcemic and hyperphosphatemic actions in animal studies. In humans, the evidence of superiority over calcitriol is more limited. A large historical cohort study did find improved survival in dialysis patients receiving paricalcitol compared with calcitriol (Teng, 2003). The initial dose in mcg per dialysis treatment can be estimated by dividing the pretreatment iPTH by 120. An oral formulation of paricalcitol is also available for patients with CKD or patients on peritoneal dialysis. A starting dose of 1 mcg daily or 2 mcg three times a week can be administered to patients with an iPTH less than or equal to 500 pg/mL (53 pmol/L). An initial dose of 2 mcg daily or 4 mcg three times a week can be started in patients with iPTH greater than 500 pg/mL (53 pmol/L).
3. Doxercalciferol (Hectorol) or 1α(OH)D

2 is a vitamin D prohormone that is metabolized by the liver to active 1,25(OH)2D2. Initial dosing is 2.5–5.0 mcg intravenously or orally each dialysis treatment.

Dose adjustments of active vitamin D products for PTH control are based on subsequent PTH determinations, which initially should be performed up to monthly

TABLE 36.4 Characteristics of Commonly used Vitamin D Analogs

Medication	Trade Name	Route	Dosing Information	Comments
Calcitriol	Rocaltrol	PO	Starting dose: 0.25 mcg daily or 0.5 mcg three 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 three times weekly Titrate by 0.5–1 mcg every 2–4 weeks	
Doxercalciferol	Hectorol	PO	Starting dose: 2.5–5.0 mcg three 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)2vitamin D2.
	Hectorol	IV	Starting dose: 2.5–5.0 mcg three times per week Titrate by 1–2 mcg q8 wk	Oral administration in dialysis patients is more hypercalcemic and hyperphosphatemic than IV administration
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 dose in mcg equal to biPTH/40 or iPTH/80 three times per week Titrate by 30%–50% at 4-week intervals	The IV preparation can also be administered on a once-weekly regimen based on the cumulative weekly dose

to establish control, then reassessed quarterly. If hypercalcemia (calcium >10.2 mg/dL [2.55 mmol/L]) develops, the dose should be decreased by 30%–50% or held until the hypercalcemia resolves then restarted at a lower dose.

F. Calcimimetics bind to the calcium sensing receptor on the parathyroid gland, making it more responsive to the ambient ionized calcium; this results in suppression of PTH, a marked decrease in serum calcium, and a slight decrease in serum phosphorus. Unlike active vitamin D products, calcimimetics result in a decrease in serum calcium and phosphorus. Cinacalcet (Sensipar), the only calcimimetic presently available, is a pill available in 30, 60, and 90 mg. Maximal PTH suppres- sion of 60 to 80% occurs 2 to 4 hours after each dose, and 30 to 50% suppression at 24 hours is observed in about two-thirds of patients. 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 <8.4 mg/dL (<2.1 mmol/L). The dose should be increased by 30-mg increments to a maximum of 180 mg per day, based on monthly or quarterly PTH results, provided the corrected calcium is >7.8 mg/dL (1.95 mmol/L). A fall in serum calcium accompanies PTH suppression, and hypo- calcemia of <7.5 mg/dL (1.87 mmol/L) occurs in about 5% of patients. Hypocalcemia is rarely symptomatic and can be managed by addition of 500 to 1,000 mg of elemental calcium on an empty stomach, an increase or addition of active vita- min D, or an increase in dialysate calcium to 3.0 or 3.5 mEq/L (1.5 or 1.75 mM). Other major side effects of cinacalcet are nausea and vomiting, which occur in up to 30% of patients, and rash.

A large outcomes trial of cinacalcet versus placebo 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), but use of cinacalcet did not reduce cardiovascular events or deaths (EVOLVE Trial Investigators, 2012).

VIII. MISCELLANEOUS THERAPIES

A. Bisphosphonates. While these agents can increase bone density in osteoporosis, they have not been adequately tested or shown to be efficacious in dialysis patients. Bisphospho- nates decrease bone resorption by inhibiting osteoclasts. This reduction in bone turnover may be deleterious in dialysis patients, creating a form of adynamic bone disease. Generally, these agents should not be used in dialysis patients.

B. Teriparatide. A synthetic form of PTH(1-34), this polypeptide induces a marked increase in bone density in osteoporotic patients when administered as a daily subcutaneous injection. It has not been tested in dialysis patients, but may be of value in the treatment of adynamic bone disease, as PTH levels usually are low in this disorder. Further studies are

needed to define the role of teriparatide in low bone turnover disease, and teriparatide has not been FDA approved in this p opul ation .

IX. PARATHYROIDECTOMY. Despite aggressive efforts to control PTH levels, surgical parathyroidectomy (PTX) continues to be necessary in those patients with severe hyperparathyroidism. PTX rates were higher among patients who were younger, female, nondiabetic, receiving peritoneal dialysis, and those with a longer duration of dialysis (Foley, 2005).

A. Indications. Failure of high-dosage intravenous active vitamin D and calcimimetic therapy to improve findings of hyperparathyroidism suggests the presence of large, poorly suppressible glands that require removal.

The indications for parathyroidectomy are listed in Table 36.5. When parathyroidectomy is being contemplated for the treatment of refractory osteitis fibrosa or hypercalcemia, very high PTH levels would be expected, and it is important to document this (e.g., iPTH usually more than 1,000 pg per mL [106 pmol/L]) before contemplating surgery. A lower serum PTH level should be suppressible using calcitriol or an active vitamin D analog. Also, lower serum PTH levels or a normal value for bone-specific alkaline phosphatase should prompt one to question the necessity for parathyroidectomy. Bone biopsy should show marked osteitis fibrosa with many osteoclasts, increased tetracycline labeling, and minimal aluminum staining.

B. Relative contraindications. Recent studies have shown that accumulation of aluminum on the bone mineralizing surface increases markedly after parathyroidectomy and suggest that parathyroidectomy should not be done in patients who are aluminum-loaded. If there is a history of long-term aluminum exposure, a bone biopsy should be performed prior to parathyroidectomy to exclude significant aluminum accumulation.

C. Surgical strategy. Parathyroid surgery is a complex endeavor and requires the services of a surgeon with experience in this procedure. Aberrantly located glands, and three, five, or even six

TABLE 36.5 Indications 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

rather than the usual four glands, may be present. An attempt may be made to localize the glands preoperatively using 10-MHz ultrasonographic scanning or thallium–technetium scanning, but this is usually not necessary.

Until recently, the operation of choice had been subtotal parathyroidectomy: total resection of three glands and 75% of the fourth. The alternative approach has been total parathyroidectomy with autotransplantation of some parathyroid tissue into the forearm or, more recently, subcutaneously in the presternal area (Kinnaert, 2000). Both procedures entail some disadvantages, including the risks of permanent hypoparathyroidism and recurrence (or lack of resolution) of bone disease or hypercalcemia. Recurrence and failure to improve are troublesome problems; often, it is uncertain whether the cause is hyperfunction of residual or transplanted parathyroid tissue or the unsuspected presence of an additional gland following surgery.

D. Chemical ablation. Percutaneous injection of ethanol or calcitriol into the parathyroid glands of patients with severe secondary hyperparathyroidism has been used to cause regression of the glands and moderate parathyroid hormone secretion. It is performed using ultrasound or color Doppler flow mapping and may be considered in those who are poor surgical risks and in centers with the appropriate expertise (Kakuta, 1999). The risk of recurrent nerve palsy has been reported to be low.

E. Postoperative hypocalcemia. Within several hours of parathyroidectomy, but especially during the first postoperative days, profound hypocalcemia can develop, the severity of which depends on the degree of osteitis fibrosa, which can be predicted by the extent of preoperative serum alkaline phosphatase elevation and bone histology. In addition to oral calcium supplements (2–4 g per day), large dosages of intravenous calcium (0.5–5.0 g per day) and oral or intravenous calcitriol (2–6 mcg per day) may be required to maintain serum calcium levels in an acceptable range (Dawborn, 1983). Some advocate starting calcitriol and oral calcium therapy a few days before the procedure even in hypercalcemic patients.

X. CALCIFIC UREMIC ARTERIOLOPATHY (CUA), previously known as "calciphylaxis," is an unusual disorder seen predominately in dialysis patients. Early signs and symptoms include livedo reticularis and extremely painful red nodules, which progress to ulcerative and necrotic lesions. Risk factors include female gender, obesity, and Caucasian race. Exposure to the uremic milieu may be responsible for altering vascular smooth muscle cells and increasing the expression of factors involved in ectopic mineralization, such as osteopontin and core-binding factor alpha (Moe & Chen, 2003). Further mineralization from elevated calcium and phosphorus levels ultimately results in arteriolar calcification, occlusion, and tissue ischemia. A high index of suspicion is necessary to identify the disease as early as possible. The

differential diagnosis includes vasculitis, coumadin-associated skin necrosis, cryoglobulinemia, calcinosis cutis, and panniculitis. Bone scan has been reported to identify calcium deposition in 97% with early plaque-only CUA (Fine & Zacharias, 2002). Skin biopsy shows characteristic arteriolar calcifications in the medial layer.

Once the diagnosis is made, calcium-containing supplements and vitamin D analogs should be discontinued, and non–calcium-based phosphorus-binders should be titrated for aggressive phosphorus control. Parathyroidectomy is recommended for those with CUA and elevated iPTH (>500 pg/ mL (53 pmol/L)), though hyperparathyroidism is not required for CUA, and patients may in fact have low to normal iPTH levels (Bleyer, 1998). Coumadin, which inhibits the calcium- regulatory matrix gla-protein, should be discontinued. Sodium thiosulfate, at a dose of 25 g IV three times per week, has been reported to completely resolve the lesions in 26% and improve the process in 47% (Nigwekar, 2013). The mechanism of action is unknown (O'Neill & Hardcastle, 2012). Pamidronate has also been cited in a single case report to effect rapid clinical improvement (Monney, 2004). Wound care is critically impor- tant in ulcerative lesions, and surgical debridement and anti- biotics may be necessary. Hyperbaric oxygen (Basile, 2002) and low-dose tissue plasminogen activator (Sewell & Pittelkow, 2004) have been reported to promote wound healing in single case studies.

XI. ALUMINUM TOxICITY. Aluminum toxicity is rarely seen today because of the development of non-aluminum phosphorus binders and improvement in water purity. Among those still exposed to aluminum-based compounds, greater risk for accumulation occurs in diabetics, the iron-deficient, children, and those with exposure to citrate (which increases aluminum absorption). Aluminum bone disease results in diffuse bone pain or fractures with low iPTH, hypercalcemia, and normal alkaline phosphatase. Confirmation of aluminum toxicity with the deferoxamine (DFO) test should be done in those with serum aluminum levels between 60 and 200 mcg/L (2,160 and 7,200 nmol/L), those with symptoms of aluminum toxicity, and prior to parathyroidectomy in those with known exposure. The combination of low iPTH and an increase in serum aluminum by 50 mcg/L (1,800 nmol/L) 2 days after a 5-mg/kg DFO administration is predictive of aluminum bone disease. Definitive diagnosis is made with bone biopsy and trabecular staining for aluminum deposition.

In all cases of aluminum toxicity, exposure to aluminum must be identified and stopped. DFO can be administered on a weekly basis at a dose of 5 mg/kg for 2 months. To prevent aluminum-related encephalopathy, those with aluminum levels greater than 200 mcg/L (7,200 nmol/L) should undergo intensive hemodialysis with high-flux membranes. Once levels are less than 200 mcg/L (7,200 nmol/L), DFO treatment can be started.

Side effects of DFO include ototoxicity, retinopathy, fatal *Mucor* infections, and precipitation of encephalopathy. For more details see the fourth edition of this Handbook (D'Haese and DeBroe, 2007).

References and Suggested Readings

Armas LAG, et al. 25-hydroxyvitamin D response to cholecalciferol supplementation in hemodialysis. Clin J Am Soc Nephrol. 2012;7:1428–1434.

Basile C, et al. Hyperbaric oxygen therapy for calcific uremic arteriolopathy: a case series. J Nephrol. 2002;16:676–680.

Bleyer AJ, et al. A case control study of proximal calciphylaxis. Am J Kidney Dis. 1998;32:376–383.

Cannata-Andia JB, et al. Use of phosphate-binding agents is associated with a lower risk of mortality. Kidney Int. 2013;84:998–1008.

Cavalier E, et al. Interpretation of serum PTH concentrations with different kits in dialysis patients according to the KDIGO guidelines: importance of the reference (normal) values. Nephrol Dial Transplant. 2012;27:1950–1956.

Chertow GM, et al. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int. 2002;62:245–252.

Cicone JS, et al. Successful treatment of calciphylaxis with intravenous sodium thiosulfate. Am J Kidney Dis. 2004;43:1104–1108.

Clark OH, et al. Localization studies in patients with persistent or recurrent hyperparathyroidism. Surgery. 1985;98:1083–1094.

Coen G, et al. PTH 1-84 and PTH "7-84" in the noninvasive diagnosis of renal bone disease. Am J Kidney Dis. 2002;40:348–354.

Cunningham J, Zehnder D. New Vitamin D analogs and changing therapeutic paradigms. Kidney Int. 2011;79:702–707.

Daugirdas JT, et al; the Frequent Hemodialysis Network Trial Group. The p hosphate binder equivalent dose. Semin Dial. 2011;24:41–49.

Daugirdas JT, et al; the FHN Trial Group. Effects of frequent hemodialysis on m easure of CKD mineral and bone disorder. J Am Soc Nephrol. 2012;23:727–738.

Dawborn JK, et al. Parathyroidectomy in chronic renal failure. Nephron. 1983;33:100–105.

D'Haese PC, DeBroe ME. Aluminum, lanthanum, and strontium. In: Daugirdas JT, Ing TS, Blake P, eds. Handbook of Dialysis, 4th ed. Philadelphia, PA: Wolters Kluwer; 2007:714–726.

de Francisco ALM, et al. Evaluation of calcium acetate/magnesium carbonate as a phosphate binder compared with sevelamer hydrochloride in haemodialysis patients: a RCT (CALMAG study) assessing efficacy and tolerability. Nephrol Dial Transplant. 2010;25:3707–3717.

Delmez JA, Slatopolsky E. Hyperphosphatemia: its consequences and treatment in patients with chronic renal disease. Am J Kidney Dis. 1992;19:303–317.

D'Haese PC, et al. A Multicenter study on the effects of lanthanum carbonate (Fosrenol) and calcium carbonate on renal bone disease in dialysis patients. Kidney Int. 2003;63:S73–S78.

D'Haese PC, et al. Use of low-dose deferrioxamine test to diagnose and differentiate between patients with aluminum-related bone disease, increased risk for aluminum toxicity, or aluminum overload. Nephrol Dial Transplant. 1995;10: 1874–1884.

Duranton F, et al. Vitamin D treatment and mortality in chronic kidney disease: a systematic review and meta-analysis. Am J Nephrol. 2013;37:239–248.

EVOLVE Trial Investigators, et al. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. N Engl J Med. 2012;367:2482-2494.

Fine A, Zacharias J. Calciphylaxis is usually non-ulcerating: risk factors, outcome and therapy. Kidney Int. 2002;61:2210–2217.

Floege J. When man turns to stone: extraosseous calcification in uremic patients. Kidney Int. 2004;65:2447–2462.

Floege J, et al. A phase III study of the efficacy and safety of a novel iron-based phosphate binder in dialysis patients. Kidney Int. 2014;86:638–647.

Foley RN, et al. The fall and rise of parathyroidectomy in U.S. hemodialysis patients, 1992 to 2002. J Am Soc Nephrol. 2005;16:210–218.

Gallieni M, et al; Italian Group for the Study of Intravenous Calcitriol. Low-dose intravenous calcitriol treatment of secondary hyperparathyroidism in hemodialysis patients. Kidney Int. 1992;42:1191–1198.

Gauci C, et al. and the NephroTest Study Group. Pitfalls of measuring total blood calcium in patients with CKD. J Am Soc Nephrol. 2008;19:1592–1598.

Goldsmith D, Ritz E, Covic A. Vascular calcification: a stiff challenge for the nephrologists. Kidney Int. 2004;66:1315–1333.

Goodman WG, et al. A calcimimetic agent lowers plasma parathyroid hormone levels in patients with secondary hyperparathyroidism. Kidney Int. 2000;58: 436–445.

Gutekunst L. Restricting protein and phosphorus: a dietitian's perspective. In: Daugirdas JT. Handbook of Chronic Kidney Disease. Philadelphia, PA; Wolters Kluw 2011:127–140.

Hutchison AJ, et al. Efficacy, tolerability, and safety of lanthanum carbonate in hyper- phosphatemia: a 6-month, randomized, comparative trial versus calcium carbon- ate. Nephron Clin Pract. 2005;100:c8–c19.

Hutchison AJ. Lanthanum carbonate treatment, for up to 6 years, is not associated with adverse effects on the liver in patients with chronic kidney disease stage 5 receiving hemodialysis. Clin Nephrol. 2009;71:286–295.

Jen G, et al. Prevention of secondary hyperparathyroidism in hemodialysis patients the key role of native vitamin D supplementation. Hemodial Int. 2010;14:486–491.

Kakuta T, et al. Prognosis of parathyroid function after successful percutaneous ethanol injection therapy guided by color Doppler flow mapping in chronic dialysis patients. Am J Kidney Dis. 1999;33:1091–1099.

Kinnaert P, et al. Long-term results of subcutaneous parathyroid grafts in uremic patients. Arch Surg. 2000;135:186–190.

Lewis JB, et al. Ferric citrate controls phosphorus and delivers iron in dialysis patient J Am Soc Nephrol. 2014; in press.

Lomashvili KA, et al. Phosphate-induced vascular calcification: role of pyrophosphate and osteopontin. J Am Soc Nephrol. 2004;15:1392–1401.

London GM, et al. Arterial calcification and bone hisomorphometry in end-stage renal disease. J Am Soc Nephrol. 2004;15:1943–1951.

Lopes AA, et al. Phosphate binder use and mortality among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS): evaluation of possible confounding by nutritional status. Am J Kidney Dis. 2012;60:80–101.

López-Hilker S, et al. Phosphorus restriction reverses hyperparathyroidism in uremia independent of changes in calcium and calcitriol. Am J Physiol. 1990;259:F432–F

Moe SM, Chen NX. Calciphylaxis and vascular calcification: a continuum of extra-skeletal osteogenesis. Pediat Nephrol. 2003;18:969–975.

Moe SM, et al. Vegetarian compared with meat dietary protein source and phosphorus homeostasis in chronic kidney disease. Clin J Am Soc Nephrol. 2011;6:257–264

Monney P, et al. Rapid improvement of calciphylaxis after intravenous pamidronate therapy in a patient with chronic renal failure. Nephrol Dial Transplant. 2004;19:2130–2132.

Mudge DW, et al. Does aluminium continue to have a role as a phosphate binder in contemporary practice? BMC Nephrol. 2011;12:20.

Nastou D, et al. Next-generation phosphate binders: focus on iron-based binders *Drugs.* 2014;74:863–877.

Navarro JF, et al. Relationship between serum magnesium and parathyroid hormone levels in hemodialysis patients. Am J Kidney Dis. 1999;34:43–48.

Nigwekar SU, et al. Sodium thiosulfate therapy for calcific uremic arteriolopathy. Clin J Am Soc Nephrol. 2013;8:1162–1170.

O'Neill WC, Hardcastle KI. The chemistry of thiosulfate and vascular calcification. Nephrol Dial Transplant. 2012;27:521–526.

Penne EL, et al; for the CONTRAST investigators. Short-term effects of online hemodi- afiltration on phosphate control: a result from the randomized Controlled Convec- tive Transport Study. Am J Kidney Dis. 2010;55:77–87.

Penne EL, et al. Role of residual renal function in phosphate control and anemia management in chronic hemodialysis patients. Clin J Am Soc Nephrol. 2011;6: 281–289.

Rastogi A. Sevelamer revisited: pleiotropic effects on endothelial and cardiovascular risk factors in chronic kidney disease and end-stage renal disease. Ther Adv Cardiovasc Dis. 2013;7:322–342.

Schaefer K, et al. Reduced risk of hypercalcemia for hemodialysis patients by administering calcitriol at night. Am J Kidney Dis. 1992;19:460–464.
Schiller LR, et al. Effect of the time of administration of calcium acetate on phosphorus binding. N Engl J Med. 1989;320:1110–1113.
Sewell LD, Pittelkow MR. Low-dose tissue plasminogen activator for calciphylaxis. Arch Dermatol. 2004;140:1045–1048.
Souberbielle JC, et al. Inter-method variability in PTH measurement: implication for the care of CKD patients. Kidney Int. 2006;70:345–350.
Spiegel DM, Farmer B. Long-term effects of magnesium carbonate on coronary artery calcification and bone mineral density in hemodialysis patients: a pilot study. Hemodial Int. 2009;13:453–459.
Teng M, et al. Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. New Engl J Med. 2003;349:446–456.
Ubara Y, et al. Histomorphogenic features of bone in patients with primary and secondary hypoparathyroidism. Kidney Int. 2003;63:1809–1816.
Wüthrich RP, et al. Randomized clinical trial of the iron-based phosphate binder PA21 in hemodialysis patients. Clin J Am Soc Nephrol. 2013;8:280–289.
Yokoyama K, et al. A randomized trial of JTT-751 versus sevelamer hydrochloride in patients on hemodialysis. Nephrol Dial Transplant. 2014a;29:1053–1060.
Yokoyama K, et al. Ferric citrate hydrate for the treatment of hyperphosphatemia in nondialysis-dependent CKD. Clin J Am Soc Nephrol. 2014b;9:543-552.

Web References

Uremic bone disease links. http://www.hdcn.com/crf/bone and http://kdigo.org/home/mineral-bone-disorder/.

37 Dialysis in Infants and Children

Susan R. Mendley

Choices in dialysis treatmentfor infants and children are wide and include the fullrangeoftherapies utilized in adult patients. Theoreti- cal considerations ofclearance, kinetic modeling, and adequacy of dialysis are equally relevantin pediatric dialysis, although they are less well studied in this population than in adults. There are impor- tant technical considerations in performing dialysis on patients whose weights may vary by as much as 50-fold. Furthermore, there are indications for and complications of the dialysis procedure that are unique to children. Finally, chronic care of children receiving dialysis is complex and requires attention to growth and cognitive develop- ment, age-appropriate nutritional interventions, consequences of metabolic disturbances, and psychosocial adjustment to achieve the goal of complete rehabilitation.

I. ACUTE DIALYSIS

A. Indications.

The indications for acute renal replacement therapy inan infant, child, or adolescent are similar to those in adults and include:

1. Oliguric acute renal failure where optimal nutritional and medical support will require fluid and/or electrolyte removal
2. Volume overload with congestive heart failure, pulmonary edema, or severe hypertension not manageable with diuretics or conservative measures; fluid overload greater than 20% of body weight in the setting of critical illness may be an independent indication
3. Hyperkalemia with electrocardiographic abnormalities
4. Metabolic acidosis that cannot be safely corrected with sodium bicarbonate administration because of risk of sodium or volume overload
5. Symptoms of uremic encephalopathy, with particular attention to seizures
6. Uremic pericarditis
7. Tumor lysis syndrome or severe hyperuricemia complicating chemotherapy for malignancy
8. Progressively rising blood urea nitrogen (BUN) level in a situation where imminent recovery is not anticipated and

uremic consequences are likely. The BUN level where concern arises will vary with the age of the child; 35–50 mg/ dL (12–18 mmol/L) is potentially dangerous in an infant, whereas 150 mg/dL (54 mmol/L) in an adolescent may necessitate initiation of dialysis.

9. Inborn error of metabolism with severe organic acidemia or hyperammonemia
10. Toxic ingestion. Guidelines for extracorporeal therapy for poisoningarefoundin Chapter 20.

B. Choice of acute dialysis modality

1. Acute peritoneal dialysis is often used in infants and young children and has several advantages. It does not require sophisticated equipment or technical expertise. One can avoid the need for vascular access, blood priming, and anti- coagulation; hemodynamic instability is uncommon. Con- tinuous peritoneal dialysis (PD) provides efficient clearance in small children. It is frequently used as adjunctive therapy to manage fluid overload in infants after cardiac surgery with cardiopulmonary bypass. However, severe hyperam- monemia, hyperphosphatemia, or hyperkalemia often require more rapid correction; in such situations, hemodial- ysis (sometimes in combination with continuous hemo[dia] filtration) may be more appropriate. Furthermore, volume removal by ultrafiltration in PD is often unpredictable and may not be rapid enough in some patients with congestive heart failure or pulmonary edema. Dialysate leakage with risk of peritonitis may limit acute PD.

There are no guidelines as to what constitutes adequate PD in acute renal failure (ARF), and one attempts maximum possible clearance to compensate for catabolic stress, utilizing continuous exchanges. The initial prescription may include hourly exchanges; more frequent exchanges can be performed, although a greater fraction of total time is then spent in filling and draining, rather than in solute exchange. An automated cycler facilitates this process, limiting nursing effort and repeated opening of the catheter. Most cyclers can deliver exchange volumes small enough for infants and young children. When a cycler is unavailable or when fill volumes <150 mL are desirable, a safe alternative is the Dialy-Nate set (Utah Medical Products, Gesco), which allows one to connect a bag of dialysate to a closed circuit, including a buretrol device (in-line sterile graduated cylinder) connected to the patient's PD catheter, and a drainage line for effluent dialysate attached to a measurement device. The desired volume fills the buretrol and is then infused into the patient; after a defined dwell, the effluent dialysate is drained and measured, and the process is repeated without opening the system. This allows one to perform closed circuit, low-volume, manual continuous PD in infants and very small children.

Exchange volumes may be targeted at 30–50 mL/kg in infants and up to 1,100 mL/m2 in children, but immediately after catheter placement, it is prudent to limit volumes to half or less of this volume to avoid leakage, which predisposes to peritonitis. Hourly exchanges may result in obligate ultrafiltration even when 1.5% dextrose concentration is used, so that parenteral or enteral fluid intake is needed to avoid volume depletion and prolongation of ARF.

2. Acute hemodialysis is performed when rapid solute clearance is of paramount importance or PD is contraindicated because of an intra-abdominal process (including recent abdominal surgery, diaphragmatic hernia, omphalocele, or gastroschisis) or respiratory limitation.

Acute hemodialysis in infants and small children requires experience and technical expertise, as well as size-appropriate dialyzers, blood lines, and vascular catheters. Very small patients may require blood or albumin priming of the hemodialysis circuit. Small patient size allows effi- cient and rapid solute clearance where appropriate (i.e., ammonia), but must be approached with caution where overly rapid osmolar shifts could precipitate seizures (reportedly more common in children than in adults). Dialyzers are available in a range of sizes for children through older adolescents (Table 37.1); however, the choices in small dialyzers have become fewer, and availability is often limit ed
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3. Continuous therapies. Continuous renal replacement therapy (CRRT) has been utilized in pediatric patients, ranging from preterm infants to older adolescents. The physiologic principles are unchanged from those in adults (see Chapter 15); because of small patient size, clearance can be extremely efficient, replacing a large fraction of endogenous renal function. Prospective registry data on CRRT in infants and children are becoming available and providing insights into practice variation and determinants of outcome (Ashkenazi, 2013). We recognize fluid overload as an independent risk factor for mortality in children with acute kidney injury (AKI) receiving CRRT and adjust ultrafiltra- tion to address that. CRRT has been successfully combined with extracorporeal membrane oxygenation support even in infants and provides better volume management than free-flow systems. Further, continuous therapies permit better phosphorus clearance than intermittent hemodi- alysis or PD and are thus frequently employed in the tumor lysis syndrome in children with Burkitt lymphoma or acute lymphoblastic leukemia.

Maintaining vascular access with adequate flow in small vessels can be problematic (Table 37.2) and is often the limiting factor. There are older reports of arteriovenous hemofiltration (CAVH), but most centers have found pump-driven venovenous treatments to perform more

TABLE 37.1 Characteristics of Low-volume Dialyzers Suitable for Pediatric Use

Dialyzer	Priming Volume (mL)	Surface Area (m2)	Urea Clearance (QB 200 or as Specified)	B12 Clearance (at Highest Tested QB)	K0A	Membrane	Manufacturer
Polyflux 6H	52	0.6	50 QB = 5097 QB = 100136 QB = 150167 QB = 200	90	465 QB= 200	Polyflux (polyarylethersulfone, polyvinylpyrrolidone, polyamide)	Gambro
CA50, CA70	35, 45	0.5, 0.7	128 (147 QB = 300), 153 (175 QB = 300)	27, 36	243, 333	Cellulose acetate	Baxter
F3, F4, F5	28, 42, 63	0.4, 0.7, 1.0	125, 155 (183 QB = 300), 170 (206 QB = 300)	20, 34, 47	231, 364, 472	Polysulfone	Fresenius
Filtryzer B3-0.8A	49	0.8	163	61	404	PMMA	Toray

PMMA, polymethylmethacrylate.

TABLE 37.2 Catheters for Use in Pediatric Extracorporeal Renal Replacement Therapy

Patient Size	Catheter Size	Access Location
Neonate	UVC—5.0 F UAC—3.5, 5.0 F or 5.0 F single lumen or 6.5, 7.0 F dual lumen	Umbilicus Umbilicus Femoral vein(s) Femoral vein(s) Femoral/subclavian vein Femoral/internal jugular/subclavian
3–15 kg	6.5, 7.0 F dual lumen	Femoral/internal jugular/subclavian
16–30 kg	7.0, 9.0 F dual lumen	
>30 kg	9.0, 11.5 F dual lumen	

UVC, umbilical vein catheter; UAC, umbilical artery catheter; F, French gauge.

reliably and to maintain circuit patency longer. As in acute hemodialysis, the entire circuit volume must be consid- ered and a blood or albumin prime used if the circuit vol- ume is >10% of the patient's estimated blood volume. The electrolyte concentrations and pH of the blood prime are far from normal values, and many infants will experience hemodynamic instability at initiation of therapy. Zero balance ultrafiltration has been proposed to bring the electrolyte concentrations in the blood prime close to physiologic values, which might avoid instability at initiation (Hackbarth, 2005). 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. Hemofilters appropriate for pediatric use are listed in Table 37.3. Ultrafiltration is controlled by volumetric pump or automated weighing to avoid errors in replacement fluid, which, if compounded over days of therapy, could be dramatic in a small, anuric patient.

Currently available machines, including the Gambro Prismaflex (Gambro Lundia AB, Lund, Sweden), the Braun Diapact (B. Braun Medical, Bethlehem, PA), and the NxStage (NxStage Medical Inc., Lawrence, MA), have been used in children, although the NxStage does not permit blood flow rates in a range appropriate for small patients. Several studies have demonstrated the success of CRRT in critically ill infants and children. Ultrafiltra- tion rates in infants and small children may be as low as 5–30 mL/hr without replacement fluid (slow continuous ultrafiltration, SCUF) or as high as 100–600 mL/hr with replacement fluid (C-HF); larger children can tolerate ultrafiltration and replacement rates near those of adults. Commercially available bicarbonate-based dialysate or replacement solution (PrismaSol, PrismaSATE, [Gambro Lundia AB, Lund, Sweden], Accusol, [Baxter Healthcare,

TABLE 37.3 Hemofilters and Sets Appropriate for Pediatric Use

Hemofilter	Priming Volume (mL)	Surface Area (m2)	Ultrafiltration Rate (mL/min, QB = 100)	Membrane	Manufacturer
Minifilter Plus	15	0.07	1–8	Polysulfone	Baxter
RenafloII HF 400, 700	28, 53	0.3, 0.7	20–35, 35–45	Polysulfone	Minntech
Prismaflex, M60, M100 set	93, 152	0.6, 0.9	38,44	AN69	Gambro
Prismaflex HF20	60	0.2		PAES	Gambro

AN69, acrylonitrile and sodium methallyl sulfonate; PAES, polyarylethersulfone.

Deerfield, IL], Pureflow (NxStage Medical, Inc., Lawrence, MA), Normocarb (Dialysis Solutions Inc., Whitby, ON), or Hemosol BO [Gambro Lundia AB, Lund, Sweden), is the safest choice; errors in local preparation of solutions in hospital pharmacies are well recognized and are no longer appropriate now that standardized solutions are available. Successful circuit anticoagulation has been reported with both heparin and citrate. 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 persis- tently 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 reported series, infants <5 kg are more often anticoa gulated with heparin. 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. Circuit life is significantly shorter in pediatric patients run without anticoagulation.

II. CHRONIC DIALYSIS

A. Indications. Optimal management of chronic kidney disease (CKD) avoids some of the historical indications for initiation of dialysis. Anemia, acidosis, hyperparathyroidism, and growth delay can often be managed medically, so nephrologists must be attuned to subtle indications of uremia, that is, diminished energy (less vigorous play), resumption of napping, anorexia (with absence of expected weight gain), and inattentiveness at school or failure to attain expected developmental milestones, in order to recognize the appropriate time to begin dialysis.

There is no consensus as to the specific level of GFR at which dialysis should be started. Symptomatic uremia or metabolic disturbances such as hyperkalemia, hyperphosphatemia, malnutrition, or growth failure that cannot be managed conservatively are agreed upon as indications for initiation of renal replacement therapy. Chronic dialysis is usually an interim measure to allow time to prepare for kidney transplantation.

B. Choice of chronic dialysis modality

1. Chronic PD is often the therapy of choice for pediatric patients. Transperitoneal solute exchange in children appears to be as efficient 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 in the category of high or high-average transport, although this observation appears to be the result of large surface area for transport rather than a difference in peritoneal membrane characteristics and can be corrected for by testing patients at fill volumes of 1,000–1,100 mL/m2. Adolescents and teenagers have PET results more typical of adults. Enhanced glucose absorption will result in relatively rapid attainment of osmotic equilibrium between dialysate and plasma, limiting ultrafiltration on long dwells. Automated forms of PD utilizing short dwells are most commonly used in children to accommodate high average peritoneal transport in young children and to improve treatment adherence in older children.

PD offers additional benefits as a chronic dialysis modality. It is technically simple and avoids the need for chronic vascular access (which is particularly difficult in infants and small children). Blood pressure and volume status may be better controlled with PD than with hemodialysis. 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.

a. Limitations to peritoneal dialysis. Previous abdominal surgery may result in intra-abdominal adhesions that make PD impossible, particularly repair of complex urogenital anomalies, which are often a cause of end-stage kidney disease (ESKD) in children. However, one can rarely predict whether adhesions will limit therapy, and a trial of PD is usually warranted. The presence of a ventriculoperitoneal shunt was once considered a relative contraindication to PD; however, multicenter data show that dialysis can be performed successfully without ascending infection even in the setting of peritonitis (Dolan, 2013). The presence of a ureterostomy, pyelostomy, or loop ileostomy is not an absolute contraindication to

performance of PD, although the risk of exit site infection and peritonitis with urinary organisms is increased.

b. Transplantation in peritoneal dialysis patients. PD is continued up to the time of renal transplantation without increased risk of infection. The PD catheter is often removed at the time of living-donor transplantation (assuming immediate graft function), but sometimes it is left in place if a deceased donor transplant is performed. The catheter will then be removed electively once graft function is stable; delay in catheter removal has been associated with posttransplantation peritonitis in the dry abdomen.

c. Complications of peritoneal dialysis. The complications of pediatric PD include those already described in adults (see Chapters 28–29). PD presents particular problems for children and families. Months or years of a demanding regimen may result in "burnout" or caregiver fatigue, which exacerbates underlying family conflicts; nonadherence to therapy becomes common, particularly among adolescents. The presence of a PD catheter may adversely affect body image. Children have a higher rate of peritonitis than adults, which further complicates therapy. Eradication of nasal *Staphylococcus aureus* carriage leads to decreased exit site infection and peritonitis in adults, but studies in children have shown no benefit. Congenital defects in the diaphragm may result in communication between the pleural and peritoneal spaces. In some cases, a change to automated peritoneal dialysis (APD) with empty periods may permit continuation of PD. Some children become obese from excessive glucose absorption from dialysate; this presents additional problems for body image as well as adversely affecting blood lipid levels and an already increased risk of cardiovascular disease. Chronic hypoalbuminemia develops in some patients, particularly with repeated peritonitis; its long-term consequences for growth in stature and lean body mass are unknown.

C. Apparatus for acute and chronic peritoneal dialysis

1. Lactate-basedPD solutions are available in a range of bag sizes appropriate for small patients who perform chronic ambulatory peritoneal dialysis and automated (cycler) PD. Calcium concentrations of 1.25 mM and 1.75 mM are used, depending on the desired calcium balance and type and amount of phosphorus binder being used. Standard dextrose concentrations (1.5%, 2.5%, and 4.25%) are uti- lized, depending on the need for ultrafiltration. Enhanced glucose absorption in small children occasionally warrants higher glucose concentration to maintain ultrafiltration, although short-dwell dialysis is usually preferred in that situation. Amino acid–containing PD solution is tolerated in children, although there remains a greater reliance on supplemental tube feeding in infants and young children.

Icodextrin-containing solutions have been used in children for long dwells to limit peritoneal glucose exposure. Neutral pH solutions of pure bicarbonate or a bicarbonate/lactate combination have been shown to be safe in children and offer the potential benefit of protection of peritoneal membrane integrity. The long-term impact of new solutions on acid–base and nutritional status is still unclear, and their role in chronic care of pediatric PD patients is still to be d et ermin ed .

2. PD catheters are available in neonatal and pediatric sizes of almost any configuration used in adults, including Tenckhoff (curled and straight), swan-neck, and Toronto-Western, usually with a choice of one or two cuffs. Most commonly placed in children is a curled Tenckhoff catheter with a straight tunnel; North American Pediatric Renal Trials and Collaborative Studies data suggest a benefit to double-cuffed catheters and downward-oriented exit sites in decreasing peritonitis rates.

a. Implantation. Chronic catheters are almost invariably implanted surgically in pediatric patients under general anesthesia. Laparoscopic placement is preferred if surgical experience is available. Laparoscopic technique allows the surgeon to see that the catheter is placed in an optimal position, and it minimizes incision size and healing time. Several technical points appear to be important:

1.Sealing the peritoneum around the catheter (to prevent leakage) by use of a pursestring suture, which is also affixed to the cuff. The exit site should be directed caudally, as shown in Figure 37.1, to facilitate drainage and to minimize the risk of exit site infection.

2.Use of a second pursestring suture to seal the posterior rectus sheath opening and fix the posterior rectus sheath to the upper part of the cuff (to prevent leakage and displacement; this is not shown in Fig. 37.1).

3.Performance of a partial omentectomy (to prevent obstruction)

4.Intraoperative search for and closure of associated hernial defects, especially a patent tunica vaginalis.

5.Intraoperative testing of the catheter to verify that there is free inflow and outflow of dialysate.

We try to allow 2 weeks for healing of the abdomen before using the catheter. It can be used immediately for acute PD or unanticipated clinical deterioration in CKD but one risks early leakage. Small exchange volumes and performance of APD in the supine position may help avoid dialysate leakage.

b. Acute “temporary” catheters can be placed after prefilling the abdomen with dialysate as in adults (see Chapter 23 for description of the technique in adults). Older acute PD catheters were much stiffer than chronic catheters,

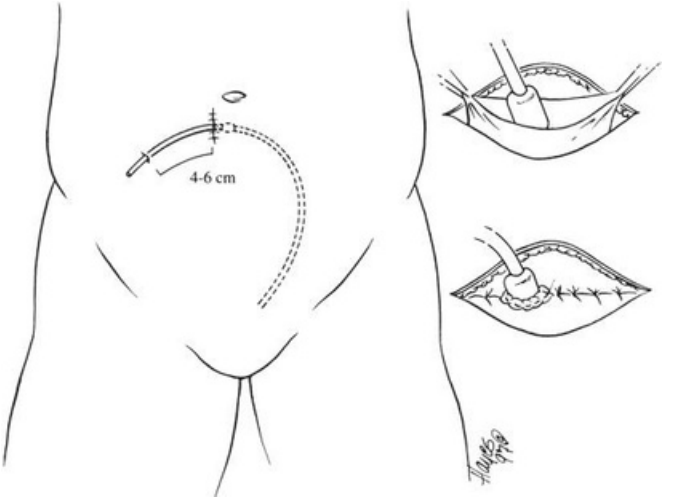


FIGURE 37.1 One method of implanting a peritoneal catheter in children. The pursestring suture used to seal the peritoneum includes the catheter cuff. A second pursestring suture (not shown) may also be used as described in the text to seal the posterior rectus sheath. (Modified from Alexander SR, et al. Clinical parameters in continuous ambulatory peritoneal dialysis for infants and children. In: Moncrief JW, Popovich RP, eds. CAPD update. New York, NY: Masson, 1981.)

conferring a greater risk of bowel injury. Newer, more flexible acute PD catheters have been developed, and some have reported success with their use with a low leakage and infection rate. However, most centers uti- lize a surgically implanted chronic PD catheter for acute peritoneal dialysis, placing it at bedside in the intensive care unit in the most unstable patients.

3. APD cyclers have facilitated PD in young patients, and all available cyclers permit sufficiently small exchange volumes to be used even in infants. Pediatric cycler tubing is available for some models of cyclers; it helps reduce dialysis inefficiency due to dead space in the tubing, which is an important consideration with very small dwell volumes (<200mL).

D. Chronic peritoneal dialysis prescription

1. Continuous ambulatory peritoneal dialysis (CAPD).

The technique for performing CAPD inthe pediatricpatient is similar to that in adults. Fill volumes are determined by patient comfort, but most children can tolerate 40–50 mL/kg or 800–1,100 mL/m2 without discomfort or leakage once their catheter exit site is well healed, although this may require assessment of intraperitoneal pressure. The choice of glucose concentration depends on ultrafiltration needs (fluid intake minus urine output and insensible losses).

a. Kinetic modeling of CAPD as *Kt/V*-urea and creatinine clearance has been performed in children; however, outcome data to define adequate clearance are not available. The NKF KDOQI (2006 update) recommendation for adequate CAPD in children is a weekly *Kt/V*-urea of 1.8 per week; if residual renal function contributes to this clearance, it should be measured regularly. Collections of effluent dialysate and residual urine output (in con- tinent patients with normal bladder function) are used to ensure that target clearance values are being achieved and that loss of kidney function is not compromising the adequacy of therapy. Patients unable to perform urine collections should be assumed to have no residual GFR to avoid inadvertent underdialysis. Many patients can achieve acceptable clearance and ultrafiltration with four exchanges per day; some will require more. The risk of noncompliance with the dialysis prescription and missing exchanges increases as the task of dialysis becomes more burdensome and intrudes on usual fam- ily activities.

2. APD is well suited for chronic PD in children, accommodating their efficient solute exchange and higher risk of peritonitis. APD can be performed without a daytime dwell (nightly intermittent peritoneal dialysis, NIPD), with a day- time dwell (continuous cycling peritoneal dialysis, CCPD), or with a daytime dwell and midday exchange if solute clearance or fluid removal necessitate. The daytime dwell is recommended to improve middle molecule clearance in those patients without residual renal function. NIPD may allow improved nutritional intake and decrease the risk of hernia formation, but clearance will likely be adequate only in patients with high or high-average transport as mea- sured by PET or those with residual renal function. The day dwell of CCPD may allow one to shorten nightly treatments (desirable in older children) or improve clearance for low and low-average transporters; yet high transporters usually absorb most of their long dwell if it is left in all day. The initial prescription is guided by transport characteristics determined by PET, typically ranging from four to eight exchanges per night with dwell times of 45 minutes to 2 hours. a. Kinetic modeling. Although kinetic modeling of PD deliv-
ery has been performed in children treated by CCPD and NIPD, outcome data to define adequate clearance are not available. Target clearance (peritoneal and renal) is the same as for CAPD, a weekly *Kt/V*-urea of 1.8. Dialysate and urine collections are performed to assess the actual delivered dialysis dose at a given prescription. Collections are repeated whenever the prescription is changed and at regular intervals to assess changes in residual renal function and peritoneal transport function. In practice,

young children with PET-defined high or high-average permeability peritoneal membranes can almost always exceed these 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.

3. Tidal dialysis is used in children; it can enhance clearance in patients with borderline values for *Kt/V* who might otherwise need to change modalities. Children with abdominal pain at the end of a drain may be more comfortable using tidal dialysis with less frequent complete drains. Tidal therapy is unwise in infants because of the risk of overfilling of the abdomen with respiratory compromise when the child cannot alert caregivers to distress.

E. Chronic hemodialysis. Chronic hemodialysis is the appropriate modality for children and families not capable of providing reliable home care. Furthermore, large adolescents with low-permeability peritoneal membranes may not achieve adequate clearance on PD without a burdensome exchange schedule, and such adolescents are appropriate candidates for hemodialysis. Because hemodialysis treatments take children out of usual activities (school and play), a hemodialysis unit must provide intensive nursing, tutoring, and play therapy during dialysis treatments.

1. Hemodialysis equipment

a. Vascular access. Vascular access remains a major limitation to successful hemodialysis in 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 treatments (with interval failed renal transplants), and one must ensure they have not depleted all options for long-term vascular access.

1. Catheters (Table 37.2). Available double-lumen hemodialysis catheters range from 7 F to 14 F in 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. The catheter tip should be radiologically positioned in the junction of the superior vena cava and right atrium.

In small infants and neonates, single-lumen catheters may be more appropriate considering vessel size. 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.

2. Fistulas and grafts. In older children, creation of an arteriovenous fistula between the radial artery and cephalic vein in the nondominant arm with an end-to-side anastomosis is a common mode of vascular access. When blood vessel size is too small for constructing an adequate fistula, a polytetrafluoroethylene (GoreTex 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 absent sensation 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.

3. Blood flows. Desired blood flow rate is targeted to urea clearance specifications for a chosen dialyzer. In a patient with advanced uremia, an initial urea clearance of 3 mL/min per kg is prudent to avoid symptomatic disequilibrium; higher urea removal rates are usually tolerated after the first few treatments. Smaller blood vessels cause higher venous resistance than in adults, which eventually limits flow, typically in the range of 50–150 mL/min in small children and 200–350 mL/min in older children. Small catheters often limit flow to 25–100 mL/min because of limited arterial inflow.

b. Dialyzers. A limited listing of dialyzers that may be appropriate for small patients is provided (Table 37.1).

c. Blood lines. Appropriately sized blood lines allow control of circuit volume. If the volume of the entire extracorporeal circuit exceeds 10% of the patient's blood volume (>8 mL/kg), a warmed blood (or albumin) prime is usually given to ensure hemodynamic stability. Small volume blood lines have become more difficult to find in an era of integrated hemodialysis machines. If small volume lines are chosen, it is important that the blood pump be properly calibrated for the chosen lines. Neona- tal lines are not compatible with most currently available volumetric dialysis machines.

d. Dialysis solution. Bicarbonate dialysis solution is standard for pediatric hemodialysis; it provides better hemodynamic stability and fewer intradialytic symptoms. Patients with small muscle mass will be unable to metabolize a large acetate load quickly.

e. Dialysis machines. Dialysis machines that provide volumetric ultrafiltration control are required. Small errors in ultrafiltration volume (of a few hundred milli- liters) may cause symptomatic hypotension or chronic volume overload. Blood flows must be accurate within the range of 30–300 mL/min, and the blood pump calibrated to different size lines.

2. Hemodialysis prescription. Small patients require a cautious approach to avoid disequilibrium by targeting urea clear- ance of 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 advis- able during initiation of hemodialysis when the BUN is extremely elevated. Once a stable, chronic dialysis prescription is attained, more efficient urea clearance is usually well tolerated, and fluid removal is more often a cause of intradialytic symptoms. With conditioning and distraction, most children can tolerate hemodialysis sessions lasting 2–4 hours. a. 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 would be used to prolong the clotting time to 125% of the population baseline value. The initial loading dosage is usually 10–20 units/kg, with higher dosages being used for infants and children weighing <15 kg. The initial maintenance heparin infusion rate (for the first 20–30 minutes) can be set at 0.3–0.5 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.

   b. 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 technical aspects of kinetic modeling are discussed in Chapter 3 and are applied similarly in children. 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.

c. Adequacy of hemodialysis. When small patients receive efficient clearance (i.e., relatively high *K/V*), there is a greater amount of postdialysis urea rebound with reequilibra- tion of urea from either the intracellular space or rela- tively underperfused tissues. Thus, single-pool modeling overestimates dose of dialysis and urea generation rate. The NKF 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 1.4–1.5 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 dialy- sis using the Tattersall equation described in Chapter 3. Yet another approach is to extrapolate from a postdi- alysis 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 total body water ratio, and alternative scaling of hemodialysis dose to body surface area would require even higher doses of Kt/V (Daugirdas, 2010). Residual renal function can significantly impact the hemodialysis prescription, espe- cially 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.

d. Complications

1. 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 per 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.

2. Hypotension. Intradialytic hypotension and cramping with fluid removal >5% of body weight are common, yet interdialytic weight gains can be large in anuric children on largely liquid diets and in noncompliant adolescents, resulting in sustained interdialytic hypertension. Volume removal must be closely monitored because blood pressure is normally lower in children than in adults and there is a narrower margin to hypotension. Infants and very young children are prone to precipitous falls in blood pressure with no warning and no ability to communicate distress. Isolated ultrafiltration or lower dialysate temperature may make fluid removal more tolerable. If hypoalbuminemia is present, intravenous albumin infusion (0.5–1.5 g/kg) will increase oncotic pressure and may permit ultrafiltration. 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.

3. Hypothermia with isolated ultrafiltration. If warmed dialysis solution is not circulated, then the extracorporeal blood circuit will function as a radiator, cooling the blood and the child. Body temperature should be monitored throughout dialysis, especially during isolated ultrafiltration.

III. CARE OF THE PEDIATRIC ESKD PATIENT

A. Nutrition. Comprehensive nutritional management is importantfor the achievement of growth and physical development through ESKD. The recommended energy intakes for pediatric dialysis patients depend on their ages and should be the same as the estimated energy requirement (EER) for their nonuremic counterparts. For infants, the EER for energy is approximately 100 kcal/kg per day. Such high intakes usually require supplementation, and gavage feeding 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 (DRI) of protein for pediatric dialysis patients is the same as that for their nonuremic counterparts plus an estimate of amino acids and protein lost through dialysis. There is an emphasis on the early use of supplements, both orally and

through gastrostomy tubes. There is limited experience with the use of amino acid–containing PD fluids, although individual patients have been treated for up to a year.

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; an appropriate multivitamin not containing vitamin A must be selected.

It is difficult to impose fluid, sodium, phosphate, and potassium restrictions on pediatric patients; however, such restrictions may be unnecessary when PD is the treatment modality. Potassium and phosphorus binders are almost always required for adolescents, yet some infants receiving efficient dialysis will require supplementation. For hemodialysis patients, restrictions depend on the amount of residual urinary output, but always require individual dietary guidance to achieve stringent fluid, sodium, and potassium intake. Infants pose a particular challenge; daily fluid intake in an anuric infant on hemodialysis should be limited to 400–500 mL/m2, and formula should be concentrated and appropriately supplemented to achieve nutritional goals. However, polyuric infants will require supplemental fluid and sodium to maintain volume status and permit growth.

Enteral feeding supplements designed for adults should be used cautiously in young children. Fortunately a whey-based infant formula lower in phosphorus and potassium is available; infants with formula allergies and intolerances present special challenges. 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 vol- ume 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 hemodi- alysis patients, 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 tempera- ture or isolated ultrafiltration may make volume removal more tolerable. Dietary and psychological counseling for the patient and family are advisable in cases of repeated nonad- herence as this may reflect more serious difficulties in cop- ing with the chronic disease process. Some patients remain hypertensive despite apparent euvolemia, and antihyperten- sive medications are indicated. All antihypertensive agents

typically prescribed for adults have been used successfully in pediatric dialysis patients, and doses should be titrated to age-appropriate blood pressure targets and reassessed frequently.

C. Anemia. Children undergoing hemodialysis tend to be anemic more often than adults and have a lower hemoglobin at the initiation of dialysis. Children respond well to erythropoietin; the indications, route of administration, and potential complications are similar for children and adults. Dosage per kilogram is often higher in very young children (150–300 units/kg per week) than in adults. Iron deficiency and repeated episodes of peritonitis adversely affect the erythropoietin response, and nonadherence to home therapy is occasionally a problem. Iron supplementation, either intravenous or oral, is usually necessary in pediatric ESKD patients; blood loss in the hemodialysis circuit is an important cause of iron deficiency in very small patients, especially when more than three treat- ments per week are prescribed. Androgen therapy, rarely used in adults, is contraindicated in prepubertal children because it will lead to premature closure of epiphyses.

D. Growth. Few longitudinal studies describing growth in pediatric patients undergoing CAPD or APD have been undertaken. Initial data comparing growth with CAPD or APD with that obtained with hemodialysis seemed to favor the PD approach; however, definitive controlled studies have not been performed. In children undergoing CAPD or APD, improvement in growth has been linked to a reduction in the degree of secondary hyperparathyroidism. Others have attributed better growth with CAPD or APD to improved nutritional intake, but increasing energy intake much above the EER will not usually be of benefit.

1. Recombinant human growth hormone (rhGH) therapy. There is evidence that rhGH treatment increases growth rate in children receiving chronic dialysis, although not as effectively as in children with nondialysis CKD. The usual dosage is 0.05 mg/kg per day or 30 IU/m2 per week as a nightly subcutaneous injection, although other dosing strategies have been used. Slipped capital femoral epiphyses and worsening of metabolic bone disease may occur with rhGH; secondary hyperparathyroidism should be controlled prior to initiation of therapy. Growth hormone therapy is often paused at the time of renal transplantation, and growth velocity reassessed with a functioning allograft. Glucocorticoid minimization or withdrawal is integral to successful growth after transplant.

2. 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 ≥22 mmol/L.

3. Renal osteodystrophy. Renal osteodystrophy can be ameliorated in children undergoing dialysis treatment by good control of serum calcium, phosphorus, bicarbonate, intact parathyroid hormone, and alkaline phosphatase levels. Calcitriol and vitamin D analogs are used to treat hyperparathyroidism and associated bone disease. There are small series reporting the use of cinacalcet 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 phosphorus level. Phosphorus intake is targeted at or below the DRI 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 choice even in infants and young children because of a greater awareness of the risks of calcium overload and recognition of early cardiac calcification in adolescents and young adults with ESKD. Calcium acetate is available in a liquid formulation, and sevelamer is available in powder, which have facilitated dosing in infants and young children. The use of aluminum-containing phosphate binders should be avoided in infants and young children with CKD because of bone and neurotoxicity. There are no long-term data on the safety of lanthanum in children.

References and Suggested Readings

AshkenaziDJ, et al. Continuousrenal replacement therapy in children ≤10 kg: a repor from the prospective pediatric continuous renal replacement therapy registry. J Pediatr. 2013;162:587–592.

Canepa A, et al. Use of new peritoneal dialysis solutions in children. Kidney Int 2008;73:S137–S144.

Daugirdas JT, et al. Dose of dialysis based on body surface area is markedly less younger children than in older adolescents. Clin J Am Soc Nephrol. 2010;5:821–827

Dolan NM, et al. Ventriculoperitoneal shunts in children on peritoneal dialysis: a survey of the International Pediatric Peritoneal Dialysis Network. Pediatr Nephrol. 2013;28:315–319.

Fischbach M, Warady, B. Peritoneal dialysis prescription in children: bedside p rincip for optimal practice. Pediatr Nephrol. 2009;24:1633–1642.

Furth SL, et al. Peritoneal dialysis catheter infections and peritonitis in children: a report of the North American Pediatric Renal Transplant Cooperative Study. Pediatr Nephrol. 2000;15:179–182.

Goldstein SL, et al. Evaluation and prediction of urea rebound and equilibrated Kt/V the pediatric hemodialysis population. Am J Kidney Dis. 1999;34:49–54.

Goldstein SL, et al. Quality of life for children with chronic kidney disease. Semin Nephrol. 2006;26:114–117.

Gorman G, et al. Clinical outcomes and dialysis adequacy in adolescent hemo dialys patients. Am J Kidney Dis. 2006;47:285–293.

Hackbarth RM, et al. Zero balance ultrafiltration (Z-BUF) in blood-primed CRRT circuits achieves electrolyte and acid-base homeostasis prior to patient connection. Pediatr Nephrol. 2005;20:1328–1333.

Kidney Disease Improving Global Outcomes. Clinical practice guildeline for chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int. 2009; 76(suppl 113):S1–S130.
Kidney Disease Improving Global Outcomes. Clinical practice guildeline for acute kidney injury. Kidney Int. 2012;2(suppl 1):1–138.
Kramer AM, et al. Demographics of blood pressure and hypertension in children on renal replacement therapy in Europe. Kidney Int. 2011;80:1092–1098.
Mendley SR. Acute dialysis in children. In: Henrich WL, ed. Principles and Practice of Dialysis, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009:641–652.
Monagle P, et al. Antithrombotic therapy in children: the Seventh ACCP C onference on antithrombotic and thrombolytic therapy. Chest. 2004;126(suppl 3):645S–687S.
National Kidney Foundation. KDOQI clinical practice guidelines for hemodialysis adequacy, update 2006. Guideline 8. Pediatric hemodialysis prescription and adequacy. Am J Kidney Dis. 2006;48(suppl 1):S45–S47.
National Kidney Foundation. KDOQI clinical practice guidelines for peritoneal dialysis adequacy, update 2006. Guideline 6. Pediatric peritoneal dialysis. Am J Kidney Dis. 2006;48(suppl 1): S127–S129.
Rees L, et al. Growth in very young children undergoing chronic peritoneal dialysis. J Am Soc Nephrol. 2011;22:2303–2312.
Schaefer F, et al. Peritoneal transport properties and dialysis dose affect growth and nutritional status in children on chronic peritoneal dialysis. Mid-European Pediatric PD Study Group. J Am Soc Nephrol. 1999;10:1786–1792.
Shmitt CP, et al. Effect of the dialysis fluid buffer on peritoneal membrane function in children. Clin J Am Soc Nephrol. 2013;8:108–115.
Smye SW, et al. Paediatric haemodialysis: estimation of treatment efficiency in the presence of urea rebound. Clin Phys Physiol Meas. 1992;13:51–62.
Sutherland SM, et al. Fluid overload and mortality in children receiving continuous renal replacement therapy: the prospective pediatric continuous renal replacement therapy registry. Am J Kidney Dis. 2010;55:316–325.
Symons JM, et al. Continuous renal replacement therapy with an automated monitor is superior to a free-flow system during extracorporeal life support. Pediatr Crit Care Med. 2013;14:e404–e408.
Warady B, et al. Pediatric Dialysis. Dordrecht: Kluwer Academic; 2004.
Warady BA, et al. Consensus guidelines for the prevention and treatment of catheter-related infections and peritonitis in pediatric patients receiving peritoneal dialysis: 2012 update. Perit Dial Int. 2012;32(suppl 2):S32–S86.

Web References

North American Pediatric Renal Trials and Collaborative Studies Annual Dialysis: https://web.emmes.com/study/ped/annlrept/annualrept2011.pdf.
Pediatric Continuous Renal Replacement Therapy website: http://www.pcrrt.com/.

38 Cardiovascular Disease

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In end stage kidneydisease (ESKD) patients, mortality due to cardiovascular disease(CVD) is 10 to 30 times higher than in the general population.Forexample, a 30-year-old dialysis patient has a similar CVD mortalityrisk to that of an 80-year-old in the general population. This increasedrisk likely reflects the very high prevalence of CVD, increased prevalence and severity of diabetes, hypertension and left ventricular hypertrophy, and nontraditional risk factors such as chronic volume overload, hyperphosphatemia, anemia, oxidant stress, and other aspects of the uremic milieu (Table 38.1). 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.

I. TRADITIONAL RISK FACTORS

A. Blood pressure. Dataon blood pressure targets and optimal strategies and agentsfor blood pressure management in dialysis remain insufficient (Inrig, 2010). These are discussed in further detail in Chapter 33.

B. Diabetes. Dialysis patients with diabetes are at higher risk for acute coronary syndromes and have worse outcomes following coronary interventions than those without diabe- tes. Additionally, there is increased prevalence of heart failure. Poor blood glucose control (as assessed by glycosylated hemoglobin levels) is associated with increased mortality in dialysis patients, although precise targets remain uncertain. Cohort data suggest that a hemoglobin A1C threshold of 8% may be a reasonable target in healthier dialysis patients for cardiovascular risk reduction (Ricks, 2012), while less stringent targets may be appropriate in those with more extensive comorbidity. See Chapter 32.

C. Smoking. Smoking is associated with progression in early stage CKD patients, and may well adversely impact residual kidney function in dialysis patients. Smoking strongly associates with all-cause mortality in dialysis patients and likely associ- ates with CVD. Critically, in USRDS data, former smokers had a similar risk as lifelong nonsmokers, suggesting a benefit of smoking cessation and a role for directed intervention.

TABLE 38.1 Traditional and Nontraditional Cardiovascular Risk Factors

Traditional Risk Factors	Nontraditional Risk Factors
Older age	Extracellular fluid volume overload
Male gender	Abnormal calcium/phosphate metabolism
Hypertension	Vitamin D deficiency Anemia Oxidant Stress
Diabetes	Inflammation Homocysteine Malnutrition
Smoking	Albuminuria Thrombogenic factors Sleep
Dyslipidemia	disturbances Altered nitric
Left ventricular hypertrophy	oxide/endothelin balance Marinobufagenin
Physical inactivity	Uremic toxins
Menopause	
Family history of cardiovascular disease	

D. Dyslipidemia

1. Lipid profile patterns. Dyslipidemia is very common in all stagesofkidney disease, including both hemodialysis and peritoneal dialysis patients. 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. In dialysis, similar to many advanced chronic disease states, the relationship of total or LDL cholesterol to mortality is "U"-shaped; patients with high cholesterol levels, likely due to increased atherogenic risk, and also patients with low levels, likely due to associated malnutrition, both are at heightened risk (Kilpatrick, 2007). Total cholesterol and, in particular, high-density lipoprotein (HDL) cholesterol levels may be reduced, and atherogenic lipoprotein remnants and lipoprotein (a) are often increased.

   Nearly one-third of dialysis patients 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 a deficiency of lipoprotein lipase, resulting in reduced lipolysis of triglyceride (TG)-rich very low-density lipoproteins (VLDL) and yielding high quantities of atherogenic remnant lipoproteins. 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.
2. Measurement. If not previously assessed, it is likely worthwhile to evaluate a lipid profile at least once in all dialysis

patients. This can establish a diagnosis of severe hypercholesterolemia or hypertriglyceridemia (i.e., 1,000 mg/dL [11.3 mmol/L] or higher) that may prompt focused treatment or evaluation for secondary causes of dyslipidemia (Miller, 2011). Lipid panels are optimally obtained in the fasting state, particularly for evaluation of serum triglyceride levels, although, as many dialysis patients receive treatments in the afternoon or evening and data on therapy efficacy are limited, a random screening may be most practical.

The current KDIGO 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, in patients already treated with a high potency statin, there is no indication to routinely measure cholesterol. Similarly, in dialysis patients not currently treated with a statin, given the data discussed below on statin efficacy for CVD prevention, there is 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 nutritionist with experience in management of kidney disease patients. Recommendations listed in Chapter 31 should generally be followed. These include consumption of a diet containing about 25%–35% of total calories as fat; of this, about 20% should be monounsatured, 10% polyunsaturated, and <7% saturated fat. 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 dialysis patients, there may be a minority where overall calorie restriction is indicated to achieve ideal body weight, especially among those receiving peritoneal dialysis. In PD patients, sodium restriction may reduce the use of higher dialysate glucose concentrations; this would yield less glucose absorption and decrease the stimulus for hypertriglyceridemia (see Chapter 29). 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 dialysis patients are in the highest risk group for CVD events, several large clinical trials have failed to show a significant benefit with statin therapy, despite substantial LDL-C lowering with therapy in these trials. Accordingly, in contrast to the prior KDOQI guideline, 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 incident dialysis patients 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 dialysis patients 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, statin/ezetimibe therapy was associated with significant cardiovascular event reduction. As many of these individuals continued on therapy following dialysis initiation, it seems reasonable to continue statin therapy in individuals treated with statins at the time of dialysis initiation. Although there are no studies evaluating dialysis patients with an acute myocardial infarction (MI) who were not previously treated with a statin, it also seems reasonable to initiate statin therapy in those with a relatively good longer-term prognosis.

One area of insufficient knowledge is peritoneal dialysis (PD). SHARP included 496 PD patients, but, aside from SHARP, PD patients have not been included in clinical trials. In SHARP, there was a trend to a benefit with lipid-lowering therapy versus placebo in this subgroup. Similarly, in a post hoc analysis of the US Renal Data System observation Dialysis Morbidity and Mortality Wave 2 cohort that used propensity score matching, lipid-l owering therapy in PD patients was associated with a significantly reduced risk of all-cause and cardiovascular death.

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 38.2). Additionally, in dialysis patients not previously prescribed a statin, in the opinion of the authors, statin treatment of those dialysis patients with longer life expectancies (i.e., individuals listed for transplantation) or those experiencing recent acute coronary syndromes may be appropriate. Given the paucity of data in peritoneal dialysis but physiology that suggests higher atherosclerosis risk, a “fire-and-forget” approach may also be beneficial in PD patients (Goldfarb-Rumyantzev, 2007).

TABLE 38.2 Lipid-lowering Medication Dose Adjustments for Reduced GFR

Agent	Dose Adjustment in Dialysis	Notes
Statinsa		
Atorvastatin	None ↓	
Fluvastatin	to 50%	Decrease dosage by half at GFR <30
Lovastatin	↓ to	Decrease dosage by half at GFR <30
Pravastatin	50%	Starting dose of 10 mg/d recommended for GFR <60
Rosuvastatin	No ↓	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 Sequestrants		
Cholestyramine	No	Not absorbed
Cholestipol	No	Not absorbed
Colesevelam	No	Not absorbed
Fibratesb		
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 May worsen glycemic control and
Nicotinic Acid	↓ to 50%	cause orthostasis, hyperuricemia, and flushing; may have phosphorus binding effects

[a] Statins may interact with other medications used in dialysis patients, including calcineurin inhibitors, several antibiotics, and, potentially, calcium channel blockers.

[b]Based on package inserts, all fibrates are contraindicated in dialysis patients. Small short-term studies have safely utilized fibrates in dialysis patients, 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 9795 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, and nicotinic acid, and are best 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 CKD. This is particularly apparent with concurrent use of fibrates, and this combination should be avoided in CKD.

c. Hypertriglyceridemia management. Statins have some effect in lowering serum triglyceride level, 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 dialysis patients, 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 that: "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 dialysis patients with very high TG levels (>500 mg/dL [>5.7 mmol/L]); accord- ingly, 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 dialysis patients as the safety of this class has not been assessed sufficiently in dialysis patients. 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 38.2) 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 (TG) are >400 mg/dL (>4.5 mmol/L), and their use is relatively contrain- dicated when TG are >200 mg/dL (>2.3 mmol/L) since they may increase triglycerides in some patients. Doses do not need to be reduced in dialysis patients (Table 38.2). Sevelamer acts by the same mechanism to

lower both total and LDL cholesterol, and may be a good choice when phosphorus binding is also desired. While not as effective for LDL lowering, nicotinic acid has the greatest favorable effects on HDL cholesterol levels of available drug therapies, and also lowers serum triglyceride levels. However, there are no data to support a benefit of nicotinic acid on CVD or mortality outcomes. Dosage should be reduced by about 50% in ESKD, given its substantial renal excretion. The potential of nicotinamide as a phosphorus binder has been advocated, but data are inadequate to support this indication. 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.

E. Left ventricular hypertrophy

1. Epidemiology. Left ventricular hypertrophy (LVH) is highly prevalent,frequently developing prior to the need for kidney replacement therapy, and likely reflecting pressure and volume overload (KDOQI 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%–75%) patients. LVH in dialysis patients is an independent risk factor for subsequent adverse cardiovascular events and death.

Most LVH is initially concentric, representing 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 hypertrophy. The endpoint is often a dilated cardiomyopathy with eventual reduction in systolic function. These end-stage patients typically have low blood pressure and may be responsible for the "J"-shaped (or "U"-shaped) relationship observed between blood pressure and mortality in dialysis patients.

LVH most often is 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 dialysis patients,

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 re- quired to estimate LV mass and volume, the increasing availability of cardiac magnetic resonance imaging likely provides the most accurate assessment of LV structure. Screening echocardiography is currently recommended for incident dialysis patients; however, 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 systolic blood pressure, strict management of volume, management of mineral and bone disorder, and use of ACE inhibitor or angiotensin receptor blocker therapy, regression of LVH may occur in dialysis patients. Data are inconsistent on whether high flow arteriovenous fistulas may lead to maladaptive cardiac remodeling. That regres- sion of LVH results in reduced CV events and decreased mortality risk appears likely, as multiple post hoc analy- ses have shown a lower risk of adverse events in partici- pants in whom LVH regressed over the course of clinical trials. Accordingly, in dialysis populations, LVH has been used both as a factor in determining study eligibility and as a surrogate outcome to infer subsequent CV and mor- tality risk reduction.

   With regard to RAAS inhibition, the largest outcomes study to date evaluating the effect of renin–angiotensin–aldosterone system blockade in dialysis patients with LVH was the Fosinopril in Dialysis Study which randomized 397 hemodialysis patients to fosinopril versus placebo, and showed no benefit on cardiovascular events over a 2-year period (Zannad, 2006). Other trials examining left ventricular mass reduction have, however, suggested a benefit. Randomized trials in CKD targeting normalization of he- moglobin levels with recombinant human erythropoietin had no effect on left ventricular mass. In hemodialysis patients enrolled in the Frequent Hemodialysis Network study, those who received more frequent hemodialysis had a significant improvement in LV mass; whether this benefit was mediated through improved control of blood pressure, volume, phosphorus, or other factors is uncertain.

II. NONTRADITIONAL RISK FACTORS. These are listed in Table 38.1. In-depth discussion of some of these is beyond the scope of the Handbook, but we briefly summarize the most pertinent issues. Volume control is discussed in chapters 12, 26, and 33.

A. Mineral and bone disorder. Mineral and bone disorders, discussed in Chapter 36, may affect the cardiovascular system in multiple ways (Lau & Ix, 2013). First, both elevated 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 promote vascular calcification. Vascular calcification occurs at both the arterial media and the intima, with medial calcification generally more pronounced among dialysis patients. 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 fill- ing. 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 as 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 precision to closely track changes over time. Use of such tests needs to be justified by their impact on clinical decision making. At the present time, there is no reliable method of reversing cardiac calcification, although some studies have suggested that use of non-calcium-containing binders results in more favorable calcium balance. Dialysis prescriptions resulting in negative phosphorus balance also may slow progression of calcification. A reasonable strategy may be to limit the use of calcium-containing phosphorus binders in patients in whom extensive vascular calcification has been documented. This is discussed in more detail in Chapter 36.

B. Anemia. Anemia is common in CKD patients, especially at dialysis initiation, and its severity correlates with the extent of LVH. While in observational studies, patients with higher hemoglobin levels have fewer cardiovascular disease events, treatment with recombinant erythropoietin to raise hemoglobin levels to the normal range may be associated with increased cardiovascular risk. Anemia management is discussed in detail in Chapter 34.

C. Sleep. Sleep abnormalities, discussed in Chapter 40, are highly prevalent in dialysis patients and are associated with coronary artery disease. 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 dialy- sis patient increase oxidant stress and inflammation burden. These include dialysis using 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 arteriovenous (AV) grafts, or kidney allografts also may be a source of continued inflam- matory 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 ther- apies in the dialysis population have been disappointing.

III. ISCHEMIC HEART DISEASE

A. Overview. Acute myocardial infarction (MI) and acute coronarysyndromes areexceedingly common in the ESKD population and associated with poor outcomes. One study in Taiwan demonstrated 30% 1-year mortality following acute coronary syndrome in dialysis patients, while US data show a 50% higher in-hospital mortality rate for dialysis patients admitted with acute MI (Herzog, 2007) and 1-year mortality of approximately 60%.

Both atherosclerosis and arteriosclerosis contribute to pathogenesis; arteriosclerosis, often synonymous with vascular stiffness and 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. Small vessel coronary artery disease also plays a role: in one study, up to 50% of nondiabetic dialysis patients 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 dialysis patients, and even screening of asymptomatic trans- plant candidates is controversial. There are no pre-operative screening guidelines specific to dialysis patients, and it is reasonable to use general population guidelines, recogniz- ing that the extent of comorbid conditions prevalent in the dialysis population is likely to place them into the highest cardiovascular risk group. Because many dialysis patients are unable to achieve adequate exercise levels for valid stress tests, pharmacologic stress tests should be used in this popu- lation. Furthermore, because of the high incidence of baseline electrocardiogram abnormalities, either nuclear or echocar- diographic 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 PD, and the associated risk of contrast nephropathy should be kept in mind.

Diagnosis of acute MI can be challenging , as cardiac biomarker levels, including troponins, may be elevated chronically (DeFilippi, 2003). Chronic troponin elevation itself is a marker of worse prognosis, likely representing ongoing injury and subclinical ischemia. The American Heart Association suggests that, if chronic, minor elevations in cardiac biomarkers in kidney failure should not be classified as injury; however, rising and/or falling cardiac biomarker levels in the appropriate clinical setting likely are consistent with acute MI (Thygesen, 2012).

C. Prevention. There are few clinical trials evaluating primary and secondary prevention strategies in dialysis patients. If hemorrhagic risk and blood pressure permit, aspirin, β-blockers, ACE inhibitors or angiotensin receptor blockers, and nitrate preparations may allbe appropriatefor secondary prevention.

D. Treatment

1. Management of angina pectoris and stable coronary artery disease.

Thepharmacologic approach to angina in dialysis patients 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 is appropriate. Usual dosages of sublingual and oral nitrates can be given to dialysis patients.

While there is strong evidence for the benefits of aspirin for secondary prevention of atherosclerotic CVD events in individuals with intact kidney function and coronary artery disease, with or without ischemic cardiomyopathy, there are conflicting reports of worse heart failure outcomes associated with aspirin use in patients with kidney disease. This may relate to attenuation of the beneficial effects of ACE inhibitors due to aspirin-mediated inhibition of kinin-mediated prostaglandin synthesis. Limited observational data in dialysis patients have not shown a beneficial effect on cardiovascular outcomes associated with low-dose aspirin, but these reports are limited by study design. Clinical trials examining aspirin use and use of other antiplatelet agents for access patency show no evidence of harm associated with aspirin or clopidogrel use, but benefit remains uncertain. At this time, given the significant benefits of aspirin use in nondialysis patients with coronary artery disease, there is insufficient evidence to recommend against the use of aspirin in dialysis patients with coronary artery disease.

2. Chest pain during the hemodialysis session. For patients who develop chest pain primarily during the hemodialysis session, 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 (Selby, 2006). 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 dialysis patients, including atenolol, which has extensive kidney clearance. Among commonly used β-blockers, atenolol and metoprolol are extensively cleared with hemodialysis, while carvedilol and labetolol 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 dialysis patients, calcium channel blockers, particularly the non-dihydropyridines (diltiazem and verapamil), should be used with caution.

3. Revascularization. The optimal treatment of coronary artery disease in dialysis patients remains uncertain. Medical management, percutaneous intervention (PCI) including angioplasty with use of either drug eluting or bare metal stents, and coronary artery bypass graft (CABG) surgery, all have roles in individualized care (Charytan, 2014).

   Given the high periprocedural risks associated with CABG, if anatomy permits and symptoms persist despite medical management, PCI is likely the better approach for patients who are not transplant candidates or at higher perioperative risk if undergoing CABG. As in the general population, CABG incorporates greater short-term risk in exchange for longer-term benefits, and balancing this trade-off is essential to individualizing therapy. For PCI, data are insufficient to support drug eluting stents over bare metal stents, and a key determination for stent type may be whether an individual dialysis patient can safely use clopidogrel for 1 year or more; if longer-term clopidogrel use is an option, many interventionalists will select a drug eluting stent based on general population and early stage CKD data. 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.

IV. CARDIOMYOPATHY AND HEART FAILURE

A. Pathophysiology. Heartfailureis highly prevalent and related to many common factors inthe 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) or diastolic dysfunction in which the LV has a normal ejection fraction but impaired filling. Diastolic dysfunction is often associ- ated with LVH and systemic hypertension, both of which are extremely common in dialysis patients. Systolic dysfunc- tion is frequently a result of ischemic disease and dilated cardiomyopathy. For obvious reasons, dialysis patients are particularly vulnerable to fluid overload, and pulmonary edema in the setting of marked fluid overload may not represent cardiac dysfunction. However, frequent pulmonary edema with minimal intradialytic weight gain may be an important clue of 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. KDOQI guidelines recommend obtaining echocardiograms at dialysis initiation after dry weight is established and every 3 years thereafter; these recommendations are opinion-based (KDOQI CVD, 2005).

B. Treatment. Chronic therapy for heart failure in dialysis patients has not been adequately studied; therefore, most recommen- dations are either extrapolated from the general population or based on smaller trials. Restriction of sodium intake, including avoidance of routine sodium modeling, is important, since, with most thrice-weekly hemodialysis schedules, the ability to remove excess fluid is limited. More frequent dialysis thera- pies, including daily hemodialysis and PD, may help optimize volume status. Maintaining a balance between fluid overload on the one hand and symptomatic hypotension on the other may be extremely difficult in some dialysis patients. In the future, newer technologies, including intradialytic blood vol- ume monitoring and bioimpedance analysis, may have more clearly delineated roles for optimizing volume management. In general, we favor maintenance of near euvolemia over phar- macologic therapy in the treatment of heart failure in dialysis patients.

1. Traditional drug therapy
   a. ACE inhibitors are beneficial in nonuremic patients with chronic heart failure and may be beneficial in dialysis patients, 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 hemo- dialysis patients with a left ventricular ejection fraction below 40%, a strategy that is not routinely recommended (Cice, 2010). On the other hand, one relatively large ran- domized 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 hyper- kalemia. If there is a contraindication to ACE inhibitor use, it seems reasonable to extrapolate from data in the general population and substitute angiotensin receptor blockers (ARBs). Most ACE inhibitors are cleared during dialysis while ARBs are not dialyzable.
   b. a-Blockers, another mainstay of heart failure therapy in the general population, also are of uncertain benefit in the dialysis population. In an Italian study, carvedilol, well studied for heart failure in the general population, reduced mortality in dialysis patients with left ventric- ular dysfunction (Cice, 2003). Carvedilol dosing is the same as in the general population. One small trial com- pared thrice weekly posthemodialysis administration of lisinopril with atenolol (Agarwal, 2014), with both groups having a similar reduction in LV mass, the primary out- come; of note, the group treated with atenolol had fewer deaths and heart failure hospitalizations, secondary outcomes for which the study was not powered. It is dif- ficult to draw treatment conclusions from this study as the dosing intervals for lisinopril were very atypical for clinical practice. Several β-blockers, including atenolol, have markedly reduced elimination rates in kidney fail- ure and should either not be used or be used at either a lower dose or increased dosing interval (Chapter 33). 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 epleronone, are beneficial in the general population with heart failure and, given the known effects of aldosterone on arterial stiffness and cardiac remodeling, could be beneficial in the dialysis population. With only one small

trial suggesting a benefit on clinical outcomes with low-dose spironolactone (Matsumoto, 2014), use of these agents has not been adequately studied in the dialysis population for safety or efficacy. Despite the lack of substantial kidney function, of theoretical concern would be a possible increased risk of hyperkalemia, particularly if aldosterone antagonists were used in conjunction with ACE inhibitors or ARBs.

d. Cardiac glycosides, namely digoxin, are frequently used in heart failure in the general population, where it has been shown that they improve morbidity but not mortality. Digoxin, when used in dialysis patients, should be utilized judiciously with careful attention to dosage and drug levels. Maintenance dosing should begin at low doses (0.0625 mg or 0.125 mg) every other day. A loading dose generally should not be used. Care should be taken in complex drug regimens as many other medications affect digoxin levels.

2. Role of arteriovenous (AV) fistulas and grafts. Although forearm fistulas occasionally lead to a high output state, 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. Bradycardia during fistula or graft occlusion (by finger pressure) suggests that the AV shunt is importantly and pathologically contributing to an increased cardiac output (Branham's sign). The test is specific, but absence of bradycardia on fistula or graft occlusion by no means exonerates the AV communication as a cause of the heart failure. Although limited data exist implicating fistulas in clinically appar- ent heart failure, flow reduction procedures can be used to address potential concerns with high flow fistulas while maintaining fistula patency.

3. Carnitine. Predominantly anecdotal evidence has suggested cardiovascular benefits with l-carnitine therapy at recommended intravenous doses of 20 mg/kg of total body weight following the dialysis procedure. Suggested indications for carnitine therapy have included anemia with extremely high erythropoietin requirements, intradialytic hypoten- sion, and muscle weakness. l-carnitine has also been rec- ommended for treatment of symptomatic cardiomyopathy with a documented impaired ejection fraction that has not responded adequately to standard medical therapy. Despite multiple suggested uses for l-carnitine, there are no strong data to support its utilization in dialysis at this time.

V. PERICARDIAL DISEASE. Pericardial disease most commonly manifests as acute uremic or dialysis-associated pericarditis although chronic constrictive pericarditis may also be seen. Most estimates of the clinical incidence of pericardial disease in prevalent dialysis patients are <20%.

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. Dialysis-associated pericarditis is a syndrome that occurs after a patient is stabilized on dialysis and is more common than uremic pericarditis. The etiology of dialysis pericarditis remains unknown, but may be at least in part dependent on inadequate dialysis and volume overload. However, other causative factors are likely present, given that intensification of dialysis frequently does not result in resolution.

1. Clinical manifestations and diagnosis. The most common symptom of pericarditis is chest pain, generally pleuritic in nature 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 signifi- cant, pericardial disease accompanied by an effusion may be characterized by hypotension, particularly during hemo- dialysis. Jugular venous distension, elevated pulsus para- doxus, and distant heart sounds may also be present. Chest radiograph may reveal an enlarged cardiac silhouette that may be difficult to distinguish from LVH. 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 peri- cardial 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 dialysis patients and require no acute intervention. Larger effusions present a risk for tamponade and need to 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 only effective approximately 50% of the time. This may be accomplished by increasing dialysis frequency to 5–7 days per week with careful attention to electrolytes, including phosphorus and magnesium, avoidance of over-alkalinization, 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.

d. Surgical drainage. Failure to recognize the need for timely surgical drainage of large pericardial effusions may have dire consequences for the patient 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 strongly 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. Surgical drainage is mandatory when overt tamponade appears. Subxiphoid pericardiostomy is the surgical drainage procedure of choice (i.e., insertion under local anesthesia of a large-bore tube into the pericardial space). The tube is left in place to closed 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 never indicated except as an emergency therapy for patients with life-threatening tamponade. Pericardiocentesis is the most common method used for pericardial fluid removal and can be performed under fluoroscopic, echocardiographic, or CT guidance. Of note, hemorrhagic effusions are poorly evacuable through the needle. 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 common complication of hemodialysis. Venous hemodialysis catheters are prone to infection and endocarditis is a frequent complication of catheter-related bacteremia; the presence of cardiovascular implantable electronic devices may also be associated with an increased risk of endocarditis. An additional recently appreciated factor predisposing to endocarditis is cannulation

of AV fistulas using a buttonhole technique. Endocarditis is relatively common in dialysis patients even without the above risk factors. The majority of 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 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. In many patients, acute bacterial endocarditis will complicate an already recognized episode of *Staphylococcus aureus* or other gram-positive bacteremia, and these bacteremias should be treated as presumed endocarditis.

Bacteremia therapy consists of an antistaphylococcal agent (nafcillin or its equivalent for methicillin-sensitive *S. aureus,* or vancomycin for methicillin-resistant *S. aureus*) with or without an additional agent for synergistic therapy (e.g., gentamicin, rifampin) for at least 4–6 weeks. First generation cephalosporins that can be dosed at hemodialysis are sometimes 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. Such prolonged antimicrobial therapy should help avoid the complication of valvular sequestration of infection in most patients with bacteremia diagnosed at an early stage.

1. Symptoms and signs. Dialysis patients with endocarditis 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 ordinary dialysis population owing to anemia, valvular calcification, and the presence of AV fistulas. Because a substantial percentage of dialysis patients are normally hypothermic, the body temperature with infection may be elevated to only slightly above the normal range or not at all. Diagnosis is chiefly dependent on
2. positive blood cultures and clinical suspicion. Transthoracic and, if echocardio- graphy windows are limited, transesophageal echocardio- graphy may be critical to making the diagnosis.
3. Treatment of endocarditis in hemodialysis patients will usually be directed at gram-positive organisms and regimens should be tailored to bacterial sensitivities. In general, 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 an aminoglycoside or third generation cephalosporin. In the presence of methi- cillin-sensitive *S. aureus*, antistaphylococcal penicillins

like nafcillin or first generation cephalosporins like cefazolin are preferable. In cases of severe *S. aureus* infection, other agents may be added for synergy, including aminoglycosides and rifampin. Care must be taken with aminoglycoside use due to the incidence of ototoxicity. 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 central venous catheters.

4. Valve replacement. ESKD 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 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 (Lei- ther, 2013). Whether a role exists for transcatheter aortic valve replacement in the setting of endocarditis remains unknown, and the literature is currently limited to case reports in the general population.

VII. VALVULAR CALCIFICATION AND STENOSIS

A. Mitral annular calcification. Mitral annular calcification may occurin as many as 50% ofpatients on dialysis and is also common in the elderly general population. 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.

B. Aortic calcification and stenosis. Aortic valve calcification occurs in 25%–55% of dialysis patients. 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.

1. 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.

2. Diagnosis is by echocardiography and cardiac catheterization, and mirrors diagnostic methods in the nondialysis p opul ation .
3. 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 replace- ment (with or without concurrent coronary artery bypass surgery) is relatively high for dialysis patients; 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. To date, several small case series have reported successful transcatheter aortic valve implantation procedures in dialysis patients, although dial- ysis patients have been excluded from clinical trials assess- ing this less invasive procedure.

VIII. VENTRICULAR ARRHYTHMIAS, CARDIAC ARREST, AND SUDDEN CARDIAC DEATH

A. Risk factors. Many comorbid conditions that are highly prevalent in dialysis patients 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. Sudden cardiac death is common among dialysis patients, with rates of 49 per 1,000 patient years in the hemodialysis population and 36 per 1,000 patient years among PD patients. According to the 2013 USRDS, cardiac arrest and arrhythmia account for ~25% of all deaths in dialysis patients. Thirty-day survival after cardiac arrest is only 32% and 1-year survival 15%. Potential strate- gies to reduce the risk of fatal cardiac risk include careful attention to fluid and electrolyte shifts. The risk of arrhyth- mias and cardiac arrest are increased in patients being dia- lyzed using a dialysate potassium level of less than 3 mEq/L (3 mM), and are most notable at lower potassium dialysate con- centrations; it is the opinion of many nephrologists that low potassium dialysate (<2 meq/L [<2 mM]) should be avoided if possible. One recent study also suggested an increased risk of sudden death associated with 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 hemodial- ysis, further suggesting that electrolyte or volume abnormali- ties 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 dialysis patients. 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 dialysis patients.

Adequate data on the benefits of implantable cardioverter defibrillators (ICD) are lacking in dialysis patients. While, intuitively, given the high risk of ventricular arrhythmia, ICD use appears sensible, ICDs are associated with an increased risk of infection and central vein stenosis (Hickson, 2014).

C. Chronic arrhythmias

1. Atrial fibrillation remains the most common arrhythmia in both the general and 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 dialysis patients.
a. 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 may be contraindicated in subjects with reduced cardiac function due to their negative inotropic effects. In these subjects, there clearly is a trade-off, as chronic control of tachycardia may offset any drug-related decrease in cardiac inotropy. Although 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 dialysis patients, extreme care must be taken to minimize electrolyte shifts and, in particular, hypokalemia. These patients should generally be on a 3 mEq/L potassium bath. Less alkaline dialysate may also be necessary 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.

b. Anticoagulation. The risks and benefits of warfarin therapy should be considered on an individual basis in all dialysis patients with chronic and paroxysmal atrial fibrillation. There are no consistent data regarding anticoagulation for atrial fibrillation in the dialysis population. Recently, warfarin use has been linked to calciphylaxis in dialysis patients (warfarin skin necrosis and calciphylaxis have similar pathologic appearance). Warfarin is also associated with an increased risk of vascular calcification. The 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation states that it's reasonable to prescribe warfarin to hemodialysis patients with nonvalvular atrial fibrillation with a CHA2DS2-VASc score of 2 or greater; implicit in the strength of the recommendation is that additional studies are needed to support this statement (January, 2014). These same guidelines are silent regarding warfarin use in PD patients.

2. Ventricular arrhythmias and ectopy are common in the dialysis population. There are no data indicating that cardiac management of patients prone to arrhythmia should be any different than in the general population. When indicated, dialysis patients may benefit from implantable defibrillators, although the cost–benefit of these devices remains uncertain given their unproven benefit in this popula- tion and potential risks as described above. Amiodarone therapy is generally well tolerated in dialysis patients, and dosing is identical to that in the general population.

IX. STROKE. Cerebrovascular disease is also very common in individuals with CKD, with 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 above, 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.

References and Suggested Readings

Agarwal R, et al. Hypertensionin hemodialysis patients treated with atenolol or lisinopril: a randomized controlled trial. Nephrol Dial Transplant. 2014;29:672–681.

Charytan DM. How is the heart best protected in chronic dialysis patients?: between scylla and charybdis: what is the appropriate role for percutaneous coronary revascularization and coronary artery bypass grafting in patients on dialysis? Semin Dial. 2014;27:325–328.

Cice G, et al. Carvedilol increases two-year survival in dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial. J Am Coll Cardiol. 2003;41:1438–1444.

Cice G, et al. Effects of telmisartan added to angiotensin-converting enzyme inhibitors on mortality and morbidity in hemodialysis patients with chronic heart failure a double-blind, placebo-controlled trial. J Am Coll Cardiol. 2010;56:1701–1708.

de Filippi C, et al. Cardiac troponin T and C-reactive protein for predicting prognosis, coronary atherosclerosis, and cardiomyopathy in patients undergoing long-term hemodialysis. JAMA. 2003;290:353–359.

Goldfarb-Rumyantzev AS, et al. The association of lipid-modifying medications with mortality in patients on long-term peritoneal dialysis. Am J Kidney Dis. 2007;50:791–802.

Herzog CA, et al. Clinical characteristics of dialysis patients with acute myocardial infarction in the United States: a collaborative project of the United States Renal Data System and the National Registry of Myocardial Infarction. Circulation. 2007;116:1465–1472.

Hickson LJ, et al. Clinical presentation and outcomes of cardiovascular implantable electronic device infections in hemodialysis patients. Am J Kidney Dis 2014;64:104–110.

Inrig JK. Antihypertensive agents in hemodialysis patients: a current perspective. Semin Dial. 2010;23:290–297.

Iseki K, et al.; Olmesartan Clinical Trial in Okinawan Patients Under OKIDS (OCTOPUS) Group. Effects of angiotensin receptor blockade (ARB) on mortality and cardiovascular outcomes in patients with long-term haemodialysis: a randomized controlled trial. Nephrol Dial Transplant. 2013;28:1579–1589.

January CT, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation. 2014, in press.

Kidney Disease: Improving Global Outcomes (KDIGO) Lipid Work Group. KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease. Kidney Int. 2013;(suppl 3):259–305.

K/DOQI. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. Am J Kidney Dis. 2005;45(suppl 3):S1–S153.

Kilpatrick RD, et al. Association between serum lipids and survival in hemodialysis patients and impact of race. J Am Soc Nephrol. 2007;18:293–303.

Lau WL, Ix JH. Clinical detection, risk factors, and cardiovascular consequences of medial arterial calcification: a pattern of vascular injury associated with aberrant mineral metabolism. Semin Nephrol. 2013;33:93–105.

Lerner MD, et al. Long-term survival of dialysis patients with bacterial endocarditis undergoing valvular replacement surgery in the United States. Circulation. 2013;128:344–351.

Matsumoto Y, et al. Spironolactone reduces cardiovascular and cerebrovascular morbidity and mortality in hemodialysis patients. J Am Coll Cardiol. 2014;63: 528–36.

Miller M, et al. American Heart Association Clinical lipidology, thrombosis, and prevention committee of the council on nutrition, physical activity, and metabolism; council on arteriosclerosis, thrombosis and vascular biology; council on cardiovascular nursing; council on the kidney in cardiovascular disease. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2011;123:2292–333.

Ricks J, et al. Glycemic control and cardiovascular mortality in hemodialysis patients with diabetes: a 6-year cohort study. Diabetes. 2012;61:708–715.

Selby NM, et al. Dialysis-induced regional left ventricular dysfunction is ameliorated by cooling the dialysate. Clin J Am Soc Nephrol. 2006;1:1216–225.

Thygesen K, et al. Joint ESC/ACCF/AHA/WHF task force for Universal definition of myocardial infarction. Third universal definition of myocardial infarction. J Am Coll Cardiol. 2012;60:1581–1598.

Zannad F, et al. Prevention of cardiovascular events in end-stage renal disease: results of a randomized trial of fosinopril and implications for future studies. Kidney Int. 2006;70:1318–1324.

39 Obstetrics and Gynecology inDialysis Patients

SusanHouandSusanGrossman

In womenwithendstagekidney disease, fertility is decreased but the possibilityof pregnancyishigh enough that it needs to be prevented if not desired andmanagedcarefully by a multidisciplinary team if it does occur. Thehypothalamic–pituitary–ovarian axis is deranged, contributing todecreasedfertility, loss of libido, and abnormal uter- ine bleeding.

I. BIRTH CONTROL

A. Indications. Forty percent of women under the age of 55 treated with dialysis menstruate, but periods may be anovulatory or characterized by a shortened luteal phase (Holley, 1997). Infer- tility is the rule, with pregnancy occurring in 0.3% to 1% per year in women aged 14–44. There is some suggestion that the use of erythropoietin and the increasing intensity of dialysis resulting from increased target *Kt/V* may have changed the hormonal abnormalities and other factors contributing to infertility in dialysis patients and that the frequency of preg- nancy may have increased. A role for increased dialysis in increasing fertility is suggested by the experience of the noc- turnal dialysis program at the University of Toronto, where, on average, women are receiving 36 hours of dialysis per week (Nadeau-Fredette, 2013). In this program, conception has occurred in 15% of women of childbearing age. Dialysis patients on standard dialysis regimens occasionally conceive, and when pregnancies occur, patient management is enor- mously complicated. Birth control is advisable for women who do not wish to conceive. It is difficult to identify women at high risk for pregnancy. Women who become pregnant once on dialysis frequently conceive again. Women who have become pregnant with renal insufficiency prior to starting dialysis, and women with regular menses are at increased risk, but pregnancies have occurred in women treated with dialysis following years of amenorrhea.

B. Methods of contraception. Diaphragms and condoms can be used as in individuals with normal renal function. The incidence of pregnancy with barrier methods is as high as 25%–29% per year in normal women, but would be expected to be much

lower in dialysis patients. Many women may opt for more effective and less cumbersome methods of contraception. Oral contraceptives can be used but are contraindicated in women with a history of thrombophlebitis or severe hyper- tension. Low-dose estrogen oral contraceptives can be used in patients with lupus who have no history of thrombosis or uncontrolled hypertension. Copper and levonorgesterone containing IUDs (intrauterine devices) can be used in women with diabetes, diabetes with nephropathy, systemic lupus ery- thematosus, and multiple cardiovascular risk factors, and are good birth control methods for women both on hemodialysis (HD) and peritoneal dialysis (PD). There are no guidelines from the U.S. Medical Eligibility Criteria for Contraceptive Use or from randomized controlled trials. There has been some concern that IUDs might increase the risk of peritonitis in women on PD, but this risk has not been well studied. There has also been concern without information on the effect of estrogen on access patency. The provision of estrogen offers the theoretical benefit of protecting bones from the effects of hypoestrogenemia seen in dialysis patients.

Many women on dialysis have prolonged periods of anovulatory bleeding, associated with the unopposed effect of estrogen on the endometrium. Estrogen–progesterone cycling might reduce the risk of endometrial cancer that is associated with unopposed estrogen. Treatment of infertility has generally not been attempted because pregnancy is dangerous for the mother and the outcome is still poor. The exception is a switch to nocturnal dialysis with higher rates of conception.

II. PREGNANCY

A. Frequency and outcome.

Estimates of the frequency of pregnancy in women ofchildbearing age treated with dialysis range from a high of 1.4% per year in Saudi Arabia to 0.44% in Japan to a low of 0.3% per year in Belgium (Nadeau-Fredette, 2013). The frequency of pregnancy in American women on dialysis is about 0.5% per year (Okundaye, 1998). For reasons that are unclear, conception occurs two to three times more frequently in hemodialysis patients than in PD patients. The likelihood of pregnancy in a dialysis patient resulting in a surviving infant, excluding elective abortions, is about 50%. The chances of success improve once she has reached the second trimester, and then it approaches 60%–70%. There is a further improve- ment in outcome with intensive dialysis. For women who start dialysis after conception, the likelihood of having a surviving infant is 75%–80%. Of unsuccessful pregnancies, 68% result in spontaneous abortion, 13% in stillbirth, 16% in neonatal death and 3% in therapeutic abortion for life-threatening maternal problems. Approximately 40% of spontaneous abortions occur in the second trimester.

B. Diagnosis. A high index of suspicion is required to make a timely diagnosis of pregnancy. Amenorrhea is common, and symptoms of early pregnancy such as nausea are often attributed to metabolic or gastrointestinal problems. A blood-based pregnancy test (serum levels of the β subunit of HCG) should be done prior to radiographic studies for abdominal complaints. Urine pregnancy tests are not reliable even if the patient is not anuric. Even with blood tests, false positives and false negatives occur. The small amounts of HCG produced by somatic cells may be excreted slowly enough in renal failure for blood levels to be borderline positive for pregnancy. Occasionally, these borderline results have led to cancellation of elective surgery. During pregnancy, β-HCG levels are more elevated than expected for gestational age, so gestational age is best assessed by ultrasound. Failure to appreciate the high β-HCG levels has led to mistaken diagnosis of a hydatidiform mole and the mistaken belief that a pregnancy was not viable when no fetal heart beat was found when high levels of β-HCG led doctors to think the pregnancy was more advanced than it was (Potluri, 2011). The reasons for false negative tests are unclear. Similarly, serum tests of α-fetoprotein done to screen for Down's syndrome may be falsely elevated in pregnant dialysis patients, and amniocentesis with karyotyping should be done to confirm abnormal results.

C. Management of hypertension during pregnancy. The major maternal risk associated with pregnancy in dialysis patients is severe hypertension. Eighty percent of pregnant dialysis patients have some degree of hypertension (BP >140/90 mm Hg). Forty percent have severe hypertension with diastolic blood pressures greater than 110 mm Hg or systolic blood pressures greater than 180 mm Hg. Seventy-five percent of severe hypertension occurs before the third trimester. Intensive care unit admissions for control of accelerated hypertension are required in 2% to 5% of pregnant dialysis patients. Patients should be taught to take their blood pressure on nondialysis days and report any increases in blood pressure promptly. Monitoring of blood pressure should continue for 6 weeks postpartum. Hypertension, even when severe, may not require the termination of pregnancy. The first step toward blood pressure control as in the nonpregnant patient is to make sure that the woman is euvolemic.

1. Drug therapy. If the blood pressure remains higher than 140/90 mm Hg when the patient is euvolemic, there are several first line drugs than can be used safely, including α-methyldopa, labetalol, and calcium channel blockers. There is less experience with β-blockers and clonidine, but, with the exception of atenolol, these are probably safe. Hydralazine can be added to any of these first line drugs, but it does not work as a single agent when given orally. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are contraindicated in pregnancy. In

animal studies, they have been associated with a fetal loss rate of 80%–93%. In humans, their use has been associated with an ossification defect in the skull, dysplastic kidneys, neonatal anuria, and death from hypoplastic lungs. One report that noted an increase in congenital anomalies with first trimester exposure to ACE inhibitors has driven prac- tice away from first trimester use (Cooper, 2006) despite contradictory data in other studies.

2. Superimposed preeclampsia and hypertensive crisis. Women treated with chronic dialysis are at increased risk for superimposed preeclampsia, but the diagnosis is difficult to make in the absence of findings of the HELLP (**H**emolysis, **E**levated **L**iver Enzymes, **L**ow **P**latelets) syndrome such as thrombocytopenia, elevated liver enzymes, or microangiopathic hemolytic anemia.

There appears to be some benefit of low-dose aspirin in preventing preeclampsia in women at high risk for the disease. Although dialysis patients have not been specifically studied, they constitute an extremely high-risk group and can be given 75 mg daily of aspirin.

a. Antihypertensive drugs. Intravenous hydralazine is the drug of first choice for hypertensive crisis in pregnant women and should be given in doses of 5–10 mg every 20–30 minutes. Labetalol is a good alternative. It can be given as a 20-mg bolus repeated every 30 minutes to a maximum of 220 mg or as a continuous infusion with 1 to 2 mg/min followed by 5–10 mg/hr to a maximum of 300 mg.

b. Magnesium. Magnesium is superior to other anticonvulsants for seizure prophylaxis in women with preeclampsia, but it must be used with extreme caution in dialysis patients. A loading dose can be given safely. Additional magnesium should not be given until after dialysis or until after a drop 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.

D. Dialysis regimen during pregnancy

1. Dialysis modality. In directcomparisons of dialysis modalities,there isno difference in outcome of pregnancy between hemodialysis patients and peritoneal dialysis patients, as measured by either infant survival or mean gestational age of live-born infants (Okundaye, 1998). How- ever, it is easier to increase the amount of dialysis delivered with hemodialysis. The higher success rates reported in more recent studies have been achieved in hemodialysis patients. Although dialysis modality should not be changed because of pregnancy, it may be easier to start hemodi- alysis in a pregnant woman than peritoneal. If peritoneal dialysis is elected, placement of a peritoneal catheter is possible at any 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. Some nephrologists have elected to supplement peritoneal dialysis with hemodialysis when pregnancy is near term.

2. Intensive dialysis. There is growing evidence that the likelihood of a surviving infant is increased with intensive dialysis. The ideal number of hours of dialysis has not been established. There was a marked improvement in outcomes for women dialyzed more than 20 hours per week, with a corresponding decrease in severe prematurity compared with less intense regimens (Hou, 2010). Infant survival was 75% for pregnancies in the group dialyzed more than 20 hours a week compared with 33% and 44% for less intensively dialyzed groups. Mean gestational age for babies born to women dialyzed more than 20 hours a week was 34 weeks compared with 30 weeks in less intensively dialyzed women. Even better outcomes have been seen in women undergoing nocturnal hemodialysis 48 hours weekly with most infants surviving and born close to term (Nadeau-Fredette, 2013). In a comparison of pregnancy results in the United States versus Canada, there was a suggestion of a "dose response" relationship between 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. 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.

Increasing the intensity of dialysis in peritoneal dialysis patients is difficult. Late in pregnancy, women have difficulty with severe abdominal distension, and exchange volume may have to be decreased. It becomes necessary to increase the frequency of exchanges even to maintain the same level of dialysis. A combination of frequent daytime exchanges and nighttime cycler is often necessary. Some have raised the question whether increased dialysis might have a detrimental effect by causing electrolyte abnormalities or by removing progesterone. Progesterone withdrawal plays a role in the initiation of labor. Measurements of serum progesterone levels during dialysis in pregnant dialysis patients are variable. Brost and colleagues (1999) measured pre- and postdialysis progesterone levels in seven pregnant dialysis patients. Changes in serum progesterone ranged from a 52% decrease in levels to an 8% increase (Brost, 1999). Changes in serum progesterone were not associated with changes in home uterine activity monitoring.

3. Dialysis solution calcium. With the recognition of the risk of soft tissue calcification in long-term dialysis patients, a

2.25 mEq/L (1.125 mM) or 2.5 mEq/L (1.25 mM) calcium concentration has replaced 3.5 mEq/L (1.75 mM) as standard. When a bath containing 2.5 mEq/L (1.25 mM) is used, the patient is usually in positive calcium balance, averag- ing about 200 mg/treatment. There is some production of calcitriol by the placenta that may increase serum calcium. Predialysis serum calcium levels should be checked weekly. The fetus needs 25 to 30 g of calcium for calcification of the fetal skeleton. With a 2.5 mEq/L (1.25 mM) bath, 25 weeks of dialysis should provide enough calcium, but premature birth is common enough, and calcium flux variable enough, that oral supplementation is advisable. If the woman requires phosphate binders, 1 to 2 g of elemental calcium should be sufficient. Over the long term, dialysate calcium should be low enough to minimize soft tissue calcification, but over the short term of pregnancy, calcium should be sufficient for the fetal skeleton. Skeletal abnormalities have been described in one baby born to a dialysis patient. For women who need phosphate binders, calcium-containing binders are the only group known to be safe in pregnancy. There is no experience with sevelamer or lanthanum car- bonate in pregnancy. Lanthanum is neurotoxic in fetal mice. Some women become hypophosphatemic. Often, phosphate binders are no longer required, and it may be necessary to add phosphorus to the bath (e.g., 4 mg/dL [1.3 mM] phosphorus or higher). For women who do not need phosphate binders, calcium can be provided in a lower dose separate from meals. Experience with cinacalcet in pregnancy is limited to a few case reports of use in primary hyperparathyroidism. Serum calcium and phosphorus should be monitored weekly. Hypercalcemia may suppress the fetal parathyroid glands and cause neonatal tetany.

4. Dialysis solution bicarbonate. With a standard bath, daily dialysis carries a theoretical risk of alkalosis. Metabolic alkalosis carries an increased risk in pregnant women who have a concurrent respiratory alkalosis; however, in the few instances where arterial blood gases have been done, compensatory hypercapnia has occurred in women with severe metabolic alkalosis. Serum bicarbonate in normal pregnancy is 18–20 mmol/L. A 25 mM bicarbonate dialy- sis 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 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 normalize serum sodium if it is high at the end of dialysis. With daily dialysis, fluid removal should be modest enough to make sodium modeling unnecessary.

6. Monitoring weight gain. Determination of optimal postdialysis weight is problematic in pregnant dialysis patients. Recommended weight gain for women who become pregnant at their ideal body weight is 11.5–16 kg. Only 1.6 kg of this weight gain occurs in the first trimester. During pregnancy, there is a 50% increase in blood volume, but vasodilatation normally prevents the development of hypertension. There is some evidence that blood volume does not increase appropriately in pregnant women with renal insufficiency, but blood volume has not been studied in pregnant dialysis patients.

   In early pregnancy, it may become difficult to dialyze the patient down to her prepregnancy dry weight, but the change should be only 0.9 to 2.3 kg, depending on the prepregnancy body mass index (BMI). Recommended weight gain in the second and third trimesters is between 0.3 and 0.5 kg per week, again depending on the prepregnancy BMI. While the nutritionist in the dialysis unit can provide dietary guidelines for appropriate weight gain during pregnancy, the most pressing question for the dialysis unit staff is determining how much of the weight change between treatments is excess fluid and how much is part of the desired pregnancy-associated weight gain.

   With daily dialysis, fluid gain between treatments should be small, but the majority of the day-to-day change in weight is still usually fluid. The woman should have a careful weekly examination to look for signs of fluid overload. With daily dialysis, volume-related hypertension should be minimized, and if there is any increase in blood pressure, particularly during dialysis, the patient should be evaluated for preeclampsia.

7. Heparinization. Clotting of the extracorporeal circuit or 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.

E. 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. Dialysis patients who become pregnant usually experience worsening anemia. Plasma volume increases while red cell mass, which increases in normal pregnancy, is limited by erythropoietin dose. While target hemoglobin levels for nonpregnant dialysis patients have decreased, a target for pregnancy has not been clearly established. However, we would choose a target of 10–11 g/dL (100–110 g/L) until more data are available, based on the World Health Organization's definition of anemia in pregnancy as a hemoglobin of 11 g/dL (110 g/L) or less.

1. Erythropoiesis stimulating agents (ESA). It has become usual practice to continue erythropoietin during pregnancy.
Prior to the availability of erythropoietin, transfusion was usually needed in any pregnancy that progressed beyond

the first trimester. All ESAs available are listed by the USA as being in "category C" in pregnancy (FDA pregnancy drug risk categories are A, B, C, D, and X, with X being the highest risk). Congenital anomalies have not been reported in the infants of the small number of women who took erythropoietin during organogenesis. In animals, congenital anomalies have been seen, but only at doses of 500 units/kg. 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. Erythropoietin has been associated with hypertension in nonpregnant patients, but it is difficult to determine what factors influence hypertension during pregnancy. Women treated with erythropoietin prior to pregnancy require increased doses during pregnancy. The hematocrit has usually dropped by the time the pregnancy is recognized. We recommend increasing the dose of eryth- ropoietin by 25% until the target hemoglobin is reached.

2. Iron therapy. While the effects of pharmacologic doses of erythropoietin stimulating agents on the fetus are unknown, there is a little known downside to treating iron deficiency. Pregnancy in normal women requires 700–1150 mg of iron. Daily hemodialysis increases iron losses over the usual amounts. We have found an increase in iron requirements during pregnancy and have given intravenous iron, but because of the high rate of transfer to the fetus, especially after 30 weeks' gestation, we limit individual doses to 62.5 mg. The FDA has labeled ferric gluconate and iron sucrose category B risk for pregnancy.
3. Folate. Folate requirements are increased in normal pregnant women. Folate deficiency is associated with an increase in neural tube defects. Folate losses increase with intensive dialysis, and folate supplementation should be quadr upl ed .

III. LABOR AND DELIVERY. Eighty percent of infants born to dialysis patients are premature. Reasons for prematurity include premature labor, maternal hypertension, and fetal distress, with premature labor being the most common.
Efforts to prevent premature labor include serial measurements of cervical length and in some cases cerclage. Progesterone has been used in other settings to prevent premature labor, and although it has not been used in dialysis patients, their risk of premature labor is so high that they should be considered candidates for its use.

Premature labor in dialysis patients has been successfully treated with terbutaline, magnesium, nifedipine, and indomethacin. Magnesium has been given intravenously in hemodialysis patients and has been added to the peritoneal dialysis solution in peritoneal dialysis patients. Magnesium must be used with extreme care in women with renal failure. Blood levels should be

monitored frequently. A loading dose can be given, but additional doses should be given only after dialysis and when the level is low. The use of magnesium in combination with nifedipine should be avoided because the combination can cause profound hypotension. Indomethacin has also been used with success, but patients must be monitored for oligohydramnios, and the fetus must be monitored for right heart dilatation. Indomethacin can be used only for a short time. While all tocolytics (a tocolytic is an anticontraction medication used to repress labor) are used for a short time, premature labor frequently recurs, and repeated use of indomethacin is problematic. In women with residual kidney function, indomethacin use may result in further deterioration in glomerular filtration rate and the need for increased dialysis.

Infants of dialysis patients are frequently small for gestational age, but it is not clear whether their growth restriction is the result of uremic toxins *per se* or of maternal hypertension. Decreased intrauterine growth restriction in nocturnal dialysis patients suggests a role for accumulated uremic toxins. There is an increased risk of stillbirth in dialysis patients, and antenatal monitoring should be started as soon as there is a chance of survival outside the mother (26 weeks).

In PD patients, caesarian section can be done extraperitoneally, leaving the catheter in place, and PD can be resumed 24 hours after delivery, starting with small exchange volumes and increasing over a 48-hour period. If there is leakage from the inci- sion, the patient can be hemodialyzed for 2–4 weeks.
Even a normal appearing infant should be monitored in a high-risk nursery. At birth, the infant, whose kidneys are normal for gestational age, will have a blood urea nitrogen (BUN) and serum creatinine levels similar to the mother's, and the infant will experience a solute diuresis, requiring careful monitoring of electrolytes and volume status.

There does not appear to be any increased risk of congenital anomalies, but information on growth and development is sketchy.

IV. DYSPAREUNIA. Some women dialysis patients may experience dyspareunia because of estrogen deficiency and resulting vaginal dryness. Postmenopausal women experiencing these symptoms can be prescribed either a conjugated estrogen cream, a sustained-release intravaginal estrogen ring or a vaginal low-dose estrogen tablet. Typical doses for local estrogen are one estradiol tablet, 10 mcg, inserted intravaginally once a day for 7 days, and then two or three times a week. A vaginal ring containing 2 mg of estradiol can be inserted and then replaced every 3 months. Conjugated estrogen cream can be used; the usual dose is 0.5 g per day for 21 days on, then 7 days off. An alternative regimen is to apply the cream twice weekly. Estrogen cream has been associated with more side effects, for example, breast tenderness, vaginal bleeding, and perineal pain. The North American Menopause Society does not recommend use of progestogen in women treated with local

estrogen therapies. Oral estrogen is rarely necessary in dialysis patients, and when needed, a daily dose of 0.3 mg of conjugated estrogen and 2.5 mg of medroxyprogesterone provides enough estrogen to prevent dyspareunia since estrogen is metabolized more slowly in dialysis patients. If there is breakthrough bleeding on this combination, progesterone can be increased to 5 mg.

V. SEXUAL DYSFUNCTION

A. Incidence and etiology. Fifty percent of female dialysis patients underthe ageof55 are sexually active. A majority of women on dialysis experience some sexual dysfunction. They suf- fer both decreased libido and decreased ability to achieve orgasm. Treatment with erythropoietin appears to be associ- ated with an improvement in sexual function, but most of the data collected have been in men. Various reasons for sexual dysfunction have been proposed, including hyperprolac- tinemia, gonadal dysfunction, depression, hyperparathyroid- ism, and change in body image.

B. Hyperprolactinemia. Studies from 30 years ago reported hyper- prolactinemia in 75%–90% of female dialysis patients. The mean serum prolactin levels in women with sexual dysfunc- tion are higher than in patients with normal sexual function. While prolactin levels have not been formally reevaluated, informal observation suggests that the frequency of hyperp- rolactinemia has decreased. Treatment of hyperprolactinemia with the dopamine agonist bromergocriptine has been reported (in limited uncontrolled studies) to improve sexual function in both men and women on dialysis. It has not come into widespread use because hemodialysis patients may be particularly susceptible to the hypotensive effects of this drug. When correctable physical problems cannot be found, dialysis patients should be referred for sex therapy, as would patients without renal failure.

VI. ABNORMAL UTERINE BLEEDING. In 2011, the International Federation of Gynecology and Obstetrics (FIGO) developed new terminology for what was previously called "Dysfunctional Uterine Bleeding," and the term Abnormal Uterine Bleeding is now preferred. A. Incidence Many women develop amenorrhea when the glomerular filtration rate falls to less than 10 mL/min. Men- struation returns in as many as 60% once dialysis is started. Regular menstruation has become more common in premeno- pausal women with end stage kidney disease (ESKD) than it was in the early days of dialysis; however, over half of women with ESKD who menstruate report hypermenorrhea. Women on HD and those on PD report similar menstrual abnor- malities. Approximately 60% of those who menstruate have irregular cycles. Abnormal uterine bleeding is common and is of concern because it may be an early sign of endometrial cancer. Blood loss may lead to severe anemia even in women treated with erythropoietin, although the introduction of

erythropoietin has made the management of abnormal uterine bleeding substantially easier.

B. Management

1. Screening for malignancy. Management depends on age and therefore risk for carcinoma. There is some suggestion that women on hemodialysis may be more likely to have endometrial hyperplasia and carcinoma compared with women without renal disease, so a high index of suspicion is warranted.

a. Women older than 40 years of age who have abnormal uterine bleeding should have endometrial sampling. In general, endometrial biopsy done in the office has replaced dilatation & curettage, because there is 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 bleeding persists after a negative biopsy, further diagnostic testing should be done.

b. Women younger than 40 years. The cancer risk is relatively small, and a yearly Papanicolaou smear is usually sufficient to screen for malignancy.

2. Anticoagulation. The lowest possible dosage of heparin should be used to perform hemodialysis when a woman is menstruating. Heparin-free techniques are described in Chapter 14.

3. Bloody peritoneal fluid during peritoneal dialysis. During menstruation or ovulation, the peritoneal fluid can become bloody (Lew, 2007). There is no specific management, except perhaps to avoid addition of heparin to the peritoneal dialysis solution. In some cases, frank hemoperitoneum may occur, requiring suppression of ovulation (Harnett, 1987). An aseptic peritonitis picture during menstruation or ovulation has also 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 dialysis patients. 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 in the form of **levonorgestrel intrauterine system** (Mirena) is probably the safest therapy and first line treatment for patients on hemodialysis who are experiencing abnormal uterine bleeding. Once the intrauterine device has been

implanted, scanty menstruation should develop within 3 months. Peritonitis has been reported after place- ment of IUDs in patients on PD, so these patients should receive prophylaxis prior to insertion of the IUD. (American College of Cardiology guidelines do not recommend antibiotic prophylaxis prior to IUD insertion to prevent endocarditis.) This system is highly effective and in the vast majority of cases will obviate the need for systemic hormonal therapy.

b. Oral contraceptives would be a second line treatment, but they should be avoided if blood pressure control or risk of thrombotic disease is a problem. The theoretical benefits of using estrogen progesterone combinations to prevent uterine cancer and osteoporosis have been discussed above.

c. Medroxypogesterone 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, IM injections on a regular basis are undesirable. Moreover, the half-life of IM medroxyprogesterone acetate in dialysis patients is unpredictable. Progestins work best in the setting of anovulatory bleeding.

d. Gonadotropin releasing hormone agonists. These can be given as an intramuscular injection once a month (leupro- lide acetate) or a daily intranasal dose. These drugs are extremely expensive and should be reserved for patients who continue to have excessive menstrual bleeding and who do not respond to intrauterine progesterone, oral contraceptives, or progestins. There is one report of ovarian hyperstimulation in a patient on chronic dialysis who received two doses of leuprolide acetate (Hampton, 1991).

e. High-dosage intravenous estrogens. In the case of acute excessive blood loss, high dose estrogen therapy can be used, giving 25 mg of conjugated estrogens IV every 6 hours. Bleeding usually subsides within 12 hours.

f. Deamino arginine vasopressin (DDAVP). In a setting of acute blood loss when bleeding time is prolonged, DDAVP should be given in a dosage of 0.3 pg/kg in 50 mL of saline every 4–8 hours for three to four doses.

6. 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 in women with ESKD Also, women with end stage kidney disease are at increased risk for gastrointestinal complications.

7. 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 3–4 weeks before the procedure to thin the endometrium. The procedure leads to permanent infertility.

8. Hysterectomy. For postmenopausal women with significant dysfunctional 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.

VII. HORMONE REPLACEMENT THERAPY. Women with end stage kidney disease treated with dialysis experience menopause on average 5 years earlier than women without renal failure. The role of hormone replacement therapy (HRT) in dialysis patients has never been clear. About 10% of postmenopausal women on dialysis take HRT. Most report that HRT was started before the initiation of dialysis. Of women not taking hormone replacement therapy, a majority say they would not take HRT if advised to do so by their doctors. Recent evidence of the risk of HRT raises concern about its use in ESKD patients. The Women's Health Initiative Study demonstrated an increased risk of breast cancer, pulmonary embolism, deep vein thrombophlebitis, and of 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 in reduced fractures.

Women with ESKD have more than a 20-fold increased incidence of cardiovascular disease compared with women without ESKD while multifactorial bone disease is also more common and more severe in dialysis patients. The risk of hip fracture is higher in dialysis patients than in healthy people of the same age and sex. 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 postmenopausal

estrogen-deficient dialysis patients, and this drug provides a safe alternative to HRT.

The use of HRT 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 HRT was small enough that many women have continued them. Unfortunately, the specific risk of HRT in hemodialysis patients has not been determined, and we can only extrapolate from the data in healthy women and women with preexisting heart disease in advising patients of the risk.

It is still the general practice to treat women with premature ovarian failure or early surgical menopause with HRT. It may be difficult to know whether a woman is postmenopausal since even women with FSH and LH in the postmenopausal range may have normalization after transplant. A very small study (13 patients) found an improvement in sexual function and general well-being as well as an improvement in L2-L4 bone density in premenopausal dialysis patients taking HRT.

HRT 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 HRT is prescribed, the dose should be adjusted in women on dialysis. Estrogen levels increase more in dialysis patients than in normal controls when estrogen is administered. If oral HRT is given to dialysis patients, 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 e strogen .

VIII.GYNECOLOGIC NEOPLASMS

A. Benign. Uterine fibroids, or leiomyomata, 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 their incidence in chronic renal failure. Uterine fibroids usually present with either menometrorrha- gia or symptoms related to the enlarging uterus pressing on nearby organs, that is, pain, pressure, and constipation. Small, asymptomatic leiomyomata 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 the size after menopause. Women still in the childbearing age range who are potential candidates for transplant should have myomectomy performed rather than hysterectomy if that is surgically feasible, to preserve childbearing potential. Recently, a number of treatments other than hysterectomy have become available, including medical therapy with mifepristone (RU486, an abortifacient), 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 when pregnancy occurs.

B. 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 is increased in women with ESKD, while the incidence of breast cancer is similar to women without kidney disease. Several recent stud- ies suggest that screening for malignancies in women with end stage kidney disease results in a negligible increase in life expectancy because of the shortened survival of women with end stage kidney disease. Such an outlook does not allow for the possibility that great strides will be made in the care of ESKD patients leading to prolonged survival. Young women, women awaiting transplantation, and women with increased risk for breast, ovarian, and 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, or women with AIDS. These women should have pap smears performed every year.

C. Evaluation of cancer in women who are symptomatic. Endometrial cancer usually presents as abnormal uterine bleeding, the investigation and management of which was 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 CA125 (cancer antigen 125) to screen for or follow ovarian cancer is of limited value in dialysis patients. It is not efficiently removed by dialysis and is also produced by mesothelial cells, giving rise to elevated levels, especially in PD patients.

D. Diagnostic procedures

1. Lower gastrointestinal X-ray series. When performing a lower gastrointestinal X-ray examination, the amount of water used to dilute the contrast material can be diluted to one-fourth the normal amount.

2. Computed tomography. Intravenous contrast infusion, if needed to perform a CT scan or angiography, is not contraindicated in dialysis patients. Although the administration of contrast involves increasing intravascular volume and osmolality, immediate dialysis following the study can be performed in the rare instance of symptoms. Dialysis can be done the following day if she is asymptomatic. A patient

on peritoneal dialysis requiring an abdominal CT scan should present for the examination with dialysis fluid in the abdomen.

3. Pelvic and abdominal ultrasonography. The patient on peritoneal dialysis 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 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, a 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. A transvaginal probe is able to furnish a more focused image of the organ of interest, but only permits effective imaging to no more than 7–10 cm in depth.

Unlike transabdominal pelvic ultrasound, it is best for the patient to have the transvaginal ultrasound study done while her bladder is empty. Since many patients on dialysis are not able to fill their bladders unless a Foley catheter is in place 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. PD patients should have the abdomen full for transabdominal ultrasound and empty for transvaginal ultrasound.

5. Magnetic Resonance Imaging. For women who are on PD, MRI of the peritoneal cavity can be done without any contrast, using the dialysate as contrast medium. This makes MRI of the abdomen and pelvic region the best modality to evaluate potential anatomic abnormalities in women on PD. Use of gadolinium as a contrast agent to enhance MRI should be done only after considering the very serious potential risk of nephrogenic systemic fibrosis. There is some evidence that with poststudy dialysis the risk of nephrogenic systemic fibrosis is not as high as once thought (Amet, 2014).

E. Management. The management of gynecologic cancers and nonmalignant tumors in women with chronic renal failure includes surgical excision and chemotherapy. 1. Surgery. In PD patients, any gynecologic procedure more invasive than a PAP smear (e.g., endometrial or cervical cone biopsy) should be performed with an empty perito- neal cavity. The patient should receive prophylactic antibi- otics 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 peritoneal dialysis solution three times daily to maintain patency. Irrigations are decreased to once daily when the fluid is no longer bloody. We wait 10 days to 2 weeks before using the catheter again, maintaining the patient by hemodialysis during the interim.

2. Chemotherapy. Use of chemotherapeutic agents in dialysis patients is beyond the scope of this Handbook.

References and Suggested Readings

Amet S, etal. Incidence ofnephrogenicsystemic fibrosis in patients undergoing dialysis after contrast-enhanced magnetic resonance imaging with gadolinium-based contrast agents: the Prospective Fibrose Nephrogénique Systémique study. Invest Radiol. 2014;49:109–115.

Ansari N, et al. Gynaecologic Nephrology. Am Med J. 2013;3:147–160.

Barua M, et al. Successful pregnancies on nocturnal home hemodialysis. Clin J Am Soc Nephrol. 2008;3:392–396.

Brost BC, et al. Effect of hemodialysis on serum progesterone level in pregnant women. Am J Kidney Dis. 1999;33:917–919.

Cooper WO, et al. Major congenital malformations after first-trimester exposure to ACE inhibitors. N Eng J Med. 2006;354:2443–2451.

Dimitriadis C, Bargman J. G ynecologic issues in peritoneal dialysis. Adv Perit Dial. 2011;27:101–105.

Hampton HL, Whitworth NS, Cowan BD. Gonadotropin-releasing hormone agonist (leuprolide acetate) induced ovarian hyperstimulation syndrome in a woman undergoing intermittent hemodialysis. Fertil Steril. 1991;55:429.

Harnett JD, et al. Recurrent hemoperitoneum in women receiving continuous ambulatory peritoneal dialysis. Ann Intern Med. 1987;107:341.

Hladunewich MA, et al. Intensive hemodialysis associates with improved pregnancy outcomes: a Canadian and United States cohort comparison. J Am Soc Nephrol. 2014;25:1103–1109.

Holley JL, et al. Gynecologic and reproductive issues in women on dialysis. Am J Kidney Dis. 1997;29:685–690.

Holley JL. Screening, diagnosis, and treatment of cancer in long-term dialysis patients. Clin J Am Soc Nephrol. 2007;2:604–610.

Hou S. Daily dialysis in pregnancy. Hemodial Int. 2004;8:167–171.

Hou S. Pregnancy in women treated with dialysis: lessons from a large series over 20 years. Am J Kidney Dis. 2010;56:5–6.

Kajbaf S, Nichol G, Zimmerman D. Cancer screening and life expectancy of Canadian patients with kidney failure. Nephrol Dial Transplant. 2002;17:1786–1789.

Kramer HM, Curhan GC, Singh A. Permanent cessation of menses and post menopausal hormone use in dialysis dependent women. Am J Kidney Dis. 2003;41:643–650.

Lew SQ. Hemoperitoneum: bloody peritoneal dialysiate in ESRD receiving peritoneal dialysis. Perit Dial Int. 2007;27:226–233.

Lin HF, et al. Increased risk of cancer in chronic dialysis patients: a population based cohort study in Taiwan. Nephrol Dial Transplant. 2012;27:1585–1590.

Ma TL, Wang CL, Hwang JC. Recurrent peritonitis episodes in a continuous ambulatory peritoneal dialysis patient after gynecologic procedures. Perit Dial Int. 2012;32:113–114.

Mattix H, Singh AK. Estrogen replacement therapy: implications for post menopausa
women with end-stage renal disease. Curr Opin Nephrol. 2000;9:207–214.
Nadeau-Fredette AC, et al. End-stage renal disease and pregnancy. Adv Chronic Ki
Dis. 2013;20:246–252.
Nakamura Y, Yoshimura Y. Treatment of uterine leiomyomas in
perimenopausal women with gonadotropin-releasing hormone agonists. In:
Pitkin RM, Scott JR,
Navaneetham SD, et al. Prevalence and correlates of self reported sexual dysfuncti
in CKD: a metaanalysis of observational studies. Am J Kidney Dis. 2010;56:670–
Okundaye IB, Abrinko P, Hou S. A Registry for Pregnancy in Dialysis Patients. Am
J Kidney Dis. 1998;31:766–773.
Poole CL et al. Aseptic peritonitis associated with menstruation and
ovulation in a peritoneal dialysis patient. In: Khanna R, et al. eds.
Advances in Continuous Ambulatory Peritoneal Dialysis. Toronto:
Peritoneal Dialysis Bulletin; 1987.
Pettiti K, et al. Beta HCG in a pregnant dialysis patient: a cautionary tale. Nephrol D
Transplant Plus. 2011;4:42–43.
Shan HY, et al. Use of circulating antiangiogenic factors to differentiate other hyper-
tensive disorders from preeclampsia in a pregnant woman on dialysis. Am J Kidn
Dis. 2008;51:1029–1032.
Stengel B. Chronic kidney disease and cancer: a troubling Connection. J Nephro
2010;23:253–262.
Strippoli GFM, et al. Sexual dysfunction in women with ESRD requiring hemodialysis
Clin J Am Soc Nephrol. 2012;7:974–981.
Weisbord SD. Female sexual dysfunction in ESRD: an underappreciated epidemic?
J Am Soc Nephrol. 2012;7:881.

Web References

National Collaborating Center for Women's and Children's Health. Hypertension in pregnancy: the management of hypertensive disorders during pregnancy. CG107 Hypertension in pregnancy: full guideline, http://www.nice.org.uk/guidance/CG107. Accessed July 7, 2014.

40 Nervous System and Sleep Disorders

Christopher W. McIntyre

Chronic kidney disease (CKD) patients 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 whilst leading a full and independent life in the hours spent not actually receiving dialysis. This chapter is limited to discussion of the brain and 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 the dialyzed uremic patient, 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. 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 CT or MRI (embracing the limitations of contrast use in this population). Heparin-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 preventative measures in hemodialysis patients. The efficacy and safety profile of all of these interventions may very well be very different in dialysis patients compared with the general population, where they were developed.

B. Subclinical brain structural abnormalities. There are several pathologies detectable by brain MRI in the brain of dialysis patients. 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). These abnormalities range from silent cerebral infarct to changes both in the white matter (leukoaraiosis) and grey matter (cortical atrophy).

1. Silent cerebral infarcts. Nakatani and coworkers examined the hypothesis that hemodialysis patients 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 hemodialysis patients and found that in those who developed SCI, associated risk factors were smoking, lower 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).

2. Cerebral atrophy. Cerebral (cortical) atrophy has been identified in hemodialysis patients 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 peritoneal dialysis patients, 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 hemodialysis patients; in fact, 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 (Eldehini, 2014).

C. Humoral abnormalities influencing brain function

1. Uremic encephalopathy. Encephalopathyis a cardinal featureof 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.

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 dialysis patient remarkably resistant to the development of severe cerebral edema as a result of abnormal tonicity. Hypoglycemia may present in diabetic patients due to inappropriate hypoglycemic therapy, or to further reductions in residual renal function with reduced insulin metabolism. In nondiabetic patients 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 s tandards

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. More information about aluminum toxicity is given in Chapter 36 on mineral bone disorders.

3. Infection and inflammation. Both systemic and local infection and inflammation can affect the brain in dialysis patients. Sepsis in this patient group not uncommonly presents without a typical pyrexial response (especially in the elderly), and the initial manifestation can be central obtundation. Dialysis patients are immunosuppressed both as a consequence of 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 CKD5D patients, and it induces a systemic proinflammatory state (McIntyre, 2011). These patients suffer 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. Hemodialysis patients 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 secondaryischemicwhite matter subcortical brain injury.

D. Acute episodic dysfunction

1. Disequilibrium syndrome .Rapid correction of advanced uremiais sometimescomplicated 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 previously undialyzed patients, 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, so as 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 effecting 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. Dialysis-
3. 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 injur y.

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 s*pina 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/sec. Events that can precipitate nonconvulsive status include alcohol, drug withdrawal, infection, hypoxia, cerebrovascular accident, menstruation, cyclosporine A therapy, malignancy, and antibiotic neurotoxicity. Antibiotics which 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 40.1. Mimics of dialysis disequilibrium are given in Table 40.2, and those for chronic dementia in Table 40.3. Proposed management strategies for acute obtundation are shown in Figure 40.1 and for chronic obtundation in Figure 40.2.

F. Diagnosis and management of epileptic seizures

1. Etiology. Seizures are not uncommon in dialysis patients. Generalized seizures are an integral feature of advanced uremic encephalopathy. Seizures can also be a manifestation of severe disequilibrium syndrome, as discussed above. Table 40.4 lists the most common associated conditions. Intracranial hemorrhage commonly leads to focal seizures, while most of the other causes lead to generalized seizures. 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

TABLE 40.1 Partial Differential Diagnoses of Acute Obtundation in Maintenance Dialysis patients

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's encephalopathy (in patients with vomiting, poor food intake)

TABLE 40.2 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 40.3 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)

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 40.4. A variety of poisonings in dialysis patients can also present with seizures, including star fruit ingestion (numbness, weakness, obtundation, seizures). Some anticonvulsant drugs may have enhanced removal by high-

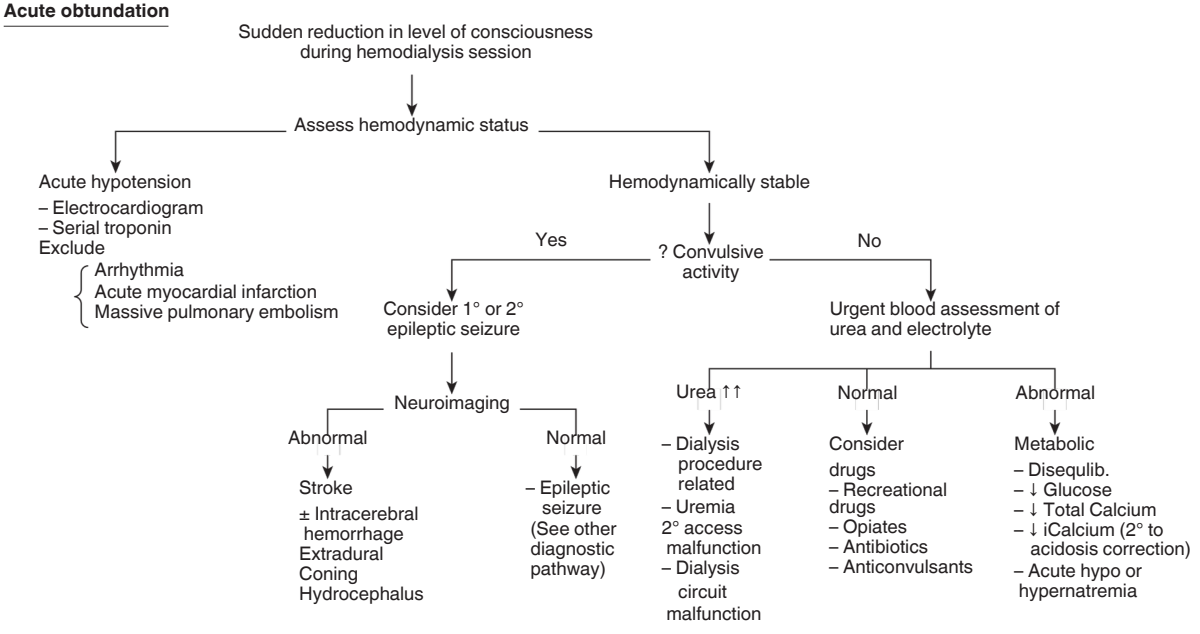


FIGURE 40.1Evaluation and Management of Acute Obtundation.

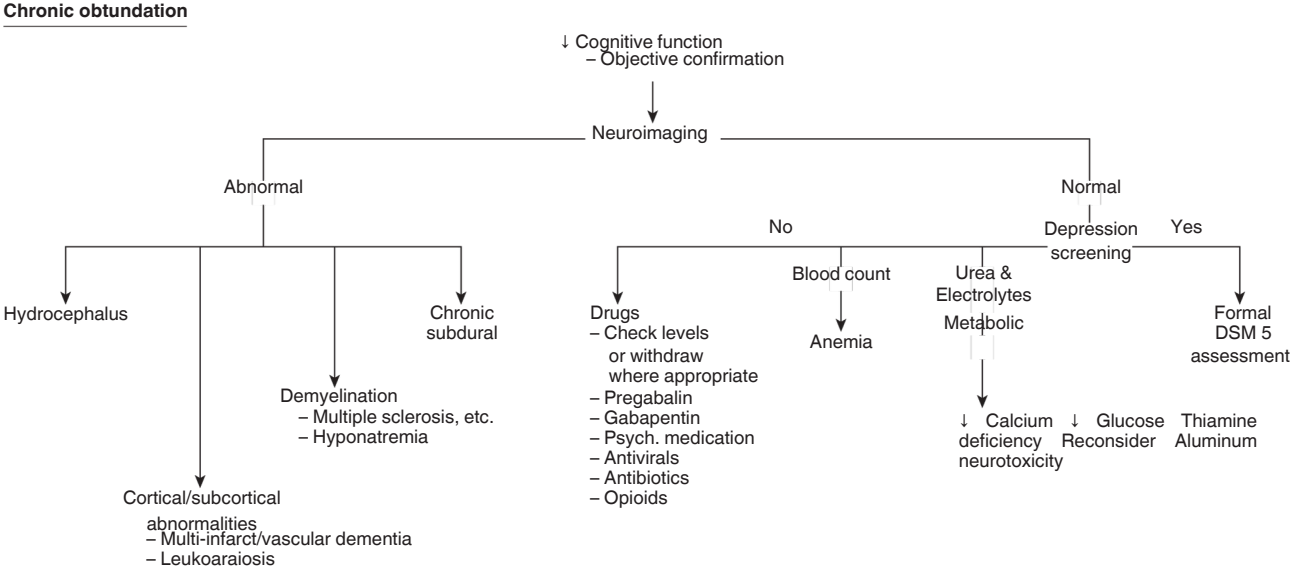


FIGURE 40.2 Evaluation and management of chronic obtundation. DSM 5, Diagnostic and Statistical Manual of Mental Disorders, 5th edition.

TABLE 40.4 Seizures in Dialysis Patients

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

efficiency hemodialysis (e.g., 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 dialysis patients. 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 40.4, 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. Prevention. Susceptible patients
3. can often be identified (see Table 40.4). 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 cal- cium concentration can be used. Blood pressure needs to be carefully regulated.

4. Management. One suggested algorithm is shown in Figure 40.3. 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, 10–15 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 conduc- tion block, or other arrhythmias. Other agents that may be appropriate include IV valproate.

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

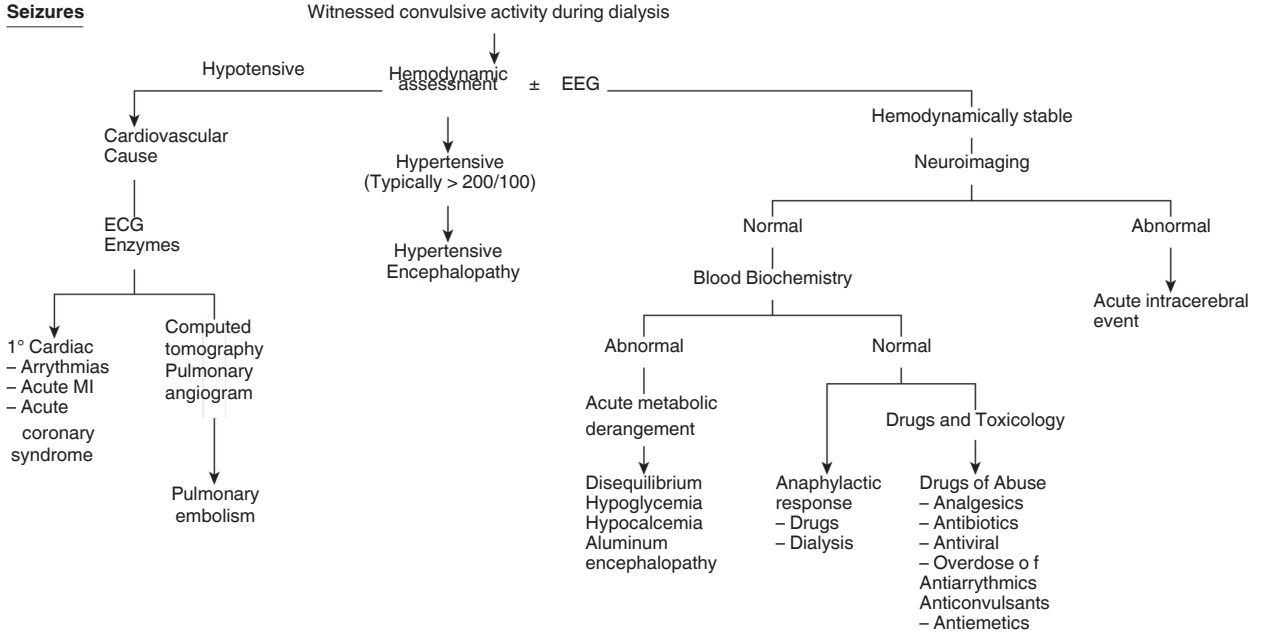


FIGURE 40.3 Evaluation and management of seizures.

drug is higher in uremic patients than in patients 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 uremic pa- tients 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 regimes). 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/CRRT (continuous renal replacement therapy) schedules. Reference to up-to-date dose modification guidelines and sources is strongly recommended. Table 40.5 is provided as initial guidance to some of the therapeutic challenges posed utilizing this group of drugs in dialysis patients.

Carbamazepine, ethosuximide, and valproic acid can be given in 75%–100% of the usual dosage to dialysis patients. 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 post-hemodialysis supplement may be required. Primidone is 40% renally excreted and is moderately dialyzable. Primidone should be used with extreme caution in dialysis patients; the need for a substantially reduced dosage should be anticipated, and a posthemodialysis supplement may be required. Phenobarbital can be given in 75%–100% of the usual dosage. Phenobarbital is dialyzable, and a dose should be scheduled after the dialysis treatment. Vigabatrin, a γ-aminobutyric acid-transaminase inhibitor, is eliminated by the kidney; major dosage reduction is necessary in dialysis patients (see Table 40.5).

G. Chronic neurologic states

1. Neurocognitive decline and dementia. Reduced cortical function and dementia is commonin dialysis patients, with characteristic patterns of memory loss and impaired cognition. This is in part due to a predominantly elderly 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

TABLE 40.5 Pharmacokinetics of Anticonvulsants in Dialysis Patients

Drug	Renal Excretion (%)	Nonuremic Dosage Range (mg/d)	Usual Dosage for ESKD Patients (% of nonuremic dose)	Plasma Half-life (hr)		Removed by Hemodialysis	Notes
				Nonuremic Patients	ESKD Patients		
Carbamazepine	3	600–1,600	10	10–20	17–28	No	NU-TPL = 4–12 mg/L
Clonazepam	<1	0.5–20.0	0	20–70	a	No	
Diazepam	<1	5–10 (IV)b	10		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	500–2,000	Caution	5–15	Same a	Yes	Avoid in ESKD patients
Valproic acid	c	750–2,000	75–100			±	NU-TPL = 50–120 mg/L
Vigabatrin	<4	2,000–4,000	25	6–16	Same a	Unknown	New drug; little experience in dialysis patients

ESKD, end-stage kidney disease; ESKD-TPL, therapeutic plasma concentration in dialysis patients; NU-TPL, therapeutic plasma concentration in nonuremic subjects.
[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%–40% of phenobarbital is excreted by the kidneys..

in dialysis patients, 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). Subclinical cognitive dysfunction and depression. Subclinical uremic encephalopathy may be present in chronic dialysis patients if inadequate dialysis is delivered. Severe depres- sion (and sometimes anxiety) can impair cognitive func- tion, but these may be detected only if detailed and regular neuropsychological assessment is undertaken.

2.

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 dialysis patients 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 hemodialysis patients 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 hemodialysis patients.

II. SLEEP-RELATED DISORDERS. Surveys of dialysis patients report that 40%–50% have one or more sleep complaints, and more than 50% studied in a sleep disorders laboratory have a sleep disorder objectively documented by polysomnography. Dialysis patients complain frequently of "insomnia" independent 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 (EDS) 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 him or her in danger while driving or operating heavy equipment.

A. Sleep apnea. Studies have found sleep apnea in 50%–75% of dialysis patients with sleep-related complaints. 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 30–60 years of age. As many as 81% of elderly nursing home patients 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 dialysis patients 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 ESKD patients 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 elderly of the general population. It

generally consists of a dorsiflexion of the foot or movement of the lower limb lasting 2–4 seconds and repeating every 20–40 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 of ESKD patients. Dialysis patients with PLMS have a much higher number of movements per hour of sleep than patients in the general population with PLMS. In one case series of 45 dialysis patients, 71% had significant PLMS, with several patients having 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 (e.g., 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 pa- tients also has 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 (e.g., 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 O2 desaturation, and more severe sleep fragmentation with consequently greater daytime fatigue.

b. Nocturnal dialysis. Both nocturnal hemodialysis and nocturnal cycler-assisted PD (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. **2**. Administration of low-flow supplemen-
Supplementary O
tal O2 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 O2 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 rateof 50%.

5. Treatment of RLS/PLMS

a. Conservative measures. Iron repletion is helpful in the generalpopulation, but is very rarely a problem in dialysis patients 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.

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 ESKD patients.

c. 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, mixedmotor 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 often are 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 six times per week nocturnal hemodialysis, 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 (e.g., amyloidosis or diabetes mellitus). Table 40.6 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 elderly Japanese dialysis patients; however, this was not a controlled study, and baseline pyridoxal 5´-phosphate levels were not decreased (Moriwaki, 2000).

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

TABLE 40.6 Principal Differential Diagnoses of Uremic Polyneuropathy

Diabetes mellitus
Ethanol abuse
Amyloidosis
Malnutrition
Polyarteritis Lupus erythematosus
Multiple myeloma
Thiamine deficiency

of the median nerve at the wrist where it passes through a narrowed carpal tunnel. Prevalence also 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 β2-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 his or her 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 longstanding 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 (EMG) 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.

IV. FINGER FLEXION CONTRACTURES. β2-Microglobulin amyloid can deposit along the flexor tendons of the hands, also. 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.

V. ATLANTO-CERVICAL SPONDYLOPATHY. Progressive neck instability and cord compression due to destructive β2-microglobulin–derived amyloidosis has been described in long-term dialysis patients. 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 β2-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 β2-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.

VI. 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 dialysis patients 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 paracetemol [called acetaminophen in the United States]) are the bedrock of chronic pain management. NSAID use may be appropriate in anephric

patients, 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, precipitat- ing 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 prepara- tions should be avoided, and access to "top up" doses may need to be limited. Transdermal release patches can be useful, espe- cially utilizing drugs such as fentanyl, which rely on hepatic dis- posal. 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 algo- rithm. Co-analgesic drugs such as antidepressants (e.g., tricyclic antidepressants) or anticonvulsants (e.g., 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 es- calation. Combination of these agents should be avoided if pos- sible. Finally, it is important that nonpharmaceutical strategies in pain management are not neglected. Patients should be closely involved in decision making, and efforts should be made to ex- plain the challenges and manage expectations. Additional inter- ventions such as psychological interventions should be given due consideration.

References and Suggested Readings

Apostolou T, Gokal R. Neuropathyandquality-of-life in diabetic continuous ambulatory peritoneal dialysis patients. Perit Dial Int. 1999;19(suppl 2):S242–S247.

Arnold R, et al. Effects of hemodiafiltration and high flux hemodialysis on nerve excitability in end-stage kidney disease. PLoS One. 2013;8:e59055.

Benz RL, et al. Potential novel predictors of mortality in end-stage renal disease patients with sleep disorders. Am J Kidney Dis. 2000;35:1052–1060.

Benz RL, Pressman MR, Wu X. Periodic limb movements in sleep revealed by treatment of sleep apnea with continuous positive airway pressure in the advanced chronic kidney disease population. Clin Nephrol. 2011;76:470–474.

Chang JM, et al. Fatal outcome after ingestion of star fruit (Averrhoa carambola) in uremic patients. Am J Kidney Dis. 2000;35:189–193.

Davison SN. Pain in hemodialysis patients: prevalence, cause, severity, and management. Am J Kidney Dis. 2003;42:1239–1247.

Dharia SM, Brown LK, Unruh ML. Recognition and treatment of obstructive sleep apnea. Semin Dial. 2013;26:273–277.

Diaz A, Deliz B, Benbadis SR. The use of newer antiepileptic drugs in patients with renal failure. Expert Rev Neurother. 2012;12:99–105.

Edmunds ME, Walls J. Pathogenesis of seizures during recombinant human erythropoietin therapy. Semin Dial. 1991;4:163.

Eldehni MT, McIntyre CW. Are there neurological consequences of recurrent intradialytic hypotension? Semin Dial. 2012;25:253–256.

Eldehini MT, Odudu A, McIntyre CW. Randomized clinical trial of dialyzate cooling and effects on brain white matter. J Am Soc Nephrol. 2014, in press.

Elias RM, et al. Relationship of pharyngeal water content and jugular volume with severity of obstructive sleep apnea in renal failure. Nephrol Dial Transplant. 2013;28:937–944.
Forsberg U, et al. Microemboli, developed during haemodialysis, pass the lung barrier and may cause ischaemic lesions in organs such as the brain. Nephrol Dial Transplant. 2010;25:2691–2695.
Glenn CM, et al. Dialysis-associated seizures in children and adolescents. Pediatr Nephrol. 1992;6:182.
Hanly PJ, et al. Daytime sleepiness in patients with CRF: impact of nocturnal hemodialysis. Am J Kidney Dis. 2003;41:403–410.
Hung SC, et al. Thiamine deficiency and unexplained encephalopathy in hemodialysis and peritoneal dialysis patients. Am J Kidney Dis. 2001;38:941–947.
Iftikhar S, Dahbour S, Nauman S. Nonconvulsive status epilepticus: high incidence in dialysis-dependent patients. Hemodial Int. 2007;11:392–397.
Kang HJ, et al. Does carpal tunnel release provide long-term relief in patients with hemodialysis-associated carpal tunnel syndrome? Clin Orthop Relat Res. 2012;470:2561–2565.
Kavanagh D, et al. Restless legs syndrome in patients on dialysis. Am J Kidney Dis. 2004;43:763–771.
Kiley JE. Residual renal and dialyser clearance, EEG slowing, and nerve conduction velocity. ASAIO J. 1981;4:1.
Lass P, et al. Cognitive impairment in patients with renal failure is associated with multiple-infarct dementia. Clin Nucl Med. 1999;24:561–565.
Marsh JT, et al. rHuEPO treatment improves brain and cognitive function of anemic dialysis patients. Kidney Int. 1991;39:155.
McIntyre CW. Recurrent circulatory stress: the dark side of dialysis. Semin Dial. 2010;23:449–451.
McIntyre CW, et al. Circulating endotoxemia: a novel factor in systemic inflammation and cardiovascular disease in chronic kidney disease. Clin J Am Soc Nephrol. 2011;6:133–141.
Molnar MZ, Novak M, Mucsi I. Management of restless legs syndrome in patients on dialysis. Drugs. 2006;66:607–624.
Moriwaki K, et al. Vitamin B6 deficiency in elderly patients on chronic peritoneal dialysis. Adv Perit Dial. 2000;16:308–312.
Nakatani T, et al. Silent cerebral infarction in hemodialysis patients. Am J Nephrol. 2003;23:86–90.
Nicholl DD, et al. Diagnostic value of screening instruments for identifying obstructive sleep apnea in kidney failure. J Clin Sleep Med. 2013;9:31–38.
Novak M, et al. Diagnosis and management of sleep apnea syndrome and restless legs syndrome in dialysis patients. Semin Dial. 2006;19:210–216.
Novak M, et al. Diagnosis and management of insomnia in dialysis patients. Semin Dial. 2006;19:25–31.
Nicholl DD, et al. Diagnostic value of screening instruments for identifying obstructive sleep apnea in kidney failure. J Clin Sleep Med. 2013;9:31–38.
Odudu A, Francis ST, McIntyre CW. MRI for the assessment of organ perfusion in patients with chronic kidney disease. Curr Opin Nephrol Hypertens. 2012;21:647–654.
Okada H, et al. Vitamin B6 supplementation can improve peripheral neuropathy in patients with chronic renal failure on high-flux hemodialysis and human recombinant erythropoietin. Nephrol Dial Transplant. 2000;16:1410–1413.
Pressman MR, Benz RL. Sleep disordered breathing in ESRD: acute beneficial effects of treatment with nasal continuous positive airway pressure. Kidney Int. 1993;43:1134–1139.
Prohovnik I, et al. Cerebrovascular effects of hemodialysis in chronic kidney disease. J Cereb Blood Flow Metab. 2007;27:1861–1869.
Santoro D, et al. Pain in end-stage renal disease: a frequent and neglected clinical problem. Clin Nephrol. 2013;79 (suppl 1):S2–S11.
Silver SM. Cerebral edema after hemodialysis: the “reverse urea effect” lives. Int J Artif Organs. 1998;21:247–250.
Tang S, et al. Alleviation of sleep apnea in patients with chronic renal failure by nocturnal cycler-assisted peritoneal dialysis compared with conventional continuous ambulatory peritoneal dialysis. J Am Soc Nephrol. 2006;17:2607–2616.
Tucker KL, et al. High homocysteine and low B vitamin predict cognitive decline in aging men: the Veterans Affairs Normative Aging Study. Am J Clin Nutr. 2005;82:627–635.

Tools for Estimating Glomerular Filtration Rate and Daily Creatinine Excretion

I. NORMALIZING GLOMERULAR FILTRATION RATE TO BODY SURFACE AREA*. Theproper size denominator to use inadjustingGlomerular Filtration Rate (GFR) to body size is a matter of debate, but traditionally, GFR is normalized in adults to body surface area (BSA)—usually per 1.73 m2 of body surface area (the aver- age BSA in early 20th century adults). BSA usually is calculated from an equation proposed by Gehan and George (1970) that de- pends 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 3 W0.51456 3 H0.422446

W h ere

W 5 weight in kg and H 5 height in cm.

When GFR is normalized to BSA, GFR/1.73 m2 in young adult men and women is similar and is in the range of 110–120 mL/min. In children as young as 2 years of age, GFR/1.73m2 also remains close to 110–120 mL/min.

Example: How to normalize GFR to 1.73 m2 BSA:

Assume raw GFR is 100 mL/min

*If BSA = 1.5 m,*2 multiply 100 by 1.73/1.50

GFR/1.73m2 = **115** mL/min

*If BSA = 2.0 m,*2 multiply 100 by 1.73/2.0

GFR/1.73m2 = **86** mL/min

The example shows two subjects with a GFR of 100 mL/min. One has a BSA of 1.5 m2 and the other of 2.0 m.2 The BSA-normalized GFR is 115 mL/min/1.73 m2 in the smaller person, and 86 mL/min/1.73 m2 in the larger person.

II. CALCULATING ESTIMATED CREATININE CLEARANCE (eCrCl) USING THE IX EQUATION*. Anewequation topredict 24-h creatinineexcretionrate was developed and validated by Ix(2011),which was validated in a number of large databases, and is also based on creatinine that was measured using an istope dilution mass

*Text in I and II cited with permission from MacGregor MS, Methven S. Assessing kidney function. In: Daugirdas JT, ed. Handbook of Chronic Kidney Disease Management. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.

spectrometry (IDMS)-calibrated assay. The new Ix equation is calculated as follows:

When creatinine excretion rate is in mg/24 h and SCr is in mg/dL:

eCrCl 5 [(24-h excretion rate in mg per day)/1440]/(0.01 3 SCr),

where:

24-h excretion rate in mg 5 880 2 6.2 3 Age 1 12.5 3 (Wt in kg)

1 (35 if Black) 2 (380 if female)

or when SCr is measured in mcmol/L:

eCrCl 5 [(24-h excretion rate in mcmol per day) / 1440] / (0.001 3 SCr)

24-h excretion rate in mcmol 5 8.84 3 [880 2 6.2 3 Age 1

12.5 3 (Wt in kg) 1 (35 if Black) 2 (380 if female)]

Note that the age correction for this new equation by Ix (2011) has a much less steep age correction than Cockcroft and Gault, and the correction for female sex is more severe than the 0.85 term commonly used with Cockcroft and Gault. 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.

III. CKD-EPI EQUATION SET FOR CALCULATING eGFR

Note:*Designed for use when SCr isenteredas mg/dL.*
To convert SCr from mcmol/L to mg/dL, multiply by 0.0113

African American Female

If serum creatinine (SCr) <= 0.7,

eGFR/1.73 m2 5 166 3 (SCr/0.7) 20.329 3 0.993 Age

If serum creatinine (SCr) > 0.7,

eGFR/1.73 m2 5 166 3 (SCr/0.7) 21.209 3 0.993 Age

African American Male

If serum creatinine (SCr) <= 0.9,

eGFR/1.73 m2 5 163 3 (SCr/0.9) 20.411 3 0.993 Age

If serum creatinine (SCr) > 0.9,

eGFR/1.73 m2 5 163 3 (SCr/0.9) 21.209 3 0.993 Age

White or other race Female

If serum creatinine (SCr) <= 0.7,

eGFR/1.73 m2 5 144 3 (SCr/0.7) 20.329 3 0.993 Age

If serum creatinine (SCr) > 0.7,

eGFR/1.73 m2 5 144 3 (SCr/0.7) 21.209 3 0.993 Age

White or other race Male
If serum creatinine (SCr) <= 0.9,

eGFR/1.73 m2 5 141 3 (SCr/0.9) 2 $^{0.411}$3 0.993^{Age}

If serum creatinine (SCr) > 0.9,

eGFR/1.73 m2 5 141 3 (SCr/0.9) 2 $^{1.209}$3 0.993^{Age}

IV. EXPECTED 24-HOUR CREATININE EXCRETION RATES (FIG. A.1) CORCORAN-

V. SALAZAR EQUATION. Thisequationis a modification ofthe Cockcroft andGault equationand can be used to esti- mate creatinine clearance (not indexed to BSA) in obese per- sons. (Fig. A.2)

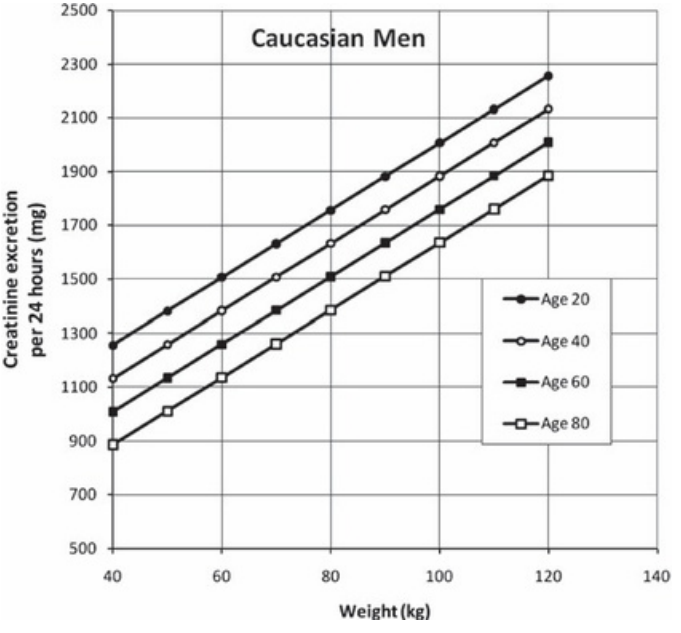


FIGURE A.1. The expected 24-hour creatinine excretion rate in Caucasians according to the new Ix equation (Ix, 2011). For African American males or females, add 35 mg/24h. (Reproduced with permission from Daugirdas JT. Handbook of Chronic Kidney Disease Management. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.)

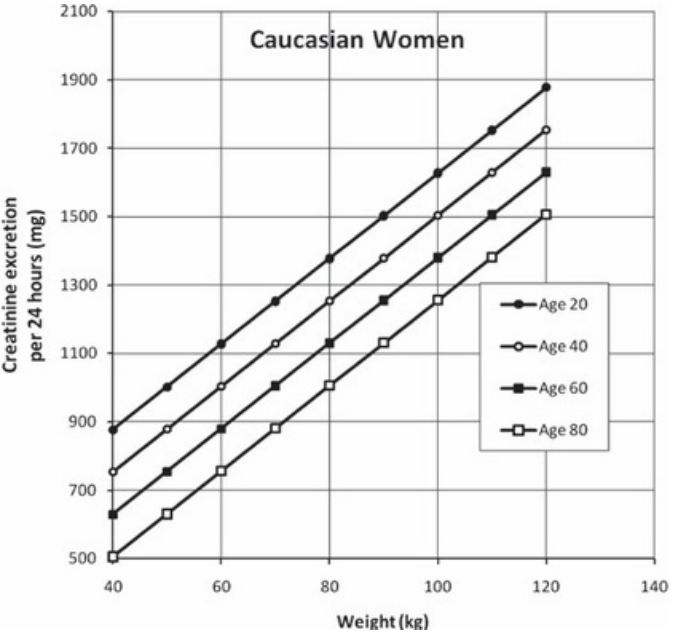


FIGURE A.1. (continued)

Male:

$$eCrCl = \frac{(137 - age) \times [(0.285 \times W) + (12.1 \times H^2)]}{51 \times SCr}$$

Female:

$$eCrCl = \frac{(146 - age) \times [(0.287 \times W) + (9.74 \times H^2)]}{60 \times SCr}$$

where eCrCl = estimated creatinine clearance, W = actual body weight in kg, H = height in meters, and SCr = serum creatinine in mg/dL.

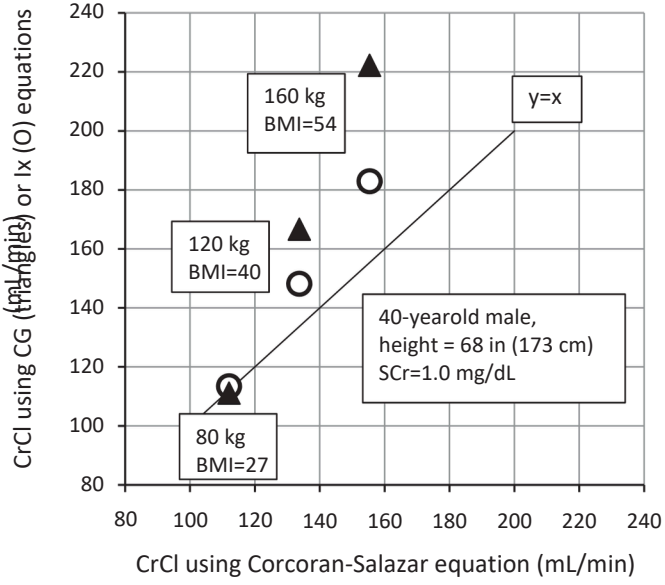


FIGURE A.2. Differences in three CrCl estimating equations in three 40-year-old male subjects all having a SCr of 1.0 mg/dL (88.4 mcmol/L) and all being of the same height, but weighing 80, 120, or 160 kg. Both the Cockcroft and Gault (CG) and Ix equations tend to overestimate CrCl in markedly obese subjects. (Reproduced with permission from Daugirdas JT. Handbook of Chronic Kidney Disease Management. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.)

References and Suggested Reading

Cockcroft DW,Gault MH.Predictionofcreatinine clearance from serum creatinine. Nephron. 1976;16:31–41.

Gehan E, George SL. Estimation of human body surface area from height and weigh Cancer Chemother Rep. 1970;54:225–235.

Ix JH, et al; for the Chronic Kidney Disease Epidemiology Collaboration. Equations to estimate creatinine excretion rate: the CKD Epidemiology Collaboration. Clin J Am Soc Nephrol. 2011;6:184–191.

Levey AS, et al; for the Chronic Kidney Disease Epidemiology Collaboration. A ne equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604–61

Salazar DE, Corcoran GB. Predicting creatinine clearance and renal drug clearance obese patients from estimated fat-free body mass. Am J Med. 1988;84:1053–106

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 kgfor each inch over 5feet.
   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. KDOQI method:

   The first, used for protein and calorie recommendations by KDOQI, is:

   adjBW = edfreeBW + (stdBW − edfreeBW) × 0.25,

   where edfreeBW is the edema-free actual body weight, and stdBW is the median standard weight from Table B.1 (below) and Table 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				
6	15	6	68	8	6	6	7	55.
2	7	4	71	2	1	8	7	8
6	16	6	71	8	6	7	8	57.
3	0	1	74	3	2	0	0	7
6	16	6	75	8	6	7	7	59.
4	3	6	77	4	3	1	7	6
6	16	6	78	8	7	7	7	61.
5	5	6	78	4	0	2	9	5
6	16	6		8	6	7	8	63.
6	8	7		4	8	4	0	4
6	17	7		8	6	7	8	65.
7	0	1		4	9	8	5	3
6	17	7		8	7	7	8	67.

(*continued*)

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). (continued)

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	
70	178	75	81	87	76	80	87	71
71	180	76	81	91	69	84	84	72.
72	183	74	84	91	76	81	90	9
73	185	79	85	93	78	88	88	74.
74	188	80	88	92	77	95	89	8
				Women				76.
5	14	5	6	8	5	5	7	7
8	7	2	3	6	4	7	8	78.
5	15	5	6	7	5	6	7	4
9	0	3	6	8	5	2	8	3
6	15	5	6	8	5	6	7	49
0	2	3	0	7	4	2	8	50.
6	15	5	6	8	5	6	7	7
1	5	4	1	1	6	4	9	52.
6	15	5	6	8	5	6	8	4
2	7	5	1	1	8	4	2	54.
6	16	5	6	8	5	6	8	1
3	0	5	2	3	8	5	0	55.
6	16	5	6	7	6	6	7	8
4	3	7	2	9	0	6	7	57.
6	16	6	6	8	6	6	8	5
5	5	0	3	1	0	7	0	59
6	16	5	6	7	6	6	8	2
6	8	8	3	5	8	6	2	60.
6	17	5	6	8	6	7	8	9
7	0	9	5	0	1	2	0	62.
6	17	6	6	7	6	7	7	6
8	3	2	7	6	5	0	9	64.
6	17	6	6	7	6	7	8	3
9	5	3	8	9	2	2	5	66
7	17	6	7	7	6	7	8	
0	8	4	0	6	3	3	5	

[a]Frame size as defined in Table B.2.
Data for median standard weight derived from the combined NHANES I and NHANES II datasets (Frisancho, 1990).
Ideal body weight computed according to Robinson (1983).
(Reproduced with permission from Daugirdas JT: *Handbook of Chronic Kidney Disease Management*. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.)

2. Based on ideal body weight: Another version, commonly used in drug dosing, is:

   Adjusted body weight = IBW 1 0.4 3 (edfreeBW 2 IBW),

   where IBW = ideal body weight calculated according to Devine or Robinson as described above.

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.
25–34	≤ 6.7	>6.7 and < 7.9	≥ 7
35–44	≤ 6.7	>6.7 and < 8.0	≥ 7.
45–54	≤ 6.7	>6.7 and < 8.1	≥ 9
55–64	≤ 6.7	>6.7 and < 8.1	≥ 8.
65–74	≤ 6.7	>6.7 and < 8.1	≥ 0
	Women		
18–24	≤ 5.6	>5.6 and < 6.5	≥ 8.
25–34	≤ 5.7	>5.7 and < 6.8	≥ 1
35–44	≤ 5.7	>5.7 and < 7.1	≥ 8.
45–54	≤ 5.7	>5.7 and < 7.2	≥ 1
55–64	≤ 5.8	>5.8 and < 7.2	≥ 8.
65–74	≤ 5.8	>5.8 and < 7.2	≥ 7.

Derived from the U.S. population in the NHANES 1 and NHANES 2 datasets.
Data from Frisancho (1984).
(Reproduced with permission from Daugirdas JT. *Handbook of Chronic Kidney Disease Management*. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.)

C. Lean body weight equations (kg):
Janmahasatian (2005):
men: 9270 × wt(kg) / (6680 + 216 × BMI)
women: 9270 × wt(kg) / (8780 + 244 × BMI)

II. BODY SURFACE AREA EQUATIONS.
SA = surfacearea,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 <18 years.

SA 5 0.0235 3 W0.51456 3 H0.422446

B. Dubois and Dubois (1916). (not as good as Gehan and George in children or in obese adults).

SA 5 0.007184 3 W0.425 3 H0.725

III. TOTAL BODY WATER ANTHROPOMETRIC EQUATIONS. (FIGS. B.1 AND B.2)
TBW = totalbodywater,W = postdialysis weight in kg, H = height in cm.

A. Watson (1980).

$$TBW_male = 2.447 - 0.09516 \times Age + 0.1074 \times H + 0.3362 \times W$$

$$TBW_female = 0 - 2.097 + 0.1069 \times H + 0.2466 \times W$$

B. Morgenstern (2006).

Use in patients <19 years of age.

$$HW = H \times W$$

$$TBW_male = 0.10 \times (HW)0.68 - 0.37 \times W$$

$$TBW_female = 0.14 \times (HW)0.64 - 0.35 \times W$$

C. Hume and Weyers (1971):

$$TBW_male = (0.194786 \times H) + (0.296785 \times W) - 14.012934$$

$$TBW_female = (0.344547 \times H) + (0.183809 \times W) - 35.270121$$

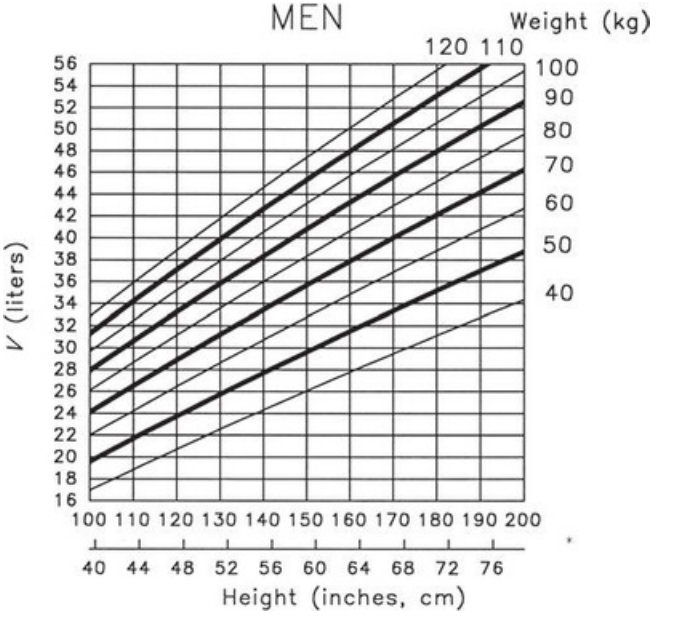


FIGURE B.1. Estimated total body water urea (V) in males as a function of weight and height. To use, find the height on the horizontal axis, rise until the appropriate weight line has been reached, and read V off the vertical axis. For urea modeling, use the postdialysis weight. The modeled V is usually 90% of the anthropometric V. The values are calculated from the Hume and Weyer equation described above. (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.)

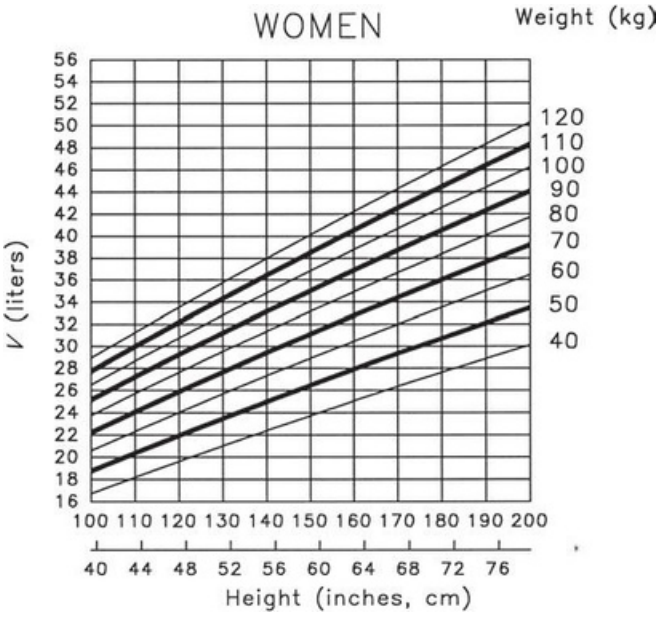


FIGURE B.2. Estimated total body water urea (V) in females as a function of height and weight. To use, find the height on the horizontal axis, rise until the appropriate weight line has been reached, and read V off the vertical axis. For urea modeling, use the postdialysis weight. The modeled V usually is 90% of the anthropometric V. The values are calculated from the Hume and Weyer equation described above. (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.)

IV. SELECTED DIET COMPOSITION TABLES.

A. Potassium
Table B.3 to TableB.8

B. Phosphorus
Table B.9 to B.11

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.

(Reproduced with permission from Daugirdas JT. *Handbook of Chronic Kidney Disease Management*. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.)

Table B.4. Potassium Content of Foods Considered to be High in Potassium

Food	Typical Serving	Potassium Content
Banana	1 small, 6"–7" long	360 mg 9.3 mmol
Cantaloupe	1 cup diced	420 mg 11 mmol
Orange juice	½ cup from frozen, reconstituted with wat er	240 mg 6.1 mmol
Prunes	5, dried, uncooked	350 mg 8.9 mmol
Avocado	Raw, ½ cup sliced	9.0 mmol
Potato	Baked, 2¼" to 3" diameter, peel eaten	350 mg 23 mmol
Potato	Baked, 2¼" to 3" diameter, peel not eat en	510 mg 13 mmol
Spinach	1 cup cooked	840 mg 21 mmol

(*continued*)

Food	Typical Serving	Potassium	Content
Brussels sprouts	1 cup cooked	490 mg	13 mmol
Broccoli	1 cup cooked flowerets	290 mg	7.4 mmol
Milk	1 cup, whole milk	350 mg	8.9 mmol
Yogurt	Fruit variety, from low-fat milk, 1 cup	440 mg	11 mmol
Dried beans	1 cup cooked, most varieties	880 mg	23 mmol

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Table B.5. Fruits: Potassium Content per 250 g Serving (about 1 cup)

mg	125–	250–	375–499	500–624	> 625
mmol	249	374	9.6–12.79	12.8–15.99	> 16.0
Listed from lower to higher within each column range	Blueberries, fro-zen or canned	Apples, raw	Strawberries, raw	Goosebe-rries, raw	Melons, cantaloupe, raw
	Apples or pears, canned	Pineapple, prickly pear, raw	Plums, canned or raw	Pummelo,	Guavas, raw
	Tangerines, canned	Rhubarb, frozen	Mangos, raw		Rhubarb, raw
	Fruit salad	Pears, rose apples, raw	Blackberries, raw	Figs, raw	Guavas, raw
	Cranberries, raw	Cherries, frozen or canned	Litchis, raw	Papayas, raw	Kiwi fruit, raw
		Apricots or peaches, canned	Cherries, raw	Apricots, raw	Currants, raw
		Lemons, raw	Oranges, raw		Passion fruit, raw

(*continued*)

Table B.5. Fruits: Potassium Ccontent per 250 g Serving (about 1 cup) (continued)

mg	125–249	250–374	375–499	500–624	> 625
mmol	3.2–6.39	6.4–9.59	9.6–12.79	12.8–15.99	> 16.0
		Grape-fruit, raw	Melons, casaba, raw Peaches, raw Grapes, raw Crabapples, quinces, raw		Bananas, raw Avocados, raw Plantains, cooked Breadfruit, raw Tamarinds, raw Persim-mons, raw Raisins Dried currants, peaches, apricots

From Nutritiondata.com, which is based on the USDA National Nutrient Database for Standard Reference, with permission.

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	7.00
Grapefruit Orange	400	10.1
Tomato	465	11.8
	500	12.3

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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
Eg g pl ant	Parsnips
Kale	Potatoes (white or sweet)
Lettuce	Pumpkin
Mixed vegetables	Rutabaga
Okra	Spinach
O nions	Squash (Hubbard)
Peas	Tomatoes
Peppers	
Radish	
Rhubarb	
Squash (summer)	
Watercress	
Water chestnuts	
Zucchini	

(Modified from the U.S. National Kidney Foundation Web site. Reproduced with permission from Daugirdas JT. *Handbook of Chronic Kidney Disease Management*. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.)

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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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) Cheddar cheese (20.6)
> 20.0	Swiss cheese (21.3) Almonds (25.3) Milk, 2% low fat (27.6) American cheese (30.7) Cashews (32.3)

(Data from: Pennington JAT, Douglas JS, eds. Bowes & Church Food Values of Portions Commonly Used. 18th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2005.
Reproduced with permission from Daugirdas JT. *Handbook of Chronic Kidney Disease Management*. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.)

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	*Diary 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*. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.)

Table B-11.Specialty Products and Supplements

Company	Product and Product Analysis
Ross Nutrition www.abbottnutrition.com	Suplena Per 8 ounce 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 Web site
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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Urea Kinetic Modeling

I. Estimating dialyzer blood water clearance from k0a, qb, and qd

Step 1: Calculate in vivo k0a from industry-reported in vitro k0a

k0a_invivo 5 0.574 3 k0a_invitro

Step 2: adjust k0a_invivo downward if dialysate flow rate <500 mL/min (because of poor penetration of dialysis solution in the fiber bundle). We no longer recommend making this adjustment for qd >500 mL/min, as manufacturers have improved penetration of dialysate into the fiber bundle at high dialysis solution flow rates. When qd <500 mL/min, the following adjustment can be used, which lowers the effective in vivo k0a. However, when qd <350 mL/min, k0a can decrease very substantially; there is little data to help quantify the adjustment needed. The minor adjustment in the equation below does not fully account for the reduction in k0a when very low qd values are used.

k0a_invivo 5 k0a_invivo 3 (1 1 0.0549 3 (qd-500)/300);

Step 3: Compute diffusive blood water clearance (kdifw) from estimated in vivo k0a, qb, and qd. Z 5 exp [k0a/(0.86 3 qb) 3 (1 – 0.86 3 qb/qd)]

kdifw 5 0.86 3 qb 3 (Z – 1) /(Z – 0.86 3 qb/qd)

Step 4: add convective clearance to diffusive clearance to calculate dialyzer clearance (kd).

qf 5 Wtlosskg 3 1000 / TD_min

kd 5 [1 2 qf/(0.86 3 qb)] 3 kdifw 1 qf

In step 4, the sign of the qf term in mL/min is positive; i .e., > 0.

The values shown in Figure 3.6 were derived using the above equations. an ultrafiltration (qf) 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, which is available free of charge to not-for-profit organizations (Daugirdas, 2012) or with a Web-based calculator

on HDCN (see Web references). a simplified approach using estimating equations can also be done as follows:

Step 1: Compute sp*Kt/V*.
This can be done by inputting the urea reduction ratio (URR), weight change, and dialysis session length into the D augirdas *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, spkt/V can be calculated using a urea modeling program.

Step 2: Compute e*Kt/V*.

This can be done using the modified Tattersall equation as described in Chapter 3.

Step 3: Use the Leypoldt equation to get a fixed-volume standard *Kt/V* (S).

$$S = \frac{1 - 2e^{-2eKt/V}}{1 - e^{-eKt/V} + \frac{t}{10080}} \Big/ \frac{10080}{N \times t} - 1$$

S = fixed volume std*Kt/V*; e*Kt/V* = equilibrated *Kt/V*; N = sessions per week; t = session length in minutes.

Step 4: adjust the standard *Kt/V* fixed volume value (S) for volume removal using the FHN equation (Daugirdas, 2010c).

std*Kt/V* 5 S/[1 2 (0.74/F) 3 UF_week / V],

where S is the simplified, fixed volume value from the Leypoldt equation, F is the frequency (sessions per week), UF_week is the weekly fluid gain between dialyses in liters, and 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.

std*Kt/V* 5 2.0/[1 2 (0.74/3.0) 3 10/35]
5 2.0/(1 2 0.247 3 0.286)
5 2.0/(1 2 0.070)
5 2.0/0.93 5 2.15

Thus, after adjusting for volume, the std*Kt/V* is 2.15 instead of 2.0. The old 2.0 minimum value of std*Kt/V* suggested by the 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*.

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 U.S. 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 George equation (Daugirdas, 2010b). M

5 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 "M." The adjustment factor is simply (V/S) / M. SaN-

std*Kt/V* 5 (V/S) / M 3 std*Kt/V*

For more information see Ramirez (2010). The target SaN-std*Kt/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 group (Daugirdas, 2010a).

References and Suggested Readings

DaugirdasJT,etal. Solute-solver: aWeb-based tool for modeling urea kinetics for a broad range of hemodialysis schedules in multiple patients. *Am J Kidney Dis*. 2009;54:798–809.

Daugirdas JT, et al. Can rescaling dose of dialysis to body surface area in the HEMO study explain the different responses to dose in women versus men? *Clin J Am Soc Nephrol*. 2010a;5:1628–1636.

Daugirdas JT, et al. Dose of dialysis based on body surface area is markedly less younger children than in older adolescents. *Clin J Am Soc Nephrol*. 2010b;5:821-

Daugirdas JT, et al; Frequent Hemodialysis Network Trial Group. Standard Kt/Vurea: a method of calculation that includes effects of fluid removal and residual kidney clearance. *Kidney Int*. 2010c;77:637–644.

Daugirdas JT,et al; FHN Trial Group. Improved equation for estimating single-pool Kt/V at higher dialysis frequencies. *Nephrol Dial Transpl*. 2013;28:2156–2160.

Daugirdas JT. Dialysis dosing for chronic hemodialysis: beyond Kt/V. *Semin Dial*. 2014;27:98–107.

Depner TA, et al. Dialyzer performance in the HEMO study: in vivo K0A and true blood flow determined from a model of cross-dialyzer urea extraction. *ASAIO J*. 2004;50:85–93.

Leypoldt JK, et al. Predicting treatment dose for novel therapies using urea standard Kt/V. *Semin Dial*. 2004;17:142–145.

Ramirez SP, et al. Dialysis dose scaled to body surface area and size-adjusted, sex-specific patient mortality. *Clin J Am Soc Nephrol*. 2012;7:1977–1987.

Web References

Solute solver:http://www.ureakinetics.org (suggest that users start with the "lite" version).

For an stdkt/V calculator see http://www.hdcn.com/calcf/ley.htm. accessed 7 July 2014.

Molecular Weights and Conversion Tables

I. TAblE D.1

Table D.1. Molecular Weights and Conversion Tables

Molecular Weights (MW) of Selected Substances	
Substance Acetylsalicylic acid (aspirin) Albumin	MW
β2-microglobulin	180
Cholesterol	68,00
Creatinine	0
Dextrose (glucose monohydrate)	11,60
Ethanol	0 386
Ethylene glycol	113
Glucose	198
Hemoglobin	46 62
Isopropyl alcohol (isopropanol)	180
Light chains	68,80
Lithium	0 60
Methanol	23,00
Myoglobin	0 7 32
Parathyroid hormone	17,80
Phenobarbital	0
Theophylline	9,500
Triglycerides	232
Urea	180
“Urea nitrogen” (blood urea nitrogen [BUN] or serum urea nitrogen [SUN])	886
Vancomycin	60 28
Vitamin B12	
Vitamin D3 (25-D3)	1,486
	1,355
	402

II. CONVERTING bETWEEN WEIGHT, VAlENCY, AND MOlARITY

A. Number ofmilligrams in1 mEqor1 mmol ofsubstance

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)

	= 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)

	= 2.4 mg/dL
	= 24 mg/L
	= 24/12 mEq/L, since 12 mg = 1mEq
	= 2 mEq/L
	= 2/2 mmol/L, since 2 mEq = 1 mmol
	= 1 mmol/L

4. Phosphorus (P) (mg/dL to mmol/L conversion)

	= 2.5 to 4 mg/dL
	= 25 to 40 mg/L
	= (25/31 to 40/31) mmol/L, since 1 mmol of P = 31 mg
	= 0.8 to 1.3 mmol/L

Because P values when expressed in mEq/L change with alterations in pH, the mEq/L unit is not ordinarily used in clinical practice.

NOTE: Page numbers followed by *f* indicate figure; those followed by *t* indicate table.

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