Review Articles

Medical Progress

Dialysis Therapy

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THE population with end-stage renal disease (ESRD) in the United States is composed of more than 200,000 patients who undergo dialysis and 70,000 patients with functioning kidney transplants.[1] With the prevalence of ESRD growing at a rate between 7 and 9 percent per year, it is projected that there will be more than 350,000 such patients by the year 2010.[2] Although the overall incidence of ESRD is 242 cases per million population per year, blacks have a disproportionately high incidence (758 per million population per year), as compared with whites (180 per million population per year).[1] Diabetes is the leading cause of ESRD (approximately 35 percent of newly diagnosed cases of ESRD are caused by diabetes), followed closely by hypertension (approximately 30 percent), but among black Americans, ESRD attributed to hypertension is most common (approximately 40 percent). Other causes of ESRD include primary and secondary glomerulopathies, cystic and interstitial renal diseases, and obstructive uropathy.[1] Human immunodeficiency virus (HIV) infection is an increasingly common cause of ESRD. Officially, it accounts for only about 1 percent of cases of ESRD, but an epidemic of HIV-related ESRD may be occurring among young black men.[3] In some inner-city dialysis units, the prevalence of HIV may be as high as 38 percent.[4]

The average cost of providing care for a patient receiving dialysis is $45,000 per year. In 1995, inpatient and outpatient expenditures for ESRD, including hemodialysis, peritoneal dialysis, and transplantation, totaled $13.1 billion, with 75 percent of this cost borne by the federal government.[1] Total life expectancy for adults with ESRD is still less than a decade, a figure similar to that for other serious chronic illnesses such as cancer (Fig. 1). In the past, U.S. mortality rates have exceeded 25 percent per year, surpassing those in both Europe and Japan. Nevertheless, recent improvements in the care of patients who are dependent on dialysis have led to improved survival. In this article, we will review basic aspects of hemodialysis and peritoneal dialysis as well as important recent advances in the field.

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THE HEMODIALYSIS PROCEDURE

During hemodialysis, diffusion of solutes between the blood and a dialysis solution results in the removal of metabolic waste products and the replenishment of body buffers. Heparinized blood is pumped through a plastic dialyzer at flow rates of 300 to 500 ml per minute, while dialysate flows in the opposite direction at 500 to 800 ml per minute in order to remove waste products. Resulting urea clearance rates of 200 to 350 ml per minute effect a 65 to 70 percent reduction in the blood urea nitrogen concentration during a three-to-four-hour treatment session; the urea clearance rate also depends on the surface area of the dialyzer and the permeability of the membrane. By means of adjustments in the transmembrane pressure across the dialyzer, removal of fluid from the plasma into the dialysate can be accurately controlled.

The composition of dialysates is listed in Table 1. Bicarbonate has replaced acetate as the dialysate buffer in the United States.[6] The potassium concentration of dialysate can be varied, but 2.0 mmol per liter is usual, with the net potassium loss largely determined by the predialysis potassium concentration. Shifts of potassium from the intracellular to the extracellular space occur more slowly than removal of potassium from the plasma by dialysis; thus the total amount of potassium that can be removed in one treatment session is limited to approximately 70 to 90 mmol.[7]

In the past, a dialysate calcium concentration of 1.75 mmol per liter (3.5 meq per liter) was used to normalize the serum calcium concentration and diminish the degree of hyperparathyroidism. Elegant studies by Henrich et al.[8] identified an increase in ionized calcium as the key factor in improving myocardial contractility during routine dialysis. Currently, oral calcium salts, predominantly calcium carbonate, have replaced aluminum compounds as the phosphate binders of choice.[9] In addition, the use of oral and intravenous calcitriol to suppress parathyroid hormone has become widespread.[10] Because these improvements cause hypercalcemia to occur more frequently, the routine use of a lower dialysate

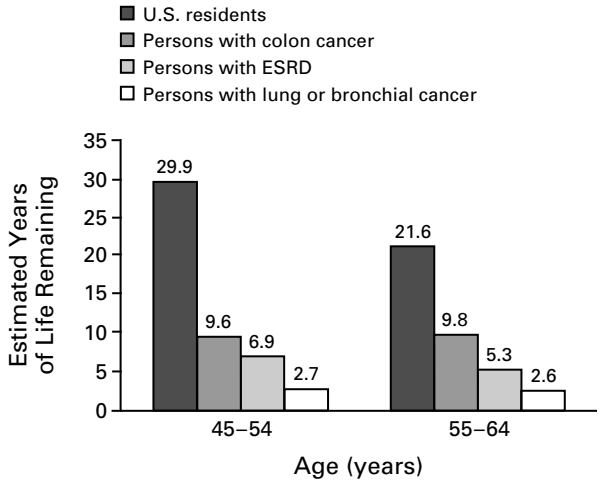

Figure 1. Life Expectancy at 45 to 54 and 55 to 64 Years of Age in the U.S. Resident Population and among Persons with Selected Chronic Diseases.

Data for the general population are for 1990, those for colon cancer are for 1983 through 1989, those for end-stage renal disease (ESRD) are for 1992, and those for lung and bronchial cancer are for 1983 through 1989. For cancer and ESRD, the ages shown are at the diagnosis of the disease. Adapted from U.S. Renal Data System,[5] with the permission of the publisher.

Table 1. Major Components of Hemodialysate and Peritoneal Dialysate.

Component*	Hemodialysate		Peritoneal Dialysate
	Range	Typical	Range
Sodium (mmol/liter)	135–155	140	130–135
Potassium (mmol/liter)	0–4.0	2.0	0
Calcium (mmol/liter)	0–2.0	1.25	0.75–1.75
Magnesium (mmol/liter)	0–0.75	0.25	0.25–0.75
Chloride (mmol/liter)	87–120	105	95–102
Bicarbonate (mmol/liter)	25–40	35	—
Lactate (mmol/liter)	—	—	35–40
Glucose (g/dl)	0–0.20	0.20	1.36–3.86†

*To convert values for calcium and magnesium to milliequivalents per liter, divide by 0.5; to convert values for glucose to millimoles per liter, multiply by 0.05551.

†These values correspond to 1.5 to 4.25 g of D-glucose monohydrate per deciliter.

calcium concentration — 1.25 mmol per liter (2.5 meq per liter) — is recommended to help prevent this complication.

A dialysate sodium concentration of approximately 140 mmol per liter is used to minimize the hypotension, cramping, nausea, vomiting, fatigue, and dizziness associated with lower dialysate sodium levels.[11] As urea is rapidly removed from the extracellular space by dialysis, an osmolar gradient is created between the extracellular and intracellular spaces. Fluid shifts result, causing both intracellular swelling and worsening of extracellular volume depletion during dialysis. These volume shifts contribute to adverse neuromuscular and hemodynamic consequences, which can be ameliorated by using dialysate with a higher sodium concentration. That a higher dialysate sodium concentration can offset osmolarity-induced fluid shifts has been confirmed by direct measurements of intracellular and extracellular volume before and after dialysis.[12] Moreover, "sodium modeling" can be used to counterbalance urea-related osmolar gradients. With this technique, an initially hypertonic dialysate sodium concentration of 148 to 160 mmol per liter is gradually lowered to isotonic levels during the treatment. In some patients, sodium modeling appears to result in an additional improvement in dialysis-related signs and symptoms, including a reduction in the frequency of hypotensive episodes.[13,14] However, not all studies have confirmed the superiority of sodium modeling to the use of a standard sodium concentration of $\geqslant$140 mmol per liter,[15] and symptoms of increased thirst with attendant weight gain between treatments negate some of the benefits of the sodium-modeling technique.[16] A dialysate glucose concentration of 200 mg per deciliter (11 mmol per liter) prevents the drop in both blood glucose and blood insulin concentrations that occurs with a glucose-free solution.[17]

Depending on the quality of the water source, water for the dialysate may be subjected to filtration, softening, and deionization, but it is ultimately purified by reverse osmosis in 98 percent of U.S. centers.[1] During the reverse-osmosis process, water is forced through a semipermeable membrane at very high pressure to remove microbiologic contaminants and more than 90 percent of dissolved ions.[18] Still, dialysate may contain low levels of bacteria or endotoxin; a maximum of 200 colony-forming units per milliliter in water purified for dialysis and 2000 colony-forming units per milliliter in dialysate is currently permitted by the Association for the Advancement of Medical Instrumentation; however, water with colony counts well below these minimally acceptable standards is recommended. Although the dialysis membrane usually prevents the passage of pyrogens or bacteria into the bloodstream, pyrogenic reactions due to contaminated dialysate still occur occasionally.[19] Careful monitoring of the water-treatment system and the dialysate must be carried out to prevent these adverse reactions.

COMPLICATIONS DURING HEMODIALYSIS

Hypotension is the most common adverse event during dialysis. Although other factors may contrib-

TABLE 2. COMMON CAUSES OF DIALYSIS-RELATED HYPOTENSION.

Ultrafiltration
Decrease in plasma osmolality
Bioincompatibility
Medication
Reflex sympathetic inhibition
Autonomic neuropathy
Temperature of dialysate
Bleeding
Electrolyte abnormalities (hypokalemia, hyperkalemia, hypocalcemia)
Acetate-based dialysate
Sepsis
Heart disease (ischemia, arrhythmias, pericardial effusion with cardiac tamponade)

ute (Table 2), ultrafiltration-induced volume depletion is the most important cause. Interestingly, some patients who are prone to hypotension undergo a paradoxical withdrawal of reflex sympathetic nervous system activity during dialysis, with a decrease in heart rate and vascular resistance and blood-pressure collapse.[20] Apart from ultrafiltration, the dialysis process itself sometimes causes hypotension. Besides the extracellular volume depletion resulting from osmolar shifts, other factors are important (Table 2). For instance, in some patients, dialysate at 37°C is associated with excess heat retention, which can cause vasodilatation and lower blood pressure. The use of a reduced-temperature dialysis bath (35°C) results in an increase in peripheral vascular resistance, elevation of plasma norepinephrine levels, improved myocardial contractility, and stable blood pressure.[21] It is particularly important to recognize that hypotensive episodes can result from coronary ischemia, arrhythmia, or pericardial effusion with tamponade. Most hypotensive episodes are successfully treated by reducing the rate of ultrafiltration, administering intravenous saline, or both.

Technical accidents and reactions to constituents of the dialyzer and to administered drugs[22] can contribute to morbidity related to dialysis. Nausea, shortness of breath, chest and back pain, and hypotension are symptoms that may be related to the first use of a new dialyzer. This first-use syndrome is particularly common with cellulose membranes and is probably related to intense complement activation.[23] Hypersensitivity reactions, with symptoms ranging from mild itching and urticaria to full-blown anaphylactic shock, can occur in two ways: as the result of allergy to the ethylene oxide used to sterilize the dialyzer, or as an adverse reaction to a specific membrane material, polyacrylonitrile. Reactions to polyacrylonitrile occur most frequently in patients taking angiotensin-converting–enzyme (ACE) inhibitors. When blood comes in contact with the polyacrylonitrile membrane, the membrane's unusually high negative surface charge stabilizes enzymes, which generate bradykinin.[24] Normally, bradykinin is quickly degraded by kininases; however, ACE inhibitors block the degradation of bradykinin, which may result in profound hypotension. Similar reactions have been reported rarely in patients taking ACE inhibitors who undergo dialysis with other types of membranes.[25] Further discussion of dialysis-related side effects can be found in two reviews.[22,26]

THE HEMODIALYSIS MEMBRANE

Two types of dialyzers are in use today. Typical hollow-fiber dialyzers are composed of bundles of capillary tubes through which blood travels, whereas other dialyzers are composed of sandwiched sheets of membrane in a parallel-plate configuration. Major advances have occurred in membrane technology with the development of more biocompatible dialyzer membranes[27,28] and of membranes that are thinner and more permeable (Table 3). High-efficiency dialyzers are dialyzers with a large surface area that are distinguished by high rates of urea clearance. High-flux dialyzers have the additional property of markedly increased hydraulic permeability, which is accompanied by an increase in diffusive permeability, particularly to solutes with molecular weights in the range of 1500 to 5000 — so-called middle molecules. High-flux dialyzers have also been defined by rates of clearance of $beta_2$-microglobulin (molecular weight, 11,800) above 20 ml per minute.

The use of large-surface-area high-efficiency or high-flux dialyzers permits high rates of urea clearance to be achieved, allows a concomitant shortening of the time required for dialysis, and offers the theoretical advantage of improved blood purification by removing the higher-molecular-weight solutes mentioned above. Furthermore, adsorption of molecules, such as $beta_2$-microglobulin, to the surface of these dialyzer membranes constitutes an additional important mechanism of blood purification.[29] Although individual programs have reported excellent survival among patients treated with high-flux dialyzers,[30,31] there are currently no data from prospective, randomized studies to support the use of such dialyzers. A study of hemodialysis, sponsored by the National Institutes of Health, that is now under way will address this issue.

Ideally, the hemodialysis membrane should not induce adverse reactions when it comes into contact with the blood; that is, the membrane should be biocompatible. Conventional dialyzers made from cellulose-based materials do induce unfavorable reactions in the blood. For instance, membrane-

TABLE 3. TYPES OF DIALYSIS MEMBRANES.

MEMBRANE TYPE	EXAMPLE MEMBRANE NAME	HIGH OR LOW FLUX	BIOCOMPATIBILITY*
Cellulose	Cuprophane	Low	−
Semi-synthetic cellulose derivatives			
Cellulose diacetate	Cellulose acetate	High and low	+
Cellulose triacetate	Cellulose triacetate	High	++
Diethylaminoethyl-substituted cellulose	Hemophan	High	+
Synthetic polymers			
Polyacrylonitrile methallyl sulfonate copolymer	PAN/AN-69	High	++
Polyacrylonitrile methacrylate copolymer	PAN	High	++
Polymethylmethacrylate	PMMA	High and low	++
Polysulfone	Polysulfone	High	++

*Biocompatibility is based on complement activation (indicated by in vivo plasma levels of C3a). The minus sign indicates that the membrane is not biocompatible, and the plus signs (+ to ++) increasing degrees of biocompatibility.

induced complement activation causes the release of C3a and C5a and causes monocytes to generate lymphokines such as interleukin-1, tumor necrosis factor α, and interleukin-6.[32] The release of these inflammatory mediators leads to such adverse consequences as vasodilatation, hypotension, fever, and activation of platelets and polymorphonuclear leukocytes (Fig. 2).

Efforts have been made to minimize these detrimental reactions by either modifying the cellulose polymer or using noncellulose-based membrane materials. Examples of polymers that can be formulated into more biocompatible membranes include acetate-substituted cellulose and noncellulose-based polyacrylonitrile, polysulfone, and polymethylmethacrylate (Table 3); membranes formulated from these polymers may also have the increased permeability discussed above. Retrospective studies have found that patients who undergo dialysis with modified cellulose or synthetic noncellulose membranes have a reduced risk of death, as compared with those for whom unmodified cellulose membranes are used.[33] It has been suggested that adverse blood–membrane interactions may therefore contribute directly to increased morbidity and mortality among patients on long-term dialysis.[34] Although this hypothesis remains unproved, about 55 percent of outpatient dialysis units in the United States use synthetic noncellulose membranes — a percentage that is steadily growing.[1] Dialyzers incorporating these new membranes are substantially more expensive than conventional dialyzers and must be reused to reduce costs. In patients with acute renal failure, membrane-induced activation of inflammatory pathways may directly prolong acute renal injury, and the use of biocompatible dialyzers may improve renal recovery and reduce mortality.[35-37]

REUSE OF DIALYZERS

Reprocessing of hemodialyzers for reuse is practiced by more than 80 percent of dialysis facilities.[1] Generally, only the dialyzer itself is reused, although some centers also reuse the blood lines. The blood and dialysate compartments are rinsed with water and then with a chemical cleaning solution. The dialyzer is then tested to ensure that more than 80 percent of the hollow fibers are still patent. Finally, the dialyzer is filled with a disinfecting agent, which is removed immediately before the next use.

Besides the cost savings, important clinical advantages of reused dialyzers over single-use dialyzers include improved biocompatibility and a decrease in the frequency of the first-use syndrome. Breach of sterility, alterations in membrane permeability, loss of structural integrity, and exposure to reprocessing chemicals are potential disadvantages of reuse; however, if reprocessing is carried out properly, the clearance characteristics of a reused dialyzer are similar to those of a new one.

Formaldehyde, peracetic acid–hydrogen peroxide, and glutaraldehyde are the most frequently used reprocessing agents, with peracetic acid–hydrogen peroxide being the most common. Each has advantages and disadvantages, but peracetic acid–hydrogen peroxide has created the most controversy, because of its possible association with higher mortality rates in some dialysis centers.[38] What had not been clarified was whether this association is due to the toxicity of the chemical sterilants or to some other variable, such as more severe coexisting illnesses among patients treated in facilities that use peracetic acid–hydrogen peroxide.

Notwithstanding this concern, reuse has been shown to be safe in a number of studies[39,40]; some studies report an overall reduction in mortality

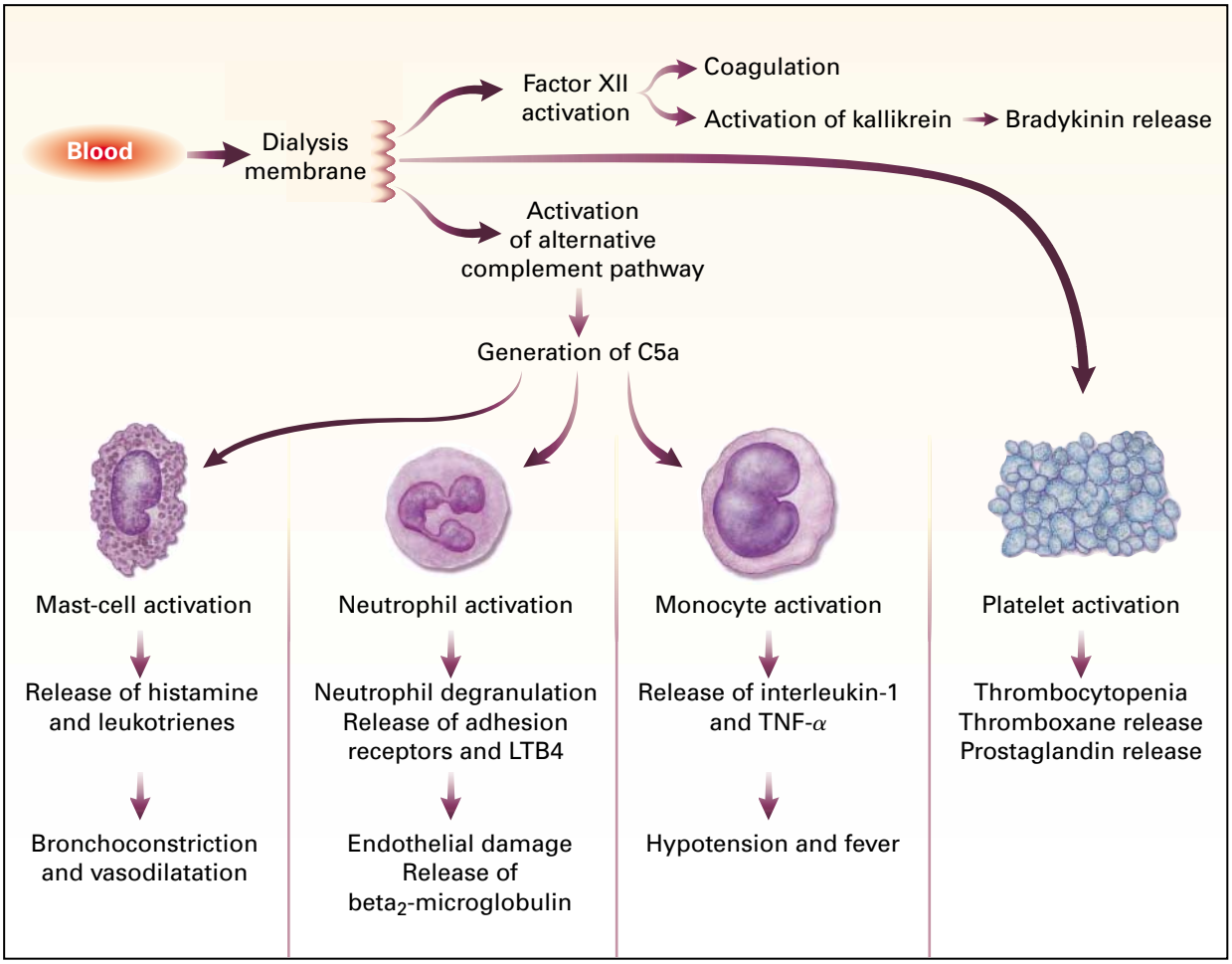

Figure 2. Pathways Involved in Blood–Membrane Interactions.
LTB4 denotes leukotriene B4, and TNF-α tumor necrosis factor α.

among patients treated with reused dialyzers.[41] Because of the lower cost, good overall safety record, and improved membrane biocompatibility, reuse will continue to be an appropriate adjunct to dialytic therapy. However, to avoid potential adverse consequences, careful attention must be paid to ensure that reprocessing and reuse follow the guidelines of both sterilant manufacturers and the Association for the Advancement of Medical Instrumentation.[42]

ACCESS FOR DIALYSIS

Obtaining and maintaining adequate access to the circulation remains a major impediment to the long-term success of hemodialysis. The fistula, conduit, or catheter (see below) through which blood is obtained for hemodialysis is often referred to as a "dialysis access." After initial placement, about $4,000 and three hospital days per patient per year are spent maintaining access for dialysis; moreover, hospitalizations related to problems with access may be increasing.[43,44] The placement of large needles (typically 15 gauge) is required to remove blood and to return it after it has passed through the dialyzer. A large, thick-walled fistula can be created by shunting blood from an artery to a vein; the result is the growth and thickening of the venous wall, which then tolerates repeated cannulation. The Cimino–Brescia fistula, in which the cephalic vein is anastomosed to the radial artery, is preferred because its two-year survival rate is higher than 75 percent. Many remain patent for several years.[45] Unfortunately, in the United States a fistula is used for access in less than 30 percent of cases.

Alternatives involving the interposition of prosthetic graft material, such as polytetrafluoroethylene, between an artery and a vein have a two-year complication-free survival rate of 30 percent; however, surgical or radiologic intervention can increase

the rate of patency to 60 percent at two years.[45] These procedures are costly.[44] The most common access-related complication is thrombosis due to intimal hyperplasia, which results in stenosis proximal to the venous anastomosis. The mechanism of smooth-muscle-cell hyperplasia that causes these anatomical abnormalities is an area of active research.[46] Stenosis in a dialysis access can also cause recirculation of blood, which diminishes the effectiveness of the prescribed treatment. Other complications related to access include infection, the formation of aneurysms and pseudoaneurysms, and ischemia of the arm.

When dialysis is urgently required, a double-lumen dialysis catheter is used. Insertion of the catheter into the subclavian vein has fallen into disfavor because such catheters are associated with a high incidence of venous stenosis or thrombosis, which can interfere with the future creation of an arteriovenous fistula or graft in the ipsilateral arm or which may cause chronic edema of the arm. Insertion into the jugular vein is becoming the method of choice because it seems to result in less central venous injury and is a safe procedure, especially when done under ultrasound guidance.[47] Temporary access can be used for two to three weeks, but clotting, low blood flow, and infection limit the life of the catheter. Because of their ease of placement, femoral-vein catheters can be inserted in patients who have respiratory distress or coagulopathy, or who require only one or two dialysis treatments. Implantation of a dual-lumen cuffed catheter is a good option for patients who have delayed recovery from acute renal failure, who require access for dialysis until a fistula matures, or who lack any other suitable site for graft placement. If carefully maintained, almost half of these catheters remain functional at one year.[48]

ADEQUACY OF HEMODIALYSIS

Determining the adequacy of dialysis therapy requires more than routine laboratory studies; malnourished and anorectic patients will make less urea and have a smaller muscle mass with deceptively low blood urea nitrogen and creatinine concentrations. Measurement of the "delivered dose" of dialysis has therefore focused on the removal of urea, an easily measured surrogate marker for uremic toxins. The two most widely used measures of the adequacy of dialysis are calculated from the decrease in the blood urea nitrogen concentration during the treatment: the urea-reduction ratio, and KT/V.[49] KT/V is a dimensionless index based on the urea clearance rate, K, and the size of the urea pool, represented as the urea-distribution volume, V. K, the sum of clearance by the dialyzer plus renal clearance, is multiplied by the time spent on dialysis, T. Currently, a urea-reduction ratio of 65 percent and a KT/V of 1.2 per treatment are minimal standards for adequacy; lower levels of dialysis treatment are associated with increased morbidity and mortality.[50,51] What constitutes an "optimal" dose of dialysis, above which no further improvement in survival or well-being can be achieved, is not known. Retrospective data show that survival rates do not rise as the urea-reduction ratio rises above 70 percent, or as KT/V rises above 1.3.[52] A prospective, randomized trial, sponsored by the National Institutes of Health, is under way to investigate the relative effects on dialysis-related morbidity and mortality of high and usual values for KT/V and of high-flux and low-flux membranes.[53]

The duration of each dialysis treatment may be an important independent factor determining efficacy, but it is hard to separate a longer dialysis treatment from a higher dose of dialysis. For example, longer treatment could facilitate removal of larger molecules as well as better control of extracellular volume and blood pressure. The National Cooperative Dialysis Study,[54] a large-scale, randomized study of the adequacy of dialysis, found a strong trend toward increasing morbidity with decreasing dialysis time. Some recent retrospective data also suggest an increase in mortality among patients whose dialysis treatments last less than 3.5 hours,[55] whereas other studies have not confirmed an independent effect of the length of treatment.[51,52] French patients receiving extremely long treatments (eight hours three times a week) have a notably high survival rate of 70 percent at 10 years.[56,57] Besides removing more waste products, longer dialysis improved blood-pressure control. However, since average KT/V values were also high in this study (1.71), it is not possible to separate the effects of time and of dose on the outcomes in this group of mostly nondiabetic patients. Factors that may adversely affect the adequacy of dialysis include recirculation in the dialysis catheter, inadequate blood or dialysate flow rates, poor-quality reprocessing of the dialyzer, and skipping or early termination of dialysis treatments.

MORTALITY AMONG PATIENTS ON DIALYSIS

On average, the yearly mortality among patients being treated with dialysis is nearly 25 percent.[1] Deaths are due mainly to cardiovascular diseases and infections (approximately 50 percent and 15 percent of deaths, respectively). Hypertension continues to be a major risk factor for cardiovascular disease; recent surveys show that more than 50 percent of patients undergoing outpatient hemodialysis have a systolic blood pressure before dialysis of more than 150 mm Hg.[58] Along with extracellular volume expansion, the administration of recombinant human erythropoietin may also worsen blood pressure in about 25 percent of the patients who receive it. When anemia is corrected, cardiac output is reduced, and there is a secondary increase in both pe-

ripheral vascular resistance and blood viscosity.[59] Nevertheless, recombinant human erythropoietin has been reported to reduce left ventricular mass by about 20 percent in patients with left ventricular hypertrophy who are undergoing dialysis.[60] Other common risk factors for cardiovascular disease include depressed high-density lipoprotein cholesterol levels, coronary-artery calcification, diabetes, and left ventricular hypertrophy.

Malnutrition has been estimated to be present in up to 50 percent of patients with ESRD and to be independently associated with increased morbidity and mortality.[61] In fact, a depressed serum albumin level, reflecting poor nutritional status, is the laboratory abnormality most strongly correlated with an excess risk of death in this population.[51] Nutritional issues in the care of patients undergoing dialysis have recently been reviewed.[61-63]

The rates of death among patients undergoing dialysis in the United States are 25 to 50 percent higher than those in Japan and Europe.[64] Acceptance of patients who are older and sicker and who have more coexisting conditions for dialysis in the United States, underreporting of adverse outcomes of ESRD in Europe, and a low rate of kidney transplantation in Japan, which results in a larger percentage of healthier patients remaining on dialysis, may explain some of the differences.[64] Reimbursement for dialysis in the United States is only 50 to 66 percent of that in Japan and Germany. Despite increases in labor costs, the average Medicare reimbursement per dialysis treatment has actually fallen, from $135 in 1973 to $126 in 1995. Reduced payments have generated intense pressure to cut costs; the results have been lower staff-to-patient ratios, widespread reuse of dialyzers, shorter dialysis treatments,[55] and lower doses of dialysis.

Nephrologists have responded, however, by improving both the delivery of dialysis services and the outcomes of patients over the past several years. The average urea-reduction ratio rose from 60 percent to 67 percent between 1990 and 1996,[65] and dialysis times have increased. Concomitantly, the adjusted mortality rate (the number of deaths per 100 patient-years at risk) fell from 25.5 in 1988 to 21.8 in 1995.[1] Unfortunately, more than 30 percent of patients still have a urea-reduction ratio of less than 65 percent (and approximately 25 percent of patients have a KT/V of less than 1.2), indicating the need for improvement in the delivered dose of dialysis.[65] In response to these dismal statistics, the National Kidney Foundation has called for an effort to reduce the annual overall mortality rate to 15 percent[66] and has published the Dialysis Outcomes Quality Initiative, a set of guidelines based on the literature and the opinion of experts on ESRD.[67,68] Ultimately, these guidelines should improve the care of patients undergoing dialysis by establishing uniform standards.

PERITONEAL DIALYSIS

Because peritoneal dialysis is simple to perform, it has gained worldwide popularity. Ninety-one percent of patients who require dialysis in Mexico, 50 percent of those in the United Kingdom, 38 percent of those in Canada, and 16 percent of those in the United States who need dialysis participate in a peritoneal dialysis program.[1,69] Typically, a plastic catheter is implanted in the peritoneal cavity and anchored in the subcutaneous tissues. A dialysis solution that contains physiologic amounts of sodium, calcium, magnesium, and (usually) lactate as the buffer (Table 1) is infused through the catheter into the peritoneum and remains in place for several hours. During that time, diffusive solute transport occurs across the peritoneal membrane until fresh fluid is exchanged for the old. Glucose added to the dialysate in concentrations of 1.5 to 4.25 percent provides an osmolar gradient that permits ultrafiltration of fluid. Approximately 1 ml of peritoneal fluid per minute is absorbed through the diaphragmatic lymphatics, limiting net ultrafiltration.

Frequently, continuous ambulatory peritoneal dialysis uses four exchanges of 2 liters each of dialysate daily, with an expected drainage volume of approximately 10 liters, including ultrafiltration; 60 percent of patients are currently treated according to this protocol. Assuming complete equilibration of urea between blood and dialysate, this regimen provides approximately 10 liters of urea clearance per day, or 7 ml per minute. In addition, residual renal urea or creatinine clearance of only a few milliliters per minute can contribute substantially, since each additional 1 ml per minute of clearance results in an extra 10 liters of clearance per week. Because residual renal function diminishes markedly during the first few years of dialysis therapy, the delivered dose of peritoneal dialysis may need to be augmented.[70] The recent Canada–USA study has aroused serious concern that many patients may currently be receiving inadequate peritoneal dialysis.[71] Weekly KT/V values under 2.2 or a creatinine clearance rate below 65 liters per week per 1.73 m^2 of body-surface area are associated with a progressive increase in mortality. Unless they have substantial residual function, patients weighing more than 60 kg usually require drainage volumes of more than 10 liters per day to achieve adequate clearance.[72]

To increase clearance, the amount of fluid and the frequency of exchange can be increased, but both may be limited by the patient's comfort and convenience. Automated peritoneal dialysis, in which a mechanized cycler infuses and drains peritoneal dialysate at night, is used in one third of patients undergoing peritoneal dialysis. When combined with one or two daytime exchanges, automated peritoneal dialysis can provide adequate clearance for most patients.

About one month after a patient begins peritoneal

dialysis, a peritoneal equilibration test is performed to help select an appropriate dialysis regimen.[73] During dialysis with a standard 2.5 percent glucose concentration and an exchange volume of 2 liters, urea, creatinine and glucose transport are measured. Ratios of urea, creatinine, and glucose in dialysate to the values in serum are compared with those in a standard population; transport is categorized as high, high-average, low-average, or low. After four hours, for instance, the concentrations in dialysate in a patient with high-average transport will be about 95 percent of the blood urea nitrogen concentration and 75 percent of the blood creatinine concentration. On the other hand, the dialysate of a patient with low transport will contain only about 75 percent as much urea nitrogen and 45 percent as much creatinine as the blood. As a result of these low transport characteristics, a patient may be precluded from undergoing peritoneal dialysis because dialysis cannot achieve adequate clearance.

The choice between peritoneal dialysis or hemodialysis for a specific patient depends on many factors. Peritoneal dialysis is ideal for patients who wish to retain an active lifestyle, since dialysis sessions can be scheduled around work or school hours and overnight automated peritoneal dialysis can allow freedom from multiple daytime exchanges. Because of the more consistent control of extracellular volume and blood pressure,[74] peritoneal dialysis may be favored for patients with congestive heart failure or unstable angina who may not be able to tolerate the rapid fluid shifts or blood-pressure swings that can accompany hemodialysis sessions. Peritoneal dialysis is also indicated for patients with extensive vascular disease that prevents the placement of a catheter for vascular access.[67]

Hemodialysis is preferred for patients with mechanical problems such as abdominal hernias or adhesions that interfere with the peritoneal dialysis procedure and for those with active gastrointestinal conditions, including inflammatory bowel disease or diverticulitis. Patients for whom peritoneal dialysis is inadequate, such as relatively large patients or those with low peritoneal clearance or ultrafiltration rates, and those who have multiple episodes of peritonitis related to peritoneal dialysis should undergo hemodialysis.[67] In addition, patients who are unable to be trained to perform peritoneal dialysis exchanges or who cannot accept the responsibility for self-care are better suited to treatment with hemodialysis at a dialysis center. Often the choice of the type of dialysis depends on subjective factors, such as the patient's preference or the physician's training and experience.

COMPLICATIONS OF PERITONEAL DIALYSIS

Peritonitis is the most common serious complication of peritoneal dialysis. Patients present with abdominal pain, fever, and cloudy peritoneal dialysate containing more than 100 white cells with more than 50 percent polymorphonuclear leukocytes. Gram's staining detects organisms in only 10 to 40 percent of cases, but it may lead to the early detection of gram-negative or fungal peritonitis. Recent improvements in dialysis tubing have reduced the incidence of peritonitis[75]; still, peritonitis occurs about once per 15 patient-months of dialysis.[76] For reasons that are unclear, black patients have higher rates of peritonitis than other groups.[77] The most common organisms causing peritonitis are gram-positive cocci, followed by gram-negative rods.

Empirical regimens containing vancomycin and either a third-generation cephalosporin or an aminoglycoside are often used until a specific organism can be targeted. Regimens based on first-generation cephalosporins are now being reemphasized, because vancomycin-resistant enterococci are emerging.[78] Currently, cefazolin or cephalothin (500 mg per liter in the first exchange as a loading dose, followed by 125 mg per liter in each subsequent exchange) plus an aminoglycoside such as gentamicin, tobramycin, or netilmicin (8 mg per liter in the first exchange, followed by 4 mg per liter in each subsequent exchange) is recommended as initial empirical therapy for peritonitis related to peritoneal dialysis.[78] Ultimately, the most effective regimen must be based on the local bacteriology of peritonitis. (Recommendations for the treatment of peritonitis are available on the Web site of the International Society for Peritoneal Dialysis at http://www.ispd.org/.) Instilled intraperitoneally, many antibiotics achieve excellent blood concentrations; the addition of heparin (500 to 1000 U per liter) prevents the formation of fibrin until the fluid is clear.

Recurrent or persistent peritonitis requires the removal of the catheter. Most episodes of peritonitis do not seriously affect the efficiency of the peritoneal membrane.[79] Yeast peritonitis presents a special problem; although some patients respond to a combination of fluconazole and flucytosine, catheter removal is often necessary.[80]

Infections at the exit site of the dialysis catheter or in the subcutaneous tunnel can be treated with oral antibiotics and local care,[81] but most tunnel infections require that the catheter be removed. Infected exit sites and nasal carriage of organisms such as *Staphylococcus aureus*[82] serve as reservoirs of pathogens that can cause peritonitis when breaks in aseptic technique occur. Additional sources of peritonitis include hematogenous seeding of the peritoneal cavity and migration of bacteria down the catheter tunnel, across the intestinal wall, or through the female reproductive tract.

Other complications include losses of amino acids and albumin (5 to 15 g per day)[83] plus absorption of glucose, resulting in hypertriglyceridemia or weight

gain. In patients with diabetes, insulin can be infused with the dialysate, a method that permits very tight regulation of blood sugar.[84] Leakage of dialysis fluid into the pleural space is indicated by an extremely high glucose concentration.

COSTS AND SURVIVAL OF PATIENTS UNDERGOING PERITONEAL DIALYSIS

Survival rates among patients treated with hemodialysis or peritoneal dialysis are similar,[85] but rates of hospitalization are higher among patients undergoing peritoneal dialysis, who average 16.6 days of hospitalization per year, as compared with 14.2 days for patients treated with hemodialysis.[1] Recent reports suggesting higher mortality among patients over 50 who have diabetes and are undergoing peritoneal dialysis rather than hemodialysis are a matter of concern.[85,86] In these studies, however, differences in the severity of coexisting conditions between the patients on peritoneal dialysis and those on hemodialysis may not have been adequately controlled for. Further investigation will therefore be required before any restrictions on peritoneal dialysis in this population are considered.

The costs of caring for patients being treated with hemodialysis ($46,000 per year) and peritoneal dialysis ($41,000 per year) are similar.[1] The costs of peritoneal dialysis are rising, however, as cycler-based regimens that use large volumes of dialysate become more widely used.

SUMMARY

The number of patients with ESRD has increased markedly over the past 10 years and continues to grow at a rate of 7 to 9 percent per year in the United States. Improvements have occurred in dialysis machines, in water-purification systems, and in the composition of dialysate and the performance and biocompatibility of dialyzers. In addition, the importance of routinely measuring the adequacy of dialysis by means of such indexes as KT/V has become clear. Despite these improvements, mortality (nearly 25 percent per year) and morbidity among patients treated with dialysis, particularly mortality related to cardiovascular diseases and morbidity resulting from complications of vascular and peritoneal access, continue to be unacceptably high. We hope that future advances will continue to address these problems and lead to longer and healthier lives for patients treated with dialysis therapy.

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