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Hemodialysis

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DEFINITION OF DIALYSIS

Dialysis is defined as the bidirectional movement of molecules across a semipermeable membrane. During dialysis, solute (molecules dissolved in a liquid) can be removed and subsequently discarded from the body. If this process takes place across an artificial membrane which is in contact with the blood during extracorporeal circulation it is called hemodialysis. Hemodialysis can be performed in treatment centers which specialize in the delivery of dialysis or, alternatively, it can be performed at home.

The ultimate goal of dialysis is to replace the function of the kidney to alleviate signs and symptoms of uremia and rehabilitate patients with end-stage renal disease (ESRD) so that they may lead productive lives. Thus far, methods of renal replacement outside of kidney transplantation have focused on mechanical methods to purify the blood of toxins, balance fluid and electrolyte levels, and correct acid–base disturbances. The downside to the currently available forms of mechanical renal replacement is they do not address the many other important endocrine and immunologic functions of the kidney. Therefore, despite our many technological advances in the field, dialysis by mechanical means does not completely replace kidney function but rather serves as a substitute.

HISTORY

In 1913 Abel, Rowntree, and Turner at Johns Hopkins University performed the first dialysis on dogs using cellulose trinitrate membranes and hirudin for anticoagulation.[1] The first human hemodialysis was performed by Hass in 1924 in Germany.[2] Hass used the radial carotid artery and portal vein for blood access. In 1943 Kolff developed the rotating drum dialyzer in Holland. Kolff used cellophane membranes (sausage casings) and an immersion bath and reported on the first patient to recover from acute renal failure after treatment. Further work by Kolff would lead to the twin coil dialyzer in 1955.[3] In 1946, Alwall developed a system for applying hydrostatic pressure to achieve ultrafiltration

allowing for fluid removal from the circulation during dialysis. In 1960 Kiil developed a flat plate dialyzer that could easily be dismantled and reassembled. The Kiil dialyzer consisted of boards of polypropylene and used more permeable cellulosic cuprophane membranes. Due to low internal resistance, a blood pump was not necessary. Meanwhile, Scribner and Quinton came up with a method to heat Teflon to bend it into a U shape. This allowed a connection between the radial artery and cephalic vein in the forearm that could be used for dialysis access.[4] Prior to this development, dialysis therapy was largely reserved for the treatment of acute renal failure in a few specialized inpatient centers. The Scribner-Quinton shunt was a crucial step that made long-term dialysis for chronic renal failure a reality. Dialysis technology was further refined in 1963 when Babb developed a central proportioning system for the delivery of dialysate to multiple patients. Access to the bloodstream was improved in 1966 when Cimino and Brescia developed the native arteriovenous fistula. More recent times have seen the development of improved technology such as ultrafiltration control, dialysate proportioning systems allowing the use of bicarbonate based dialysate, improved safety mechanisms, more biocompatible dialysis membranes, high flux dialyzers, simplified home dialysis technologies, and even development of wearable artificial kidneys. Advances by researchers and industry coupled with financial support through government subsidized care have led to the expansion of dialysis as we know it today and have solidified chronic hemodialysis as a feasible life-sustaining treatment for thousands of patients who would otherwise be facing terminal ESRD.

EPIDEMIOLOGY

According to the United States Renal Data System (USRDS) atlas of ESRD report,[5] in the year 2008 there were 109,832 new ESRD patients. The rate of ESRD incidence reached 322 per million population for hemodialysis, 20.7 for peritoneal dialysis, and 7.9 for transplant. In the United States, hemodialysis remains the most common form of chronic renal replacement therapy. Hemodialysis as the modality of renal replacement

therapy accounted for the bulk of the incident dialysis patients with peritoneal dialysis initiated in only 6,577 patients and renal transplant in only 2,644. Trends over the past few decades have seen increases in percentages of incident hemodialysis patients and decreases or plateauing of the incident patients on peritoneal dialysis. In-center hemodialysis therapies were more frequently utilized with more than 347,000 patients receiving hemodialysis and only 3,826 performing home hemodialysis.

Hemodialysis Outcomes: Morbidity and Mortality

Patients with ESRD are frequently hospitalized for medical complications. Numbers from the USRDS reveal 12.8 hospital days per patient year on hemodialysis (HD), compared with 13.3 hospital days per patient year on peritoneal dialysis (PD) and 5.9 for transplant patients. Over the last few years, hospital admission rates have remained the same for HD (approximately two admissions per year) and declined 9.6% in PD patients. Women appear 16% more likely to be hospitalized than their male counterparts. Common causes for admission to the hospital are cardiovascular complications, infectious complications, and access complications. Admission rates for infection (pneumonia, bacteremia) have risen 19% whereas admission rates for cardiovascular disease have remained similar and admissions for vascular access issues have fallen as more procedures are now performed in the outpatient setting.[5]

ESRD patients have high mortality rates. Adjusted rates for all-cause mortality in dialysis patients are approximately six to eight times higher than in the general population. Five-year probability of survival (1999–2003) among incident ESRD patients was 0.39. This improved 8.4% when compared with 1994–1998. The greatest amount of improvement was seen in the PD population with a 17.6% increase compared with an 8.4% increase in HD patients. There is a large racial disparity in risk for death when comparing Caucasians (21%), African Americans (17%), and other racial groups (14%), with minorities having a clear survival advantage.[5]

MECHANISMS OF SOLUTE REMOVAL

Removal of solute (molecules dissolved in liquid, such as urea) from solvent (the liquid which contains the molecules, such as the bloodstream) is the major function of dialysis. Removal of solute from the body can be accomplished by diffusion, convection, or osmosis.

Diffusion

Diffusion is the movement of particles from areas of higher concentration to areas of lower concentration through random motion. In the example of hemodialytic therapy, diffusion is the driving force that is responsible for the movement of solute dissolved in blood (such as urea) across the membrane of the dialyzer to the area of lower concentration, the dialysate (Fig. 84.1).
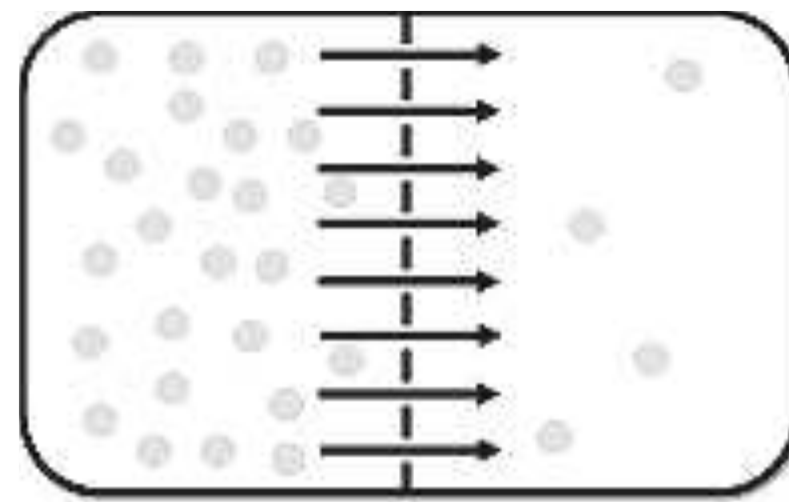
FIGURE 84.1 Diffusion. If two compartments are separated by a semipermeable membrane (*dashed line*) solute tends to move down a concentration gradient from areas of high concentration to areas of lower concentration. For example, in the case of hemodialysis, solute (e.g., urea) dissolved in solvent (blood) passes the semipermeable membrane (dialyzer) to an area of lower solute concentration (dialysate).

Convection

Convection is the movement of molecules within fluids, also known as "solute drag." Convection occurs in hemofiltration when a transmembrane pressure is applied to the blood side of a membrane forcing plasma water through the pores in the membrane. Any solute dissolved in the plasma water smaller than the membrane pore size is subsequently transported (Fig. 84.2). The ability for a particular solute to be removed through convection is dependent on the solute size and the membrane pore size, compared to the diffusive process where removal is also dependent on concentration gradients. The sieving coefficient describes the membrane passage of a particular solute during convection and can be determined by dividing the concentration of the solute in the effluent by the concentration in the blood. For example, urea (small molecule) generally will have a sieving coefficient of 1 which indicates that the
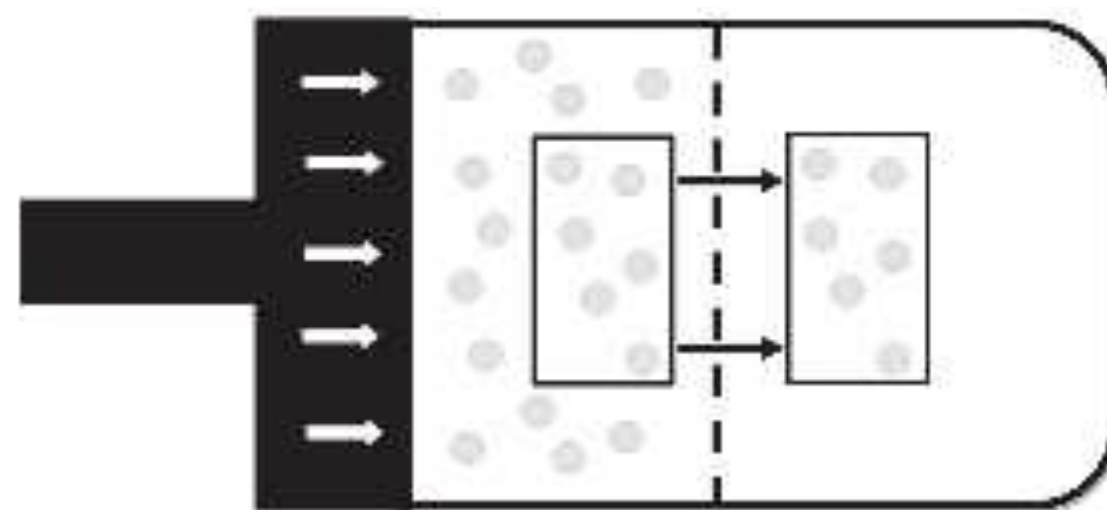
FIGURE 84.2 Convection is the movement of molecules within fluid. In the case of hemofiltration, solute (e.g., urea) is dissolved in plasma water. If a hydrostatic pressure is applied to one side of the semipermeable membrane, water will be forced through the pores of the membrane bringing along the solute which is dissolved in it if the solute particles are smaller than the membrane pore size. This is also known as solute drag.

concentration in the blood is equal to the concentration in the effluent whereas albumin, a molecule which is too large to pass traditionally used membranes, will have a sieving coefficient of 0.

Osmosis

Osmosis is the movement of water molecules across a semipermeable membrane down a water gradient. In other words, osmosis is the movement of water across a semipermeable membrane from an area of low solute concentration to an area of high solute concentration. A clinical example of osmosis is PD where a high dextrose containing fluid is instilled into the peritoneal cavity which creates a osmotic gradient moving water into the peritoneal space.

Ultrafiltration

Ultrafiltration is the movement of fluid across a semipermeable membrane which is caused by a pressure difference. This pressure difference can be a result of osmotic pressure (as is the case with PD) or hydrostatic pressure (as is the case with HD). Ultrafiltration is a form of convective clearance in traditional HD but does not typically account for a significant volume of clearance.

Concept of Clearance in Dialysis

The clearance of a solute is defined as the volume from which the solute is completely removed in a specified period of time and is often expressed in units of milliliters per minute. In HD, the processes of diffusion, convection, and, to a lesser extent, membrane adsorption each contribute to the total clearance of solute. Numerous factors affect the clearance of solute in dialysis including the concentration differences between the blood and dialysate, the rate at which blood is delivered to the dialyzer, and the intrinsic properties of the dialyzer such as surface area, permeability, membrane thickness, pore size, and solute size.

Concentration is the ratio of the amount of solute in a given solvent volume. The clearance of a solute is dependent on the concentration of the solute. It is also important to recognize the relationship between concentration and generation of a solute. Both generation and removal of a solute from the body will affect the concentration and therefore has an effect on clearance. The concept of mass balance and the relationship between concentration, generation, and clearance forms the basis for many of the equations that have been derived to assess the adequacy of dialysis (discussed in more detail below).

DIALYSIS TECHNIQUE

The HD equipment typically consists of a tubing set, dialyzer, and the hemodialysis machine. The tubing set connects the patient's source of blood access to the dialyzer which contains the semipermeable membrane. The entire circuit is connected to the dialysis machine. After negative pressure is applied to the access by a mechanically driven blood pump on the dialysis machine, blood circulates through the arterial limb of the blood tubing and past the dialysis membrane. It is then sent through the venous limb of the tubing and back to the patient via the vascular access (Fig. 84.3).
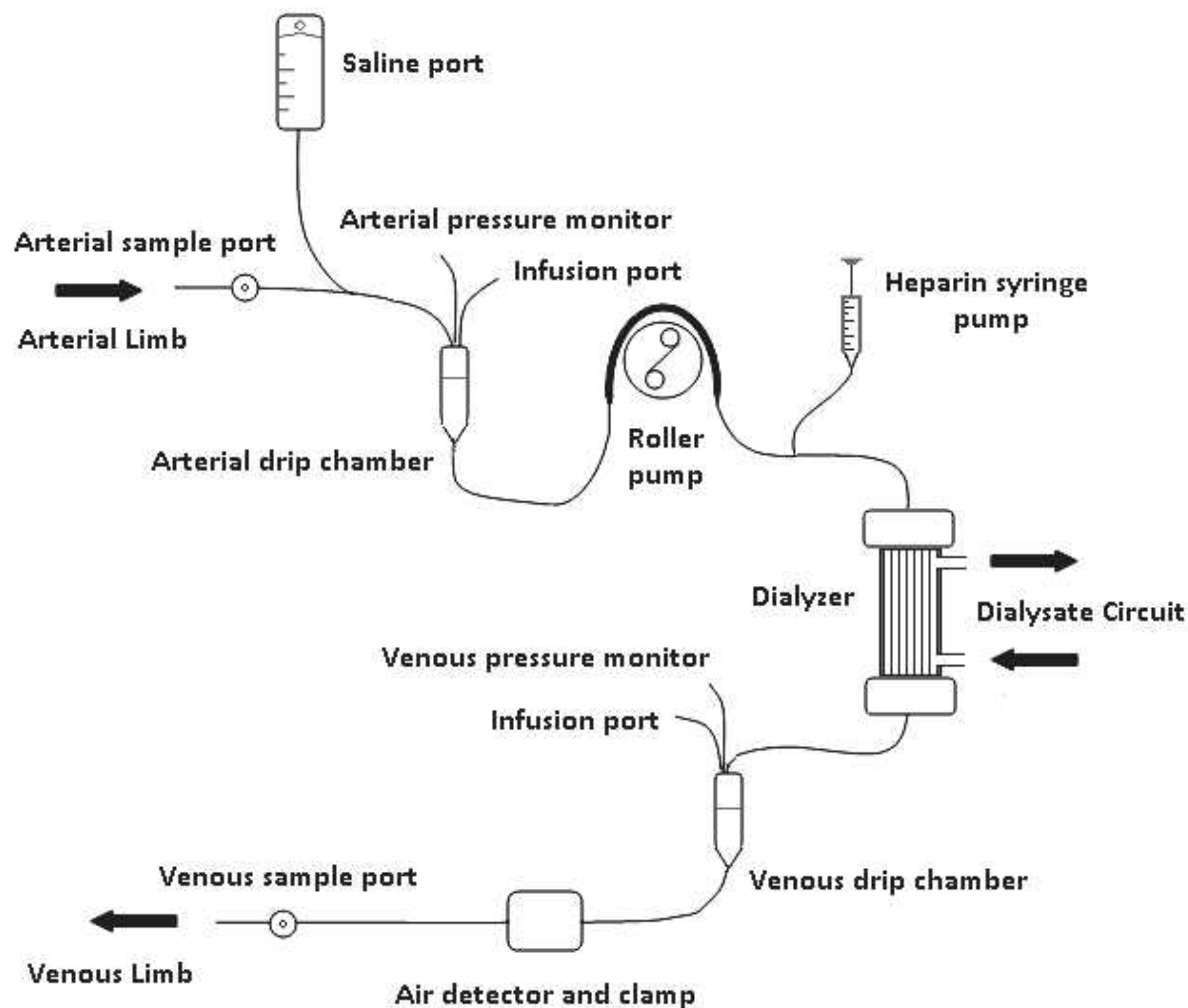
Blood Access

Ideally HD is performed through a connection between the arterial circulation and the venous system in the form of an arteriovenous fistula (AVF) or an arteriovenous graft (AVG). The AVF is the preferred form of access. The use of the arteriovenous circulation allows intradialytic blood flows that can easily support achieving adequate solute clearance during the dialysis procedure. In the case of the AVF and AVG, needles are placed into the access during each dialysis session. Hemodialysis needles range in size but usually are 17 to 15 gauge with larger needles (15 g) being used in stable accesses with lower risk of bleeding and smaller needles (17 g) used in situations of small diameter access, developing accesses (especially for first cannulation), or higher bleeding risk. Typically two needles are placed in the access, one needle for the inflow to the dialysis machine, and the other needle for the outflow from the dialysis machine. Single needles with a dual lumen are also available but are rarely used due to a higher degree of access recirculation.

The buttonholing technique of dialysis access is sometimes used in patients with an AVF. Through this technique, the AVF is accessed in the same location at the same angle during each dialysis session, preferably by the patients themselves or by the same dialysis caregiver. Over time, the patient develops a scarred tract that eventually allows for the placement of blunt needles down the tract after removal of the scab that serves as a plug. Once established, buttonholes have the advantage of ease of obtaining access, less pain, reduced aneurysm formation, and reduced incidence of hematoma formation.[6] The downside of buttonholes is higher rates of infection, particularly, Staphylococcus aureus bacteremia. This increased risk may be mitigated by diligent topical care and the use of agents such as mupirocin.[7]

Catheters placed in the central veins can also be used for dialysis access. Typically these catheters are placed within the internal jugular or femoral vein. The subclavian vein position is associated with greater rates of central stenosis and should be avoided if possible.[8,9] Catheters are less desirable than AVF or AVG due to increased rates of infection,[10] clotting,[11] recirculation,[12] poor blood flows,[13] and higher potential to cause stenosis of the central veins.[14] Catheters that are tunneled and cuffed have lower rates of infectious complications than noncuffed, nontunneled catheters, and, when possible, are preferable in patients

FIGURE 84.3 Drawing of a hemodialysis circuit. Blood flows from the patient access into the arterial limb of the circuit, passes the dialyzer, then is delivered to the venous limb and back to the patient. Note that the location of the arterial drip chamber, which is drawn prepump in this picture, is occasionally postpump in some designs. The location of the infusion ports and sample ports can vary as well.

who have an anticipated need for dialysis that is longer than 2 weeks.[15]

Blood Circuit

The blood circuit is composed of tubing which carries blood from the patient access through the dialyzer and back to the patient. There are two main portions of the dialysis circuit: the arterial and venous limbs. The arterial limb carries blood under negative pressure provided by the blood pump from the access to the dialyzer. It usually includes a drip chamber which serves to remove air from the dialysis circuit. The arterial pressure monitor is frequently located at the top of the arterial drip chamber and blood flows out of the bottom of the drip chamber toward the blood pump. The blood pump is commonly designed in a circular roller fashion that squeezes segments of blood through a portion of arterial tubing as the rollers apply pressure to the line. This configuration leads to an irregular vacillating flow of blood through the circuit. The portion of the arterial limb tubing that comes in contact with the rollers from the pump is reinforced to withstand the extra stress applied by the rollers. The blood pump typically operates at speeds ranging from 150–500 mL per min. There is usually a branching line that connects to an automated heparin syringe pump, typically located after the blood pump.

After the blood passes through the arterial circuit it is delivered to the dialyzer. Post dialyzer the blood enters the venous circuit. Similar to the arterial limb, the venous limb also has a drip chamber and pressure monitor. Furthermore, the venous limb has an air detector and a portion of line which passes through an automated clamp. If air is detected in the venous line, the clamp will be triggered, preventing delivery of air to the patient. This portion of equipment is crucial as an air embolus is a potentially lethal complication. The arterial and venous pressure monitors play an important function in monitoring the progress of dialysis. Arterial pressures are typically negative with pressures ranging from −80 to −200 mm Hg. Venous pressures are usually positive, ranging from 50 to 250 mm Hg. Pressures that fall outside of the acceptable ranges should trigger machine alarms that will stop the blood pump. Tables 84.1 and 84.2 list potential reasons for arterial and venous pressure alarms, respectively.

The ideal tubing set has a smooth inner surface to reduce blood turbulence, is biologically compatible to prevent allergic reactions, and does not narrow or kink. Care should be taken to ensure that the tubing is rinsed completely prior to initiation of dialysis especially in the case of tubing that is sterilized with ethylene oxide. Failure to do so can result in an allergic reaction. For example, if there is a faulty or

84.1	Arterial Pressure Alarms

Arterial Pressure (normal −80 to −200)	Potential Problem
0 to −80	Pump speed too low Arterial needle dislodged Saline line open
−200 or more negative	Kink in line or catheter ports Catheter or needle placement suboptimal Clotting of access Vasospasm Infiltration Low patient blood pressure

84.2	Venous Pressure Alarms

Venous Pressure (normal 50–250 mm Hg)	Potential Problem
<50	Pump speed too slow Postpump clotting (clotted dialyzer) Dialyzer membrane rupture Kink in line (postpump, prepressure monitor) Venous needle or catheter dislodged
>250	Access stenosis Kink in line or catheter (postpressure monitor) Catheter or needle placement suboptimal Venous drip chamber clotting Clotting of access Access hematoma formation Access vasospasm Bad arm positioning Pump speed too fast

misplaced clamp on a side branch of the circuit, such as the heparin branch, ethylene oxide can backfill into the tubing during rinsing and later is delivered to the patient.

Shear stress applied to blood in dialysis tubing has been associated with hemolysis and should be avoided. Narrowing or kinking of the blood tubing can cause hemolysis.[16] In the past faulty tubing sets were linked to outbreaks of hemolysis in patients on dialysis.[17] High blood flows using small gauge needles,[18] excessively negative arterial pressures, and misalignment of the blood tubing with the blood pump can theoretically cause hemolysis as well.

Dialyzer

The dialyzer is a crucial portion of the hemodialysis apparatus that provides a site for solute transport. Dialyzers are composed of blood and dialysate compartments. These two compartments are separated by a semipermeable membrane and form a closed self-contained system. Although dialysis membranes initially used the parallel plate design, the hollow fiber design is now used almost exclusively (Fig. 84.4). Hollow fiber dialyzers consist of a cylindrical plastic shell. At the opposing ends of the cylinder are headers which provide ports for the blood flow. Blood flows through the header to the potting compound which encases thousands of tiny hollow fibers through which the blood flows. On the side of the cylinder are two ports for the dialysate connections. Blood and dialysate flows are typically run in opposite directions (countercurrent) to improve clearance, but can be run in the same direction if less solute clearance is desired. The hollow fibers are the site of diffusion and convection as each of the hollow fibers contain pores which allow the passage of molecules.

Dialysis membrane biomaterials can be divided into four different types: cellulose, substituted cellulose, mixed cellulose synthetic, and pure synthetic. Cellulose membranes are formed from plant (usually cotton) polysaccharide. They are considered to be less biocompatible and are therefore now used less frequently. Substituted cellulose membranes are formed by removing free hydroxyl groups from cellulose membranes. The removal of these hydroxyl groups attenuates complement activation and therefore is more biocompatible. Cellulosynthetic membranes are cellulose membranes with a synthetic material (tertiary amine structure) added to the surface. Pure synthetic membranes do not contain cellulose materials and are the most commonly used membranes today.

Dialyzer solute clearance characteristics are primarily dependent on surface area and porosity. Dialyzer properties are provided by the manufacturer via dialyzer specification sheets. It is worthy to note that reported clearance data for the dialyzer is based on in vitro testing which tends to overestimate in vivo clearances. It is also important to note that clearance is affected by blood flow, therefore analysis of clearance at varying blood flows is of relevance. In general, the clearance values provided by the manufacturer can give the practitioner an idea of the performance of a particular dialyzer. For example, urea can be used as a marker of small molecule removal, whereas clearance values for B12 provide information about the middle molecule removal. Flux refers to the ability to remove or ultrafilter plasma water. High-flux dialyzers have larger pores capable of removing greater volumes of plasma water. This is denoted by the ultrafiltration coefficient, or K_{uf}, of a dialyzer. Low-flux dialyzers have a K_{uf} of <10 mL/h/mm Hg and high flux dialyzers >20 mL/h/mm Hg. High-flux membranes, by nature of their larger pore sizes, also have higher clearance
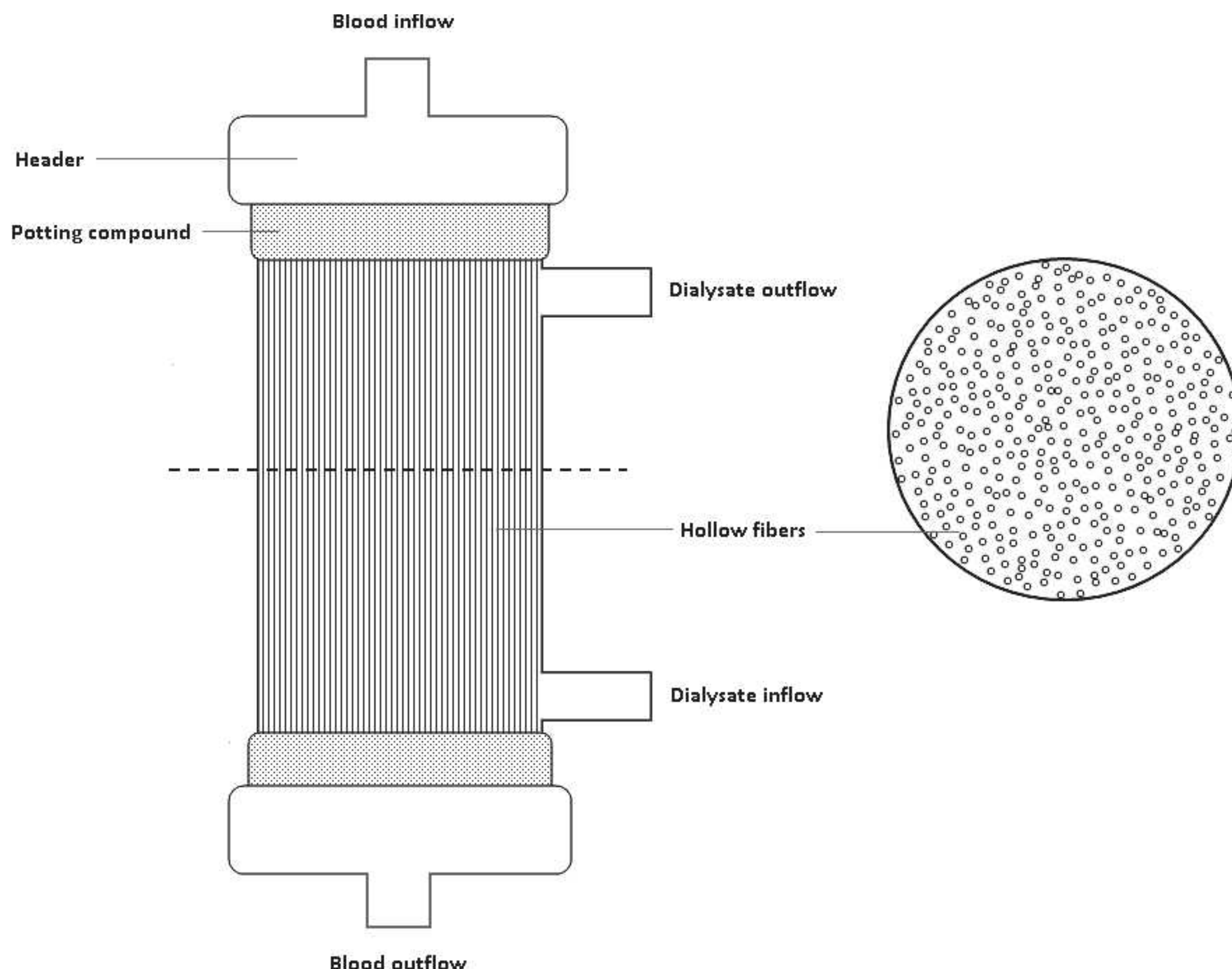
FIGURE 84.4 Hollow fiber dialyzer. In modern times nearly all dialysis setups utilize hollow fiber dialyzers as the membrane site of dialysis. The dialyzer is usually designed as a cylindrical tube which encases hollow fibers. The fibers serve as semipermeable membranes. Blood flows through the cavity of the hollow fiber and dialysate bathes the outside of the fibers. The fibers are held in place by the impermeable potting compound and the dialyzer is capped off by two headers which also serve as the site for the blood hookups. The dashed line above indicates the site of cross-section that is illustrated on the right. Note that blood and dialysate usually run in a countercurrent (opposite) direction to optimize exposure of the blood to fresh dialysate and improve clearance; however, dialysate can also be run in the same direction as the blood if less efficient therapy is required.

of middle molecules with sizes similar to molecules such as vitamin B12 (MW ∼1400 Da) and β2-microglobulin (MW ∼12000 Da). The efficiency of a dialyzer refers to its ability to remove small molecular solutes such as urea; this is usually denoted by the KoA of urea. The KoA is related to the clearance of a dialyzer (Ko) and the surface area of the dialyzer (A). It should be recognized that the manufacturer-provided clearance values for different dialyzers at different blood flows can be useful to help compare performance, but cannot reliably be used to calculate the dose of dialysis.

The priming volume of the dialyzer and the sterilization method of the dialyzer will also be listed in the dialyzer specifications. The average priming volume ranges from 50 to 150 mL. Sterilization methods of dialyzers include ethylene oxide, gamma beam radiation, and heat/steam sterilization. Sterilization with ethylene oxide has fallen out of favor due to increased rates of allergic reactions. Certain dialyzers can

be reprocessed and reused. Reused dialyzers are cleaned with bleach, hydrogen peroxide, or peracetic acid and sterilized with formaldehyde, glutaraldehyde, or heat. Before reuse, the dialyzers have to be tested for residual chemical agents and ability to withstand pressure. Fiber bundle volume is also calculated to ensure the dialyzer has an adequate number of patent hollow fibers to achieve adequate solute clearance. This process can be tedious and labor intensive and can sometimes outweigh the cost of the dialyzer—as a consequence, many dialysis units choose single-use dialyzers.

Dialysate Circuit

The main components of a typical dialysis circuit include the dialysate concentrate, the water input, a proportioning system, and a volumetric control system. The dialysate circuit is usually fitted with monitors including the conductivity monitor, temperature monitor, and a blood leak detector (Fig. 84.5).
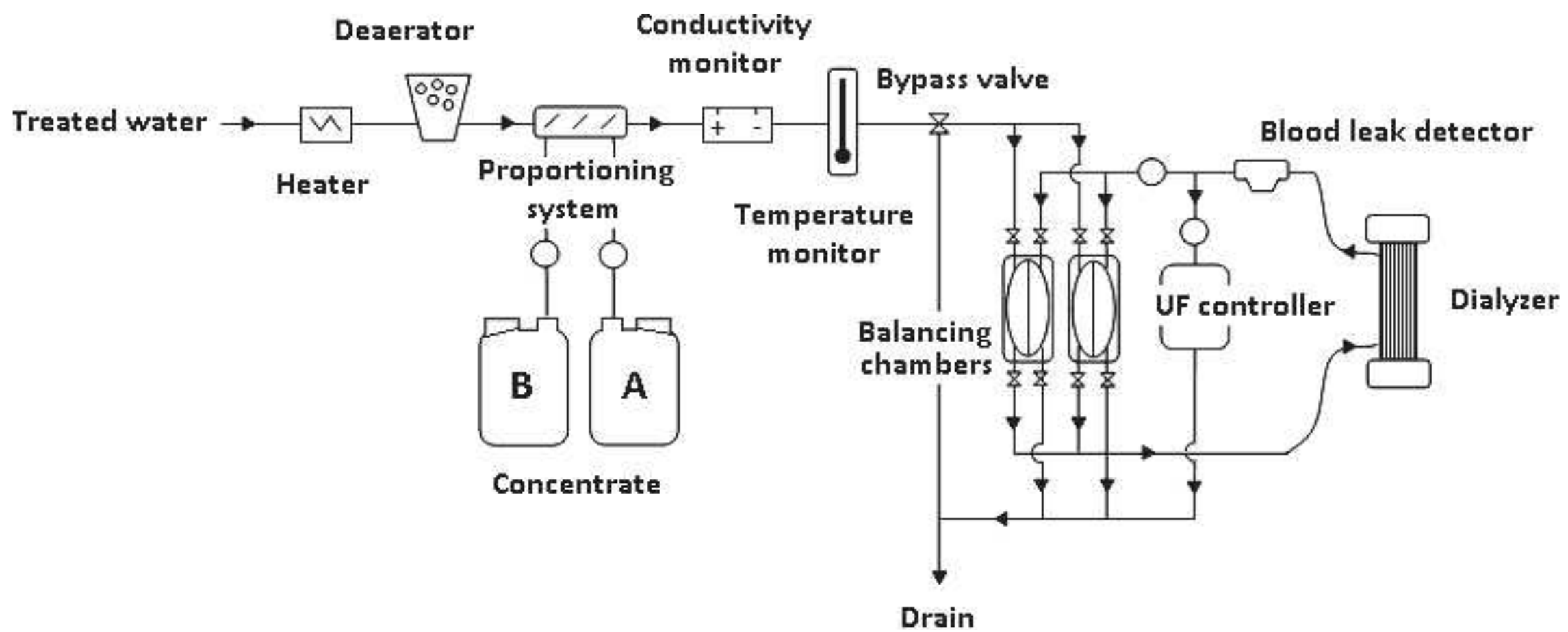
FIGURE 84.5 Drawing of the typical components in a dialysate circuit. Treated water is heated to an appropriate temperature (~35.5°–38℃) and any air bubbles in the water are removed by the deaerator. The water is then mixed with concentrate. In dynamic proportioning systems bicarbonate is usually added followed by the acid concentrate through the proportioning system. The mixed product is then tested by the conductivity monitor and tested to ensure that temperature is appropriate. pH sensors are also sometimes used. If the product is not within acceptable conductivity or temperature range the bypass valve is opened and the dialysate is delivered to the drain preventing delivery to the patient. If the product passes the tests, then it is delivered to the balancing chambers. The balancing chambers are an intricate set of chambers separated by impermeable membranes and inflow and outflow valves. The purpose of the balancing chambers is to balance dialyzer inflow with dialyzer outflow to ensure that the amount of dialysate entering the dialyzer and the amount leaving the dialyzer are equal. The ultrafiltration (UF) controller uses pressure measurements and a separate pump to remove any additional desired volume from the dialyzer effluent. The blood leak detector located on the effluent outflow tract serves to ensure dialyzer membrane integrity.

The job of the proportioning system is to take pretreated pure water and mix it with the bicarbonate and acid concentrates to make final dialysate for delivery to the dialyzer. The common range of components for bicarbonate dialysate are listed in Table 84.3. The level of sodium or bicarbonate in the dialysate can be adjusted by the proportioning system from input provided to the dialysate machine, whereas the concentration of the other electrolytes such as potassium and calcium are relatively fixed and require a change in the concentration in the concentrate. Dialysis machines rely on conductivity to test the dialysate and appropriately proportion the bicarbonate concentrate, acid concentrate, and water prior to delivery to the patient. The flow of electricity through solution is proportional to the amount of ions dissolved in the solution. Pure water is a poor conductor of electricity and salty water conducts electricity more readily. The conductivity monitor ensures that the conductivity of the dialysate, and therefore the overall electrolyte concentrations, are within the appropriate range. If out of range, the dialysate is delivered to the drain via a bypass valve. Machine alarms due to altered conductivity usually represent either inaccurate input of the concentrations of electrolytes in the concentrate, an inappropriately calibrated machine, or problems with the water purification system. These alarms can indicate malfunction of proportioning or contaminated water which can be potentially fatal to the patient if the bypass system is not evoked.

In most dialysis machines, treated water flows through the dialysate circuit at a constant rate and bicarbonate concentrate is metered into the water at a ratio around 1:20 to 1:30. After mixing of the bicarbonate with the water there is a conductivity check, then the acid concentrate is metered and added to the water in a ratio around 1:33 to 1:45. The product dialysate then undergoes further conductivity testing. It is important to understand that current dialysis technology is not sophisticated enough to measure the exact concentration of electrolytes in the dialysate but rather it

84.3	Typical Dialysate Composition Ranges	
Sodium (mEq/L)	130–145	
Potassium (mEq/L)	0–4	
Chloride (mEq/L)	98–112	
Bicarbonate (mEq/L)	30–40	
Magnesium (mEq/L)	0.5–1.5	
Calcium (mEq/L)	2.5–3.5	
Glucose (mg/dL)	100–200	

relies on conductivity to ensure the correct preparation of dialysate. For example, if a lower bicarbonate concentration is desired in the dialysate then the bicarbonate pump will deliver less of the bicarbonate concentrate to the water stream, therefore, there will be less sodium delivered as well. In order for the machine to prepare dialysate with appropriate conductivity it will need to deliver additional sodium from the acid concentrate, subsequently, other cations in the acid concentrate will also be delivered in a larger proportion as well (e.g., potassium and calcium).

The volumetric control system regulates the amount of plasma water removed (ultrafiltration) during dialysis. It consists of an intricate set of valves coupled with balancing chamber(s), an ultrafiltration pump, pressure monitors, and a computerized ultrafiltration controller. If no ultrafiltration is desired, these components act together to ensure that the amount of fluid entering the dialyzer matches the amount of fluid that leaves the dialyzer. If fluid removal is desired, the amount of fluid in the dialyzer outflow will exceed the dialysate input.

Other safety systems included in the dialysate circuit include the temperature monitor, the blood leak detector, and sometimes a pH detector. Standard dialysate temperature is around 37°C. Lower temperature is associated with shivering and discomfort but may reduce intradialytic hypotension. Higher temperatures (>42°C) can lead to protein denaturation and hemolysis.[19,20] The blood leak detector serves as a method to detect the presence of blood in the dialysate. Given that dialysate water is not sterile, blood should not come in direct contact with the dialysate. If there is a rupture in the dialysis membrane blood will be found in the dialysate effluent. Additionally, high levels of myoglobin or hemoglobin in the dialysate effluent can set off the blood leak detector if a significant amount of pigment is able to pass through the membrane.

Methods of Dialysis

Traditional Intermittent Hemodialysis

In traditional intermittent hemodialysis (IHD) blood flows through a dialyzer at rates from 300 to 500 mL per min against countercurrent flow of dialysate at 500 to 800 mL per min. Typically this is done in 4-hour treatments three to four times weekly. Solute removal in IHD is predominantly from diffusive clearance. Ultrafiltration is usually performed concurrently for volume removal. The resulting convective removal of solute by ultrafiltration is only a small fraction of the overall clearance.

Slow Low Efficiency Dialysis

Slow low efficiency dialysis (SLED) or sustained low efficiency dialysis is an option for patients who are hemodynamically unstable and would not otherwise tolerate traditional intermittent hemodialysis. With SLED, the speed and efficiency of dialysis is decreased and this decreases the rate of osmolar shifts while still providing for solute removal and

volume removal if necessary. Blood pump speeds are typically 100 to 200 mL per min and dialysate flows 100 to 300 mL per min. SLED is typically done for longer periods of time or continuously with lower rates of ultrafiltration (0–400 mL per hr), and is primarily used in inpatient hospital settings for the treatment of acute kidney injury (AKI).

Hemofiltration

In hemofiltration (Fig. 84.6) large quantities of plasma water are removed with ultrafiltration by hydrostatic pressure (typically 1–5 L per hr). There is no dialysate, thus, diffusive clearance is nonexistent and resulting solute clearance is primarily convective. Blood pump speeds can vary from slow (100 mL per min) to speeds similar to IHD. The large amount of ultrafiltration performed necessitates use of a replacement fluid; otherwise, plasma volume would be rapidly depleted using this technique. Replacement fluid is added back to the blood circuit either pre- or postfilter (or both). The replacement fluid needs to be sterile or "ultrapure" as it will be delivered directly to the patient. Hemofiltration can be intermittent or slow and continuous. Slow continuous hemofiltration is also known as continuous arteriovenous hemofiltration (CAVH) or continuous venovenous hemofiltration (CVVH). CAVH requires arterial access and has fallen out of favor in recent years. These continuous techniques are primarily used for the treatment of critically ill patients with AKI.

Typically the dose of replacement fluid is set in liters per hour. The ideal dose is controversial but, in general, around 20 to 35 mL/kg/hr is recommended. Care should be taken to account for the difference between the actual delivered dose and the prescribed dose as the two can often be off by 20% due to a variety of technical and logistic problems such as breaks in therapy and clotting issues.[21] There does not seem to be any improvement in outcomes when using higher delivered dosages (>30 mL/kg/hr) for AKI.[21–24] Volume removal in hemofiltration can be achieved by decreasing the amount of replacement fluid given back to the patient in relation to the amount of fluid that is removed.

Hemodiafiltration

Combining diffusive clearance with large amounts of convective clearance (in other words, combining hemofiltration with dialysis) is termed hemodiafiltration. With hemodiafiltration, both use of dialysate and ultrapure replacement fluid administration are necessary. If performed continuously, hemodiafiltration is termed continuous veno-venous hemodiafiltration or CVVHDF (also CVVHD). Hemodiafiltration can be used for the treatment of ESRD and is also frequently used continuously for critically ill patients with AKI.

Pure Ultrafiltration

In patients who require fluid removal without solute clearance, removal of plasma water alone or ultrafiltration can be performed. Fluid removal without simultaneous dialysis has the added benefit of conferring more hemodynamic stability as
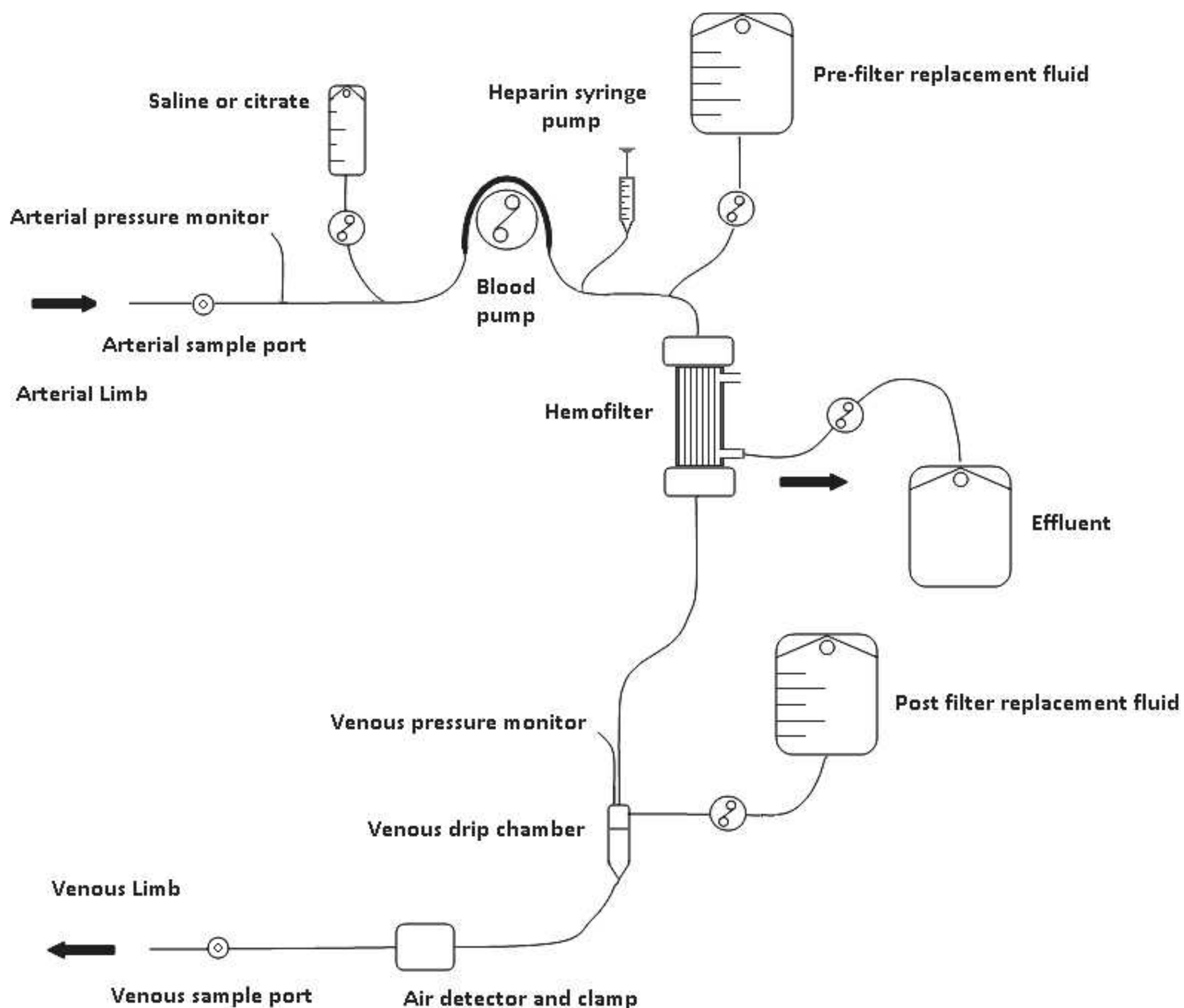
FIGURE 84.6 Drawing of a hemofiltration circuit. Blood enters the arterial limb from the patient dialysis access and flows through a hemofilter where plasma water and solute that is smaller than the hemofilter pore size passes the membrane via convection and is discarded in the effluent bag. Blood then continues to flow through the venous limb and back to the patient. To achieve meaningful clearance of solute, large volumes of plasma water removal are required, thus the need for replacement fluid to prevent excessive volume removal from the patient. Replacement fluid can be delivered prefilter, postfilter, or both pre- and postfilter as illustrated. Anticoagulation options typically include either heparin delivered by a syringe pump or citrate delivered to the arterial limb by a separate pump. Note that the illustration only shows a hemofiltration setup which is similar to setups used for continuous venovenous hemofiltration (CVVH). Many different arrangements are available. If dialysate is hooked up to the filter, the technique can be modified to perform dialysis at the same time as hemofiltration, also known as hemodiafiltration.

osmolar shifts are not taking place in the circulation due to lack of diffusive clearance. For patients who are particularly hemodynamically unstable, slow continuous ultrafiltration (SCUF) is an option. With SCUF blood flows are typically 100–200 mL per min with fluid removal (ultrafiltration rate) ranging from 100–500 mL per hr as tolerated. Small amounts of convective clearance of solute occur with this technique but not at a level that is clinically significant. Pure ultrafiltration or SCUF has also been termed aquaphresis by non-nephrologists.

Water Treatment Systems

To perform hemodialysis, a large amount of pure water is needed. At a dialysate flow rate of 500 to 800 mL per min a standard 4-hour dialysis session will require 120 to 192 L

of water. Inpatient and outpatient dialysis units operate using water treatment systems that are able to meet this demand for water (Fig. 84.7). Regular city or well water can contain many contaminants. Some of these contaminants include particulate matter such as sand, clay, and plant matter or metals such as copper, zinc, and lead which can be leeched from pipes during water transport. Water obtained in proximity of agriculture may be contaminated with fertilizers and pesticides. Further, heath authorities of city water systems frequently add agents to water to make it safer or more palpable for consumption. Chlorine and chloramines are added to control microbial contamination, fluorides for dental prophylaxis, and occasionally aluminum sulfate and iron salts are added as flocculating agents to decrease water turbidity.[25] These contaminants and
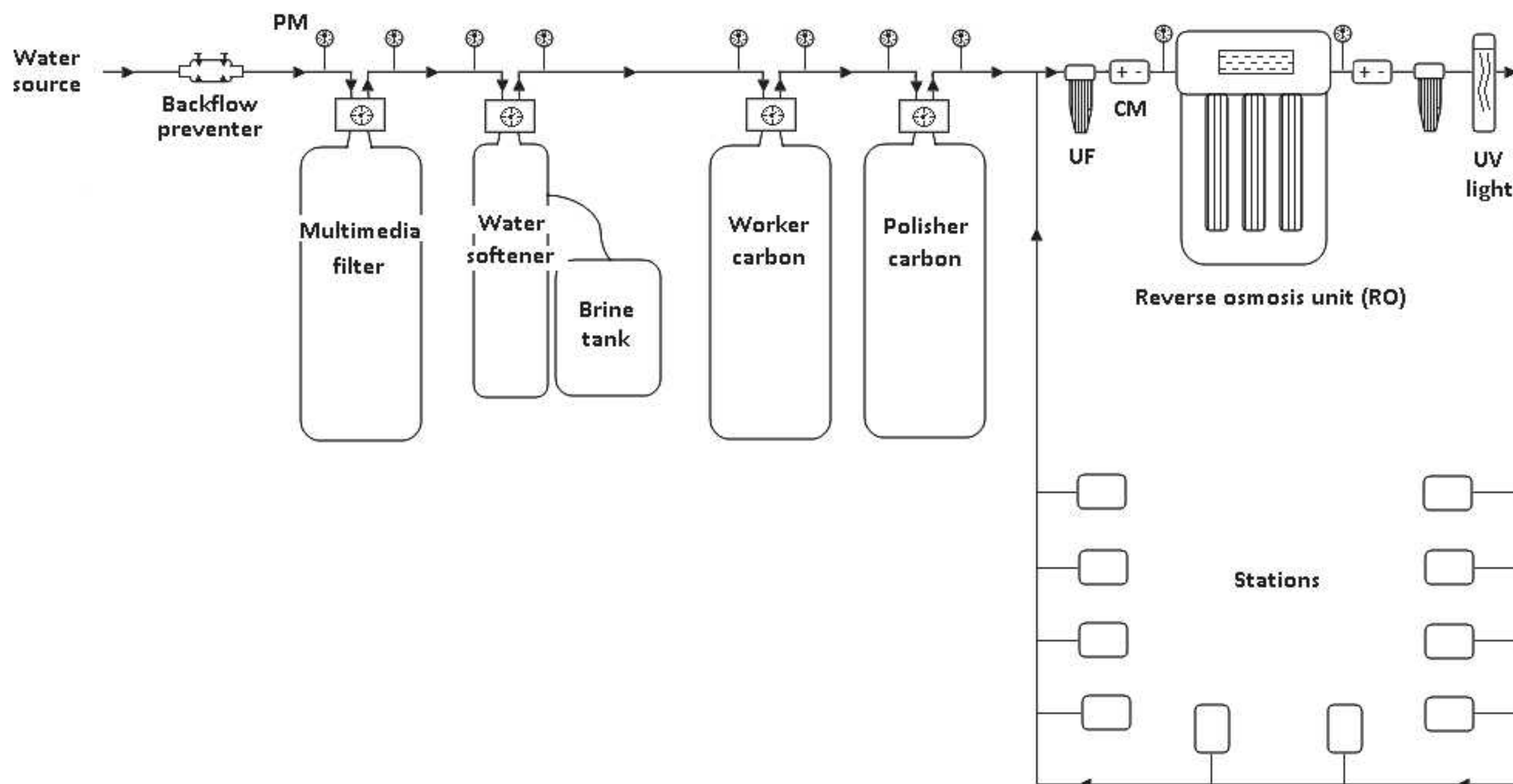
FIGURE 84.7 Simplified drawing of the components of a typical direct feed water treatment system. *Arrows* indicate the direction of flow. City water enters the system and runs through a backflow preventer. Pressure is monitored (PM) at multiple points in the circuit to ensure filtration integrity of the various components. Conductivity monitors (CM) are placed before and after treatment with the reverse osmosis unit. Ultrafilters (UF) and a ultraviolet (UV) light are placed in the loop to prevent microbiologic contamination. Water not used at the dialysis stations in the loop is returned to the circuit pre-RO for reuse. Not drawn but occasionally included in the water treatment system is the storage tank (for indirect feed systems), pressure tank, booster pump, and acid feed system.

additives need to be removed from the water source prior to being used in the production of dialysate.

Treatment guidelines for water purification have been set by the Association for the Advancement of Medical Instrumentation (AAMI) and the European Pharmacopeia. Water treatment systems can vary among institutions and differ based on water supply and local requirements. The water purification circuit generally consists of a back flow preventer, multimedia filter, water softener, activated carbon filters, and a final purification device which can be a de-ionizer or more commonly a reverse osmosis system. The backflow preventer serves to keep water in the circuit from regurgitating into the plumbing circuit of the building. The multimedia filter contains sand and gravel of varying sizes and serves to remove large particulate matter and debris from the water. The water softener contains anion exchange beads which exchange calcium and magnesium in the city water for sodium from the brine tank. Carbon tanks remove chlorine and chloramines from the city water. After passing through these initial steps the water is sent to the final purification unit. Reverse osmosis (RO) is a filtration process by which water is actively forced through a membrane with very small pore sizes that do not allow solute (including sodium) and other organic matter to pass through. De-ionization, an alternative to reverse osmosis, uses an ion exchange process to form water. Supply water percolates around cationic and anionic exchange resins which exchange hydrogen and hydroxide ions for other ions. The H+ and OH− ions then form pure water. De-ionization is effective in removing inorganic ions but has the downside of ineffective removal of organic contaminants and potential bacterial contamination. Water also can be passed through a UV light and ultrafilters to aid in the sterilization process. Once purified, typically, water is sent through a loop which feeds dialysis stations. Depending on the dialysis machine, there may also be a filter at the machine for the dialysate after the water has mixed with the concentrate.[26,27]

Water Quality Issues

Clinical events can manifest when there is a problem with chemical or microbiologic impurities in water. Aluminum, chloramines, and fluoride intoxication have been reported in recent years in hemodialysis units. Aluminum toxicity can lead to progressive central nervous system (CNS) effects, anemia, and low turnover bone disease. High levels can lead to permanent CNS toxicity, dementia, and even death.[27] Blood exposure to chloride and chloramines in the dialysate can lead to symptoms of nausea, vomiting, hypotension, dyspnea, and hemolytic anemia. Patients with hemolysis may present with dark blood in the hemodialysis line. Chloramines are not completely removed by de-ionization or reverse osmosis and require functional activated charcoal

columns for removal. Charcoal columns can be exhausted over time and if water flow is too rapid through them, chloramines can pass into the product water. For this reason, purified water for dialysis should be checked every dialysis shift or every 4 hours for chloramines to ensure that this complication is avoided. Fluoride is removed by reverse osmosis and de-ionization. However, if the de-ionizer becomes saturated, large quantities of fluoride can be released into the water as the anion resin preferentially exchanges bound fluoride for anions of higher affinity such as chloride. In the body, fluoride binds to calcium and can disrupt cell membranes leading to hyperkalemia. Toxic effects of fluoride can manifest with pruritus, painful gastrointestinal (GI) symptoms, syncope, tetany, neurologic symptoms, cardiac arrhythmia, and death.[28]

Dialysate water does not have to be sterile because the dialysis membrane does not have pore sizes large enough for transport of microbes. Even so, water-related febrile reactions and related inflammatory problems can occur if the water is excessively contaminated with microorganisms, lipopolysaccharides, or endotoxins. The AAMI recommends that water used for dialysate has less than 200 colony forming units (CFU) per milliliter of water. The European Pharmacopeia guidelines are more strict, recommending less than 100 CFU per mL. Water contaminated with high levels of endotoxins or lipopolysaccharides can cause fevers, chills, and systemic inflammatory response. The acceptable level for endotoxin measured by the LAL test is less than 0.1 EU per mL.[27,29]

The term "ultrapure dialysate" describes fluid that is nearly free of bacteria and endotoxin but should not be confused with sterile fluid which is completely free of pyrogen and bacteria. Ultrapure dialysate has been suggested as beneficial in dialysis patients due to a decreased burden of microbial contamination resulting in less inflammatory response.[30] Ultrapure dialysate water contains bacterial concentrations less than 0.1 CFU per mL if standard techniques are used or less than 0.03 IU per mL if sensitive assays are used.[31] Improving water purification methods have allowed for more interest in online generation of replacement fluid for hemofiltration or hemodiafiltration.[32,33] These techniques usually involve an extra ultrafilter at the dialysis machine to generate ultrapure replacement fluid for infusion into the patient.

Uremic Toxins

Uremic retention compounds are usually classified by molecular weight and degree of protein binding. Many of the known uremic toxins are generated by metabolism of proteins and by modification of amino acids by gut microbes.

Urea, measured by blood urea nitrogen (BUN), is a low molecular weight solute (60 daltons) which is linked to protein metabolism and has been used as a surrogate marker for small, water soluble uremic toxins. Urea itself is not highly toxic and its generation is influenced by many factors such as dietary intake and liver function. In current practice, urea is the predominant marker used to evaluate clearance in dialysis and urea clearance is accordingly associated with dose of dialysis or dialysis adequacy. However, the clinical picture of uremia is complex and involves more than just small molecules.

Middle molecules (500 daltons to 60 kDa) have also been suggested as an important component of the uremic syndrome.[34] This proposal was based, in part, on the observation that peritoneal dialysis patients did quite well with high BUN and creatinine levels and the peritoneal membrane is more permeable to middle size molecules than the dialysis membranes used early on in dialytic therapy.[35] Most middle molecules are peptides. Clearance of middle molecules has improved in recent years with the use of high-flux dialyzers that have larger pore sizes. Clearance of middle molecules can also be improved by lengthening treatment time. Further, convective methods of clearance are gaining in popularity and are more effective than diffusive methods for clearance of middle molecules. The prototype middle molecule is β2–microglobulin (12 kDa). Many of the middle molecules are involved in leukocyte, endothelial cell, smooth muscle cell, and/or thrombocyte function and therefore they likely have an impact on cardiovascular health.[36]

Protein-bound uremic toxins can be of variable size but due to their binding to large molecular weight plasma proteins such as albumin (68 kDa), they are not well cleared with current dialysis technology. Only the smaller, free fraction of these solutes is cleared with diffusion or convection. Phenols, indoles, hippurates, and advanced glycation end products are some examples of uremic toxins that are protein bound.[37] Many uremic toxins, protein bound and otherwise, appear to be generated in the gastrointestinal tract as a result of altered intestinal absorption of nutrients in the uremic state leading to changes in gut flora and microbial metabolism.[38]

Urea as a Marker of Dialysis Adequacy

Single Pool Kt/V (spKt/V)

To quantify the effect dialysis has on the removal of urea over time we can multiply clearance (K, mL/min) by time (t, min) which gives us the expression Kt which is a volume (mL) cleared. To generalize this expression among patients, Kt can be normalized to the volume of distribution of urea or total body water (V, mL) which results in a dimensionless expression of Kt/V.[39] In hemodialysis, this can be thought of as a ratio of the volume cleared of urea to the volume of distribution of urea. In other words, a Kt/V of 1.0 means that a volume of blood equal to the volume of total body water was cleared of urea. The clearance of urea from the blood over time during dialysis follows an exponential pattern. The following equation models the clearance of a substance from the body where that substance decreases in an exponential fashion:

$$Kt/V = \ln(C_{pre} / C_{post})$$

where C_{pre} is predialysis urea and C_{post} is postdialysis urea. This simplified equation provides the basis for urea

kinetic modeling. It should be noted that it does not take into account the minimal generation of urea that happens during dialysis, nor does it take into account fluid that is removed with ultrafiltration during dialysis (changing V). It also assumes that the postdialysis urea is equilibrated across all body compartments or a "single pool." This is an erroneous assumption as urea is not distributed equally throughout all body compartments, especially during dialysis with high blood and dialysate flow rates. Other more complex formulas attempt to improve on accuracy and can also be used for the calculation of single pool Kt/V (Table 84.4).[40]

Equilibrated Kt/V (eKt/V)

The concentration of solute removal will be the greatest in the compartments of the body which have the largest amount of blood flow in continuity with the dialysis access—for example, the cardiopulmonary circuit. Other less well perfused areas such as the peripheral capillary beds will equilibrate urea more slowly with the vascular space. The method described above for calculation of Kt/V is the single pool method (spKt/V). This method treats the volume of distribution of urea as if it was a single pool that urea moves in and out of easily. In reality this is not true as solute gradients form between the various body compartments during dialysis and equilibration occurs in a delayed fashion after dialysis is complete. Although access recirculation and the cardiopulmonary circuit are quickly equilibrated, movement from less well perfused areas and cellular compartments continues for up to 60 minutes after dialysis.[41]

Keeping the phenomenon of recirculation in mind, it becomes important to be consistent about the timing of the postdialysis sample. Although measuring the urea concentration 60 minutes after dialysis would allow for equilibration to occur, this expenditure of patient and staff time is not practical in everyday practice. Alternate methods have been developed to estimate the degree of equilibration which are not so time consuming. In one such method ultrafiltration is stopped and the blood pump is slowed to

84.4 Formulae for the Calculation of Single Pool Kt/V

Kt/V = (4 × URR) − 1.2
Kt/V = 1.18 × −ln(R)
Kt/V = 2.2 − 3.3 × (R − 0.03 − UF/W)
Kt/V = −ln(R − 0.03) + (4 − 3.5 × R) × UF/W

Accuracy of formulae increases from top to bottom.
URR, pre-post BUN/pre-BUN; UF, volume of fluid removed (L); W, postdialysis weight (kg); R, post/pre-BUN ratio.
From Daugirdas JT. Chronic hemodialysis prescription: a urea kinetic approach. In: Daugirdas JT, Ing TD, eds. *Handbook of dialysis*. 2nd ed. Boston: Little, Brown and Company; 1994:92; with permission.

84.5 Formulae for the Calculation of Equilibrated Kt/V[42]

Arteriovenous access	eKt/V = spKt/V − 0.6(K/V) + 0.03
Venous catheter	eKt/V = spKt/V − 0.47(K/V) + 0.02

100 mL per min for 10 seconds, after which a sample is drawn from the arterial port. This maneuver allows for access recirculation to resolve and will yield a measurement that can be used in the calculation of the spKt/V. To account for equilibration of urea between body compartments after dialysis, equations have been developed to estimate the equilibrated Kt/V (eKt/V).[42] These equations (Table 84.5) were developed to serve as estimations extrapolated from urea rebound curves. The lack of significant cardiopulmonary recirculation in patients dialyzing with catheters necessitates the use of a separate formula.

Standard Kt/V

Measuring the single pool Kt/V (spKt/V) or equilibrated Kt/V (eKt/V) provides data for a single dialysis treatment, and this has limited value for comparing different treatment frequency strategies or for comparing peritoneal dialysis to hemodialysis. In an effort to quantify the dose of dialysis that is delivered continuously, the standard Kt/V (stdKt/V) was developed.[43,44] One can think of the standard Kt/V urea as a continuous clearance over a week of therapy rather than an intermittent clearance, similar to continuous urea clearance provided by residual renal function. The clearance is calculated based on the mean (peak) urea concentrations and the generation rate of urea over a week. It is then normalized to the volume of distribution of urea. This method of quantifying dialysis dose has utility particularly when comparing (or standardizing) patients on continuous therapies such as peritoneal dialysis or those who are receiving more frequent hemodialysis. Equations for calculation of stdKt/V are described in Table 84.6.[44,45]

Urea Reduction Ratio

Compared to formal urea kinetic modeling, the amount of urea removed in a single dialysis treatment can be expressed in a simple way as the fractional reduction of urea. The urea reduction ratio (URR) can then be converted into a percentage of urea reduction for a given dialysis session:

$$\%UR = C_{pre} - C_{post} / C_{pre} * 100$$

Roughly, a %UR of 65 correlates with a single pool Kt/V of 1.2. The URR does not take into account changes

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84.6 **Formulae for the Calculation of Standard Kt/V**

Equation 1: Gotch formula[43]

$$stdKt/V = 7*1440[0.184(PCRn - 0.17)]/Co \text{ weekly}$$

PCRn is the normalized protein catabolic rate, Co is the mean peak urea concentration

Equation 2: Leypoldt formula[44]

$$stdKt/V = \frac{10{,}080 \dfrac{1 - e^{-eKt/V}}{t}}{\dfrac{1 - e^{-eKt/V}}{eKt/V} + \dfrac{10{,}080}{Ft} - 1}$$

eKt/V is the equilibrated Kt/V, t is treatment time in minutes, and F is the frequency of dialysis treatments per week

Equation 3: Adjustment for ultrafiltration and residual renal function[45]

$$stdKt/V = S/(1 - (0.74/F) * UFw/V) + Kru * (0.974/(spKt/V + 1.62) + 0.4) * 10{,}080/V$$

Where t is the treatment time in minutes, S is the result of equation 1, F is the number of sessions per week, UFw is the weekly fluid removal in liters, spKt/V is the single pool Kt/V, Kru is residual renal function, and V is the volume of distribution of urea.

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in volume. Larger amounts of fluid removed with dialysis will result in a lower URR. This effect should be realized in patients with large intradialytic weight gains and high ultra-filtration rates.

Protein Catabolic Rate

Measurement of pre- and postdialysis urea concentration also allows the ability to calculate the amount of urea that is generated in the intradialytic period. This in turn can be used as a surrogate measure of protein intake and/or nutritional status. As protein is metabolized by the body, urea is generated. Therefore, measurement of the amount of urea in the body can be viewed as a measurement of net protein breakdown and, in the nutritional steady state, net protein catabolism is equal to dietary protein intake.[46]

There are many equations available for the calculation of normalized protein catabolic rate (Table 84.7). It should be noted that the equations do not take into account the

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84.7 **Formula for the Calculation of Normalized Protein Catabolic Rate[217]**

PCRn = 5.42 G / V + 0.168
G is the urea generation rate and V the volume of distribution of urea.

Three times weekly dialysis	
Beginning of week	$C_o / [36.3 + 5.48Kt/V + 53.5/(Kt/V)] + 0.168$
Mid week	$C_o / [25.8 + 1.15Kt/V + 56.4/(Kt/V)] + 0.168$
End of week	$C_o / [16.3 + 4.3Kt/V + 56.6/(Kt/V)] + 0.168$
Twice weekly dialysis	
Beginning of week	$C_o / [48 + 5.14Kt/V + 79/(Kt/V)] + 0.168$
End of week	$C_o / [33 + 3.6Kt/V + 83.2/(Kt/V)] + 0.168$

C_o is the predialysis concentration of urea.

clearance of urea that takes place by native kidneys in persons with residual kidney function. If a significant amount of urea clearance is still present through the native kidneys the PCRn will appear low. Further care should be taken when relating the PCRn to nutrition. Each patient needs to be evaluated for other clinical factors that can affect serum urea levels because the equation assumes that the patient is in a steady state of protein balance. For example, in states of increased protein catabolism, such as acute illness, urea levels will be increased and do not represent increased dietary intake. Taking these potential confounders into account, in general, an nPCR of greater than 1.0 g/kg/day would indicate that the patient has adequate protein intake. Goal PCRn should be in the range of 0.8 g/kg/day to 1.4 g/kg/day.[47]

Pitfalls with Urea-based Measures of Dialysis Adequacy

Urea is used as a surrogate marker of dialysis adequacy but urea itself does not describe the entirety of the uremic milieu. Urea is attractive as a marker of uremic toxicity because levels correlate with protein catabolism and many uremic toxins have been linked to protein metabolism. Urea is also easily measured by blood chemistry. However, urea levels may not correlate with the level of all uremic toxins, particularly in the case of uremic toxins that are not small solutes. Middle molecules and uremic toxins which are protein bound are largely ignored when using urea based methods of measurement of adequacy. Further, putting these inherent properties of urea aside, many other potential inaccuracies exist in the calculation of Kt/V (Table 84.8).

Timing of Initiation of Dialysis

The ideal timing for the initiation of dialysis in the patient with chronic kidney disease (CKD) is dependent on sound clinical judgment which accounts for factors such as age, residual kidney function, rate of progression to ESRD, modality choice, and patient preference. Examples of clear indications for the initiation of dialysis include uremia, uremic pericarditis, and volume excess refractory to diuretic therapy. Over time in the United States, the estimated glomerular filtration rate (eGFR) at which patients are initiated on dialysis continues to increase. In 1996 the mean eGFR at dialysis initiation was between 7 and 8 mL per min whereas in 2008 the mean eGFR was 11 mL per min.[5] It is possible that this increase in eGFR represents changing nephrologist attitudes toward offering dialysis care with a general shift in practice patterns toward offering dialysis earlier. Patients starting dialysis at higher eGFRs may also be sicker than appreciated or sicker than historical patients. Patients starting dialysis with a higher eGFR are generally older, diabetic, and have a higher number of premorbid conditions.[5]

Many recent clinical guidelines and recommendations focus on the estimated GFR as calculated by Cockcroft-Gault or MDRD formulae as a tool to assist with the timing of initiation of dialysis. Use of eGFR is fraught with difficulties because the eGFR does not always correlate well with the actual GFR, particularly at very low levels of renal function as is seen in patients nearing the need for renal replacement therapy. Often patients with malnutrition will have lower creatinine levels reflective of decreased muscle mass and MDRD eGFRs which appear to be higher.

The trend toward starting dialysis earlier based on eGFR is alarming due to lack of clear demonstration of benefit in early start situations. In a prospective registry study comparing the MDRD eGFR and mortality, in a subgroup of patients with measured creatinine clearances, mortality rates were higher in patients with a higher eGFR but this relationship did not hold up when the GFR was calculated by measured creatinine clearance.[48] Furthermore, higher eGFR at initiation of dialysis has been correlated with a greater risk for death. In an evaluation of registry data from Scotland and British Columbia, a progressively increasing hazard ratio of death was seen with increasing eGFR.[49] In a cohort of over 25,000 patients from Canada between 2001 and 2007, increased mortality was seen in the early start group (eGFR $>$10.5) compared with late start (eGFR $<$10.5). After adjustment for comorbidities, the increased risk persisted.[50] Retrospective analysis of the USRDS revealed similar associations between increased mortality and early dialysis start when using eGFR $>$15 mL per min as the definition for early start and $<$5 mL per min late start, arguing against early start of dialysis based on eGFR alone.[51] Recently, a randomized controlled trial of patients from Australia and New Zealand attempted to define the ideal timing of dialysis based on the eGFR calculated by the Cockcroft-Gault formula (IDEAL study).[52] Patients were randomized to two groups, early start (eGFR 10–14 mL per min) and late start (5–7 mL per min). Enrollment included 828 patients followed between 2000 and 2008. The results showed no difference between early versus late start with regard to death from any cause, cardiovascular complications, infectious complications, or dialysis complications. The conclusion was early start based on eGFR considerations alone does not confer clinical benefit.

The weight of the evidence seems to point away from using eGFR as the sole factor to determine the appropriate timing for initiation of dialysis. Rather, decisions regarding timing of the initiation of dialysis should remain a clinical judgment call made by a physician trained in kidney disease and individualized to meet the patient's needs.

Clinical Trials to Define the Optimal Dialysis Dose

Over the years, clinicians and researchers have attempted to define the optimal dose of dialytic therapy for ESRD patients. Currently, dialysis therapy is delivered in a relatively uniform fashion to nearly all dialysis patients (3 to 4 days a week for 3 to 4 hours). Realization that the appropriate dose of volume and solute removal in dialysis is probably

84.8	Some Potential Pitfalls with Urea-based Methods of Dialysis Adequacy and Their Solutions	
	Problem	**Potential Solution**
Expected K_{urea}	Clearance data for specific dialyzers relies on information provided by manufacturers measured in artificial situations with urea solutions, not in vivo.	Anticipate that manufacturer listed clearances overestimate in vivo clearances
Sampling error	Clearance calculations can be affected by sampling, if sample is not drawn correctly or there is significant access recirculation results can be overestimated.	Develop consistent quality driven protocols for measurement of pre- and postdialysis urea
Discrepancy between prescribed vs. delivered dose	Loss of fiber bundle volume due to clotting can reduce amount of clearance. This is more of an issue near the end of the dialysis run or in dialyzers that are reused. Lost dialysis time. Staff or patient related factors may create a discrepancy between the prescribed dose of dialysis and the amount of dialysis actually delivered.	Urea kinetic modeling should not be used alone to prescribe a dose of dialysis
Urea rebound	Urea rebound occurs after dialysis. Initially urea is equilibrated in the dialysis access as recirculation is negated, in the following minutes recirculation from the cardiopulmonary circuit resolves and over the following hour urea is redistributed completely from various tissue compartments and cellular spaces. Urea levels drawn immediately after dialysis do not allow enough time for equilibration to occur.	The calculation of equilibrated Kt/V attempts to address this problem
Modeled after traditional intermittent HD	Single pool Kt/V measures the effectiveness of a single dialysis session and is modeled after patients undergoing thrice weekly dialysis for 3–4 hours. The applicability of this method in persons on differing dialysis regimens particularly in cases of more frequent dialysis is unclear.	The calculation of standard Kt/V attempts to address this problem

not the same for every patient led to expanded concepts for adequacy of dialysis by measurement of patient specific factors which could quantify the amount of dialysis delivered.

The National Cooperative Dialysis Study (NCDS) in 1981 was a seminal early study seeking to provide a means for quantitative measurement of the optimal dose for thrice weekly dialysis.[53] Investigators compared time averaged urea clearances (TAC_{urea}) with long or short treatment durations using a factorial randomized study design. Patients were divided into four groups based on their TAC_{urea} and dialysis time (Table 84.9). The TAC_{urea} provides a value for the mean concentration of urea over a dialysis cycle (Fig. 84.8). Investigators found that the patients in groups 2 and 4 with higher TAC_{urea} had more frequent hospitalizations, most commonly due to nausea, anorexia, and other uremic symptoms. As a result, more patients were withdrawn from the high TAC_{urea} groups for medical reasons. With regard to the length of therapy, in the high TAC_{urea} patients (groups 2 and 4), the short duration dialysis group (group 4) was hospitalized more frequently than the long duration dialysis group (group 2). The benefit of longer dialysis was not seen in the two groups with low TAC_{urea} (groups 1 and 3).

The NCDS findings were widely interpreted as suggesting that to prevent morbidity, clearance of urea is more

| 84.9	Four Groups of the National Cooperative Dialysis Study (NCDS)			
Group	**Td (h)**	**Predialysis BUN (mg/dL)**	**TAC_{urea} (mg/dL)**	**Patients (%)**
1 Long Td, low BUN	4.5 to 5.0	60 to 80	50	86
2 Long Td, high BUN	4.5 to 5.0	110 to 130	100	46
3 Short Td, low BUN	2.5 to 3.5	60 to 80	50	69
4 Short Td, high BUN	2.5 to 3.5	110 to 130	100	31

Td, dialysis time; BUN, blood urea nitrogen; TAC_{urea}, time-averaged concentration of BUN.

important than dialysis treatment time. This led to the assumption by many clinicians that dialysis time could be shortened so long as urea clearance remained adequate. Notable caveats of the NCDS study include relatively low urea clearances across all groups, a patient population that was healthier when compared to the dialysis population in more recent times, and the small size of the study which was underpowered to make mortality comparisons.

Following the NCDS study numerous large observational studies, most of them performed in the 1990s, challenged the NCDS findings and suggested that higher Kt/V urea values and higher flux dialysis is associated with better outcomes.[54–61] Subsequently, there was a trend toward lengthening dialysis time and the utilization of high flux membranes.

The Hemodialysis (HEMO) study[62] in 2002 sought to evaluate the effect of dialysis dose and membrane flux on death from any cause. In a schedule of thrice weekly dialysis, investigators used a two by two factorial design to randomize patients to high dose or low dose groups and high flux or low flux groups. They achieved an equilibrated Kt/V (eKt/V) in the low dose group of 1.16 and 1.53 in the high dose group. The low flux and high flux groups had similar mean eKt/V at 1.34. There was no significant improvement in survival seen between standard dose, high dose, low flux, or high flux dialysis groups. The results of the HEMO study were surprisingly negative in contrast to the earlier observational data. Even so, it is notable that on secondary analysis of the HEMO study, high flux dialysis was associated with improved cardiovascular[63] and cerebrovascular outcomes.[64]
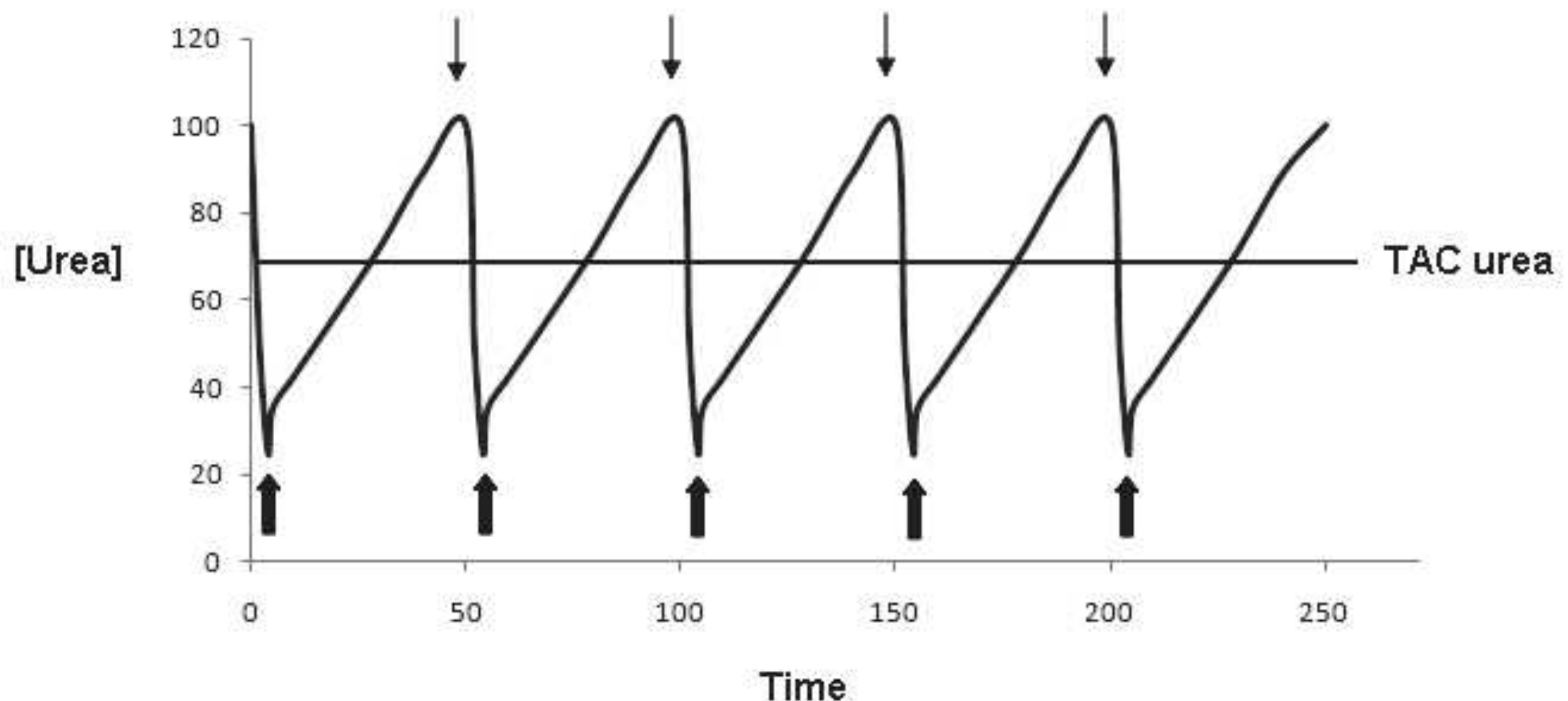
FIGURE 84.8 Time averaged concentration of urea (TAC_{urea}). Graphical representation of the time averaged urea concentration. On the *y* axis is urea concentration (mg/dL), on the *x* axis time (hours). The *thin arrows* indicate the urea concentration predialysis and *thick arrows* postdialysis. The *black line* intersecting the urea curve is the time-averaged urea concentration (approximately 70 mg/dL in this example). Note the brisk upstroke of the urea curve postdialysis which represents equilibration (described previously under equilibrated Kt/V).

The Membrane Permeability Outcome Study Group (MPO study)[65] was also undertaken with a goal of evaluating the effect of membrane permeability on outcomes. Patients were randomized to dialysis with low flux or high flux membranes and stratified according to their serum albumin level (albumin <4 g per dL or albumin >4 g per dL). Both groups were treated with a minimum single pool Kt/V of 1.2. Findings revealed that patients in the low albumin group (<4 g per dL) had significantly higher survival rates when treated with a high flux dialyzer. Further, high flux dialyzers in secondary analysis seemed to improve survival of diabetics regardless of serum albumin. This survival benefit was not seen in patients with higher serum albumin levels or across the group as a whole.

Effect of extended duration of dialysis therapy on patient outcome was not assessed in the aforementioned clinical trials. In 2010 data from the Frequent Hemodialysis Network (FHN) trial[66] was released to help address the issue of the appropriate duration of dialysis. The rationale for the currently used duration of dialysis (three times weekly) is based on limited studies, logistic practicality, cost, and patient acceptance rather than on sound science. The FHN randomized subjects to in-center hemodialysis six times weekly compared with standard thrice weekly dialysis with the hypothesis that more frequent dialysis would improve outcomes. As expected, solute clearance was improved in the frequent dialysis group (weekly standard Kt/V 3.54 vs. 2.49). Results revealed that more frequent dialysis was associated with improvement in left ventricular mass, physical composite health score, hypertension, and phosphorus control. The study was only conducted for 12 months and was underpowered to detect any differences in mortality. There was no difference in the rates of hospitalizations with more frequent dialysis. Results of a trial of extended daily dialysis (nocturnal dialysis) are currently pending and may also contribute to this clinical question.

Anticoagulation

Systemic anticoagulation is usually necessary in hemodialysis patients to prevent clotting of the extracorporeal blood circuit. Due to underlying renal disease, patients with ESRD often have abnormalities of the clotting system. Most classically this is thought of as a bleeding disorder, related to uremic platelet dysfunction. However, it is also worthwhile to note that patients with renal failure frequently have coagulation abnormalities that predispose to clot formation. This may be related to underlying systemic inflammation and endothelial injury which can activate the clotting cascade.[4] The clotting cascade is composed of intrinsic and extrinsic pathways which converge at factor X. Activated factor X (factor Xa) catalyzes the formation of thrombin from prothrombin. Thrombin then converts soluble fibrinogen to fibrin which can be cross-linked to form a clot. The extrinsic pathway is endogenously activated by trauma or injury and endothelial release of tissue factor. The intrinsic pathway, also known as the contact pathway, is activated by artificial surfaces, such as

occurs during extracorporeal circulation in hemodialysis.[67] Therefore, the process of dialysis itself can activate the clotting cascade as blood comes in contact with needles, plastic tubing, and dialyzer materials. The movement of blood through the extracorporeal circuit also leads to increased shear stress and turbulent flow, mechanical factors that can activate platelets, and the clotting cascade. Granulocytes and monocytes can adhere to artificial surfaces and subsequently release granules containing tissue factor which can stimulate the coagulation cascade.[26] Risk factors for clotting on hemodialysis include slow blood flow, high hematocrit, and blood transfusion into the extracorporeal circuit. The drip chambers, particularly on the venous limb, are more prone to clotting due to slow blood flow, relative stasis, and air interface which can activate the clotting cascade.

The most widely used agent for anticoagulation during the dialysis procedure is unfractionated heparin (UFH). There is no standard dose for heparin given with dialysis and the prescription should be modified to fit the patient's needs taking into account the risk of bleeding from anticoagulation. As an example, one prescription for low dose heparinization would be a bolus dose of heparin (25–30 U per kg) given at the beginning of dialysis followed by 500–1000 U hourly during the treatment. Heparin can be stopped 30 to 60 minutes before the end of a treatment for the purpose of achieving hemostasis after needles are removed from the dialysis access. For extended or continuous hemodialysis sessions in inpatient settings heparin dosing should be monitored by periodically checking aPTT and titrating to a goal level of anticoagulation (usually between 40 and 60). Heparin has the advantage of being relatively inexpensive, easy to administer and monitor, and there is an available antidote in protamine sulfate. Adverse effects of heparin include osteoporosis, hyperkalemia, hyperlipidemia, and allergic reactions. Heparin related allergic reactions take two main forms: acute allergic reactions (type 1 hypersensitivity reactions) and heparin induced thrombocytopenia (HIT). HIT is estimated to affect 10% of patients who receive heparin though only 17% of patients with HIT experience adverse clinical effects.[68] HIT usually manifests 5 to 10 days after exposure to heparin and presents with a drop in the platelet count and a propensity to form clots ("white clots").

Low molecular weight heparins (LMWH) are also an option for anticoagulation. LMWH has the advantage of more predictable dose effects, ease of subcutaneous administration, and less of the traditional side effects associated with heparin such as HIT. However, LMWH has a long duration of action leading to anticoagulation effects lasting long after dialysis is completed. Furthermore, the effects of anticoagulation are not readily reversible. LMWH is not approved for use with dialysis in the United States but is frequently used in Europe.[26,67]

Occasionally patients cannot receive systemic anticoagulation with heparin while on dialysis due to excessive bleeding risk or allergies. In these cases, often heparin-free dialysis with frequent saline rinses of the circuit (e.g., 200 mL

of normal saline every 20 to 30 minutes) is enough to prevent excessive clotting. If this is ineffective, alternative methods of anticoagulation are available but often not utilized in outpatient dialysis units due to technical difficulty and/or excessive cost. Regional forms of anticoagulation involving the dialysis circuit have been developed; the most commonly used is regional citrate anticoagulation. Citrate is infused into the arterial limb of the circuit and acts by chelating free calcium which in turn inhibits the coagulation cascade. Some of the citrate is removed from the circuit as it passes through the dialyzer but diffusion of citrate across the membrane is not complete and some of it is delivered to the patient. Citrate anticoagulation is often very effective at keeping the circuit patent and with proper monitoring can be accomplished safely.[69] Regional citrate anticoagulation is frequently used in inpatient settings when continuous renal replacement therapy is employed but it can also be used for intermittent hemodialysis. Citrate infusion should be monitored closely to ensure that the patient does not develop systemic citrate toxicity. In citrate toxicity, serum total calcium levels will be normal or elevated but ionized calcium levels can be low due to the binding of free ionized calcium to circulating citrate. Patients with liver disease are at particular risk for citrate toxicity over time due to inadequate hepatic citrate metabolism.[70] Citrate toxicity can manifest with all of the symptoms of hypocalcemia such as fatigue, weakness, tetany, cramping, seizures, prolonged QT interval, and arrhythmias. An alternative to administration of citrate in the blood circuit is adding citrate to the dialysate, a method of anticoagulation that is effective, safe, and relatively easy to perform.[71] Other options include direct thrombin inhibitors such as argatroban, heparinoids such as danaparoid, and regional heparin-protamine setups. These options are infrequently used due to cost and difficulty with administration in outpatient settings.

Vascular Access

Establishing reliable, functional, and infection free access to the bloodstream for dialysis has often been described as the Achilles heel of hemodialysis. Recent clinical practice guidelines and clinical initiatives have recognized the importance of appropriate vascular access with goals to increase the numbers of patients with fistulas (the "fistula first" initiative) and decrease the usage of hemodialysis catheters. These guidelines are in part a response to the mortality and morbidity that has been realized in hemodialysis patients with suboptimal access. It is estimated that 20% of hospitalizations in dialysis patients are related to dialysis access problems.[72] Infection is the second leading cause of mortality in dialysis patients and is often related to the dialysis access. Adjusted mortality rates in patients who dialyze through a catheter as opposed to a fistula are 40% to 70% higher,[73] and these rates improve after being switched from a catheter to a fistula or graft.[74] Placement of dialysis access requires close collaboration between nephrologists, primary care physicians, and vascular surgeons to ensure that

it happens in a timely fashion. In general, access planning should take into account the level of kidney function, rate of decline, and the time needed for the selected dialysis access to mature.

Fistulas are typically created using a side-to-end anastomosis of the vein to the artery or less frequently a side-to-side anastomosis. Fistulas have the lowest complication rates, the longest patency rates, and require fewer interventions. Maturation time differs among accesses. Fistulas usually take at least 6 to 12 weeks to mature and may take as long as 8 to 9 months. In particular, fistulas tend to take longer to mature in diabetics.[75] Venous mapping through imaging with ultrasonography or venography is recommended to provide surgical planning.[76] In general, for fistula placement, a minimum vein diameter of 2.5 mm is necessary. For grafts the minimum vein diameter is 4 mm. The artery diameter should be at least 2 mm for both fistulas and grafts.[77] Stenosis or thrombosis of proximal portions of the vein that is to be used should be ruled out prior to fistula placement.

If the patient does not have anatomy that is amenable to placement of a native arteriovenous fistula then placement of a graft should be considered. AV grafts are usually composed of synthetic material, most often polytetrafluoroethylene (PTFE). Occasionally deceased donor vein grafts (cryoveins) or bovine carotid arteries are used; however, these have not been found to be superior to synthetic PTFE.[78,79] More recent work using stem cells to create artificial veins has the hope of providing more biocompatible graft materials for use in dialysis access in the future. Grafts often can be used as early as 2 to 3 weeks. Grafts are more prone to infectious complications than native fistulas. If graft material becomes infected the graft needs to be removed and the dialysis access will be lost. Problems with stenoses and thrombosis are also more common with grafts. Stenosis in grafts usually happens at the graft-vein anastomosis.

Catheters should be considered the last resort in patients who need long-term hemodialysis access. Catheters which are used for long-term access are tunneled under the skin and have a cuff whereas temporary catheters usually do not have a cuff or tunnel. The preferred site of insertion is the right internal jugular vein followed by the left internal jugular vein. In patients with difficult access, placement in the femoral veins or translumbar placement into the inferior vena cava can be considered. Subclavian catheters have been associated with higher rates of central stenosis and should be avoided.[8] Catheters should be locked with heparin, citrate, or thrombolytic agents to maintain patency between dialysis sessions.

ACUTE COMPLICATIONS OF DIALYSIS

Intradialytic Hypotension

Hypotension is a common complication of the hemodialysis procedure (Table 84.10) and is estimated to occur in 10% to 50% of treatments.[80] Intradialytic hypotension has been reported to occur more commonly in women, the elderly, diabetics, and patients with autonomic dysfunction.[81] Usually

84.10   Acute Complications of Hemodialysis

Complication	Potential Cause
Hypotension	Excessive fluid removal, excessive antihypertensive medication regimen, infection, myocardial infarction, tamponade, anaphylactic reaction
Hypertension	Sodium and water excess, inadequate ultrafiltration
Allergic reactions	Dialyzer, tubing, heparin, iron (especially dextrans), latex or tape reaction
Arrhythmias	Electrolyte imbalance, rapid fluid shifts, dialytic removal of antiarrhythmic medications
Muscle cramping	Rapid ultrafiltration, electrolyte imbalances
Air embolism	Air entry into blood circuit
Dialysis disequilibrium	Osmotic shifts between intracellular and extracellular space leading to cell swelling, cerebral edema. Rapid drop in plasma urea concentration
Dialysate/Water Quality Problems	
Chlorine/chloramines	Hemolysis, usually due to depletion of charcoal columns
Fluoride contamination	Itching, gastrointestinal symptoms, syncope, tetany, neurologic symptoms, arrhythmia; due to exhaustion of de-ionizer, usually not a complication if reverse osmosis is used
Bacterial/endotoxin contamination	Fever, rigors, hypotension; due to contamination of dialysate or water circuit

hypotension is related to aggressive ultrafiltration rates, but intradialytic hypotension can also be a sign of other clinical problems such as underlying infection, myocardial ischemia, or, if severe, an anaphylactic reaction to dialysis components. Excessive removal of volume from the plasma through an ultrafiltration rate that exceeds the plasma refill rate can lead to decreased circulatory volume. If the patient is subsequently not able to increase cardiac output to keep up with the volume lost or move fluid from the interstitium into the plasma compartment quickly enough then hypotension and hemodynamic collapse ensues. In hemodialysis patients there may also be a reduction in the ability of the venous system to appropriately vasoconstrict, possibly due to cardiopulmonary redistribution of blood flow that occurs in patients with arteriovenous accesses.[81] Left ventricular hypertrophy is thought to be a significant factor in intradialytic hypotension. Myocardial hypertrophy can impair ventricular filling by narrowing the ventricular cavity and leading to lower filling volumes. Myocardial hypertrophy and fibrosis can result in a stiff ventricular wall that requires a higher filling pressure to expand. Presence of atrial fibrillation can lead to intradialytic hypotension through decreased ventricular filling due to loss of atrial kick.[82] Autonomic nervous system dysfunction is seen frequently in ESRD, and in patients with

intradialytic hypotension, autonomic dysfunction is usually more severe, particularly in diabetic patients.[80]

Treatment of intradialytic hypotension involves measures aimed at restoration of blood volume or vascular tone. If the hypotension is mild and asymptomatic, patients may respond with improvement in blood pressure after simply discontinuing the ultrafiltration for a period of time sufficient enough to allow plasma refill and restoration of blood pressure. In more severe cases of symptomatic hypotension, administration of normal saline is indicated to restore blood volume. Placing the patient in the Trendelenburg position to improve vital cerebral perfusion can also be considered if the patient is symptomatic.

Accurate assessment of dry weight by the clinician is important to prevent iatrogenic excessive ultrafiltration. Key to the avoidance of intradialytic hypotension is patient control of interdialytic weight gains to prevent the need for excessive ultrafiltration rates. This can be accomplished through tight dietary sodium restriction and clinical attention to the amount of sodium delivered through dialysate during the dialysis process. Dialysate sodium levels should be kept low to prevent a net sodium gain during dialysis. Rapid ultrafiltration rates during dialysis (ultrafiltration rate of >10 mL/kg/hr) are associated with higher odds of intradialytic hypotension and a higher risk of mortality.[83]

Intradialytic hypotension can usually be avoided and dry weight goals still met in patients by decreasing the ultrafiltration rate and prolonging dialysis time. This simple yet time and resource intensive maneuver is perhaps the most effective intervention in the prevention of intradialytic hypotension. Cool dialysate has been shown to be an effective method for prevention of hypotension.[84] Alteration of the dialysate chemistry can improve stability as well. Increasing dialysate sodium or sodium modeling has been associated with greater stability but should be avoided to prevent sodium loading and rebound fluid excess. Higher calcium dialysate (3–3.5 mEq per L) may also be helpful but may lead to a positive calcium balance over time. Other methods frequently employed with little definitive data to support their use include colloid infusions such as albumin and medications such as midodrine. Careful adjustment of blood pressure altering medications is necessary when managing intradialytic hypotension.

Intradialytic Hypertension

Changes in blood pressure during dialysis are not always in the hypotensive direction. In approximately 10% to 15% of patients on hemodialysis blood pressure increases during the dialysis run or shortly thereafter. Increased predialysis blood pressure has been shown to have an inverse relationship with mortality in cross-sectional studies.[85] Perhaps this relationship is seen because healthier dialysis patients start out with higher blood pressures. However, this mortality benefit does not seem to hold true when the patient starts out with low or normal blood pressures and the blood pressure elevates with dialysis. In one study of over 400 patients on dialysis there was a twofold increase in the odds of hospitalization or death at 6 months in patients who had a blood pressure that increased with dialysis or failed to decrease by the end of the dialysis run when compared with patients who had a blood pressure decrease with dialysis.[86] Intradialytic hypertension seems more common in patients who are older, lower body weight, lower creatinine, lower albumin, and those on more antihypertensive medications.[87] The mechanism of intradialytic hypertension is unclear but most likely represents a state of salt and volume excess.[88] Other proposed mechanisms include increased sympathetic activity, activation of the renin-angiotensin-aldosterone system, endothelial cell dysfunction, vascular stiffness, erythropoietin stimulating agents, and dialysis related factors such as sodium loading, hypercalcemia, hypokalemia, and removal of antihypertensive medications during dialysis.[87] The majority of cases of hypertension during dialysis reported in the literature respond to increased ultrafiltration or prolonged slow ultrafiltration, suggesting volume excess as the predominant factor.[89]

Allergic Reactions

Allergic or hypersensitivity reactions are fortunately rare in hemodialysis patients but can be clinically devastating if not promptly recognized and treated appropriately. Over the course of hemodialysis technological advances, numerous types of anaphylactic (IgE mediated) and anaphylactoid (non-IgE mediated) reactions have been described. Anaphylactic reactions typically present as an acute event with pruritus, erythema, flushing, urticaria, and angioedema. If the episode is severe patients can develop hypotension, shock, laryngeal edema, and respiratory failure. Generally symptoms happen within minutes of starting dialysis but can manifest 30 to 45 minutes into the dialysis treatment. Ethylene oxide (EtO), an agent used in the sterilization of dialyzers, has been associated with allergic type reactions. This can be seen as a "first use" syndrome of dialyzers sterilized with EtO seen on the first dialysis run and not on subsequent uses of the dialyzer. The majority of dialyzers on the market currently are sterilized with steam or radiation, making this entity less frequent. Formaldehyde can be used in the sterilization and preservation of reuse dialyzers and has also been associated with IgE type anaphylactic reactions as well as delayed hypersensitivity reactions.[90] Dialyzer membranes can also be a source of immune stimulation. Polyacrylonitrile membranes are negatively charged and have been shown to increase bradykinin levels via the contact activation pathway. This reaction can be worsened if the patient is taking angiotensin-converting enzyme (ACE) inhibitors concomitantly due to the prolongation of the biologic half-life of bradykinin and other kinins.[91] Newer "biocompatible" synthetic membranes are generally well tolerated and only rarely precipitate an allergic reaction.[92] Heparin administered to dialysis patients can rarely induce anaphylactoid reactions. Heparin-induced thrombocytopenia (HIT) is a more common immune response to heparin leading to thrombocytopenia and a hypercoagulable state. Iron infusion is common in dialysis patients and known to cause allergic reactions, particularly with the administration of iron dextran. Iron preparations free of dextrans such as iron sucrose and sodium ferric gluconate are well tolerated and only rarely associated with allergic reactions. Patients can form allergies to latex from gloves and contact allergies to tape and adhesive products.

The management of allergic reactions depends on the severity of the reaction. In patients with severe reactions, dialysis should be stopped immediately and the blood in the dialysis circuit should be discarded. Acute management of life threatening situations should include the administration of epinephrine, antihistamines, corticosteroids, and attention to supporting potential airway compromise and hemodynamic collapse.[90]

Arrhythmias

Arrhythmias are a common cause of sudden cardiac death in dialysis patients. In a retrospective review of dialysis patients, ventricular arrhythmias were among the most common causes of cardiac arrest.[93] As one may expect, ventricular arrhythmias are a bad prognostic sign. Approximately one half of the patients survived 24 hours after the arrest, one third survived to discharge from hospital, and only 15%

survived 1 year after the arrest. Another review of a large number of dialysis patients provides insight into the risk factors that are associated with cardiac arrest while on dialysis. Older age, dialysis early in the week (Monday), low (0 or 1 mEq/L) potassium dialysate, diabetes, and use of a catheter for dialysis were all associated with higher risk for cardiac arrest and sudden death.[94]

Arrhythmias during the intradialytic period can be related to electrolyte disturbances. Rapid intradialytic shifts of potassium may play a role in precipitating intradialytic arrhythmias. One group looked at 30 arrhythmia-prone dialysis patients and noted that there was a tendency for ventricular ectopy in patients who dialyzed with a constant potassium level in the dialysate as opposed to a tapering potassium level in the dialysate.[95] Potassium profiling may be useful for patients prone to ventricular arrhythmias.

Atrial fibrillation is often present in dialysis patients. In a retrospective review of 488 Italian dialysis patients, atrial fibrillation was reported in approximately 30%.[96] Atrial fibrillation tended to be more common in older patients, patients with an older dialysis vintage, patients with ischemic heart disease, episodes of pulmonary edema, valvular heart disease, cerebrovascular accidents, increased left atrial diameter, and hyperkalemia. Interestingly, diabetes and hypertension were not associated with higher incidence of atrial fibrillation in this series, in contrast to the association seen in the normal population. In a review of USRDS data a prevalence of 10% was noted. One year mortality was noted to be 39% in the patients with atrial fibrillation compared with 19% in those who did not have the diagnosis.[97] The role of anticoagulation for atrial fibrillation in patients with advanced kidney disease is unclear. Patients with advanced kidney disease have increased incidence of both thromboembolism and bleeding events.[98] Previous studies evaluating the use of warfarin to prevent stroke for atrial fibrillation excluded patients with advanced kidney disease and caution should be used before extrapolating their results to dialysis patients.[99] In a cohort of incident HD patients with atrial fibrillation warfarin use was associated with increased incidence of stroke.[100] The risk–benefit balance should be carefully weighed on an individual basis when treating dialysis patients with warfarin.

Muscle Cramps

Muscle cramps are a common cause of intradialytic discomfort and a frequent patient complaint. Cramping can be a sign that the patient has reached an ideal dry body weight or it can be a sign of ultrafiltration rate that is too rapid. Cramps usually can be remedied by administration of normal saline and by discontinuing the ultrafiltration for a period of time. Hypertonic solutions (saline, dextrose, mannitol) may be useful.[101] Manual techniques such as massage or sequential compression also have a role in the prevention of cramps.[102] Avoidance of cramping during dialysis is of utmost importance. Often, cramping leads to patient dissatisfaction with the dialysis procedure and

can cause alienation from dialysis caretakers interfering with the ability to attain adequate dialysis. L-carnitine,[103] vitamin E,[104,105] and quinine sulfate[106] have all been suggested to help treat cramps but clear data to support their routine use is lacking. In the evaluation of persistent muscle cramping with dialysis, other reversible causes of cramping should be investigated and ruled out. These include thyroid disorders, hypomagnesemia, hyponatremia, hypocalcemia, and hypokalemia.

Dialysis Disequilibrium Syndrome

Dialysis disequilibrium syndrome (DDS) is a constellation of acute symptoms that was initially described early on in the history of dialysis in the 1960s.[107] DDS can manifest as a variety of symptoms including headache, nausea, vomiting, dizziness, and, in more severe forms, alteration in mentation, seizures, hypotension, shock, and coma. Symptoms are usually mild, transient, and only rarely have been associated with adverse clinical outcomes such as cerebral demyelination or death. Patients at greater risk for DDS include those with a history of previous CNS lesions, children, and persons with hyponatremia. DDS is caused by the development of cerebral edema in dialysis patients during the end of their dialysis session or shortly after dialysis is complete. The mechanism of DDS is hypothesized to involve urea effect, idiogenic osmoles, and/or changes in pH. Rapid removal of urea from the plasma space during dialysis creates a gradient between the intracellular space (high urea concentration) and the extracellular space (lower concentration) in the brain. If cellular mechanisms to move urea out of the cell have been adaptively suppressed due to chronically high urea concentrations then the movement of urea back into the extracellular space will be delayed allowing water to move up an osmotic gradient into the intracellular space causing cell swelling and cerebral edema. The diagnosis of DDS is largely clinical. DDS usually occurs in patients with chronic uremia when first initiated on dialysis. Rapid intradialytic drop in the plasma BUN concentration can precipitate DDS. Management of DDS is largely supportive and revolves around prevention by starting patients with chronic uremia on slow gentle dialysis initially to bring the urea levels down slowly. In cases where the dialysis needs to be performed more rapidly, consideration can be given to adding urea to the dialysate at a concentration that is 10% less than the serum concentration. Hemofiltration, hemodiafiltration, and PD have not been associated with DDS.[108]

Air Embolism

Air embolism is exceedingly rare but a potentially lethal complication of the hemodialysis procedure. Development of a pump-driven dialysis machine with negative arterial pressures created a higher potential for the introduction of air into the hemodialysis circuit. To remedy this potential problem standard hemodialysis machines come equipped with an air detector on the venous limb. This air detector is associated with a clamping mechanism that will clamp the line if

air is detected, preventing delivery to the patient. Due to this technological safeguard, machine-related air embolism in dialysis patients has become exceedingly rare. There are other potential causes of air embolism in dialysis patients that are not machine driven. In a fatal case of flawed technique, air was inadvertently administered to a dialysis patient after saline was pushed into a line full of air.[109] Air embolism can also be a complication of intravenous catheters. In one case of inadvertent laceration of a hemodialysis catheter, a patient presented with air embolism and respiratory compromise.[110] Air embolism can happen after catheter removal, particularly if a well-formed tract is present between the skin and the central vein, as is seen in catheters that have been in place for prolonged periods of time. If the patient has an intracardiac shunt, such as a patent foramen ovale, air can be introduced into the arterial system which can have devastating cerebrovascular effects.[111] To prevent air embolism during catheter removal, it is advisable to place the patient in the Trendelenburg position so that the venous pressure elevates and exceeds the atmospheric pressure thereby preventing a negative pressure which can draw air into the vein. If air embolism is suspected, the patient should be immediately placed in the Trendelenburg and left lateral decubitus position to move the air to the apex of the right ventricle and out of the pulmonary circuit. If a catheter is in place, attempts can be made to aspirate the air from the central line.

84.11 Chronic Complications of Hemodialysis
Cardiac disease
Protein calorie malnutrition
Hypertension/volume excess
Anemia
Renal osteodystrophy
Neuropathy
Reproductive dysfunction
Access complications
Bleeding diathesis
Infection
Amyloidosis
Acquired cystic kidney disease

CHRONIC COMPLICATIONS OF END-STAGE RENAL DISEASE

The following chronic complications of advanced renal failure (Table 84.11) are described in detail in other chapters of this text: cardiac disease (see Chapter 79), protein calorie malnutrition (see Chapter 85), anemia (see Chapter 76), neuropathy (see Chapter 78), renal osteodystrophy (see Chapter 77), and reproductive dysfunction (see Chapter 80).

Underdialysis

Inadequate delivery of dialysis can be a cause of morbidity in dialysis patients. Underdialysis usually presents subtly with a lack of appetite that can progress to more severe problems such as protein calorie malnutrition. If underdialysis is severe, patients experience the full range of symptoms associated with uremia. Clues to underdialysis lie in the history where patients may complain of pruritus or fatigue in addition to anorexia. Laboratory parameters and urea kinetic modeling may reveal measures of declining solute clearance or even inability to meet monthly adequacy goals. Worsening phosphorus levels or decline in hemoglobin may also be present. Alternatively, if protein calorie malnutrition progresses and is severe enough, patients can have low BUN and phosphorus levels which indicate poor nutrition as opposed to good clearance with dialysis. Underdialysis is most commonly a result of a dysfunctional dialysis access or an inadequate dialysis prescription. Workup of underdialysis should include a close review of the dialysis access for functional problems such as recirculation. In the setting of recirculation, dialysis efficiency is reduced due to blood which is leaving the extracorporeal circuit via the venous limb being taken up by the arterial inflow. In this situation blood which has already been dialyzed is sent through the dialyzer repeatedly leading to a decrease in the overall effectiveness of the therapy systemically. Doppler ultrasonography can be used to evaluate a dysfunctional dialysis access and decide if further intervention is needed to repair or replace it. Recirculation can also be calculated through measurements of arterial, venous, and peripheral blood samples (three-needle method) which can be used to calculate a percent recirculation:

$$\% \text{ Recirculation} = [C_{periph} - C_a / C_{periph} - C_v] * 100$$

Identification of significant recirculation (greater than 15% to 20%) should prompt further investigation of the dialysis access. Recirculation rates tend to be higher when catheters are used for hemodialysis due to the nature of their configuration with the arterial inflow in close proximity of the venous return. Location of the venous catheter tip can also have an effect on catheter recirculation.

After careful evaluation and repair of hemodialysis access problems, treatment of underdialysis involves increasing the dose of dialysis. This most readily can be accomplished by increasing the frequency of dialysis treatments, increasing blood, and/or dialysate flows or by increasing the duration of each dialysis treatment.

Hypertension in End-Stage Renal Disease

The Mechanism of Hypertension in End-Stage Renal Disease *(see also Chapter 41)*

Hypertension is present in 75% to 90% of dialysis patients.[112,113] As a potential risk factor for cardiovascular disease, hypertension has been associated with increased left ventricular mass in dialysis patients.[114,115] Excess sodium and fluid balance is thought to play the predominant role in driving hypertension in ESRD. In particular, large intradialytic weight gains contribute to hypertension in ESRD and may be associated with mortality.[116] In a large cohort study of over 85% of dialysis patients who gained more than 1.5 kg of weight in between dialysis sessions, after controlling for demographics and nutritional factors, higher weight gains were incrementally associated with all-cause and cardiovascular mortality.[117] Endothelial dysfunction, vascular stiffness, activation of the renin–angiotensin–aldosterone system, and increased sympathetic nervous system activity may also contribute.

Ideal Blood Pressure in End-Stage Renal Disease

According to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) the blood pressure goal for persons with hypertension, diabetes, or renal disease is less than 130/80 mm Hg.[118] These recommendations do not include the ESRD population. In an effort to find the ideal blood pressure for hemodialysis patients, one group studied 5,433 dialysis patients. In the analysis of postdialysis blood pressures they noted a U-shaped curve when graphing relative death rate on the y-axis and systolic blood pressure on the x-axis. The most favorable postdialysis systolic blood pressures were between 120 and 160 mm Hg. In analysis of the predialysis blood pressures this relationship held true when the blood pressure was low (lower blood pressure was associated with higher mortality). However, higher predialysis systolic hypertension was not associated with higher mortality, forming a J-shaped curve.[85] This relationship between predialysis blood pressures and mortality was confirmed in a study of over 4,000 dialysis patients that were randomly selected[112] and in a subsequent analysis of the HEMO study.[119] Others have argued that blood pressure measurements taken in the ambulatory setting are likely to have a higher prognostic significance than blood pressures that are obtained in center.[120] The relationship between blood pressure and mortality over time may be of importance as well. In a large cohort of nearly 17,000 incident dialysis patients, low systolic blood pressure (<120) was associated with increased mortality in years 1 and 2 after starting dialysis. High blood pressure (>150) was not associated with increased mortality early on but the association was seen in patients who survived over 3 years.[121] Despite these studies, the ideal target for blood pressure in ESRD remains unknown and more study will be needed to define appropriate clinical guidelines.

Treatment Options for Hypertension in End-Stage Renal Disease

Salt restriction and ultrafiltration (preferably through slow, longer dialysis sessions or daily dialysis treatments) are among the most effective options for treatment of hypertension in ESRD. Experience with dialysis patients in Tassin, France, has shown a time-dependent relationship between dialysis and volume control with longer dialysis sessions leading to superior volume control. The benefit of tight volume control has been seen in patients through improved blood pressure values and improved mortality.[122] In a cross-sectional study of ESRD patients from two dialysis centers (~200 patients per center) the differences between a medication intensive therapy versus increased ultrafiltration were evaluated. In one center patients practiced a salt-restricted diet and aggressive ultrafiltration without blood pressure medications. In the other center patients were treated with antihypertensive medications. Blood pressures were similar in both groups but the ultrafiltration group had lower left ventricular mass, lower frequency of left ventricular hypertrophy, and less frequent episodes of intradialytic hypotension.[123] One group performed a randomized controlled trial of 150 hypertensive hemodialysis patients who were randomized to routine dialysis care versus more intensive ultrafiltration to reduce dry weight without increasing duration or frequency of dialysis treatments. Systolic and diastolic blood pressure was reduced in the group with more aggressive ultrafiltration.[89] The downside of aggressive ultrafiltration without increasing the time spent on dialysis is the development of more symptoms associated with rapid fluid removal such as nausea, cramping, dizziness, and intradialytic hypotension. Even so, reduction of dry weight is an effective first step to decreasing blood pressure in dialysis patients.

Therapy with antihypertensive medication is rarely effective without concomitant control of volume status in hemodialysis patients. Often due to financial or time constraints and dietary indiscretion, adequate volume control cannot be achieved in hemodialysis patients through ultrafiltration alone. In such cases, medical therapy may be indicated. First line agents are RAAS blockers, especially in cases with coexisting diabetes and heart disease. RAAS blockers may also be of benefit in preservation of residual renal function. Choosing medical therapies for hypertension in ESRD requires attention to the timing of the dose of medication as well as the clearance of medications with dialysis so as to prevent episodes of intradialytic hypotension. Excessive prescription of antihypertensive agents can lead to the inability to ultrafiltrate and, therefore, inability to achieve adequate volume status.

Vascular Access Complications

Failure of Arteriovenous Fistulae to Mature

The rates of primary fistula failure to mature vary by patient population and center but are estimated to be around 40%.[124] Factors associated with a higher rate of failure to

mature include age >65, white race, coronary artery disease, peripheral vascular disease,[125] female gender, and forearm location.[124] Others have found that predialysis vein diameter is the major predictive element in fistula maturity.[126] Fistulae are usually ready for use when they meet the rule of sixes: minimum of 6 mm in diameter, less than 6 mm deep, and blood flows of >600 mL per min. The vessel walls of the fistula should be tough and firm to touch. Reasons for primary failure of fistulae to mature include inadequate anastomosis limiting flow to the fistula, collateral branches off the fistula diverting flow from the main conduit, and thrombosis. Management of fistulae that are failing to mature depends on the clinical scenario but likely will consist of Doppler ultrasonography of the access to evaluate blood flow and identify collateral veins as well as evaluation by a surgeon or nephrologist familiar with the placement of dialysis access.

Access Thrombosis

Access thrombosis can occur at any time in the lifespan of a fistula. Thrombosis is usually due to decreased flow through the fistula which allows blood more time to pool and clot. This can be due to venous outflow stenosis, extrinsic compression to the fistula, or due to arteriovenous anastomotic failure limiting flow to the fistula. Thrombosis occurs more frequently in grafts than native fistulae.[127,128] Patients with thrombosed accesses can present to medical attention following periods of systemic hypotension which precipitated the thrombosis.[129] Access thrombosis can usually be managed by angiography and local mechanical and/or pharmacologic thrombolysis. Percutaneous therapy has been found effective in prolonging survival of fistulae with primary failure due to thrombosis.[130]

Access Stenosis

Vessel intimal and fibromuscular hyperplasia can lead to stenosis of the dialysis access. In the case of PTFE grafts, up to 90% of cases of thrombosis are attributed to venous outflow stenosis developing within 2 to 3 cm of the venous anastomosis of the graft.[131,132] Central venous stenosis is also a common complication of dialysis access with the stenotic lesion developing in the more central venous location in the axillary, subclavian, brachiocephalic, or superior vena cava. Patients who have central vein stenosis can present with facial or neck swelling, extremity swelling, or superficial venous prominence across the chest wall and shoulder. Central venous stenosis is more common in patients with a history of multiple central lines, particularly in the case of central lines placed in the subclavian position or central lines placed on the left side, as well as in patients with pacemakers.[133,134]

Ischemic Injury

Arterial steal is a feared complication of the formation of an arteriovenous access. Particularly in the case of radial artery fistulas, blood can be diverted away from the hand and preferentially circulate through the fistula. Also, a low pressure palmar arch can provide preferential flow for the ulnar artery further diverting blood from the interosseous supply stealing the blood supply to the digits. The end result is ischemic injury to the hand. Symptoms of steal include paresthesias, cool digits, pain, and skin changes. If allowed to persist, steal can result in tissue loss and muscle wasting. Steal syndrome is more common in patients with a history of vascular disease, diabetes, lupus, and hypertension.[135] Steal can occur immediately after the surgical procedure to create the fistula or can present more insidiously over time. Occasionally, a procedure to improve fistula flow such as an angioplasty can exacerbate or unmask symptoms of steal. Treatment of severe steal syndrome usually involves surgical assessment for ligation of the fistula. In certain cases, consideration can be given to performing a distal revascularization and interval ligation (DRIL) procedure which can alleviate the steal while sparing the use of the fistula.[136–139]

Ischemic monomelic neuropathy is a rare form of access steal syndrome where multiple distal neuropathies develop in the limb following placement of the dialysis access. Classically ischemic monomelic neuropathy affects the radial, median, and ulnar nerve distributions (a pan-neuropathy) resulting in loss of motor function, paresthesias, and nerve deficits that are out of proportion to the ischemic findings in other tissues of the hand. As a result, patients can develop functional limitations and a "claw hand." The symptoms usually occur immediately after surgery. Treatment includes efforts at improvement of vascular perfusion and early reversal of the fistula or graft may improve symptoms.[140]

Venous hypertension can also occur in dialysis accesses with chronic thrombosis or stenosis.[141] This typically presents with swelling of the arm or hand distal to the access or distal to the stenotic lesion which can sometimes be in a central location. Digits can also appear cyanotic due to poor venous flow and pooling. Angioplasty of venous stenoses can improve venous hypertension though frequent intervention is often required after a stenosis has been identified in order to maintain the access.[142]

Aneurysms and Pseudoaneurysms

Aneurysms are common late complications of AV fistulas. Most of the time true aneurysms are of little clinical consequence; however, aneurysms can grow to be quite large and should be taken seriously if there are signs of altered integrity that may herald impending rupture. Such signs include skin changes overlying the fistula consistent with thinning, pigment changes, or overt tissue breakdown and scabbing. The presence of a firm aneurysm, pulsatile fistula, or inability of the fistula to collapse upon extremity elevation may point to a venous outflow stenosis or central venous stenosis as the etiology for expansion of an aneurysm. Occasionally, aneurysms can be revised, sparing the function of the fistula.[143] Pseudoaneurysms can be seen with grafts after needle puncture, and if there is an inability to seal off the graft puncture blood can collect under the skin in a hematoma. Rapidly expanding pseudoaneurysms, pain or throbbing, infection, or

loss of skin integrity should be taken seriously and require surgical or endovascular repair.[144]

Access Infection

Vascular access infection is common, with infection rates being the highest in catheters, followed by grafts. Infections are rare in the case of the native AVF.[128] Infectious organisms usually are skin flora such as S. aureus, S. epidermis, and Streptococcal species. Catheters with evidence of a tunnel infection (redness, pus expressed from tunnel, or fluctuance over tunnel) and infected graft material usually need to be removed in order to eradicate the infection.[145] Antibiotic therapy should be tailored to the cultured organism keeping in mind local resistance patterns if culture data is not available. Patients often require prolonged courses of intravenous (IV) antibiotics (6–8 weeks) if endovascular infection is suspected.

Bleeding Diathesis

Under normal conditions, hemostasis is dependent on intricate interplay between the platelet receptor glycoproteins (GPIb, GP IIb/IIIa), von Willebrand factor (vWF), fibrinogen, and the damaged endothelial surface. At areas of injury the subendothelial surface is exposed, vWF binds to the injured surface, platelet glycoprotein GP1b binds vWF, and GP IIb/III3 binds fibrinogen creating a mesh-like network that precipitates further platelet and fibrin aggregation as well as activation of the clotting cascade. Shear stress is required for affinity of the binding of vWF to GPIb.

In uremic states, platelet function is impaired and the normal clotting mechanism is altered. Platelets tend to be hyporesponsive in the setting of bleeding.[146] Typically this results in prolonged bleeding times[147]; however, it should be noted that other defects in platelet and coagulation cascade have been associated with an increased risk of thrombosis in dialysis patients as well.[148] The underlying mechanisms of platelet dysfunction in the uremic environment are unclear. Platelet aggregation may be impaired due to GP IIb/IIIa dysfunction or a uremic toxin that inhibits binding of GP IIb/IIIa to fibrinogen.[149] Abnormalities in the interaction between GPIb and vWF may also play a role. Increased levels of glycocalicin, a cleavage product of GPIb, has been demonstrated in dialysis patients.[150] Other mechanisms involved could include higher levels of prostacyclins and nitric oxide, reduction in platelet ADP levels, abnormal calcium signaling, altered blood rheology, and altered thromboxane-A2 production.[151] It is clear that uremic bleeding is not caused by elevated BUN as evidenced by studies of patients with rare urea disorders in the setting of normal renal function.[152]

Treatment of bleeding diathesis revolves around improvement of the uremic condition. Peritoneal dialysis seems to have a stronger association with clotting abnormalities as opposed to bleeding abnormalities when compared with hemodialysis, possibly due to increased middle molecule clearance, decreased platelet activation via dialysis membranes, and lack of need for anticoagulation with agents such as heparin.[153,154] Correction of anemia is also important as anemia is associated with prolonged bleeding times. In situations of active uremic bleeding, desmopressin (DDAVP) can be administered. DDAVP induces the release of vWF, leading to increased platelet adhesion and has been shown to be effective.[155] Recommended dose is 0.3 μg per kg given IV in 50 mL of NS over 30 minutes. DDAVP will act within 1 hour and the effect lasts up to 8 hours. More than two successive administrations of DDAVP are not likely to be effective due to depletion of vWF stores. Conjugated estrogens, cryoprecipitate, and activated factor VII can also be considered in cases of serious uremic bleeding.[156]

Infectious Complications

The following section is limited to infectious issues pertinent to the dialysis patient but not related to dialysis access.

Tuberculosis

Infection with Mycobacterium tuberculosis is more common in dialysis patients than the general population. The increased risk of tuberculosis in dialysis patients is believed to be due to impaired cellular immunity.[157] Risk factors for tuberculosis in dialysis patients in the United States include advanced age, unemployment, Medicaid insurance, reduced body mass index, decreased serum albumin, Asian and Native American race, ischemic heart disease, smoking, illicit drug use, and anemia.[158] Active tuberculosis in dialysis patients often presents with extrapulmonary manifestations which can make the diagnosis difficult.[159] Latent tuberculosis infection (LTBI) is believed to affect anywhere from 20% to 70% of patients.[158] Diagnosis of LTBI can be difficult but is of paramount importance as patients with LTBI on dialysis should be aggressively treated to prevent reactivation of infection and transmission to other patients in the dialysis center. Traditionally, diagnosis of LTBI has relied on the tuberculin skin test; however, this method is less sensitive in dialysis patients owing to high rates of anergy (up to 44%).[160,161] Newer testing strategies with interferon gamma release assays (TSPOT and QuantiFERON-TB) take advantage of two proteins which are specific to M. tuberculosis (not found in other forms of mycobacterium, including the BCG vaccine) known as early secretory antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10). ESAT-6 and CFP-10 are antigenic targets for T cells. When T cells encounter these proteins they release interferon gamma (IFN-γ). Therefore, by measuring T cell secretion of IFN-γ when exposed to ESAT-6 and CFP-10 one can indirectly test for the presence of M. tuberculosis. The role of IFN-γ release assays is unclear in the diagnosis of LTBI in dialysis patients; however, they appear to be useful in the setting of previous BCG vaccination,[162] recent exposure,[163] or active infection.[164] Treatment of tuberculosis in hemodialysis patients varies depending upon the activity of disease and location of infection. Care should be taken to dose anti-tuberculin medications after dialysis.[165]

Hepatitis B

Historically, hepatitis B has been a significant pathogen in the hemodialysis population. In 1974, the incidence of newly acquired hepatitis B infection in dialysis patients was 6.2%; this number dropped to 0.06% by 1999 after widespread implementation of guidelines to prevent the spread of hepatitis B in dialysis units.[166] Hepatitis B can cause acute and/ or chronic hepatitis and usually has an insidious onset. The hepatitis B virus is transmitted by percutaneous or mucosal transfer of blood or bodily fluids. Hepatitis B is remarkable in that it is stable at room temperature for up to 7 days on artificial surfaces.[167] Due to the potential ability of dialysis staff to transfer virus from one patient to another, guidelines have been developed by the Centers for Disease Control and Prevention (CDC) and endorsed by the Centers for Medicare and Medicaid Services (CMS) as a condition for coverage of a dialysis unit. These guidelines include isolation of dialysis patients with hepatitis B in a separate room, assignment of specific staff to hepatitis B patients alone (preventing simultaneous care for any patients who are hepatitis B susceptible), assignment of dialysis equipment to hepatitis B patients alone without sharing with other patients, assignment of a separate set of supplies, cleaning and disinfection of all equipment before use on another patient, use of gloves and glove changes between patients, and routine cleaning of all environmental surfaces. Dialyzers should not be reused in patients with hepatitis B infection. The guidelines also recommend routine serologic screening for hepatitis B and, in particular, monthly screening for patients who are hepatitis B susceptible.[167] Hepatitis B serologic status should be known for all patients prior to admission to a dialysis unit and testing should be repeated upon transfer to a different dialysis unit.

Hepatitis C

The hepatitis C virus can cause acute and chronic hepatitis. The course of hepatitis C is variable but the disease seems to be milder in dialysis patients. Patients tend to have lower viral loads, lower inflammatory activity, and lower amounts of fibrosis on liver biopsy.[168] Hepatitis C is transmitted through exposure to infected blood. Risk factors for infection include history of blood transfusions, intravenous drug use, and dialysis vintage. The CDC recommends routine screening for hepatitis C with monthly liver enzyme tests and every 6-month checks of hepatitis C antibodies. Liver function tests are of use in screening for hepatitis C because around 90% of hemodialysis patients with hepatitis C will have elevated ALT levels.[166] If unexplained liver enzyme elevations are noted, hepatitis C testing should be pursued with addition of polymerase chain reaction (PCR) for hepatitis C RNA if the enzyme-linked immunosorbent assay (ELISA) for hepatitis C antibody is negative. It has been proposed that hepatitis C infection can be occult in hemodialysis patients manifesting as a negative serum antibody, negative serum PCR for hepatitis C RNA, but detectable hepatitis C virus in mononuclear cells and liver tissue.[169] Occult hepatitis C is a consideration in patients with unexplained persistently elevated ALT levels; however, the clinical significance of occult infection remains unclear. Unlike hepatitis B patients, patients with hepatitis C do not require strict isolation. Rather, they require adherence to routine infection prevention practices applicable to all dialysis patients. Dedicated machines for patients with hepatitis C are not necessary and dialyzers can be reused if processed appropriately.

Patients on hemodialysis can be considered for treatment of hepatitis C, particularly if they are kidney transplant candidates. Typically ESRD patients are treated with dose adjusted standard interferon (IFN): 3 MU three times weekly subcutaneously (SQ) as monotherapy. Length of therapy depends on the genotype and is usually around 48 weeks for genotypes 1 and 4 and 24 weeks for genotypes 2 and 3. Viral load is typically checked at 12 weeks to evaluate the response to therapy.[170] Sustained virologic response to monotherapy in dialysis patients is around 37%,[171] which is higher than rates of persons with normal renal function treated with standard IFN (7% to 16%) and lower than persons treated with dual therapy including ribavirin. Proposed mechanisms for improved efficacy of IFN in dialysis patients include lower viral load, milder histologic disease, lower clearance of IFN, and increased endogenous release of IFN.[172] Pegylated IFN has not been extensively studied in the dialysis population but appears to provide no additional benefit when compared to standard IFN.[170] Ribavirin is usually not used as clearance is impaired in kidney disease and the drug carries an increased risk of hemolytic anemia. Even so, limited case reports have reported on successful use of dual therapy with careful monitoring.[173] Patients on dialysis seem to suffer from higher rates of side effects due to IFN therapy. Dropout rate due to side effects is around 17% for dialysis patients compared with 5% to 9% in patients without kidney disease.[170]

Vaccinations

Clinical practice guidelines recommend annual influenza immunization, hepatitis B immunization, and pneumococcal immunization for all dialysis patients.

Influenza vaccination is recommended on an annual basis. Live attenuated virus should not be used in dialysis patients. Immunization against influenza provides approximately the same rates of seroprotection in dialysis patients as the general population (~80%).[174]

In the general population, 90% to 95% of adults develop protective antibodies to hepatitis B after immunization. The effectiveness of the vaccine in dialysis patients is much lower and patients on dialysis require a higher dose of vaccine or an increased number of administrations. Studies have shown only 64% protection after a standard three dose regimen of hepatitis B vaccination, but this number can be improved to 86% if the vaccine series is increased to four doses. A special hepatitis B vaccine has been developed for dialysis patients which is higher dose (Recombivax HB 40 μg per mL).

Testing for immunogenicity can be performed 1 to 2 months after the last dose of vaccine to ensure patient response (goal hepatitis B surface antibody titer >10 mIU per mL). Booster doses should be administered to patients previously vaccinated if their hepatitis B surface antibody titers fall below 10 mIU per mL.[175] Based on the observation that combined hepatitis A and B immunization improves immunogenicity to hepatitis B in the general population, a randomized controlled clinical trial comparing combined hepatitis A and hepatitis B vaccination with hepatitis B vaccination alone was performed in dialysis patients which showed improvement in seroprotection when hepatitis A was added.[176] Therefore, it is advisable to administer hepatitis A vaccination at the same time or in combination with hepatitis B vaccination.

Pneumococcal vaccination is recommended every 5 years for dialysis patients; however, this interval can be shortened to 3 years if it is felt that the patient is at high risk for a pneumococcal infection.[175] Pneumococcal vaccination in dialysis patients has been associated with lower mortality risk.[177]

Amyloidosis

Dialysis-related amyloidosis is a disease entity seen only in ESRD patients and differs from other forms of systemic amyloidosis. In persons without renal disease, β2-microglobulin is freely filtered by the glomerulus then taken up in the proximal tubule and metabolized.[178] In ESRD clearance of β2-microglobulin is impaired and serum levels rise and accumulation of β2-microglobulin subsequently forms fibrils in tissues. Deposition of amyloid fibrils seems to have a predilection for articular tissues and bone but can deposit in all tissues. Clinically, the afflicted manifest joint pain and stiffness. Chronic arthralgias can progress to a destructive arthropathy. Most commonly the carpal tunnel is involved. The shoulders are another site of frequent involvement. Amyloid can also involve the synovial membranes and tendons of the hand leading to trigger finger or contractures. Amyloid deposits in bone can lead to pathologic fracture of long bones. Vascular deposition of amyloid may play a role in the vascular disease seen in patients with ESRD. Clinically significant visceral involvement is less common but can be found in the GI tract, heart, lung, liver, ovaries, ureter, and subcutaneous tissue.[179] Amyloid has been associated with GI bleeding, bowel infarction, and pseudo-obstruction.[180,181] Amyloidosis of ESRD usually manifests in patients who have been on dialysis for more than 10 years and becomes more common (up to 100%) in patients who have been on dialysis for more than 30 years.[182] The disease appears to be uncommon as the majority of dialysis patients do not live long enough for it to become clinically relevant. Even so, amyloid deposition appears to occur early in the course of ESRD. This observation has been noted on histologic autopsy studies demonstrating presence of amyloid prior to clinically evident disease.[183] Clearance of β2-microglobulin may be better in peritoneal dialysis.[184] Regardless, the histologic prevalence of amyloid in peritoneal dialysis patients did not differ from HD patients in one study of joint samples from continuous ambulatory peritoneal dialysis (CAPD) patients.[185] Newer, commonly used high flux dialyzers are more effective at removing β2-microglobulin from the circulation and probably account for the declining incidence of clinically relevant disease.[186–188] Convective forms of solute removal such as hemofiltration, in combination with dialysis (hemodiafiltration) are also more effective at middle molecule clearance. Management of the dialysis patient with amyloidosis centers around symptomatic treatments and local procedures such as carpal tunnel release. Patients who receive a renal transplantation usually have improvement in symptoms.[189]

Acquired Cystic Kidney Disease

Under circumstances of normal health, even persons without renal disease can acquire cysts in the renal parenchyma as they age. Acquired cystic kidney disease (ACKD) refers to persons with ESRD who develop at least three cysts in a kidney which were not present before the onset of renal failure and which cannot be explained by other inherited renal cystic conditions. Renal cysts are seen in over 80% of patients who have been on dialysis for more than 10 years.[190] Longer time on dialysis is a risk factor for the development of ACKD and this risk is also associated with higher rates of renal cell carcinoma (RCC).[191] The progression of ACKD may exist along a spectrum where cystic lesions evolve from simple to complex and on to form carcinoma.[192] The specific cause of ACKD is unknown but may be related to an increase in proliferation of renal tubular epithelial cells. The observation that cysts can improve after renal transplantation has led some to believe that the underlying mechanism of cyst formation may be related to the uremic environment.[193] Patients with RCC associated with ACKD often have multifocal and bilateral lesions. Clinical features of ACKD are often silent. Rarely patients can present with hematuria, flank pain, or spontaneous retroperitoneal bleeding. ESRD patients rarely die from metastatic RCC. Therefore, screening for disease is controversial and guidelines for screening in ACKD are not universally agreed upon, even in the post-kidney transplantation population.[194]

Neoplasia

It has been proposed that ESRD patients may be at a higher risk for cancer than the general population due to multiple factors. The uremic milieu may contribute to tumor formation. Increased oxidant stress and chronic inflammation seen in dialysis patients can lead to DNA alteration. Depressed immune system function may allow cancerous cells to grow unchecked and allow cancers that are associated with infectious pathogens to proliferate. Further, previous treatment with immunomodulatory medications may predispose to development of cancer (e.g., cyclophosphamide which has been associated with genitourinary cancers or rituximab which has been associated with lymphoproliferative disorders). Early reports and case series did not support the findings of increased rates of cancer in dialysis patients[195,196] but more recent and larger series seem to point toward an

association between certain types of cancer and ESRD. In a population-based cohort study an association was seen between patients with ESRD who were receiving renal replacement therapy and higher rates of RCC, liver carcinoma, and lymphomas.[197] In an international collaborative study[198] 831,804 patients who received dialysis from 1980 to 1994 were reviewed. They observed that 25,044 patients were diagnosed with cancer compared with the expected number of 21,185 patients if using normal population incidences. Higher risk was seen in younger patients and decreased with age. Significantly increased cancer risk was confined to specific tissues with cancers of the kidney, bladder, thyroid, tongue, liver, lymphoma, and multiple myeloma being more common. They noted that tumors in these areas are often associated with viral infections (human papilloma virus, Epstein Barr virus, hepatitis C), which suggests a role of impaired immunologic function in tumor pathogenesis. Cancers of the lung, prostate, breast, stomach, and colorectum were not increased compared to the general population. There is also an association between increased risk of kidney and urinary tract cancers in toxic nephropathies such as analgesic nephropathy and Balkan nephropathy. Risk for developing RCC increases with increasing time spent on dialysis whereas risk for developing bladder cancer decreases with time on dialysis.[199]

Consensus screening guidelines for cancer in ESRD do not exist currently. Given that malignancy is not a major cause of mortality in dialysis patients, cancer pathology in ESRD seems to differ from pathology in the general population. Furthermore, the expected longevity of the dialysis population is much less compared with that of the general population. Therefore, applying screening guidelines from the general population to dialysis patients seems inappropriate. The decision to screen ESRD patients for cancer should be customized to the individual dialysis patient taking into account inherent risks, the usefulness of the results obtained with the screening study, and its impact on future management.[200] Over time, as dialysis technology and medical therapy improves, and dialysis patients live longer, further study should guide recommendations for screening which will become more of a clinical necessity to protect the longevity of dialysis patients.

Psychosocial Problems

Psychiatric illnesses seem to be more common in patients with ESRD. When compared with patients with other chronic illnesses, hospitalization with mental disorders was 1.5 to 3 times higher in patients with renal failure. Of all psychosocial problems that dialysis patients suffer from, depression is the most common with estimates of 20% to 30% of dialysis patients afflicted with depression.[201]

Depression in dialysis patients may be driven by feelings of futility, loss of hope, fear, loss of control, loss of employment, financial stress, and altered family relationships. Higher prevalence of comorbid conditions and lower body

mass index is associated with depression.[202] Patients on dialysis who have depression have been found to have impaired cognitive function.[203] Elective withdrawal from dialysis has been linked to depression and occurs in 9% to 20% of ESRD patients. Stopping dialysis is a decision seen more often in the elderly, white patients, or women. High disease burden associated with malnutrition, dementia, malignancy, and other chronic disease states is also a risk factor.[204] Withdrawal from dialysis is not considered suicide; however, actual suicide rates are higher in dialysis patients compared with those of the general population. One study showed patients on dialysis were found to have an 84% higher rate of active suicide compared with that of the general population.[205] This was true for all age groups except age 15 to 29 which had lower suicide rates. The increased rate of suicide did not hold true across all races. Whereas whites and Asians had higher suicide rates, African American suicide rates were similar to those of the general population.

Anxiety also appears to be common with 18% seen in the national comorbidity survey[206] and rates up to 27% in other studies.[201,202] Anxiety can adversely affect dialysis patients, particularly when it interferes with their ability to complete a dialysis treatment session.

HOME HEMODIALYSIS

Home hemodialysis has been available since the early days of chronic renal replacement therapy when physicians realized that more patients could be offered hemodialysis if the patient was willing to shoulder some of the burden and cost involved in the administration of their care.[207] Limitations in the availability of in-center dialysis at the time drove many patients to home dialysis. Later, when dialysis therapy began to be financially supported by governments around the world, there was a shift from home to in-center therapies.

The benefits of home hemodialysis may include improved patient independence, flexibility with dialysis schedule, ability to provide more dialysis than what is offered in-center, improved health and quality of life,[208] as well as better survival.[209] Hospitalization rates are lower in home hemodialysis patients when compared to peritoneal dialysis patients.[210] Although these findings may represent a selection bias of healthier patients on home hemodialysis it may also be due to improved well-being and improved dialysis therapy. Home hemodialysis is considered an adequate bridge to transplantation and may even be an adequate substitution for transplant. A cohort study of the USRDS over 12 years showed no difference in survival between patients on home hemodialysis and patients who received a deceased donor transplant.[211] On the other hand, recipients of a living donor transplant tended to do better than home hemodialysis patients.

Home hemodialysis provides flexibility in schedules which can be adjusted to fit the patient. Short daily hemodialysis (SDHD) is usually done 5 to 6 days per week for 2 to 3 hours and nocturnal home hemodialysis (NHHD) is usually

done 5 to 6 nights per week for more than 6 hours. Home dialysis can also be done on the more traditional schedule of three times weekly for 4 hours per treatment. NHHD has the added benefit of extended time on dialysis without much intrusion into day-to-day life. Significant barriers exist to implementation of home hemodialysis including the patient's physical capabilities, fear, anxiety, and feelings of being a burden to their family. Remote monitoring, patient counseling, and education can help alleviate some of those fears.[212]

Home hemodialysis is somewhat hindered by access to water purification systems which are expensive to set up and can require extensive plumbing changes. Development of newer compact dialysis technologies using slow dialysate flow and dialysate saturation as well as newer sorbent-based systems should help to work around this problem by providing water-efficient dialysis. Currently used water-efficient dialysis technologies often use sterile dialysate in preformed bags. The anionic base used in the dialysate can be lactate as opposed to bicarbonate. This should be kept in mind in patients with liver disease as metabolism of lactate will be impaired, potentially leading to increased serum lactate concentrations. Other systems utilize streamlined water treatment systems for in-home generation of smaller quantities of dialysate.

Medication changes are common after starting patients on home hemodialysis. Volume control with frequent or daily dialysis is often superior and subsequently there is less need for antihypertensive medications.[213] Phosphorus levels decrease and binder medications often need to be adjusted or discontinued, particularly in patients on NHHD.[214] With more frequent hemodialysis bone marrow responsiveness to erythropoietin therapy improves,[215] although patients on more frequent dialysis may require higher iron and erythropoietin doses to keep up with increased blood loss involved with an increased frequency of dialysis treatment.[216]

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