CHAPTER 48

Hemodialysis and Peritoneal Dialysis

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KEY CONCEPTS

1. The hemodialysis procedure involves the perfusion of blood and dialysate on opposite sides of a semipermeable membrane. Substances are removed from the blood by diffusion and convection. Excess plasma water is removed via ultrafiltration.
2. The native arteriovenous fistula is the preferred access for hemodialysis because of fewer complications and a longer survival rate. Venous catheters are plagued by complications such as infection and thrombosis and often deliver relatively poor blood flow rates.
3. Adequacy of hemodialysis can be assessed by the *Kt/V* and urea reduction ratio (URR). The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative has set the minimum goal *Kt/V* at greater than 1.2 per treatment and the URR at greater than 65%. In practice, most patients on hemodialysis exceed this goal.
4. During hemodialysis, patients commonly experience hypotension and cramps. Other more serious complications include infection and thrombosis of the vascular access.
5. The peritoneal dialysis procedure involves the instillation of dialysate into the peritoneal cavity via a permanent peritoneal catheter. The peritoneal membrane lines the highly vascularized abdominal viscera and acts as the semipermeable membrane across which diffusion and ultrafiltration occur. Substances are removed from the blood across the peritoneum via diffusion and ultrafiltration. Excess plasma water is removed via ultrafiltration created by osmotic pressure generated by various dextrose or icodextrin concentrations.
6. Patients on peritoneal dialysis are required to instill and drain, manually or via automated systems, several liters of fresh dialysate each day. The more exchanges a patient completes each day results in greater solute removal.
7. Peritonitis is a common complication of peritoneal dialysis. Initial empiric therapy for peritonitis should include intraperitoneal antibiotics that are effective against both gram-positive and gram-negative organisms.
8. Nasal carriage of *Staphylococcus aureus* is associated with an increased risk of catheter-related infections and peritonitis. Prophylaxis with intranasal mupirocin (twice a day for 5 days every month) or mupirocin (daily) at the exit site can effectively reduce *S. aureus* infections.

The three primary treatment options for patients with end-stage renal disease (ESRD) are hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation. The United States Renal Data System is the national system that "collects, analyzes, and distributes" data relating to the United States ESRD program.[1] According to the United States Renal Data System, at the end of 2005 (the most recent data available), there were 483,750 patients in the United States with ESRD. Of these, 314,162 and 25,895 patients were being treated with HD and PD, respectively, and 143,693 had a functioning kidney transplant. The vast majority of incident (new) dialysis patients are treated with HD. Since mid-1990, the number of prevalent PD patients has decreased. Although the number of patients who have received a kidney transplant has risen steadily, transplantation has not kept pace with the growing prevalence of ESRD in the United States.

Since 1972, the treatment of ESRD (both dialysis and kidney transplantation) has been covered by Medicare. Total spending for ESRD in 2005 was $32 billion; approximately one-third of this was from non-Medicare payers. ESRD patients consume a disproportionate amount of healthcare dollars. Approximately 1% of the patients in the Medicare program have ESRD, yet 8.2% of the budget is consumed by the ESRD program. Although total spending for ESRD treatment continues to climb, per-patient spending (after adjusting for inflation) was fairly flat between 2004 and 2005.

There are some positive signs as it relates to public health and ESRD. Although the total number of dialysis patients is increasing in the United States, the incident rate (number of new dialysis patients per total population) has stabilized or slightly decreased from the highest value observed in 1997. The prevalent population of ESRD continues to climb, reflective of reduced mortality and enhanced patient care. The primary diagnosis for incident patients with ESRD is diabetes.[1] Chapter 46 provides a thorough discussion on the epidemiology of chronic kidney disease.

This chapter serves as a primer on the principles and practice of dialysis. The chapter focuses on HD and PD as the dialysis modalities most commonly employed for the management of ESRD (see Chap. 45 for a discussion of the role of dialysis in the management of acute renal failure). The pertinent factors which should be considered before the initiation of dialysis are described. The morbidity and mortality associated with HD and PD are compared, as these considerations may influence the dialysis method chosen by patients and clinicians. Because dialysis by either method is not a generic procedure, the variants of HD and PD are detailed. The multiple types of

vascular and peritoneal access used to provide HD and PD, including various catheters and surgical techniques, are illustrated. The concept of dialysis adequacy for each modality is briefly reviewed. Finally, the clinical presentation of the common complications of both dialytic therapies is presented, along with pertinent nonpharmacologic and pharmacologic therapeutic approaches.

MORBIDITY AND MORTALITY IN DIALYSIS

Morbidity in patients with dialysis can be assessed by the number of hospitalizations per patient-year, the number of days hospitalized, or the incidence of certain complications such as cardiovascular events. Among dialysis patients, the number of all-cause hospital admissions per patient-year has remained fairly constant since 1993. Trends in hospitalization demonstrate an increase in hospitalization as a consequence of infection and cardiovascular disease and a decrease in hospitalizations as a consequence of vascular access problems. Overall, patients with a functioning kidney transplant have a lower rate of hospitalization and shorter length of stay. Hospitalizations are more frequent for whites than for blacks, and the frequency and duration increase with age in both dialysis modality groups.[1]

The life expectancy of U.S. dialysis patients is markedly lower than that of healthy subjects of the same age and gender. In comparison to the general population, dialysis patients have one-fourth to one-fifth the expected remaining lifetime. Approximately 50% of deaths in dialysis patients are cardiovascular related. Infections, usually related to the dialysis access, are the second most common cause of death in dialysis patients. Although mortality is high in this patient population, improvement has been made and the overall patient mortality rate has fallen 13% among dialysis patients since 1988. The changes in mortality rates are more impressive when dialysis vintage is examined. In patients receiving dialysis for fewer than 2 years, mortality rates decreased 25% since 1988. However, in those treated for 5 years or more, mortality rates increased 10%. These changes suggest that death is occurring later in the course of dialysis therapy.[1]

There is significant debate on the relative mortality differences between HD and PD. A recent trial examining mortality in dialysis patients in the Netherlands found no difference between modalities in the first 2 years, but after that mortality rates were higher in patients on PD.[2] This was particularly evident in patients older than 60 years of age. Similar results were found in a prospective cohort study of 1,041 dialysis patients (274 who were receiving PD) which found that the risk of death at 1 year was similar between the treatment modalities, but in the second year, the risk of death was significantly higher in the group of patients on PD.[3] Recent reports suggest that PD should be avoided in ESRD patients with certain comorbid conditions. ESRD patients with coronary artery disease treated with PD have significantly poorer survival compared with patients receiving HD.[4] Mortality is also higher in patients on PD compared to HD among those who have chronic heart failure (diabetics, relative risk [RR] = 1.30, 95% CI 1.20 to 1.41; nondiabetics, RR = 1.24, 95% CI 1.14 to 1.35).[5] Among patients without congestive heart failure, adjusted mortality risks were higher only for diabetic patients treated with PD compared with HD (RR = 1.11, 95% CI 1.02 to 1.21); nondiabetics had similar survival on PD or HD (RR = 0.97, 95% CI 0.91 to 1.04). A major problem with all morbidity and mortality studies comparing dialysis modalities is that none were prospectively randomized. Therefore differences noted in outcome may be related to a wide array of confounding factors, such as the dose of dialysis, baseline patient health status, physician bias in modality selection, patient compliance, or other unknown confounders. In fact, there is evidence that healthier patients tend to be directed toward PD and factors such as age, duration of dialysis, and comorbidities play an important role in the complex relationship between patient outcomes and mortality.[6,7]

Without clear distinction between modalities in terms of many important outcomes, the selection of the optimal therapy for a given patient must be individualized.

CLINICAL CONTROVERSY

There is much debate over which dialysis modality—hemodialysis or PD—is best in terms of morbidity and mortality. Outcome studies have provided conflicting results. Although only 7% of U.S. patients are treated with PD, surveyed nephrologists report that as many as 45% of prevalent end-stage renal disease patients could be treated with PD.

INDICATIONS FOR DIALYSIS

As recommended by the National Kidney Foundation's Kidney Disease Outcome Quality Initiative (K/DOQI), planning for dialysis should begin once the patient's glomerular filtration rate (GFR) or creatinine clearance (CL_{cr}) drops below 30 mL/min per 1.73 m^2.[8] Beginning the preparation process at this point allows adequate time for proper education of the patient and family and for the creation of a suitable vascular or peritoneal access. For patients choosing HD, a permanent arteriovenous (AV) access (preferably a fistula) should be surgically created 6 months prior to the anticipated need for dialysis.

The primary criterion for initiation of dialysis is the patient's clinical status: the presence of persistent anorexia, nausea, and vomiting, especially if accompanied by weight loss, fatigue, declining serum albumin levels, uncontrolled hypertension or congestive heart failure, and neurologic deficits or pruritus. Some nephrologists use critical lab values of serum creatinine or blood urea nitrogen as indicators of when to initiate dialysis. The 2006 update of the K/DOQI guidelines suggest that benefits and risks of dialysis should be evaluated when estimated GFR or CL_{cr} is <15 mL/min per 1.73 m^2.[8] The advantages and disadvantages of hemodialysis and peritoneal dialysis are depicted in Tables 48–1 and 48–2, respectively. These factors, along with the patients' concomitant diseases, personal preferences, and support environments, are the principal determinants of the dialysis mode they will receive.

HEMODIALYSIS

Although hemodialysis was first successfully used in 1940, the procedure was not used widely until the Korean War in 1952. Permanent dialysis access was developed in the 1960s, which allowed routine use

TABLE 48-1 Advantages and Disadvantages of Hemodialysis

Advantages

1. Higher solute clearance allows intermittent treatment.
2. Parameters of adequacy of dialysis are better defined and therefore underdialysis can be detected early.
3. Technique failure rate is low.
4. Even though intermittent heparinization is required, hemostasis parameters are better corrected with hemodialysis than peritoneal dialysis.
5. In-center hemodialysis enables closer monitoring of the patient.

Disadvantages

1. Requires multiple visits each week to the hemodialysis center, which translates into loss of control by the patient.
2. Disequilibrium, dialysis hypotension, and muscle cramps are common. May require months before the patient adjusts to hemodialysis.
3. Infections in hemodialysis patients may be related to the choice of membranes, the complement-activating membranes being more deleterious.
4. Vascular access is frequently associated with infection and thrombosis.
5. Decline of residual renal function is more rapid compared to peritoneal dialysis.

TABLE 48-2 Advantages and Disadvantages of Peritoneal Dialysis

Advantages

1. More hemodynamic stability (blood pressure) due to slow ultrafiltration rate.
2. Increased clearance of larger solutes, which may explain good clinical status in spite of lower urea clearance.
3. Better preservation of residual renal function.
4. Convenient intraperitoneal route for administration of drugs such as antibiotics and insulin.
5. Suitable for elderly and very young patients who may not tolerate hemodialysis well.
6. Freedom from the "machine" gives the patient a sense of independence (for continuous ambulatory peritoneal dialysis).
7. Less blood loss and iron deficiency, resulting in easier management of anemia or reduced requirements for erythropoietin and parenteral iron.
8. No systemic heparinization required.
9. Subcutaneous versus intravenous erythropoietin or darbepoetin is usual, which may reduce overall doses and be more physiologic.

Disadvantages

1. Protein and amino acid losses through peritoneum and reduced appetite owing to continuous glucose load and sense of abdominal fullness predispose to malnutrition.
2. Risk of peritonitis.
3. Catheter malfunction, exit site, and tunnel infection.
4. Inadequate ultrafiltration and solute dialysis in patients with a large body size, unless large volumes and frequent exchanges are employed.
5. Patient burnout and high rate of technique failure.
6. Risk of obesity with excessive glucose absorption.
7. Mechanical problems such as hernias, dialysate leaks, hemorrhoids, or back pain more common than HD.
8. Extensive abdominal surgery may preclude peritoneal dialysis.
9. No convenient access for intravenous iron administration.

of dialysis in patients with ESRD. Subsequent decades brought advances in dialysis technology, including the use of more efficient and biocompatible dialyzer membranes and safer techniques. Hemodialysis is now the most common type of renal replacement therapy for patients with acute renal failure and those with ESRD. Although there are variants of the procedure, the basic principles and operations are similar.

PRINCIPLES OF HEMODIALYSIS

❶ Hemodialysis consists of the perfusion of blood and a physiologic salt solution on opposite sides of a semipermeable membrane. Multiple substances, such as water, urea, creatinine, uremic toxins, and drugs, move from the blood into the dialysate, by either passive diffusion or convection as the result of ultrafiltration. Diffusion is the movement of substances along a concentration gradient; the rate of diffusion depends on the difference between the concentration of solute in blood and dialysate, solute characteristics, the dialyzer membrane composition, and blood and dialysate flow rates. Ultrafiltration is the movement of water across the dialyzer membrane as a consequence of hydrostatic or osmotic pressure and is the primary means for removal of excess body water. Convection occurs when dissolved solutes are "dragged" across a membrane with fluid transport (as long as the pores in the dialyzer are large enough to allow them to pass). Convection can be maximized by increasing the hydrostatic pressure gradient across the dialysis membrane, or by changing to a dialyzer that is more permeable to water transport. These two processes can be controlled independently, and thus a patient's hemodialysis prescription can be individualized to attain the desired degree of solute and fluid removal.

HEMODIALYSIS ACCESS

❷ A brief overview of hemodialysis access is provided here. Permanent access to the bloodstream for hemodialysis may be accomplished by several techniques, including creation of an AV fistula, an AV graft, or by the use of venous catheters (Fig. 48–1).[9] The native AV fistula is created by the anastomosis of a vein and artery (ideally the radial artery and cephalic vein in the forearm). The native AV fistula has many advantages over other access methods. Fistulas have the longest survival of all blood-access devices and are associated with the lowest rate of complications such as infection and thrombosis. In addition, patients with fistulas have increased survival and lower hospitalization rates compared to other hemodialysis patients. Finally, the use of AV fistulas is the most cost-effective in terms of placement and long-term maintenance. Ideally, the most distal site (the wrist) is used to construct the fistula. This fistula is the easiest to create, and in the case of access failure, more proximal sites on the arm are preserved. Unfortunately, fistulas require 1 to 2 months or more to mature before they can be routinely utilized for dialysis. In addition, creation of an AV fistula may be difficult in elderly patients and in patients with peripheral vascular disease (which is particularly common in patients with diabetes).

Synthetic AV grafts, usually made of polytetrafluoroethylene, are another option for permanent AV access. In general, grafts require only 2 to 3 weeks to endothelialize before they can be routinely used. The primary disadvantages of this type of access are the shorter survival, and the fact that they have higher rates of infection and thrombosis than do AV fistulas. The least-desirable hemodialysis access is via central venous catheters, which, unfortunately, are commonly used in chronic HD patients. Venous catheters can be placed in the femoral, subclavian, or internal jugular vein. The main advantage of catheters is that they can be used immediately. Catheters are often used in small children, diabetic patients with severe vascular disease, the morbidly obese, and other patients who have no viable sites for permanent AV access. Late referrals to a nephrology specialist and delayed placement of a more appropriate long-term access contribute to the overuse of venous catheters in chronic HD patients. The major problem with all venous catheters is they have a short life span and are more prone to infection and thrombosis than either AV grafts or fistulas. Furthermore, some catheters are not able to provide adequate blood flow rates, which can limit the amount of dialysis delivered.[9–12]

The Centers for Medicare and Medicaid Services developed a series of healthcare quality improvement programs in 1993. Now called the ESRD Clinical Performance Measures (CPM) Project, this program examines markers of the quality of dialysis care, including anemia management, serum albumin, vascular access (for hemodialysis), and adequacy of dialysis. The 2006 report studied a sample population of 8,915 adult, in-center HD and 1,469 PD patients.[13] At the end of 2005, 54% and 44% of incident and prevalent patients, respectively, were using AV fistulas for hemodialysis. The CPM Project's goal is that 50% and 40% of incident and prevalent hemodialysis patients, respectively, should be using an AV fistula. This makes the first year that CPM's goal for the use of fistulas has been reached. For instance, in 2000 only 27% and 30% of incident and prevalent hemodialysis patients had a working fistula. That is the good news; the bad news is that 21% of hemodialysis patients were using chronic catheters in 2005. The percent of patients using catheters is at least stable, but still higher than the 17% in 2000 and much higher than the CPM Project's goal of <10%. The extensive use of catheters may be a result of the large population of patients who are not candidates for AV access, or that they are being used until permanent AV access can be accomplished. As noted earlier, timely referral to a nephrologist and vascular surgeon makes it easier to place the most appropriate access.

HEMODIALYSIS PROCEDURES

The HD system consists of an external vascular circuit through which the patient's blood is transferred in sterile polyethylene tubing to the

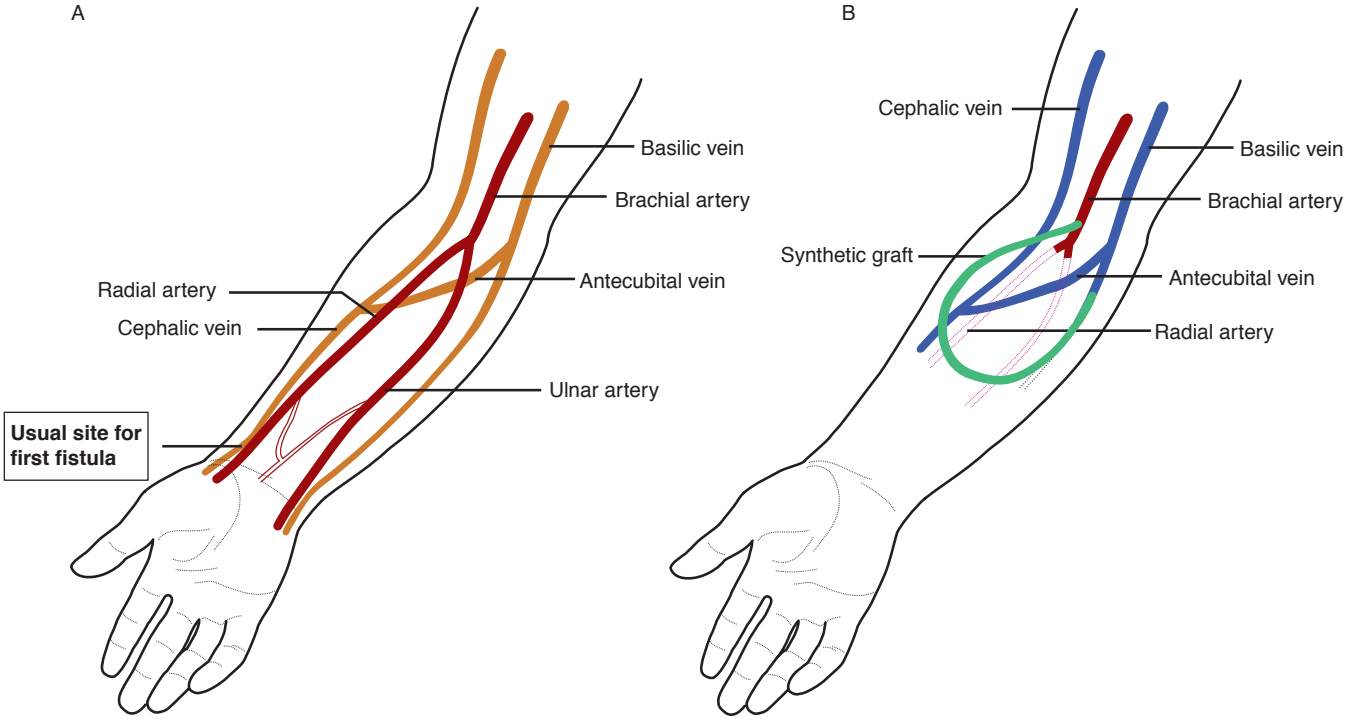

FIGURE 48-1. The predominant types of vascular access for chronic dialysis patients are *(A)* the arteriovenous fistula and *(B)* the synthetic arteriovenous forearm graft. The first primary arteriovenous fistula is usually created by the surgical anastomosis of the cephalic vein with the radial artery. The flow of blood from the higher-pressure arterial system results in hypertrophy of the vein. The most common AV graft (depicted in green) is between the brachial artery and the basilic or cephalic vein. The flow of blood may be diminished in the radial and ulnar arteries since it preferentially flows into the low pressure graft.

dialysis filter or membrane (dialyzer) via a mechanical pump (Fig. 48–2). The patient's blood then passes through the dialyzer on one side of the semipermeable membrane and is returned to the patient. The dialysate solution, which consists of purified water and electrolytes, is pumped through the dialyzer countercurrent to the flow of blood on the other side of the semipermeable membrane. In most cases, systemic anticoagulation (with heparin) is used to prevent clotting of the hemodialysis circuit.

Dialysis membranes are classified as conventional or standard, high efficiency, and high flux. Conventional dialyzers, mostly made of cuprophane or cellulose acetate, have small pores that limit clearance to relatively small molecules (size ≤500 daltons) such as urea and creatinine. High-efficiency membranes have large surface areas and thus have a greater ability to remove water, urea, and other small molecules from the blood. High-flux membranes have large pores that are capable of removing high-molecular-weight substances, such as β_2-microglobulin, and certain drugs, such as vancomycin.[14,15] The primary reason to use high-efficiency and/or high-flux membranes is that clearance of both low- and high-molecular-weight substances is much greater than with the conventional membranes, so treatment times can be shorter. The use of high-flux and high-efficiency dialysis increased significantly in the United States during the 1990s. High-efficiency and high-flux dialysis require blood flow rates greater than 400 mL/min, dialysate flow rates greater than 500 mL/min, and the use of strict controls on the rate of fluid removal. Typically these dialyzers are composed of

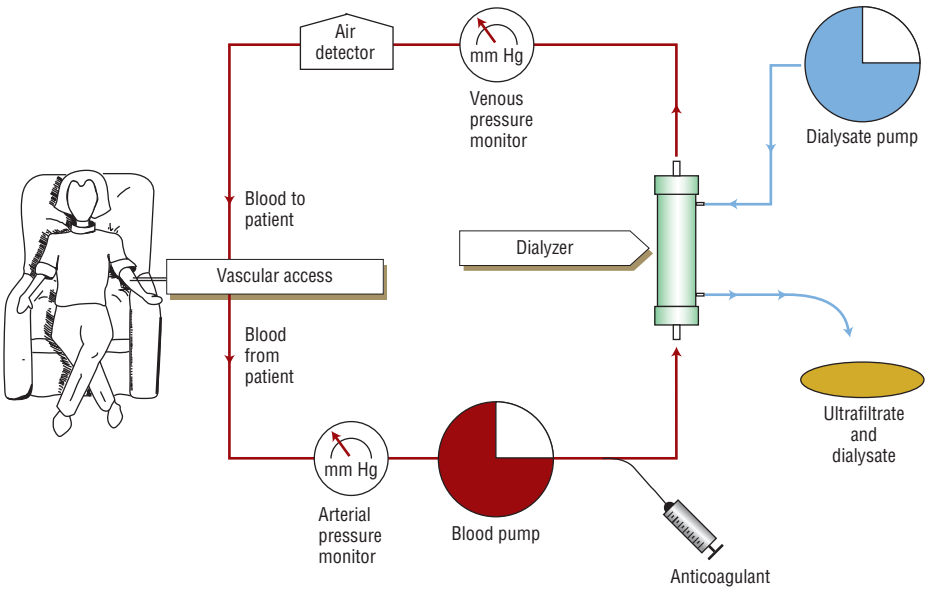

FIGURE 48-2. In hemodialysis, the patient's blood is pumped to the dialyzer at a rate of 300 to 600 mL/min. An anticoagulant (usually heparin) is administered to prevent clotting in the dialyzer. The dialysate is pumped at a rate of 500 to 1,000 mL/min through the dialyzer countercurrent to the flow of blood. The rate of fluid removal from the patient is controlled by adjusting the pressure in the dialysate compartment.

polysulfone, polymethylmethacrylate, polyamide, cellulose triacetate, and polyacrylonitrile.[14]

Hemodialysis is traditionally prescribed three times weekly for 3 to 5 hours. The mean dialysis treatment session duration in the United States in 2005 was 3.6 ± 0.5 hours.[13] Generally, larger patients require longer treatment times for adequate solute removal. Quotidian dialysis is a variant of HD in which dialysis is administered daily for shorter periods of time (2 hours) or as long-slow nocturnal treatments. There is some evidence that quotidian dialysis results in improved clinical outcomes and that it may be a more cost-effective dialysis procedure.[16] Both daily HD and nocturnal HD are usually done in the home. Home hemodialysis is most commonly used in New Zealand (14.3% of prevalent dialysis patients). In Canada, 1.9% of prevalent dialysis patients are on home HD. Despite the perceived advantages, the use of home HD is very uncommon in the United States, only 0.6% of the prevalent dialysis patients receive hemodialysis at home.[1]

ADEQUACY OF HEMODIALYSIS

The optimal dose of hemodialysis for each individual patient, is that amount of therapy above which there is no cost-effective increment in the patient's quality-adjusted life expectancy. The two key goals of the prescription are to achieve the desired dry weight and the adequate removal of endogenous waste products such as urea. Dry weight is the target postdialysis weight at which the patient is normotensive and free of edema.

1 The desired dose of dialysis in terms of solute removal can be expressed as the urea reduction ratio (URR) or the *Kt/V* (pronounced "K-T-over-V"). The URR is a simple concept and is easily calculated as:

$$URR = \frac{\text{Predialysis BUN} - \text{Postdialysis BUN}}{\text{Predialysis BUN}} \times 100$$

The URR is frequently used to measure the delivered dialysis dose, however, it does not account for the contribution of convective removal of urea. The *Kt/V* is the dialyzer clearance of urea (*K*) in L/h multiplied by the duration of dialysis (*t*) in hours, divided by the urea distribution volume of the patient (*V*) in liters.[17] *Kt/V* is a unitless parameter that quantitates the fraction of the patient's total body water that is cleared of urea during a dialysis session. Urea kinetic modeling, using special computer software, is the optimal means to calculate the *Kt/V*.[18] An in-depth discussion of the pros and cons of various methods of calculating and interpreting *Kt/V* is beyond the scope of this chapter. The reader is referred to other sources for more information.[18,19]

The K/DOQI recommends that the delivered dose of dialysis be at least a *Kt/V* of 1.2 (equivalent to an average URR of 65%).[8] To achieve this goal, the recommended target/prescribed *Kt/V* must be 1.4 (equivalent to an average URR of 70%). Many nephrologists believed that even greater doses of dialysis would have positive outcomes in dialysis patients, and so the average dose of dialysis has been increasing in the United States. In 2004, the mean delivered *Kt/V* as reported by the CPM was 1.55.[13] The HEMO study was designed to determine the effects of high-dose dialysis and the use of high-flux hemodialysis membranes on morbidity and mortality.[20] The results of this prospective, randomized trial that assigned patients to either standard (*Kt/V* = 1.25) or high-dose (*Kt/V* = 1.65) dialysis with high-flux or low-flux membranes revealed that the risk of death was similar in both the standard and high-dose therapy and the low- and high-flux groups. Thus there does not appear to be any benefit in increasing the amount of dialysis above the current recommendations. Although many patients in the United States are well above the target *Kt/V* range, there is no reason to believe that nephrologists will begin to decrease their dose of dialysis. The HEMO study only enrolled patients who were on traditional thrice-weekly dialysis, thus the applicability of these findings to patients on more intensive regimens such as daily or nocturnal HD regimens which provide long, frequent dialysis remain to be determined.[21,22] Although early data indicate that these intensive HD regimens result in better blood pressure, anemia, and phosphate control,[21] currently these HD regimens are not widely used in part because of Medicare reimbursement issues. In those relatively few patients who are below the adequacy goal, the deficiency may be related to patient compliance with dialysis prescription (ending dialysis early) or low blood flow rates caused by access stenosis or thrombosis, or as a result of the use of catheters. Adequate dialysis may not be achieved in some patients despite compliance and sufficient blood flow. For these patients there are really only two options to increase urea clearance: use a larger membrane or increase the treatment time.

CLINICAL CONTROVERSY

It remains to be determined what type of hemodialysis is best. Intensive hemodialysis treatments (nocturnal and daily dialysis) may provide better outcomes in hemodialysis patients. Studies on the value of these regimens are currently in development.

COMPLICATIONS OF HEMODIALYSIS

Complications associated with the hemodialysis procedure are significant and account for many of the associated costs of dialysis. Those complications which occur during the actual procedure (intradialytic), as well as those associated with vascular access are discussed in this chapter.[23–25]

Intradialytic Complications

4 The most common complications that occur during the hemodialysis procedure include hypotension, cramps, nausea and vomiting, headache, chest pain, back pain, and fever or chills. Table 48–3 lists these complications and the etiology with predisposing factors.[26]

Hypotension is the most common complication during HD and is primarily related to the large amount of fluid removed during typical treatments, although other causes, as listed in Table 48–3, are important.[25,27] Intradialytic hypotension is more common in the elderly and patients with diabetes. Other symptoms such as nausea and cramping are often present during acute hypotensive episodes. The replacement of acetate with bicarbonate as the dialysate buffer, the use of volumetric ultrafiltration controllers, as well as individualized dialysate sodium levels, have helped to reduce the incidence of hypotension.

Skeletal muscle cramps complicate 5% to 20% of hemodialysis treatments.[26] Although the pathogenesis of cramps is multifactorial, plasma volume contraction and decreased muscle perfusion caused by excessive ultrafiltration are frequently the initiating events. Although pruritus may appear to be worse during the HD treatment, it is actually a complication of chronic kidney disease and the management of this condition is discussed in Chap. 47.

Complications of Vascular Access: Thrombosis and Infection

Vascular access thrombosis is a major problem in chronic HD. Although thrombosis occurs in grafts, and to lesser extent fistulas, thrombosis associated with central venous catheters is the most problematic and is the focus of discussion here. Early dysfunction (less than 5 days after placement) of an HD catheter is usually associated with an intracatheter or catheter-tip thrombosis, or a malpositioned catheter. Thrombi that occur after approximately 1 week can be outside the

TABLE 48-3 Common Complications during Hemodialysis

	Incidence (%)	Etiology/Predisposing Factors
Hypotension	20–30	Hypovolemia and excessive ultrafiltration Antihypertensive medications prior to dialysis Target dry weight too low Diastolic dysfunction Autonomic dysfunction Low calcium and sodium in dialysate High dialysate temperature Meal ingestion prior to dialysis
Cramps	5–20	Muscle hypoperfusion due to ultrafiltration and hypovolemia Hypotension Electrolyte imbalance Acid–base imbalance
Nausea and vomiting	5–15	Hypotension Dialyzer reaction
Headache	5	Disequilibrium syndrome Caffeine withdrawal due to dialysis removal
Chest and back pain	2–5	Unknown
Pruritus	5	Inadequate dialysis Skin dryness Secondary hyperparathyroidism Abnormal skin levels of electrolytes Histamine release Mast cell proliferation
Fever and chills	<1	Endotoxin release Infection of dialysis catheter

From Bregmental.[26]

catheter (extrinsic) or within the catheter (intrinsic). Intrinsic thrombosis is the major cause of catheter failure and can occur within the lumen of the catheter, at the tip of the catheter, or can present as a fibrin sleeve surrounding the catheter. Fibrin sleeves can obstruct the catheter and be a nidus for infection. Continuous monitoring for catheter dysfunction is critical. Catheter dysfunction can be assessed in a number of ways but reduced access blood flow (<300 mL/min) over time is an important predictor of thrombosis. A late manifestation of catheter dysfunction occurs when blood cannot be aspirated from the catheter yet saline flows in freely. Catheter-related thrombosis can be definitely diagnosed using ultrasonography, venography, or computed tomography scans.[8,10,11,24]

Infections of the vascular access are also a significant problem in patients on HD. The most common cause of access infection is *Staphylococcus aureus* (which is often methicillin-resistant) although gram-negative organisms are common and other organisms can be isolated. The type of access is one of the most important risk factors for infection. AV fistulas have the lowest rate of infection followed by grafts, tunneled catheters, and temporary catheters. Catheters in general have more than a sevenfold risk of infection versus fistulas.[28,29] Catheter-related infections can be exit site or catheter-related bacteremia.[30] Patients with diabetes, immunosuppression, a history of bacteremia, and those with *S. aureus* nasal carriage are at highest risk for catheter-related bacteremia. Bacteria can seed distant sites and cause endocarditis, osteomyelitis, and septic arthritis.[31] Clinically, patients present with fever and chills. If fever and chills occur after catheter manipulation, it is highly suggestive of catheter-related bacteremia.[28,29,32]

MANAGEMENT OF HEMODIALYSIS COMPLICATIONS

HYPOTENSION

Acute management of hypotension includes placing the patient in the Trendelenburg position, decreasing the ultrafiltration rate, and/or administering normal or hypertonic saline.[25,26] A careful review of antihypertensive medications in these patients is usually warranted. In general, patients should not take their blood pressure medications prior to the HD session but sometimes even hypertensive medications given the day prior might be contributing to the intradialytic hypotension.

TABLE 48-4 Management of Hypotension

Acute treatment	Place patient in Trendelenburg position Decrease ultrafiltration rate Give 100–200 mL bolus of normal saline intravenous Give 10–20 mL of hypertonic saline (23.4%) intravenous over 3–5 min 12.5 g mannitol
Prevention	
Nonpharmacologic	Accurately set "dry weight" Use steady constant ultrafiltration rate Keep dialysate sodium greater than serum sodium Use cool dialysate Use bicarbonate dialysate Avoid food before or during hemodialysis
Pharmacologic	Midodrine 2.5–10 mg orally 30 min before hemodialysis (start at 2.5 mg and titrate) Other options (not well studied): Levocarnitine 20 mg/kg IV after hemodialysis Sertraline 50–100 mg daily Fludrocortisone 0.1 mg before hemodialysis

Numerous nonpharmacologic and pharmacotherapeutic interventions have been used to prevent or reduce the incidence of symptomatic dialysis hypotension (Table 48–4). Randomized, blinded, prospective trials are rare and thus comparisons between therapeutic alternatives are difficult to quantify. If patients remain symptomatic after nonpharmacologic interventions, oral midodrine, an α_1-adrenergic agonist prodrug with peripheral vasoconstrictive properties may be considered. A recent systematic review of the literature suggested that midodrine, when administered in doses ranging from 2.5 to 10 mg prior to dialysis, resulted in elevations of postdialysis systolic and diastolic blood pressures of 12.4 and 7.3 mm Hg above the values in controls, and also resulted in improvement in symptoms.[33] A long-term study of the benefits of midodrine found that 10 mg given 30 minutes prior to dialysis resulted in correction of hypotension over an 8-month period without any adverse events.[34] Some HD patients have chronic hypotension and experience low blood pressure even when not on dialysis. Oral midodrine given 5 mg twice daily can increase blood pressure in these patients as well.[35] It is important to note that the effects of midodrine are probably best in patients with hypotension related to autonomic dysfunction as opposed to other causes of hypotension.

Other medications have also been studied in hypotension. The intravenous administration of levocarnitine (20 mg/kg at the end of each dialysis session) reduced the number of hypotensive episodes from 17 to 7 (P <0.02) in a study of 38 patients.[36] The high cost and fairly limited data on levocarnitine precludes a strong recommendation for its use. Sertraline has demonstrated efficacy in some studies,[37,38] but not in all studies.[39] In addition, fludrocortisone has been suggested as a potential agent for symptomatic hypotension.[40,41] These medications may be tried in individual patients with hypotension, but clearly more studies are required before they can be broadly recommended.

MUSCLE CRAMPS

Although there are no comparative data regarding the efficacy of nonpharmacologic and pharmacotherapeutic interventions, the former should be the first line of treatment because the adverse consequences are minimal (Table 48–5).

TABLE 48-5 Management of Cramps

Acute treatment	Give 100–200 mL bolus of intravenous normal saline
	Give 10–20 mL of intravenous hypertonic saline (23.4%) over 3–5 min
	Give 50 mL of 50% intravenous glucose (nondiabetic patients)
Prevention	
Nonpharmacologic	Accurately set "dry weight"
	Keep dialysate sodium greater than serum sodium
	Stretching exercises
Pharmacologic	Vitamin E 400 international units at bedtime.
	Quinine 325 mg daily (second-line therapy)

Both vitamin E and quinine significantly reduce the incidence of cramps. Quinine is usually well tolerated, but rarely may cause temporary sight and hearing disturbances, thrombocytopenia, or gastrointestinal distress. Furthermore, quinine tends to increase plasma digoxin levels and may enhance the effect of warfarin. This constellation of adverse events prompted the withdrawal of quinine from the over-the-counter market in 1995. Prescription quinine can no longer be marketed for leg cramps. Despite these concerns, quinine is still used fairly frequently in HD patients.

A recent randomized, double-blind, placebo-controlled trial demonstrated that both vitamin E (400 mg) and vitamin C (250 mg) reduce the frequency of cramps in dialysis patients.[42] The combination of these two drugs had an additive effect. Although these data further strengthen the case for vitamin E, it is unclear what role oral vitamin C would play since many patients are on a renal multiple vitamin that contains vitamin C (the current study restricted all vitamin products for 1 month prior to the study). Furthermore, there is some concern that oxalate, a metabolite of vitamin C, may accumulate in dialysis patients.

Creatine might have some beneficial effects on muscle cramps in dialysis patients.[43] Ten patients with intradialytic muscle cramps were randomized to either creatine (12 mg before dialysis) or placebo.[43] The frequency of muscle cramps decreased 60% in the creatine group, while there were no differences in the placebo group. Although serum creatinine concentrations rose in the treatment group, no side effects were noted. Certainly more research in this area is needed before creatine supplementation can be broadly recommended for the prevention and treatment of muscle cramps during HD.

Thus vitamin E appears to be the first choice among these therapeutic options because of the accumulated evidence in clinical trials and because of its better safety profile. Low-dose quinine (300 to 325 mg daily either at bedtime or 1 hour prior to hemodialysis) can be tried as well, but the clinician should be aware of potential side effects and drug interactions.

THROMBOSIS OF VENOUS CATHETERS

Prevention of catheter-related thrombosis is important. Locking the dialysis access port that is filling it with heparin is a standard-of-care, although, surprisingly, there is little data in the literature to support its use in hemodialysis patients, and K/DOQI guidelines do not specifically address the issue of catheter locking. The use of oral antiplatelet agents to prevent thrombosis is also discouraged because of a lack of efficacy and an increased risk of bleeding.[8] A recent study compared the efficacy of 2,000 units of heparin and 2 mg of alteplase as locking solutions. Access blood flow and pressures were significantly better in patients given alteplase. In addition, there were fewer clotting problems and need for lytic therapy in the alteplase group. This study was relatively small and limited to a single dialysis center. The Pre-CLOT (Prevention of Catheter Lumen Occlusion with rT-PA Versus Heparin) study is designed to compare the efficacy of heparin and alteplase in the prevention of catheter dysfunction.[44] This protocol will use lower doses of alteplase (1 mg per lumen once per week, with 5,000 units of heparin the other 2 days). In addition, an economic analysis is planned to determine the cost-effectiveness of using alteplase in this setting.

TABLE 48-6 Management of Hemodialysis Catheter Thrombosis

Nonpharmacologic therapy
Forced saline flush
Referral to vascular surgeon
Pharmacologic therapy
Alteplase: instill 2 mg/2 mL per catheter port; attempt to aspirate after 30 min; may repeat dose if catheter function not restored in 120 min; longer durations of instillation have been used

The therapeutic alternatives for a thrombosed venous catheter are listed in Table 48–6. If a catheter-related thrombus is suspected, a forced saline flush should be used to clear the catheter, followed by installation of a thrombolytic. The thrombolytic with the most data is urokinase, but this agent was withdrawn from the U.S. market in 1999 because of the risks of transmitting infectious agents. Urokinase was reintroduced in the U.S. market in 2002, but is only available as a 250,000-international unit vial (prior to 1999 there was a 5,000-international unit vial specifically designed for catheter clearance). A number of studies have been published using alteplase[45–51] and reteplase[52,53] for thrombosed hemodialysis catheters. Two studies that compared alteplase versus urokinase suggest that alteplase might be more effective.[45,47] The initial rates of reperfusion for both alteplase and reteplase is approximately 90%. However, there are no data available that directly compare the two agents for management of dialysis catheter thrombosis. Alteplase (but not reteplase) is FDA approved for restoration of function to thrombosed central venous catheters, and is commercially available as a 2-mg vial. Alteplase is often administered as a short dwell for 30 to 60 minutes, or it may be given as a long dwell, left in the catheter between treatments. One small study suggested there is no difference in patency rates at the subsequent treatment when alteplase was used as either a short or long dwell.[54] Alteplase has also been given as a short infusion. Infusion doses reported in the literature include 10 mg over 2 hours[51] and 4 to 8 mg over 4 hours.[49] Infusions may theoretically be more efficacious because with the dwell technique only the lytic agent at the very tip of the catheter is exposed to the thrombus.[8] There have been no comparisons between dwells and infusions of alteplase.

INFECTION

Patients who experience fever during HD should immediately have blood cultures collected. If a temporary catheter is being used, it should be removed and the tip of the catheter cultured. Commonly used preventative approaches to catheter-related infections include minimizing use and duration of catheters, proper disinfection and sterile technique, and use of exit-site mupirocin or povidone-iodine ointment. Adopting strict unit protocols that employ universal precautions, limiting manipulation of the catheter, using disinfection with povidone-iodine, and requiring the use of face masks by the patient and caregiver can significantly reduce the incidence of catheter-related bacteremia.[30] There are no published guidelines for the treatment of HD access-related infections. The most recent K/DOQI guidelines do not address specific antimicrobial choices for catheter-related infections. Table 48–7 outlines a reasonable approach, which is partly based on the 2000 K/DOQI guidelines.[9,55] Many clinicians also add an aminoglycoside to the regimen for empiric therapy in catheter-related bacteremia. If the isolated organism is methicillin-sensitive *S. aureus*, therapy may be changed to intravenous cefazolin (20 mg/kg, rounded to the nearest 500 mg) after each dialysis session.[31]

TABLE 48-7 Management of Hemodialysis Access Infection

I. Primary arteriovenous fistula
- A. Treat as subacute bacterial endocarditis for 6 weeks.
- B. Initial antibiotic choice should always cover gram-positive organisms, (e.g., vancomycin 20 mg/kg IV with serum concentration monitoring or cefazolin 20 mg/kg IV 3 times per week.)
- C. Gram-negative coverage is indicated for patients with diabetes, human immunodeficiency virus infection, prosthetic valves, or those receiving immunosuppressive agents, gentamicin 2 mg/kg IV with serum concentration monitoring.

II. Synthetic arteriovenous grafts
- A. Local infection–empiric antibiotic coverage for gram-positive, gram-negative, and *Enterococcus* (e.g., gentamicin plus vancomycin then individualized after culture results available). Continue for 2 to 4 weeks.
- B. Extensive infection–antibiotics as above plus total resection.
- C. If access is less than 1 month old, antibiotics as above plus remove the graft.

III. Tunneled cuffed catheters (internal jugular, subclavians)
- A. Infection localized to catheter exit site.
  1. No drainage–topical antibiotics, (e.g., mupirocin ointment.)
  2. Drainage present–gram-positive antibiotic coverage, (e.g., cefazolin 20 mg/kg IV three times per week.)
- B. Bacteremia with or without systemic signs or symptoms.
  1. Gram-positive antibiotic coverage as in III.A.2.
  2. If symptomatic at 36 hours, remove the catheter.
  3. If stable and asymptomatic, change catheter and provide culture-specific antibiotic coverage for a minimum of 3 weeks.

There has been an increased interest in salvaging venous catheters by using antibiotic lock solutions in conjunction with systemic antibiotics.[32] Recent studies have suggested that between 62% and 70% of catheters can be salvaged using this technique (as defined by absence of fever without loss of catheter).[56–58] However, this approach is not used widely in clinical practice.

As opposed to treatment, catheter locking has also been studied to prevent infection and thrombosis in hemodialysis catheters. In one study, cefotaxime plus heparin was compared to heparin alone.[59] There was an overall risk reduction of 56.5% for catheter thrombosis when the antibiotic-heparin solution was used as compared to just heparin alone. There was also a 50.5% relative risk reduction in catheter-related infections. Finally, the combination extended the life span of the dialysis access. Another study demonstrated a decreased bacteremia rate when gentamicin-citrate was used as a locking solution.[60] Although initial data looks promising, antibiotic resistance is a concern with the wide use of antibiotics in locks. K/DOQI does not recommend routine locking of catheters with antibiotics.

PERITONEAL DIALYSIS

Although the concept of peritoneal lavage has been described as far back as 1744, it wasn't until 1923 that PD was first employed as an acute treatment for uremia. It was used infrequently during subsequent years until the concept of PD as a chronic therapy for ESRD was proposed in 1975. Over the ensuing years the number of patients receiving PD increased slowly until the early 1980s. At that time, several innovations in PD delivery systems were introduced, such as improved catheters and dialysate bags. These innovations led to improved outcomes, decreased morbidity, and a corresponding increase in the use of PD as a viable alternative to HD for the treatment of ESRD.

Some patients—such as those with more hemodynamic instability (e.g., hypotension) or significant residual kidney function (RRF), and perhaps patients who desire to maintain a significant degree of self-care may be better suited to PD rather than to HD. As discussed earlier, there is some debate over important outcomes for patients on PD. Table 48–2 shows the advantages and disadvantages of PD.

PRINCIPLES OF PERITONEAL DIALYSIS

5 The three basic components of HD—namely, a blood-filled compartment separated from a dialysate-filled compartment by a semipermeable membrane—are also used for PD. In PD, the dialysate-filled compartment is the peritoneal cavity, into which dialysate is instilled via a permanent peritoneal catheter that traverses the abdominal wall. The contiguous peritoneal membrane surrounds the peritoneal cavity. The cavity, which normally contains about 100 mL of lipid-rich lubricating fluid, can expand to a capacity of several liters. The peritoneal membrane that lines the cavity functions as the semipermeable membrane, across which diffusion and ultrafiltration occur. The membrane is classically described as a monocellular layer of peritoneal mesothelial cells. However, the dialyzing membrane is also comprised of the basement membrane and underlying connective and interstitial tissue. The peritoneal membrane has a total area that approximates body surface area (approximately 1 to 2 m^2). Blood vessels supplying and draining the abdominal viscera, musculature, and mesentery constitute the blood-filled compartment.

Because the blood is not in intimate contact with the dialysis membrane as it is in HD, metabolic waste products must travel a considerable distance to the dialysate-filled compartment. In addition, unlike HD, there is no easy method to regulate blood flow to the surface of the peritoneal membrane, nor is there a countercurrent flow of blood and dialysate to increase diffusion and ultrafiltration via changes in hydrostatic pressure. For these reasons, PD is a much-less-efficient process per unit time as compared with HD, and must, therefore, be a virtually continuous procedure to achieve acceptable goals for clearance of metabolic waste products.

PERITONEAL DIALYSIS ACCESS

Access to the peritoneal cavity is via the placement of an indwelling catheter. Many types are available and Fig. 48–3 shows a typical example. Most catheters are manufactured from silastic, which is soft, flexible, and biocompatible. A typical adult catheter is approximately 40 to 45 cm long, 20 to 22 cm of which are inside the peritoneal cavity. Placement of the catheter is such that the distal end lies low in a pelvic gutter. The center section of the catheter has one or two cuffs made of a porous material. This section is tunneled inside the anterior abdominal wall so that the cuffs provide mechanical support and stability to the catheter, a mechanical barrier to skin organisms, and prevent their migration along the catheter into the peritoneal cavity. The cuffs are placed at different sites surrounding the abdominal rectus muscle. The remainder of the central section of the catheter is tunneled subcutaneously before exiting the abdominal surface, usually a few centimeters below and to one side of the umbilicus.

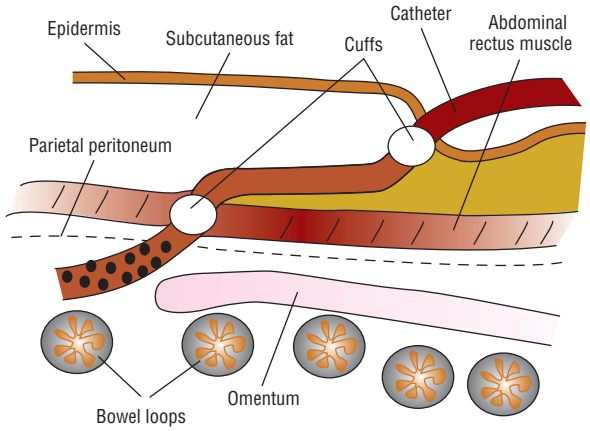

FIGURE 48-3. Diagram of the placement of a peritoneal dialysis catheter through the abdominal wall into the peritoneal cavity.

The placement of the catheter exit site is one of the factors related to the development or prevention of exit-site infections and peritonitis. The external section of most peritoneal catheters ends with a Luer-Lok connector, which can be connected to a variety of administration sets. These catheters can be used immediately if necessary, provided small initial volumes are instilled; however, a maturation period of 2 to 6 weeks is preferred.

PERITONEAL DIALYSIS PROCEDURES

6 In the United States, several variants of PD are clinically utilized. All variants of PD require the placement of a dialysis solution to dwell in the peritoneal cavity for some period, removing the spent dialysate, and then repeating the process. The prescribed dose of PD may be altered by changing the number of exchanges per day, by altering the volume of each exchange, or by altering the strength of dextrose in the dialysate for some or all exchanges. Increasing any one of these variables increases the effective osmotic gradient across the peritoneum, leading to increased ultrafiltration and diffusion (solute removal). If the dwell time is extended, equilibrium may be reached, after which time there will be no further water or solute removal. Indeed, after a critical period, reverse water movement may occur.

The number of patients using automated systems, in 2005, (collectively termed automated peritoneal dialysis [APD]) surpasses those prescribed traditional continuous ambulatory peritoneal dialysis (CAPD).[1] APD systems are designed for patients who are unable or unwilling to perform the necessary aseptic manipulations, and for those who require more dialysis. APD provides an automated cycler that performs the exchanges. The device is set up in the evening, and the patient attaches the peritoneal catheter to it at bedtime. The machine performs several short-dwell exchanges (usually 1 to 2 hours) during the night. This permits a long cycle-free daytime dwell of up to 12 to 14 hours. Typical APD regimens involve total 24-hour exchanges of approximately 12 L, which include one or more daytime dwells.[13] This type of regimen is sometimes referred to as APD with a "wet" day. The APD variant, nightly intermittent peritoneal dialysis, has a similar theme, except that the peritoneal cavity tends to be dialysate free during the day. This type of regimen is frequently referred to as APD with a "dry" day. A number of variants exist and depend largely on equipment availability, patient and prescriber preference, and whether the patient retains any residual renal function, which influences the quantity of dialysis prescribed.[61]

The APD systems include continuous cycling peritoneal dialysis, nocturnal tidal peritoneal dialysis, and nightly intermittent PD.[61] The prototypic form of APD is usually a hybrid between CAPD and continuous cycling PD, in which some of the daily exchanges (usually the overnight exchanges) are completed using an automated device. Recent advances in PD procedures involve using continuous flow peritoneal dialysate.[62] This technique maintains a fixed intraperitoneal volume and rapid, continuous movement of dialysate into and out of the peritoneal cavity. To accomplish this, two PD catheters (an inlet and outlet catheter) and means of generating a large volume of sterile dialysate are required. Dialysate is generated via conventional HD equipment or sorbent technology. In continuous flow peritoneal dialysate, clearance of small solutes is three to eight times greater than with APD, and approximates that with daily HD.[62] Potential applications of continuous flow peritoneal dialysate include daily home dialysis, treatment of acute renal failure in the intensive care unit, and ultrafiltration of ascites.[62]

In a basic CAPD system, the patient or caregiver is manually responsible for delivering the prescribed number of dialysate exchanges. The patient is connected to a bag of prewarmed peritoneal dialysate via the PD catheter, by a length of tubing called a transfer set. The most common transfer set used is the Y transfer set. This consists of a Y-shaped piece of tubing that is attached at its stem to the patient's catheter, leaving the remaining two limbs of the Y attached to dialysate bags, one filled with fresh dialysate and the other empty. The spent dialysate from the previous dwell is drained into the empty bag, and the peritoneum is subsequently refilled from the bag containing fresh dialysate. The Y set is then disconnected and the bag containing the spent fluid and the empty bag that had contained fresh dialysate are detached and discarded. Typically a patient instills 2 to 3 L of dialysate three times during the day with each exchange lasting 4 to 6 hours, and then a single dialysate exchange overnight lasting 8 to 12 hours. At the end of the prescribed dwell period a new Y set is attached and the process is repeated. The process of outflow, aseptic manipulation of the administration set and catheter, and inflow requires a total time of approximately 30 minutes.[61]

Peritoneal Dialysis Solutions

All forms of PD use the same dialysate solutions, which are commercially available in volumes of 1 to 3 L in flexible polyvinyl chloride plastic bags. Commercial PD solutions include varying concentrations of electrolytes, such as sodium (132 mEq/L), chloride (96 to 102 mEq/L), calcium (0 to 3.5 mEq/L), magnesium (0.5 mEq/L), and lactate (35 to 40 mEq/L). Dialysate pH is maintained at 5.2.[63]

The PD dialysate solution may contain 1.5%, 2.5%, 3.86%, or 4.25% dextrose or icodextrin (a glucose polymer) at a concentration of 7.5%. The dextrose solutions are hyperosmolar (osmolarity ranges from 346 to 485 mOsm/L) and induce ultrafiltration (removal of free water) by crystalline osmosis. Dextrose is not the ideal osmotic agent for peritoneal dialysate because these solutions are not biocompatible with peritoneal mesothelial cells or with peritoneal leukocytes.[64] The cytotoxic effects on these cells are mediated by the osmolar load and the low pH of the solutions, as well as the presence of glucose degradation products formed during heat sterilization of these products.

Icodextrin PD solution contains icodextrin, a starch-derived glucose polymer. It has an osmolality of 282 to 286 mOsm/L, which is isoosmolar with serum. Icodextrin produces prolonged ultrafiltration by a mechanism resembling colloid osmosis resulting in ultrafiltration volumes similar to those with 4.25% dextrose. Icodextrin may have fewer of the metabolic effects associated with dextrose, such as hyperglycemia and weight gain. It is indicated for use during the long (8 to 16 hours) dwell of a single daily exchange in CAPD and APD patients.[65]

Additives to Peritoneal Dialysis Solutions: Insulin and Heparin

Possible advantages of intraperitoneal versus subcutaneous insulin include the avoidance of erratic absorption (both rate and extent of absorption), convenience, avoidance of subcutaneous injection site-related complications, and prevention of peripheral hyperinsulinemia.[66] A number of studies have demonstrated the bioavailability of intraperitoneal insulin to be approximately 25% to 30%, although none clearly compares the clinical effectiveness of intraperitoneal versus subcutaneous insulin in diabetes control. Insulin requirements for PD patients may be greater than in hemodialysis patients because of the continued absorption of dextrose from the peritoneal cavity. Furthermore, because of adsorption of insulin to the polyvinyl chloride bag and administration set, the intraperitoneal dose of insulin often needs to be two to three times the subcutaneous maintenance dose.

Many PD patients secrete large quantities of fibrinogen into the peritoneal cavity, which results in fibrin formation. This can lead to intraperitoneal adhesions and outflow obstruction. Intraperitoneal heparin 500 to 1,000 units/L may prevent this complication as a result of its local antifibrin effect. Because standard heparin has a

molecular weight of 12,000 to 15,000 daltons, it is minimally absorbed and thereby has limited systemic effects.[67]

ADEQUACY OF PERITONEAL DIALYSIS

As in HD, the clearance of urea, a product of protein catabolism, can be quantified by calculating *Kt/V*. Calculation of *Kt/V* for PD patients can be accomplished by using various formulas or software programs. The outcome of these calculations results in a value per day which must be multiplied by 7 before it is reported as a weekly value that is relevant for PD patients.[68]

PD adequacy is a major issue which has received considerable attention during the last 10 years. The most recent K/DOQI guidelines recommend that patients on PD have at least a total *Kt/V* of 1.7 per week.[8] It is important to note that RRF may provide a significant component of the total *Kt/V*. Patients may commence PD with a residual $CL_{cr\ renal}$ of approximately 9 to 12 mL/min, which contributes a Kt/V_{renal} of 0.2 to 0.4. Over a period of 1 to 2 years, RRF tends to progressively deteriorate to zero. Because Kt/V_{total} is the sum of Kt/V_{PD} and Kt/V_{renal}, the Kt/V_{total} will progressively diminish unless Kt/V_{PD} is increased (by increasing the prescribed dose of PD) to compensate for the reduced Kt/V_{renal}.

For patients producing <100 mL urine per day, the weekly Kt/V_{urea} dose of 1.7 must be provided entirely by peritoneal clearance. For patients producing >100 mL urine per day, combined renal and peritoneal urea clearances must exceed the weekly Kt/V_{urea} dose of 1.7.[8] The weekly *Kt/V* dose should be measured within the first month of PD initiation and at least once every 4 months thereafter. The rationale for this is that it is imperative to detect subtle decreases in RRF and noncompliance and to make the necessary alterations to the prescribed PD dose to compensate for them.

The K/DOQI guidelines also stress the importance of preserving RRF in PD patients because it is associated with decreased mortality in PD patients. Typical measures to maintain RRF include preferential use of angiotensin-converting enzyme inhibitors or receptor blockers in all patients, regardless of blood pressure, and avoidance of medications or procedures that are associated with insults to the kidney (e.g., nonsteroidal antiinflammatory drugs, cyclooxygenase-2 inhibitors, aminoglycosides, radiocontrast dyes, withdrawal of immunosuppressant therapies from a transplanted kidney, hypovolemia, urinary tract obstruction, and hypercalcemia).[8]

COMPLICATIONS OF PERITONEAL DIALYSIS

Mechanical, medical, and infectious problems complicate PD therapy. Mechanical complications include kinking of the catheter and inflow and outflow obstruction; excessive catheter motion at the exit site, leading to induration and possible infection and aggravation of tissues; pain from impingement of the catheter tip on the viscera; or inflow pain resulting from a jet effect of too rapid dialysate inflow.

Table 48–8 lists the numerous medical complications of PD. An average PD patient absorbs up to 60% of the dextrose in each exchange. This continuous supply of calories leads to increased adipose tissue deposition, decreased appetite, malnutrition, and altered requirements for insulin in diabetic patients. Fibrin formation in dialysate is common and can lead to obstruction of catheter outflow. Infectious complications of PD are a major cause of morbidity and mortality and are the leading cause of technique failure and transfer from PD to hemodialysis. The two predominant infectious complications are peritonitis and catheter-related infections, which include both exit-site and tunnel infections.

Peritonitis

The incidence of peritonitis is influenced by connector technology, by the composition of patient populations, and by the use of APD versus CAPD. The incidence of peritonitis reported by most dialysis centers in the United States is about 1 episode every 24 patient-months, although it may be as low as 1 episode every 60 patient-months.[69] Within 1 year of starting CAPD, 40% to 60% of patients develop their first episode of peritonitis (although the incidence is significantly lower in APD patients).

Peritonitis is a major cause of catheter loss in PD patients. A statistically significant correlation between infectious complications and death rates has been reported. Of patients who had more than 1 peritonitis episode per year, 0.5 to 1 episode per year, or less than 0.5 episode per year, 50% died after 3, 4, and 5 years of therapy, respectively. It is important to note that these relationships are not necessarily cause and effect, as many of these patients succumb to cardiovascular events.[69]

TABLE 48-8 Medical Complications of Peritoneal Dialysis

Cause	Complication	Treatment
Glucose load	Exacerbation of diabetes mellitus	IP insulin
Fluid overload	Exacerbation of congestive heart failure	Increase ultrafiltration
	Edema	Diuretics, if the patient has residual renal function
	Pulmonary congestion	
Electrolyte abnormalities	Hypercalcemia	Alter dialysate calcium content
	Hypocalcemia	
PD additives	Chemical peritonitis	Discontinue PD additives
Malnutrition	Albumin loss	Dietary changes
	Loss of amino acids	Parenteral nutrition
	Muscle wasting	Discontinue PD
	Increased adipose tissue	
Unknown	Fibrin formation in dialysate	IP heparin

IP, intraperitoneal; PD, peritoneal dialysis.

CLINICAL PRESENTATION OF PERITONEAL DIALYSIS–RELATED PERITONITIS

General

- Patients generally present with abdominal pain and cloudy effluent

Symptoms

- The patient may complain of abdominal tenderness, abdominal pain, fever, nausea and vomiting, and chills

Signs

- Cloudy dialysate effluent may be observed
- Temperature may or may not be elevated

Laboratory Tests

- Dialysate white blood cell count >100/mm^3, of which at least 50% are polymorphonuclear neutrophils
- Gram stain of a centrifuged dialysate specimen

Other Diagnostic Tests

- Culture and sensitivity of dialysate should be obtained

Peritonitis has several imprecise definitions, but guidelines suggest that an elevated dialysate white blood cell count of greater than 100 per microliter with at least 50% polymorphonuclear neutrophils indicates the presence of inflammation, of which peritonitis is the most likely cause. A patient who presents with abdominal pain and a cloudy effluent is usually given a provisional diagnosis of peritonitis. Inherent in this definition is a number of false-positive and false-negative diagnoses, because a small percentage of patients with culture-proven peritonitis will have clear dialysate, and some patients, such as menstruating females, may have cloudy PD effluent without clinical infection. Sterile culture peritonitis remains problematic; it is defined as an

episode in which there is clinical suspicion of peritonitis, but for which the culture of the dialysate reveals no organism. There are several postulates for the high incidence (up to 20% of episodes) of culture-negative peritonitis. Many peritonitis-producing organisms are slime producers and may adhere to the peritoneal membrane or to the catheter surface and be protected from exogenous antibiotics. Sufficient numbers of these bacteria may proliferate to cause peritoneal membrane inflammation and clinical peritonitis, but an inadequate number may seed into the peritoneal cavity to be recovered by conventional microbiologic techniques. In addition, free-floating planktonic bacteria may be rapidly phagocytosed by peritoneal white blood cells, thereby rendering them unavailable for culture.[70]

Contemporary methods have increased the recovery rate of organisms and decreased the culture-negative rate. Centrifugation is currently recommended as the optimum culture method. Centrifugation of a large volume of dialysate (50 mL), resuspension of the sediment in 3 to 5 mL of sterile saline, and subsequent inoculation in culture media produce a culture-negative rate less than 5%. If centrifuge equipment is not available, blood culture bottles can be directly injected with 5 to 10 mL of dialysate effluent. However, this method results in a culture-negative rate of up to 20%.[70]

The majority of infections are caused by gram-positive bacteria, of which *Staphylococcus epidermidis* is the predominant organism. There is no single predominant gram-negative organism. Together, gram-positive and gram-negative organisms account for 80% to 90% of all episodes of peritonitis, and constitute the spectrum against which initial empiric therapy is directed. In APD, there is a relative increase in the percentage of infections caused by polymicrobial and fungal organisms.[70]

Catheter-Related Infections

PD patients experience an exit-site infection approximately once every 24 to 48 months. Patients with previous infections tend to have a higher subsequent incidence. The majority of exit-site infections are caused by *S. aureus*. In contrast to peritonitis, *S. epidermidis* accounts for less than 20% of exit-site infections. Although gram-negative organisms, such as *Pseudomonas*, are less common, they can result in significant morbidity. The diagnostic characteristics of these infections are somewhat vague but generally include the presence of purulent drainage, with or without erythema at the catheter exit site. The risk of exit-site infections is increased several-fold in patients who are nasal carriers of *S. aureus*.[70]

MANAGEMENT OF PERITONEAL DIALYSIS COMPLICATIONS

PERITONITIS

7 The International Society of Peritoneal Dialysis (ISPD) Ad Hoc Advisory Committee on Peritoneal Dialysis Related Infections evaluates the diagnostic and therapeutic literature periodically. The most recent report, published in 2005, provides guidelines for the diagnosis and pharmacotherapy of PD-associated infections (Fig. 48–4).[70]

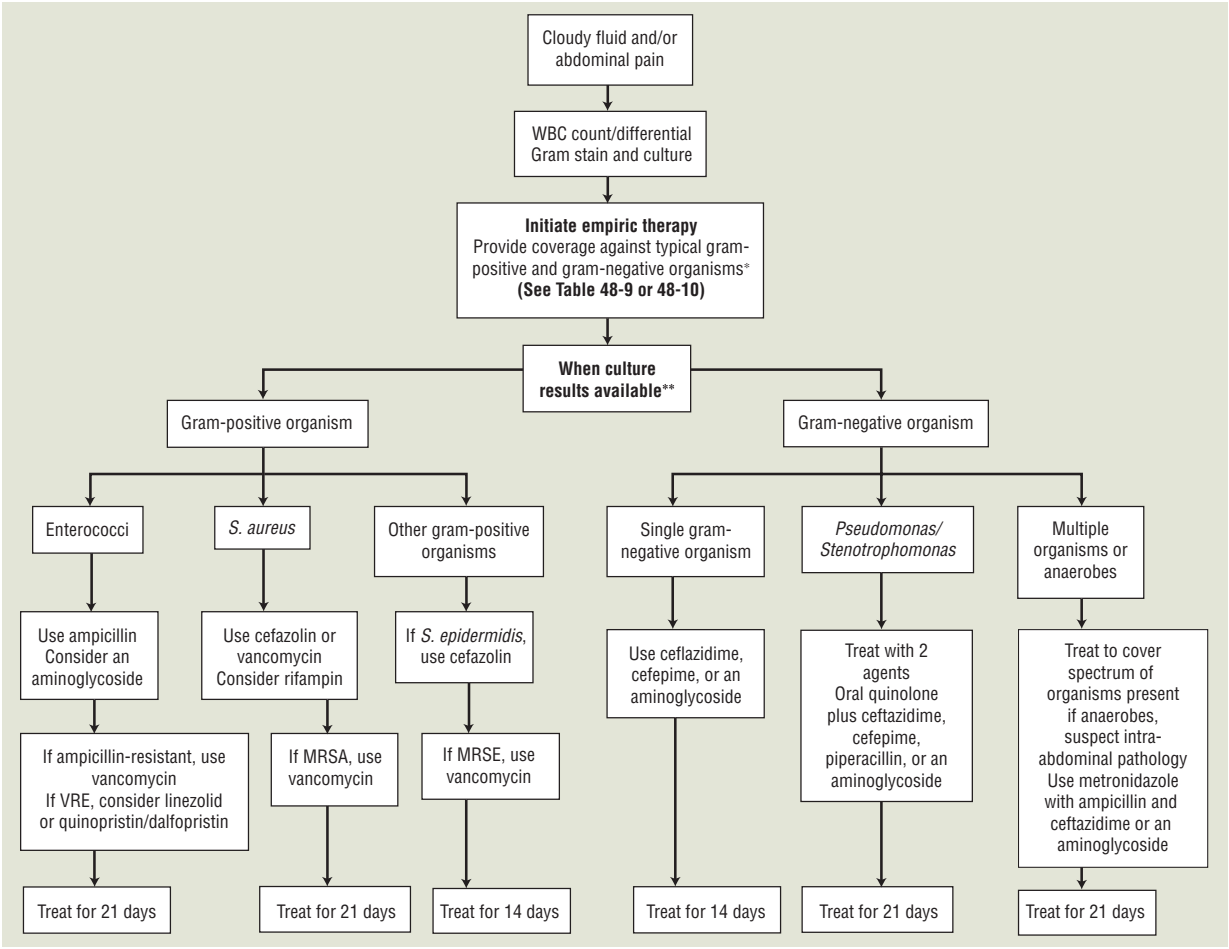

FIGURE 48-4. Pharmacotherapy recommendations for the treatment of bacterial peritonitis in peritoneal dialysis patients. *Choice of empiric treatment should be made based on the dialysis center's and the patient's history of infecting organisms and their sensitivities. **Final choice of therapy should always be guided by culture and sensitivity results. (MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*; *S. aureus*, *Staphylococcus aureus*; *S. epidermidis*, *Staphylococcus epidermidis*; VRE, vancomycin-resistant enterococci; WBC, white blood cell.)

These guidelines include several significant changes from the previous version and specifically address the increasing importance of dialysis center specific antibiotic selection, the effect of residual renal function on the pharmacokinetics of antibiotics, and updated recommendations regarding the use of aminoglycosides and vancomycin.

Intraperitoneal (IP) administration of antibiotics remains the preferred route over IV therapy. The guidelines provide dosing recommendations for intermittent (1 large dose into 1 exchange per day) and continuous therapy (antibiotic addition to each exchange). In addition, dosing recommendations are modified on the basis of the patient's PD modality (CAPD or APD) and whether or not the patient has residual renal function (>100 mL/day urine output).

The choice between intermittent and continuous therapies requires careful consideration for several reasons. The dialysate and serum concentrations achieved after these regimens are very different. The pharmacokinetics of intermittent intraperitoneal ceftazidime and cefazolin are well described. Single daily doses of cefazolin and ceftazidime in CAPD are effective in achieving serum concentrations greater than the minimum inhibitory concentration for sensitive organisms over 48 hours. In CAPD, it is usual to add the single daily dose into the exchange with the longest dwell, to ensure maximal bioavailability. Intermittent (once-daily) IP dosing of antibiotics is recommended for CAPD patients with peritonitis. However, APD dosing strategies are different, because of the increased clearances of solutes in such systems. This appears to be particularly important for first generation cephalosporins. The ISPD guidelines recommend continuous dosing of first-generation cephalosporins because of concerns over inadequate IP drug concentration during the shorter APD dialysate dwells. With regard to residual renal function, in patients with daily urine output greater than 100 mL, the dose should be empirically increased by 25% for drugs that are renally eliminated. The ISPD dosing recommendations for IP antibiotics in CAPD and APD patients are shown in Table 48–9 and Table 48–10, respectively.

The stability of antibiotics added to peritoneal dialysate is important. In dextrose solutions, most antibiotic additives appear to be stable (usually defined as retaining at least 90% of initial activity) for about 1 week if refrigerated, or 1 to 2 days if left at room temperature. Recent data suggests that cefepime, cefazolin, vancomycin, gentamicin, tobramycin, netilmicin, and heparin are stable in icodextrin.[71–73] It is important to note that some studies may not be indicative of stability, that is, they may assay total concentration of an agent, which may include parent-drug degradation products as well as the active drug product, which, as a result, may not maintain the same degree of pharmacologic activity.

The systemic toxicities of IP regimens remain unclear, but are likely similar to those associated with IV and oral antibiotic administration. Intermittent (once-daily) IP dosing of drugs, such as aminoglycosides, may reduce the risk of systemic toxicity (ototoxicity and nephrotoxicity).[70] This is based on a study that showed rapid loss of RRF in PD patients treated with aminoglycosides.[74] However, a later study concluded that aminoglycosides do not accelerate the decline of residual renal function.[75] As a result, the current ISPD guidelines state that there is no convincing evidence that short courses of aminoglycosides lead to loss of RRF. They also state that prolonged or repeated courses are probably inadvisable if an alternative approach is possible.[70] This latter controversial recommendation was based on the opinion of the committee and restated in the recent K/DOQI document. Since the preservation of RRF is very important for PD patients, routine use of aminoglycosides should be avoided in patients with significant RRF (producing >100 mL urine per day) if other antibiotic choices are available.[70]

TABLE 48-9 Intraperitoneal Antibiotic Dosing Recommendations for Continuous Ambulatory Peritoneal Dialysis Patients

Drug	Intermittent (per exchange, once daily)	Continuous (mg/L, all exchanges)
Aminoglycosides		
Amikacin[a]	2 mg/kg	LD 25, MD 12
Gentamicin[a]	0.6 mg/kg	LD 8, MD 4
Netilmicin[a]	0.6 mg/kg	LD 8, MD 4
Tobramycin[a]	0.6 mg/kg	LD 8, MD 4
Cephalosporins		
Cefazolin[a]	15 mg/kg	LD 500, MD 125
Cefepime[a]	1,000 mg	LD 500, MD 125
Cephalothin[a]	15 mg/kg	LD 500, MD 125
Cephradine[a]	15 mg/kg	LD 500, MD 125
Ceftazidime[a]	1,000–1,500 mg	LD 500, MD 125
Ceftizoxime[a]	1,000 mg	LD 250, MD 125
Penicillins		
Azlocillin[a]	ND	LD 500, MD 250
Ampicillin[a]	ND	MD 125
Oxacillin[a]	ND	MD 125
Nafcillin[a]	ND	MD 125
Amoxicillin[a]	ND	LD 250–500, MD 50
Penicillin G[a]	ND	LD 50,000 units, MD 25,000 units
Quinolones		
Ciprofloxacin[a]	ND	LD 50, MD 25
Others		
Vancomycin[a]	15–30 mg/kg Q5-7d	LD 1,000, MD 25
Aztreonam[a]	ND	LD 1,000, MD 250
Antifungals		
Amphotericin B	NA	MD 1.5
Combinations		
Ampicillin/sulbactam[a]	2 g q 12 h	LD 1,000, MD 100
Imipenem/cilastatin[a]	1 g twice daily	LD 500, MD 200
Quinupristin/dalfopristin[b]	25 mg/L in alternate bags	

LD, loading dose in mg; MD, maintenance dose in mg; NA, not applicable; ND, no data.
[a]Dosing of these drugs with renal clearance in patients with residual renal function (defined as more than 100 mL/day urine output) dose should be empirically increased by 25%.
[b]Given in conjunction with 500 mg IV twice daily.
From Piraino et al.[70]

CLINICAL CONTROVERSY

The ISPD guidelines for peritonitis treatment state that patients with significant residual renal function should not receive aminoglycosides if other antibiotic choices are available. Aminoglycosides were found to increase the rate of decline in residual renal function in one study. However, another study refuted this claim. It seems reasonable to withhold aminoglycosides if appropriate alternative antibiotics are available.

TABLE 48-10 Intermittent Intraperitoneal Antibiotic Dosing Recommendations for Automated Peritoneal Dialysis Patients

Drug	Intraperitoneal Dose
Vancomycin	Loading dose 30 mg/kg IP in long dwell, repeat dosing 15 mg/kg IP in long dwell every 3–5 days, following levels
Tobramycin	Loading dose 1.5 mg/kg IP in long dwell, then 0.5 mg/kg IP each day in long day dwell
Fluconazole	200 mg IP in one exchange per day every 24–48 h
Cefepime	1 g IP in one exchange per day

IP, intraperitoneal.
From Piraino et al.[70]

Initial empiric therapy for peritonitis, regardless of whether a Gram stain was performed or organisms were identified, should include agents effective against both gram-positive and gram-negative organisms. Antibiotic selection should be made with consideration given to the dialysis center's and the patient's history of infecting organisms and the antibiotic sensitivity profile of the organisms. In many cases, a first-generation cephalosporin such as cefazolin in combination with a second drug that provides broader gram-negative coverage, such as ceftazidime, cefepime, or an aminoglycoside, will prove suitable. Patients with documented allergy to cephalosporin antibiotics can be treated with vancomycin and an aminoglycoside. High rates of methicillin resistance have been reported by many dialysis centers and vancomycin should be used as first-line therapy against gram-positive organisms for patients treated at these centers. Monotherapy with agents providing both gram-positive and gram-negative coverage is an alternative option. Both imipenem-cilastin and cefepime are effective in treating CAPD-related peritonitis.

After culture and sensitivity results are obtained, antibiotic therapy should be adjusted appropriately (see Fig. 48–4). Tables 48–9 and 48–10 list doses for antibiotics. Treatment should be continued for 14 to 21 days. If the patient does not show a sign of clinical improvement within 72 hours after antibiotic treatment is initiated, the culture should be repeated and the patient reevaluated. If the peritoneal dialysate white blood cell count remains high after 4 days of appropriate antibiotic therapy, clinicians should consider removing the peritoneal catheter and placing the patient on HD and starting IV antibiotics.

Fungal peritonitis is associated with a poor prognosis and high morbidity and mortality. One problem with prospective assessment of antifungal regimens is the infrequency with which these infections occur. This makes it difficult to design and implement comparative studies. Most literature about antifungal treatment is therefore retrospective or limited to reports of local experience.[76] As a result, the ISPD recommendations for treatment of fungal peritonitis are somewhat vague and treatment should be based on culture and sensitivity results. However, one area that has been clarified is the question as to whether the PD catheter should be removed. The ISPD recommendations are to remove the catheter immediately after identifying fungi. If the Gram stain indicates the presence of yeast, treatment may be initiated with amphotericin B and oral flucytosine. Once culture and sensitivity results are available, fluconazole, caspofungin, or voriconazole may replace amphotericin B. Treatment with these agents should be continued orally for an additional 10 days after catheter removal. It remains unclear whether there is any benefit from fungal prophylaxis.[77] Recommendations are also provided for the treatment of mycobacterial, or tuberculous, peritonitis. Although this infection is a rare complication, it can be difficult to diagnose, and treatment requires multiple drugs.

CATHETER EXIT-SITE INFECTIONS

Topical antibiotics and disinfectants appear to be effective agents for the prevention of exit-site infections.[78–80] Gram-positive organisms should be treated with an oral penicillinase-resistant penicillin or a first-generation cephalosporin such as cephalexin (Fig. 48–5). Rifampin may be added if necessary, in slowly resolving or particularly severe *S. aureus* infections. Vancomycin should be avoided in routine or empiric treatment of gram-positive catheter-related infections, but will be necessary for methicillin-resistant *S. aureus*. Gram-negative organisms should be treated with oral quinolones. The effectiveness of oral quinolones may be diminished owing to the chelation drug interactions with divalent and trivalent metal ions, which are commonly taken by dialysis patients. Administration of quinolones should occur at least 2 hours prior to these drugs.

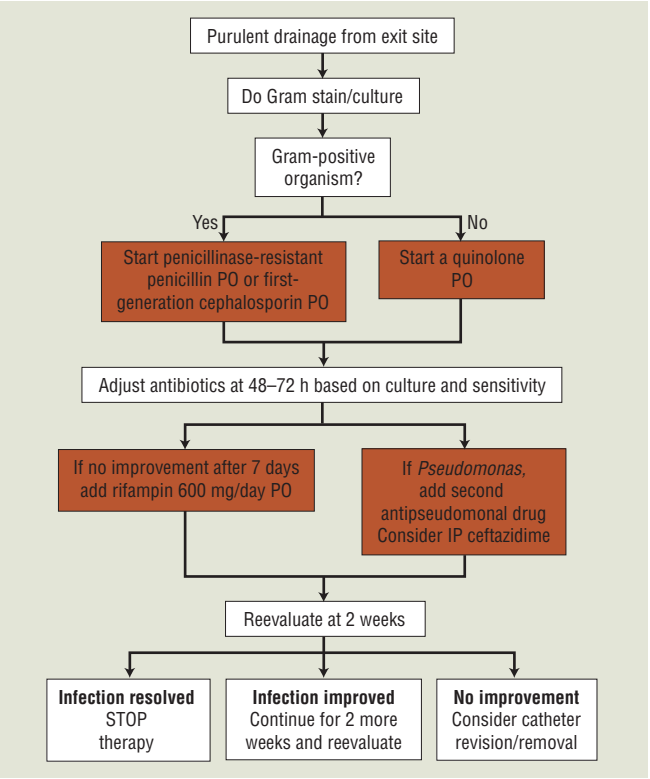

FIGURE 48-5. Management strategy of exit-site infections for peritoneal dialysis patients. (IP, intraperitoneal; PO, orally.[70])

In cases where *Pseudomonas aeruginosa* is the pathogen, a second antipseudomonal drug should be added. IP ceftazidime may be considered. In all cases antibiotics should be continued until the exit site appears normal; 2 to 3 weeks of therapy may be necessary. A patient with a catheter-related infection that progresses to peritonitis will usually require catheter removal.[70]

PREVENTION OF PERITONITIS AND CATHETER EXIT-SITE INFECTIONS

8 Attempts to prevent peritonitis and catheter-related infections have included refinement of connector system technology and the use of prophylactic antibiotic regimens and vaccines. Several studies have examined the impact of antibacterial agents as prophylaxis against both peritonitis and tunnel-related infections. Intermittent rifampin, 300 mg orally twice a day for 5 days, repeated every 3 months, appears to decrease the number of catheter-related infections, but not the incidence of peritonitis. The efficacy of other antibiotic prophylaxis for peritonitis and catheter-related infections is limited. Long-term, extended-duration prophylaxis with penicillins or cephalosporins is not effective.[70]

Nasal carriage of *S. aureus* is associated with an increased risk of catheter-related infections and peritonitis. In addition, diabetic patients and those on immunosuppressive therapy are at increased risk for *S. aureus* catheter infections. Prophylaxis with intranasal mupirocin (twice daily for 5 to 7 days every month), mupirocin (daily) at the exit site, or oral rifampin can effectively reduce *S. aureus* exit-site infections. Because of the minimal toxicity of mupirocin and the risk of rifampin resistance, mupirocin regimens are preferred.[70] However, it is important to note that *S. aureus* isolates with a high degree of resistance to mupirocin have been isolated from PD patients using prophylactic mupirocin at the peritoneal catheter exit site.[81] In addition, gentamicin cream applied daily to the exit site has been found to effectively reduce both *S. aureus* and *P. aeruginosa* exit-site infection.[70]

CONCLUSIONS

Because of the limitation of available kidneys for transplantation, dialysis (HD and PD) remains the most widely available and commonly used means of ESRD treatment. Despite continual advances in dialysis and transplantation, kidney failure is associated with significant morbidity and mortality. Given the lack of a true cure for kidney failure, emphasis recently has been placed on the prevention and early detection of kidney disease. Goals set by the K/DOQI, the Healthy People 2010 initiative, and the Centers for Medicare and Medicaid Services' CPM Project provide guidance and direction for all healthcare practitioners. In fact, there have been some significant gains in recent years in terms of incidence rate of ESRD, optimal access placement, and mortality and morbidity.[1,8,13] For patients with ESRD, a focus on quality of life and rehabilitation may be a valuable and viable goal toward which the nephrology community should direct its research resources. Although prevention of ESRD is the primary goal for clinicians and adequate access to renal transplantation is secondary, dialysis will likely be a part of the treatment paradigm for ESRD for the near- and long-term.

ABBREVIATIONS

APD: automated peritoneal dialysis

AV: arteriovenous

CAPD: continuous ambulatory peritoneal dialysis

CI: confidence interval

CL_{cr}: creatinine clearance

CPM: clinical performance measures

ESRD: end-stage renal disease

GFR: glomerular filtration rate

HD: hemodialysis

IP: intraperitoneal

ISPD: The International Society of Peritoneal Dialysis

NKF-K/DOQI: National Kidney Foundation's Kidney Disease/Dialysis Outcome Quality Initiative

PD: peritoneal dialysis

RRF: residual kidney function

URR: urea reduction ratio

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