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Dialysis in the Treatment

of Kidney Failure Dialysis may be required for the treatment of either acute or chronic kidney disease (CKD). The use of continuous renal replacement thera pies (CRRTs) and prolonged intermittent renal replacement therapy (PIRRT)/slow low-efficiency dialysis (SLED) is specific to the manage ment of acute kidney injury/acute kidney disease and is discussed in Chap. 321. These modalities are performed continuously (CRRT) or over 6–12 h per session (PIRRT/SLED), in contrast to the 3–4 h of an intermittent hemodialysis session. Advantages and disadvantages of CRRT and PIRRT/SLED are discussed in Chap. 321. Peritoneal dialysis is rarely used in developed countries for the treatment of acute kidney injury/acute kidney disease because of the increased risk of infection and (as will be discussed in more detail below) less efficient clearance per unit of time. The focus of this chap ter will be on the use of peritoneal and hemodialysis for end-stage kidney disease (ESKD). PART 9 Disorders of the Kidney and Urinary Tract With the widespread availability of dialysis, the lives of hundreds of thousands of patients with ESKD have been prolonged. In the United States alone, there are now >800,000 patients with treated ESKD (kidney failure requiring dialysis or transplantation), the vast majority of whom require dialysis. Since 2000, the prevalence of treated ESKD has increased 65%, which predominantly reflects enhanced survival of patients receiving dialysis. The crude incidence rate for treated ESKD in the United States is 363 cases per million population per year; this incidence has slowly fallen over time. ESKD is disproportionately higher in African Americans as compared with white Americans. In the United States, the leading cause of ESKD is diabetes mellitus, currently accounting for ~45% of newly diagnosed cases of ESKD. Approximately 30% of patients have ESKD that has been attributed to hypertension, although it is unclear whether in these cases hypertension is the cause or a consequence of vascular disease or other unknown causes of kidney failure. Other prevalent causes of ESKD include glomerulonephritis, polycystic kidney disease, and obstructive uropathy. A fraction of the excess incidence of ESKD in African Americans is likely related to trans mission of high-risk alleles for the APOL1 gene. Globally, mortality rates for patients with ESKD are lowest in Europe and Japan but

very high in the developing world because of the limited availability of dialysis. In the United States, the mortality rate of patients on dialysis had decreased somewhat but remained extremely high prior to the COVID-19 pandemic. During the pandemic, there was a signifi cant increase in the mortality of patients receiving hemodialysis or peri toneal dialysis, but we remove the point estimates. Deaths are due mainly to cardiovascular diseases and infections. Older age, male sex, nonblack race, diabetes mellitus, malnutrition, and underlying heart disease are important predictors of death. TREATMENT OPTIONS FOR PATIENTS WITH ESKD Commonly accepted criteria for initiating patients on maintenance dialysis include the presence of uremic symptoms, the presence of hyperkalemia unresponsive to conservative measures, persistent extra cellular volume expansion despite diuretic therapy, acidosis refractory to medical therapy, a bleeding diathesis, and a creatinine clearance or estimated glomerular filtration rate (GFR) <10 mL/min per 1.73 m2, although we should emphasize that there is no absolute level of serum creatinine, cystatin C, blood urea nitrogen (BUN), or estimated GFR that should be considered an absolute indication (see Chap. 322 for estimating equations). Timely referral to a nephrologist for advanced planning and creation of a dialysis access, education about ESKD treat ment options, and management of the complications of advanced CKD, including hypertension, anemia, metabolic acidosis, and disorders of

bone and mineral metabolism, including secondary hyperparathyroid ism, is advisable. Recent data have suggested that a sizable fraction of ESKD cases result following episodes of acute kidney injury, particu larly among persons with underlying CKD. Furthermore, there is no benefit to initiating dialysis preemptively at a GFR of 10–14 mL/min per 1.73 m2 compared to initiating dialysis for symptoms of uremia. In ESKD, treatment options include hemodialysis (in a center or at home); peritoneal dialysis, as either continuous ambulatory peritoneal dialysis (CAPD) or continuous cyclic peritoneal dialysis (CCPD); or transplantation (Chap. 325). Although there are significant geographic variations and differences in practice patterns, in-center hemodialysis remains the most common therapeutic modality for ESKD (>80% of patients) in the United States. In contrast to hemodialysis, peritoneal dialysis is continuous, but much less efficient in terms of solute clear ance. While no large-scale clinical trials have been completed compar ing outcomes among patients randomized to either hemodialysis or peritoneal dialysis, outcomes associated with both therapies are similar in most reports, and the decision of which modality to select is often based on personal preferences and quality-of-life considerations. HEMODIALYSIS Hemodialysis relies on the principles of solute diffusion across a semi permeable membrane. Movement of by-products of metabolism (often referred to as “waste products” or “toxins”—terms that may under standably create anxiety in patients) takes place down a concentration gradient from the circulation into the dialysate. The rate of diffusive transport increases in response to several factors, including the mag nitude of the concentration gradient, the membrane surface area, and the mass transfer coefficient of the membrane. The latter is a function of the porosity and thickness of the membrane, the size of the solute molecule, and the conditions of flow on the two sides of the membrane. According to laws of diffusion, the larger the molecule, the slower is its rate of transfer across the membrane. A small molecule, such as urea (60 Da), undergoes substantial clearance, whereas a larger molecule, such as creatinine (113 Da), is cleared less efficiently. In addition to dif fusive clearance, movement of waste products from the circulation into the dialysate may occur as a result of ultrafiltration. Convective clear ance occurs because of solvent drag, with solutes being swept along with water across the semipermeable dialysis membrane. ■ ■THE DIALYZER There are three essential components to hemodialysis: the dialyzer, the composition and

delivery of the dialysate, and the blood delivery system (Fig. 323-1). The dialyzer is a plastic chamber with the ability to perfuse blood and dialysate compartments simultaneously at very high flow rates. The hollow-fiber dialyzer is the most common in use in the United States. These dialyzers are composed of bundles of capil lary tubes through which blood circulates while dialysate travels on the outside of the fiber bundle. Virtually all dialyzers now manufactured in the United States are “biocompatible” synthetic membranes derived from polysulfone or related compounds (versus older cellulose “bioin compatible” membranes that activated the complement cascade). The frequency of reprocessing and reuse of hemodialyzers and blood lines varies across the world. In general, as the cost of disposable supplies has decreased, the use of single-use dialyzers has increased. In the United States, reprocessing of dialyzers is now extremely rare. Formal dehyde, peracetic acid–hydrogen peroxide, glutaraldehyde, and bleach have all been used as reprocessing agents. ■ ■DIALYSATE The potassium concentration of dialysate may be varied from 0–4 mmol/L depending on the predialysis serum potassium concentration. The use of 0- or 1-mmol/L potassium dialysate is becoming much less common owing to data suggesting that patients who undergo treatments with very low potassium dialysate have an increased risk of sudden death, perhaps due to arrhythmias in the setting of potassium shifts. The usual dialysate calcium concentration is 1.25 mmol/L (2.5 mEq/L), although modification may be required in selected settings (e.g., higher dialysate calcium concentrations may be used in patients with hypocalcemia

Venous Arterial Dialysate V Arteriovenous fistula A Venous line Hollow fiber dialyzer Arterial line FIGURE 323-1 Schema for hemodialysis. associated with secondary hyperparathyroidism or with “hungry bone syndrome” following parathyroidectomy). The usual dialysate sodium concentration is 135–140 mmol/L. In patients who frequently develop hypotension during their dialysis run, “sodium modeling” to coun terbalance urea-related osmolar gradients may be employed. With sodium modeling, the dialysate sodium concentration is gradually lowered from the range of 145–155 mmol/L to isotonic concentrations (135–140 mmol/L) near the end of the dialysis treatment, typically declining either in steps or in a linear or exponential fashion. However, higher dialysate sodium concentrations and sodium modeling may predispose patients to positive sodium balance and increased thirst; thus, these strategies to ameliorate intradialytic hypotension may be undesirable in patients with hypertension or in patients with large interdialytic weight gains. Because patients are exposed to ~120 L of water during each dialysis treatment, water used for the dialysate is subjected to filtration, softening, deionization, and, ultimately, reverse osmosis to remove microbiologic contaminants and dissolved ions. ■ ■BLOOD DELIVERY SYSTEM The blood delivery system is composed of the extracorporeal circuit and the dialysis access. The dialysis machine consists of a blood pump, dialysis solution delivery system, and various safety monitors. The blood pump moves blood from the access site, through the dialyzer, and back to the patient. The blood flow rate typically ranges from 250– 450 mL/min, depending on the type and integrity of the vascular access and needle gauge. Negative hydrostatic pressure on the dialysate side can be manipulated to achieve desirable fluid removal or ultrafiltration. Dialysis membranes have different ultrafiltration coefficients (i.e., mL removed/min per mmHg) so that along with hydrostatic changes, fluid removal can be varied. The dialysis solution delivery system dilutes the concentrated dialysate with water and monitors the temperature, conductivity, and flow of dialysate. ■ ■DIALYSIS ACCESS The fistula, graft, or catheter through which blood is obtained for hemodialysis is often referred to as a hemodialysis (or vascular) access. A native fistula created by the anastomosis of an artery to a vein (e.g., the Brescia-Cimino fistula, in which the cephalic vein at the

wrist is anas tomosed end-to-side to the radial artery) results in arterialization of the

Acid concentrate Water treatment (deionization and reverse osmosis) Na+ Cl– K+ Acetate– Ca2+ Mg2+ NaBicarb NaCl Dialysate Dialysate flow rate Dialysate pressure Dialysate conductivity Blood (leak) detection CHAPTER 323 Arterial pressure Venous pressure Blood flow rate Air (leak) detection “Delivery” system Dialysate drain Dialysis in the Treatment of Kidney Failure vein. This facilitates its subsequent use in the placement of large needles (typically 15 or 16 gauge) to access the circulation. Fistulas have the highest long-term patency rate of all hemodialysis access options. For patients in whom fistulas fail to mature or in patients whose vasculature does not allow creation of a successful fistula (i.e., poor arterial inflow or recipient veins of inadequate caliber), patients undergo placement of an arteriovenous graft (i.e., the interposition of prosthetic material, usually polytetrafluoroethylene, between an artery and a vein) or a tunneled hemodialysis catheter. Nephrologists, vascular surgeons, and health care policymakers in the United States have encouraged creation of arteriovenous fistulas in a larger fraction of patients (the “fistula first” initiative). Unfortunately, even when created, arteriovenous fistulas may not mature sufficiently to provide reliable access to the circulation, or they may thrombose early in their development. The most important complication of arteriovenous grafts is throm bosis of the graft and graft failure, due principally to intimal hyper plasia at the anastomosis between the graft and recipient vein. When grafts (or fistulas) fail, catheter-guided angioplasty can be used to dilate stenoses; monitoring of venous pressures on dialysis and of access flow, although not universally performed, may assist in the early recognition of impending vascular access failure. In addition to increased rates of access failure, grafts and (in particular) catheters are associated with much higher rates of infection than fistulas. Intravenous large-bore catheters are often used in patients with acute renal failure and CKD. For persons on maintenance hemodialy sis, tunneled catheters (either two separate catheters or a single catheter with two lumens) are often used when arteriovenous fistulas and grafts have failed or are not feasible due to anatomic considerations. These catheters are tunneled under the skin; the tunnel reduces bacterial translocation from the skin, resulting in a lower infection rate than with nontunneled temporary catheters. Most tunneled catheters are placed in the internal jugular veins; the external jugular, femoral, and subclavian veins may also be used. Infection, venous thrombosis, and venous stenosis resulting in swelling of the extremity or superior vena cava syndrome are complications best avoided by limiting the time during which catheters are employed. Nephrologists, interventional radiologists, and vascular surgeons generally prefer to avoid placement of catheters into the subclavian

veins; while flow rates are usually excellent, subclavian stenosis is a frequent complication and, if present, will likely prohibit permanent vascular access (i.e., a fistula or graft) in the ipsilateral extremity. Infec tion rates may be higher with femoral catheters. For patients with mul tiple vascular access complications and no other options for permanent vascular access, tunneled catheters may be the last “lifeline” for hemo dialysis. Translumbar or transhepatic approaches into the inferior vena cava may be required if the superior vena cava or other central veins draining the upper extremities are stenosed or thrombosed.

■ ■GOALS OF DIALYSIS The hemodialysis procedure consists of pumping heparinized blood through the dialyzer at a flow rate of 250–450 mL/min, while dialysate flows in an opposite counter-current direction at 500–800 mL/min. The efficiency of dialysis is determined by blood and dialysate flow through the dialyzer as well as dialyzer characteristics (i.e., its efficiency in removing

solute). The dose of dialysis, which is currently defined as a derivation of the fractional urea clearance during a single treatment, is further governed by patient size (in particular, the total body water or urea volume of distribution, which resides to large extent in the skeletal muscle), residual kidney function, dietary protein intake, the degree of anabolism or catabolism, and the presence of comorbid conditions, including, in particular, heart failure. Since the landmark studies of Sargent and Gotch relating the mea surement of the dose of dialysis using urea concentrations with mor bidity in the National Cooperative Dialysis Study, the delivered dose of dialysis has been measured and considered as a quality assurance and improvement tool. While the fractional removal of urea nitrogen and derivations thereof are considered to be the standard methods by which “adequacy of dialysis” is measured, a large multicenter random ized clinical trial (the HEMO study) failed to show a difference in mor tality associated with a large difference in per-session urea clearance. Current targets include a urea reduction ratio (the fractional reduction in blood urea nitrogen per hemodialysis session) of >65–70% and a total body water–indexed clearance × time product (Kt/V) >1.2 or 1.05, depending on whether urea concentrations are “equilibrated.” For the majority of patients with ESKD, 9–12 h of dialysis are required each week, usually divided into three equal sessions. Several studies have suggested that longer hemodialysis session lengths may be ben eficial (independent of urea clearance), although these studies are con founded by a variety of patient characteristics, including body size and nutritional status. Hemodialysis “dose” should be individualized, and factors other than the urea nitrogen should be considered, including the adequacy of ultrafiltration or fluid removal and control of hyper kalemia, hyperphosphatemia, and metabolic acidosis. A randomized clinical trial comparing hemodialysis performed 6 versus 3 times per week (the Frequent Hemodialysis Network Daily Trial) demonstrated improved control of hypertension and hyperphosphatemia, reduced left ventricular mass, and improved self-reported physical health with more frequent hemodialysis. Secondary analyses also demonstrated improvements in other metrics of health-related quality of life, includ ing improved self-reported general health and a reduced “time to recovery” (time until usual activities can be resumed) among patients randomized to more frequent hemodialysis. A companion trial in which frequent nocturnal hemodialysis was compared to conventional hemodialysis at home showed no significant effect on left ventricular mass or self-reported physical health. Finally, an evaluation of the U.S. Renal Data System registry showed a significant increase in mortality and hospitalization for heart failure after the longer interdialytic inter val that occurs over the dialysis “weekend.” PART 9 Disorders of the Kidney and Urinary Tract ■ ■COMPLICATIONS DURING HEMODIALYSIS Hypotension is the most common acute complication of hemodialysis, particularly among patients with diabetes mellitus. Numerous fac tors appear to increase the risk of hypotension, including excessive ultrafiltration with inadequate compensatory vascular filling, impaired vasoactive or autonomic responses, osmolar shifts, overzealous use of antihypertensive agents, and reduced cardiac reserve. Patients with arteriovenous fistulas and grafts may develop high-output cardiac failure due to shunting of blood through the dialysis access; on rare occasions,

this may necessitate ligation of the fistula or graft. The management of hypotension during dialysis consists of discontinuing ultrafiltration, the administration of 100–250 mL of isotonic saline, or administration of salt-poor albumin, although the latter is generally unavailable in outpa tient settings. Hypotension during dialysis can frequently be prevented by careful evaluation of the dry weight and by ultrafiltration modeling, such that more fluid is removed at the beginning rather than the end of the dialysis procedure. Excessively rapid fluid removal (>13 mL/kg per h) should be avoided, as rapid fluid removal has been associated with adverse outcomes, including

cardiovascular deaths. Additional maneuvers to prevent intradialytic hypotension include the performance of sequential ultrafiltration followed by dialysis, cooling of the dialysate during dialysis treatment, and avoiding heavy meals during dialysis. Midodrine, an oral selective α1 adrenergic agent, has been advocated by some practitioners, although there is insufficient evidence of its safety and efficacy to support its routine use. Muscle cramps during dialysis are also a common complication. The etiology of dialysis-associated cramps remains obscure. Changes in muscle perfusion because of excessively rapid volume removal or targeted removal below the patient's estimated dry weight often precip itate dialysis-associated cramps. Strategies that may be used to prevent cramps include reducing volume removal during dialysis, ultrafiltra tion profiling, and the use of sodium modeling (see above). Anaphylactoid reactions to the dialyzer, particularly on its first use, have been reported, most frequently with the bioincompatible cellulosic-containing membranes, which are rarely used today. Dialyzer reactions can be divided into two types, A and B. Type A reactions are attributed to an IgE-mediated intermediate hypersensitivity reaction to ethylene oxide used in the sterilization of new dialyzers. This reaction typically occurs soon after the initiation of a treatment (within the first few minutes) and can progress to full-blown anaphylaxis. The type B reaction consists of a symptom complex of nonspecific chest and back pain, which appears to result from complement activation and cytokine release. These symptoms typically occur several minutes into the dialy sis run and typically resolve over time with continued dialysis. PERITONEAL DIALYSIS In peritoneal dialysis, 1.5–3 L of a dextrose-containing solution is infused into the peritoneal cavity and allowed to dwell for a set period of time, usually 2–4 h. As with hemodialysis, metabolic by-products are removed through a combination of convective clearance generated through ultrafiltration and diffusive clearance down a concentration gradient. The clearance of solutes and water during a peritoneal dialysis exchange depends on the balance between the movement of solute and water into the peritoneal cavity versus absorption from the peritoneal cavity. The rate of diffusion diminishes with time and eventually stops when equilibration between plasma and dialysate is reached. Absorp tion of solutes and water from the peritoneal cavity occurs across the peritoneal membrane into the peritoneal capillary circulation and via peritoneal lymphatics into the lymphatic circulation. The rate of perito neal solute transport varies from patient to patient and may be altered by the presence of infection (peritonitis), drugs, and physical factors such as position and exercise. ■ ■FORMS OF PERITONEAL DIALYSIS Peritoneal dialysis may be carried out as CAPD, CCPD, or a combination of both. In CAPD, dialysate is manually infused into the peritoneal cav ity and exchanged three to five times during the day. A nighttime dwell is frequently instilled at bedtime and remains in the peritoneal cavity through the night. In CCPD, exchanges are performed in an automated fashion, usually at night; the patient is connected to an automated cycler that performs a series of exchange cycles while the patient sleeps. The number of exchange cycles required to optimize peritoneal solute clear ance varies by the peritoneal membrane characteristics; as with hemodi alysis, solute clearance should be tracked to ensure dialysis "adequacy." Peritoneal dialysis solutions are available in volumes typically rang ing from 1.5–3 L. The major difference between the dialysate used for peritoneal dialysis rather than hemodialysis is that the hypertonicity of peritoneal dialysis solutions drives solute and fluid removal, whereas

solute removal in hemodialysis depends on concentration gradients, and fluid removal requires transmembrane pressure. Typically, dex trose at varying concentrations contributes to the hypertonicity of peritoneal dialysate. In some cases in which patients have developed severe protein-energy malnutrition or have struggled with insufficient ultrafiltration, amino acid–containing

peritoneal dialysis solutions have been added to the CAPD or CCPD regimen. Icodextrin is a nonabsorbable carbohydrate that is frequently used in place of dex trose during a single daily exchange. Studies have demonstrated more efficient ultrafiltration with icodextrin than with dextrose-containing solutions. Icodextrin is typically used as the “last fill” for patients on CCPD or for the longest dwell in patients on CAPD. The most com mon additives to peritoneal dialysis solutions are heparin to prevent obstruction of the dialysis catheter lumen with fibrin and antibiotics during an episode of acute peritonitis. Insulin may also be added in patients with diabetes mellitus. ■ ■ACCESS TO THE PERITONEAL CAVITY Access to the peritoneal cavity is obtained through a peritoneal cath eter. Catheters used for maintenance peritoneal dialysis are flexible, being made of silicone rubber with numerous side holes at the distal end. These catheters usually have two Dacron cuffs. The scarring that occurs around the cuffs anchors the catheter and seals it from bacteria tracking from the skin surface into the peritoneal cavity; it also pre vents the external leakage of fluid from the peritoneal cavity. The cuffs are placed in the preperitoneal plane and ~2 cm from the skin surface. The peritoneal equilibrium test is a formal evaluation of peritoneal membrane characteristics that measures the transfer rates of creatinine and glucose across the peritoneal membrane. Patients are classified as low, low–average, high–average, and high transporters. Patients with rapid equilibration (i.e., high transporters) tend to absorb more glucose and lose efficiency of ultrafiltration with long daytime dwells. High transport ers also tend to lose larger quantities of albumin and other proteins across the peritoneal membrane. In general, patients with rapid transporting characteristics require more frequent, shorter dwell-time exchanges, nearly always obligating use of a cycler. Slower (low and low–average) transporters tend to do well with fewer exchanges. The efficiency of solute clearance also depends on the volume of dialysate infused. Larger volumes allow for greater solute clearance, particularly with CAPD in patients with low and low–average transport characteristics. As with hemodialysis, the optimal dose of peritoneal dialysis is unknown. Several observational studies have suggested that higher rates of urea and creatinine clearance (the latter generally measured in L/week) are associated with lower mortality rates and fewer uremic complications. However, a randomized clinical trial (Adequacy of Peritoneal Dialysis in Mexico [ADEMEX]) failed to show a significant reduction in mortality or complications with a relatively large incre ment in urea clearance. In general, patients on peritoneal dialysis do well when they retain residual kidney function. Rates of technique fail ure increase with years on dialysis and have been correlated with loss of residual function to a greater extent than loss of peritoneal membrane capacity. For some patients in whom CCPD does not provide suffi cient solute clearance, a hybrid approach can be adopted where one or more daytime exchanges are added to the CCPD regimen. While this approach can enhance solute clearance and prolong a patient’s capacity to remain on peritoneal dialysis, the burden of the hybrid approach can be overwhelming. ■ ■COMPLICATIONS DURING PERITONEAL DIALYSIS The major complications of peritoneal dialysis are peritonitis, catheterassociated nonperitonitis infections, weight gain and other metabolic disturbances, and residual uremia (especially among patients with little or no residual kidney function). Peritonitis typically develops when there has been a break in sterile technique during one or more of the exchange procedures. Peritonitis is usually defined by an elevated peritoneal fluid leukocyte count (100/mm3, of which at least 50% are polymorphonuclear neutrophils); these cutoffs are lower than in spontaneous bacterial peritonitis because of the presence of dextrose in peritoneal dialysis solutions and rapid bacterial proliferation in this environment without antibiotic

therapy. The clinical presentation typically consists of pain and cloudy dialysate, often with fever and other constitutional symptoms. The most common culprit organisms are gram-positive cocci, including Staphylococcus, reflecting the origin from the skin. Gram-negative rod infections are less common; fungal and mycobacterial infections can be seen in selected patients, particularly after antibacterial therapy. Most cases of peritonitis can be managed either with intraperitoneal or oral antibiotics, depending on the organism; many patients with peri tonitis do not require hospitalization. In cases where peritonitis is due to hydrophilic gram-negative rods (e.g., Pseudomonas spp.) or yeast, antimicrobial therapy is usually not sufficient, and catheter removal is required to ensure complete eradication of infection. Nonperitonitis catheter-associated infections (often termed tunnel infections) vary widely in severity. Some cases can be managed with local antibiotic or silver nitrate administration, while others are severe enough to require parenteral antibiotic therapy and catheter removal.

Peritoneal dialysis is associated with a variety of metabolic compli cations. Albumin and other proteins can be lost across the peritoneal membrane in concert with the loss of metabolic wastes. Hypoprotein emia obligates a higher dietary protein intake in order to maintain nitrogen balance. Hyperglycemia and weight gain are also common complications of peritoneal dialysis. Several hundred calories in the form of dextrose are absorbed each day, depending on the concentra tion of dextrose employed. Patients receiving peritoneal dialysis, par ticularly those with diabetes mellitus, are prone to other complications of insulin resistance, including hypertriglyceridemia. On the positive side, the continuous nature of peritoneal dialysis usually allows for a more liberal diet due to continuous removal of potassium and phos phorus—two major dietary components whose accumulation can be hazardous in ESKD. CHAPTER 323 Dialysis in the Treatment of Kidney Failure LONG-TERM OUTCOMES IN ESKD Cardiovascular disease constitutes the major cause of death in patients with ESKD. Cardiovascular mortality and event rates are higher in patients receiving dialysis than in patients posttransplantation, although rates are extraordinarily high in both populations. The underlying cause of cardiovascular disease is unclear but may be related to shared risk factors (e.g., diabetes mellitus, hypertension, atherosclerotic and arteriosclerotic vascular disease), chronic inflam mation, massive changes in extracellular volume (especially with high interdialytic weight gains), inadequate treatment of hypertension, dyslipidemia, anemia, dystrophic (vascular) calcification, and, perhaps, alterations in cardiovascular dynamics during the dialysis treatment. Few studies have targeted cardiovascular risk reduction in patients with ESKD; none has demonstrated consistent benefit. Two clinical trials of statin agents in ESKD demonstrated significant reductions in low-density lipoprotein (LDL) cholesterol concentrations but no significant reductions in death or cardiovascular events (Die Deutsche Diabetes Dialyse Studie [4D] and AURORA studies). The Study of Heart and Renal Protection (SHARP), which included patients on dialysis and others with non-dialysis-requiring CKD, showed a 17% reduction in the rate of major cardiovascular events or cardiovascular death with simvastatin-ezetimibe treatment. Most experts recommend conventional cardioprotective strategies (e.g., lipid-lowering agents, aspirin, inhibitors of the renin-angiotensin-aldosterone system, and β-adrenergic antagonists) in patients receiving dialysis based on the patients' cardiovascular risk profile, which appears to be increased by more than an order of magnitude relative to persons unaffected by kidney disease. To date, sodium-glucose cotransporter 2 (SGLT-2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists have not been formally studied in the context of ESKD for cardiovascular risk reduction. Other complications of ESKD include a high incidence of infection, progressive debility and frailty, protein-energy malnutri tion, and impaired cognitive function. GLOBAL PERSPECTIVE The incidence of ESKD is increasing worldwide with longer life expectancies and improved care of infectious and

cardiovascular dis eases. The management of ESKD varies widely by country and within

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