CHAPTER 154

Technical and Clinical Complications of Intermittent Hemodialysis in the Intensive Care Unit

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OBJECTIVES

This chapter will:
1. Discuss the technical and clinical complications of hemodialysis in the intensive care unit.
2. Explain how to recognize and treat clinical and technical complications of this treatment.

Acute kidney injury (AKI) requiring renal replacement therapy (RRT) in the intensive care unit (ICU) is a serious condition with a reported mortality rate as high as 50% to 80%.[1,2] The choice of RRT depends on logistics and the patient's clinical condition. Although intermittent hemodialysis (IHD) may be used to manage AKI in the ICU, sustained low-efficiency dialysis (SLED) is also a popular therapy for critically ill patients. This latter modality has evolved as a conceptual and technical hybrid of continuous and intermittent therapies, with therapeutic aims that combine the desirable properties of each of the following component modalities[3]:

- A lower rate of ultrafiltration for optimized hemodynamic stability
- Low-efficiency removal of solutes to minimize solute dysequilibrium
- Intermittent treatments allowing patients to leave the unit for diagnostic and therapeutic procedures during scheduled down time.

This chapter reviews the various hazards complicating the course of IHD/SLED in patients with AKI receiving treatment in the ICU. Complications may be classified generally into two broad categories, clinical and technical. The clinical complications are vascular access problems, air embolism, hemolysis, and electrolyte and acid-base disorders. The clinical complications are bleeding, thrombosis, hypotension, hypoxemia, bioincompatibility, and allergic reactions, arrhythmias, febrile reactions, and dialysis dysequilibrium syndrome. The chapter also discusses other miscellaneous issues related to dialysis in AKI, including recovery of renal function, nutrition, and dialysis dosing.

TECHNICAL COMPLICATIONS

Vascular Access Problems

Table 154.1 lists the vascular access problems associated with hemodialysis performed to treat AKI in patients receiving intensive care.

At present, double-lumen, noncuffed dialysis catheters are the preferred means of obtaining acute dialysis vascular access. If it is anticipated that a catheter will be needed for more than a week, a tunneled cuffed catheter should be inserted to take advantage of the lower infection rates and higher blood flow rates associated with such catheters.[4] Noncuffed, double-lumen catheters are inserted percutaneously,

TABLE 154.1

Types of Vascular Access for Hemodialysis in the Intensive Care Unit

	FEMORAL CATHETER	INTERNAL JUGULAR CATHETER	SUBCLAVIAN CATHETER
Complications of insertion	Puncture of the femoral artery Groin hematoma Retroperitoneal hematoma Increased risk of infection	Puncture of the carotid artery Local hematoma Risk of pneumothorax, hemothorax Rupture of the superior vena cava Pericardial tamponade	Puncture of subclavian artery Risk of pneumothorax, hemothorax Rupture of the superior vena cava Pericardial tamponade Lesions of the brachial plexus
Advantages	Technically easy procedure; used by inexperienced operators Used when the cardiovascular condition of patient (pulmonary edema) does not allow thoracic catheterization	Low recirculation rate Low venous stenosis rate Ambulation possible	Low recirculation rate Low infection rate Ambulation possible
Disadvantages	Highest infection rate Highest recirculation rate (longer catheters [>19 cm] required) Used only in bed-bound patients Should not be left in place longer than 5 days	Technically difficult More prone to infectious complications, particularly in patient with tracheotomy Trendelenburg position required for placement	Technically difficult High rate of central venous stenosis Trendelenburg position required for placement

by means of the Seldinger insertion method, at any of three different deep venous sites: femoral, internal jugular, or subclavian. The anatomic venous site usually is chosen according to the clinical context and the physician's experience. Ideally, such dialysis catheters should be placed in the internal jugular or femoral position, the right internal jugular being the preferred site. Insertion into the right jugular vein is associated with a lower probability of major complications, because there is an almost straight venous path from the insertion site to the right atrium.[5,6] The subclavian route should be avoided whenever possible, because insertion of subclavian catheters is associated with an unacceptable rate of central venous thrombosis and stenosis, leading to loss of potential sites for future arteriovenous fistulas and grafts. This issue is of particular importance, because it is frequently difficult to determine which patients with AKI need continuous renal replacement therapy either at the time of discharge or in the future. The stenosis that forms in association with a subclavian catheter may be silent until an arteriovenous fistula or graft is created on the ipsilateral arm; the most common clinical presentation in this situation is ipsilateral arm swelling with subclavian vein stenosis. In patients with preexisting cardiovascular implantable electronic devices placed via the subclavian approach, it is easier as well as simpler to place the dialysis catheter on the contralateral side.

The causes of dialysis catheter malfunction depend on the time of introduction. In general, immediate catheter malfunctions are related to catheter position, whereas late malfunctions (more than 2 weeks after insertion) are related more often to thrombus or fibrin sheath formation.[7]

Thrombosed, noncuffed catheters can be exchanged over a guidewire or treated with thrombolytics as long as the exit site and tunnel are not infected. Exit site, tunnel tract, or systemic infections should prompt the removal of noncuffed catheters.[8] The thrombolytic agent used to treat thrombosis of a catheter varies with local practice. In the United States, for example, tissue plasminogen activator (tPA) is used commonly for catheter thrombolysis. This agent may be effective even in low doses of 1 mg per lumen.[9] Thrombosis of cannulated veins is another complication of indwelling catheters. The incidence of venous thrombosis ranges from 20% to 70%, depending on the site and diagnostic modalities used.[7,10] Deep vein thrombosis develops after activation of the coagulation cascade by an inflammatory process, which is triggered by the presence of the intraluminal foreign body and venous endothelial lesions. The patient has edema of the ipsilateral limb, which may be tender and painful. The presence of venous thrombosis is confirmed by ultrasonography. Treatment consists of catheter removal and anticoagulation.[11]

Infection

Infection is a common complication in dialysis-dependent patients in whom a catheter is used. Bacteremia usually results either from migration of microorganisms from the skin through the exit site and down the catheter into the bloodstream or from contamination of the catheter lumen.[12] The cuff represents a significant barrier for periluminal bacterial penetration, and infection rates with cuffed catheters are markedly lower than those with uncuffed catheters. Reported bacteremia rates vary from 3.8 to 6.5 per 1000 catheter-days[13,14] for uncuffed catheters and 1.6 to 5.5 for tunneled cuffed catheters.[15,16] In one study, the risk of bacteremia was higher after 1 week at the femoral site and after 3 weeks at the internal jugular site, and increased three-fold with the use of the femoral rather than the internal jugular site.[13] In another study, this risk was increased sixfold by the use of the internal jugular rather than the subclavian site (no femoral catheters were used in this study), likely because of a difference in the density of skin flora between the insertion sites.[14] A third study that compared the outcomes of uncuffed and cuffed catheters found an infection rate of 2.9 per 1000 catheter-days for tunneled cuffed catheters, 15.6 for uncuffed jugular catheters, and 20.2 for uncuffed femoral catheters.[17]

Prevention of infection requires strict aseptic care at the time of catheter insertion as well as optimal exit site care with regular review of the exit site and aseptic dressing change. The use of either povidone-iodine ointment or mupirocin ointment has been shown in randomized controlled trials to significantly reduce the risk of bacteremia from tunneled cuffed catheters. For temporary catheters, povidone-iodine and mupirocin ointments with dry gauze exit site dressings are reported to be similarly useful.[18–22] Use of a chlorhexidine-impregnated sponge (Biopatch) over the site of short-term arterial and central venous catheters (CVCs) has been shown to decrease the risk of catheter-related bloodstream infections (CRBSI) in a multicenter study.[23]

Access Recirculation

Access recirculation has not been as well defined for temporary cuffed catheters as for tunneled cuffed catheters. Access recirculation depends on the design and site of the catheter. Access recirculation is higher in femoral catheters than in those located elsewhere, especially if the catheter is shorter than 20 cm. Recirculation rates of 4%, 5%, and 10% (depending on whether the site was internal jugular, subclavian, or femoral) have been reported with temporary venous catheters and a fixed blood flow of 250 mL/min.[24] Interestingly, these recirculation rates did not significantly change at higher blood flow rates (up to 400 mL/min). On the other hand, short femoral catheters (15 cm) exhibit higher recirculation rates, which rise further with higher blood flow rates.[24] Finally, it is worth remembering that in up to half of the treatments, catheters will have to be used with inflow and outflow lines in reversed configuration—using the arterial line for venous return and the venous line for blood aspiration. In this context, recirculation rates of about 20% to 30% have been measured.[18] The impact of access recirculation on dialysis dose has been shown by the study of Leblanc et al.,[25] who reported that the urea reduction ratio (URR) was significantly higher with subclavian catheters (62.5%) than with femoral catheters (54.5%) despite identical IHD operating parameters for both sites.

Air Embolism

With the development of modern hemodialysis machines, the incidence of life-threatening air embolism has diminished. Modern machines contain air bubble detectors, which can stop the pump when air is detected in the system. The two types of air embolism—venous and arterial—are distinguished by the mechanism of air entry and the site where the embolism ultimately lodges.

The two common sites for air entry through the hemodialysis circuit are as follows:

1. The arterial line, into which air can be sucked because of subatmospheric pressure between the arterial access and the blood pump. Leaks in this segment, which may occur from a loose connector or a crack in the polymeric

silicone (Silastic) tubing of the blood pump, may result in air embolism.
2. Central venous catheters

Occasionally, air in the dialysate fluid may diffuse across the dialysis membrane into the blood, forming bubbles in the venous air trap.

Most causes of air embolism are reported during catheter insertion, incorrect catheter removal, or disconnection of central venous catheters.[26] During dialysis, the air emboli are typically venous. The clinical severity depends on the quantity of the injected air, the rate of air entry, and the site of entry. The patient's body position at the time of embolization determines the clinical manifestations. With the patient in the sitting position, the air first may migrate to the cerebral blood vessels, causing neurologic decompensation and unconsciousness. With the patient in the recumbent position, air reaches the right atrium and right ventricle; foam develops in those chambers and flows into the pulmonary vasculature, which becomes occluded, causing pulmonary hypertension. Symptoms of this complication are dyspnea, chest pain, and cough followed by cardiovascular collapse.[27,28] In rare cases, air that has entered venous circulation can reach the left heart and then the systemic arterial circulation, where it may provoke coronary and cerebral embolization. Embolization can happen through "paradoxical embolism" via a patent foramen ovale, through passage through physiologic pulmonary arteriovenous shunts, or from incomplete filtering of a large air embolus by the pulmonary capillaries.

Because the majority of affected patients have nonspecific symptoms, air embolism may be difficult to diagnose in the absence of a high level of suspicion for such a possibility. Air embolism should be suspected in dialysis-dependent patients after insertion, manipulation, or removal of a central venous catheter in whom sudden onset of cardiopulmonary or neurologic decompensation develops. Transesophageal echocardiography is a definitive method for detecting intracardiac air. If an air embolism occurs, the venous blood line should be clamped immediately to prevent further entry of air. Management is supportive, with the patient being placed in flat, supine position for arterial air embolism. For venous air embolism, patients may be placed in either a left lateral decubitus position (Durant's maneuver), Trendelenburg position, or left lateral decubitus head down position).[29] Adequate oxygenation is often possible only with an increase in the oxygen concentration of the inspired gas up to 100%. If the patient does not show response within minutes, mechanical ventilation and inotropic support may be needed. If significant foaming has occurred in the right ventricle, causing cardiac arrest, cardiac puncture and aspiration should be performed to remove the foam. Hyperbaric oxygen therapy is an additional aid in treating air embolism.[30,31] In addition, because chest compressions can force air out of the pulmonary outflow tract and into smaller pulmonary vessels, improving forward blood flow, they can be used as a last-resort maneuver in patients with severe hemodynamic instability.[32,33]

Hemolysis

Clinically significant hemolysis can occur during the dialysis procedure. There are numerous reported causes of acute hemolysis, including oxidant damage (from chloramines, zinc, copper, or nitrate contamination of the dialysate), reduction injury (from formaldehyde used to disinfect reprocessed dialyzers or water treatment system), osmolar injury (from hypotonic or hypertonic dialysate), thermal injury (from overheated dialysate), and mechanical injury (e.g., kinking of blood lines, narrowed aperture of the blood tubing set, pump malocclusion, and the presence of a blood clot at the tip of a subclavian catheter). Clinical manifestations include headache, abdominal pain, nausea, vomiting, chest or back pain, malaise, shortness of breath, and severe hyperkalemia resulting from hemolysis. Immediately after acute hemolysis is suspected or diagnosed, the blood pump should be stopped, the venous blood lines clamped, and the blood discarded. Dialysis should be restarted as soon as the patient is stable, owing to potential fatal hyperkalemia if it is not.[30,34]

Electrolyte and Acid-Base Disorders

Hyponatremia or hypernatremia can occur if there is an error with the preparation of electrolyte solution and the conductivity monitors fail or the alarms are not set properly. Acute hyponatremia causes water intoxication, cerebral edema, and hemolysis. Its clinical manifestations include neurologic symptoms, abdominal pain, leg cramps, and hyperkalemia. Treatment consists of stopping the dialysis session and starting another dialysis using a dialysate sodium concentration level of 120 to 130 mEq/L or, if hyponatremia is life-threatening, a hypertonic saline infusion to raise the plasma sodium concentration to 120 to 125 mEq/L. Complete normalization of plasma sodium concentration should be avoided to reduce the level of cerebral edema.[27]

Hypernatremia causes intracellular (including cerebral) volume depletion as water shifts into the extracellular space. Its symptoms include thirst, headache, nausea and vomiting, seizures, hot flushes, weakness, and even coma and death. If severe hypernatremia occurs, the dialysis treatment should be stopped. Oral water or an infusion of 5% glucose should be given, and dialysis restarted with an appropriate sodium concentration in the dialysate. To prevent cerebral edema, plasma sodium levels should not be allowed to fall below 145 mEq/L.[27]

Hypokalemia can occur when patients, especially those with acidemia, undergo dialysis with a low-potassium dialysate, because the correction of acidosis results in a rapid shift of potassium from the extracellular space to the intracellular space. Hypokalemia is associated with muscle weakness, fatigue, cardiac arrhythmias, and cardiac arrest. Dialysis-induced hypokalemia can be prevented by raising the dialysate potassium concentration. Intravenous potassium can be administered during dialysis when needed. The serum potassium level should be determined frequently to minimize the risk of hyperkalemia.[30] Dialysis-induced hyperkalemia is rare. Theoretically, the use of high-potassium dialysate or inadvertent potassium supplementation could lead to hyperkalemia during dialysis. The most common cause of hyperkalemia is hemolysis. Hyperkalemia should be suspected in any patient undergoing dialysis who has weakness, dysrhythmia, or hypotension. Treatment consists of dialysis with a low-potassium dialysate.[30]

Hypophosphatemia can become a significant problem in patients undergoing daily IHD or SLED in the ICU setting. Phosphorus is removed during dialysis, and hypophosphatemic patients require phosphorus supplementation during dialysis to prevent muscle weakness and cardiac arrhythmias.[34] Because phosphate is distributed predominantly intracellularly, its removal is enhanced by more frequent and longer dialysis, which may require monitoring and replacement.

Hypercalcemia can occur because of faults in the ICU water supply. In absence of proper safeguards and/or faults

in the deionized/water softener systems, dialysate calcium or magnesium concentration may rise inappropriately, leading to what some call hard water syndrome. Symptoms of this condition consist of nausea, vomiting, increased warmth, headache, tachycardia, and hypotension. The dialysate concentration should be immediately checked for any patient exhibiting such symptoms and corrected if necessary.

Metabolic acidosis resulting from dialysis is not a common complication. It occurs as a consequence either of defective conductivity or defective pH sensors in the dialysis equipment or of incorrect buffer concentration. Metabolic acidosis causes nonspecific symptoms, including malaise, nausea, headache, and hypotension. It also predisposes to ventricular arrhythmias. Treatment consists of administration of sodium bicarbonate and the use of dialysis fluid with the correct concentration of buffer.[27]

Metabolic alkalosis can occur on HD/SLED if the final dialysate buffer base concentration delivered to the patient (bicarbonate precursors such as acetate/citrate provided by the acid component and bicarbonate provided by the bicarbonate component) is not monitored carefully. Citrate-induced metabolic alkalosis also can occur in case of multiple blood transfusions.

CLINICAL COMPLICATIONS

Bleeding and Thrombosis

Anticoagulation is an essential component of all extracorporeal therapies. The passage of blood through an extracorporeal circuit causes platelet activation and induces a variety of inflammatory and prothrombotic mediators, resulting in fibrin deposition on filter membranes. The extracorporeal circuit is prone to clotting during acute treatments, unless some form of anticoagulation is employed. Clotting of the system leads to loss of blood, decreased delivery of therapy and/or reduced clearance, and higher costs of therapy. On the other hand, excessive anticoagulation may result in bleeding complications. Patients with AKI can have many comorbidities that further raise hemorrhagic risk, such as disseminated intravascular coagulation, sepsis, and hepatic failure. Uremia is thought to cause bleeding diathesis by impairing platelet aggregation and platelet–vessel wall interaction.[35] Studies over the last 30 years suggest that gastrointestinal bleeding is the most common bleeding complication of AKI observed in 10% to 36% of cases.[36] Other, less common manifestations are intracranial bleeding, hemorrhage of surgical wounds, retroperitoneal hematoma, hemorrhagic pleural effusion, subcapsular hepatic hematoma, and hemopericardium.

Systemic anticoagulation with heparin is used commonly for anticoagulation in patients undergoing dialysis in the ICU. However, the major drawback of systemic heparin therapy is the risk of life-threatening bleeding episodes, which ranges from 25% to 30%.[37,38] Alternative methods for anticoagulation have been proposed, such as regional heparinization with protamine, low-molecular-weight heparin, regional citrate anticoagulation, prostacyclin, and saline flushes with no anticoagulant. Combination regimens using heparin and prostacyclin are more popular in Europe and are reported to be fairly efficacious.[39,40] Regional citrate anticoagulation has been found to be an effective alternative to heparin anticoagulation in patients at high risk for bleeding.[38,41,42] Regional citrate anticoagulation may be complicated by metabolic alkalosis, particularly if high doses of citrate are required; therefore frequent monitoring of the acid-base status is mandatory with its use.[43] Dialysis with citrate may induce a rise in total calcium concentration during and after dialysis.[44] If citrate cannot be metabolized (e.g., in liver dysfunction), it complexes with calcium, leading to an increase in total serum calcium with a corresponding fall in ionized fraction (calcium gap).

Compared with continuous CRRT, SLED has some important advantages with regard to anticoagulation and bleeding risk. One study found that patients treated with SLED required significantly less heparin than those treated with CRRT; 31.9% of the subjects receiving SLED could be dialyzed without anticoagulation, compared with 2.7% of those undergoing CRRT.[45] SLED using saline flushes also can be performed safely and efficiently without anticoagulation.[46,47]

Treatment of patients with bleeding who are undergoing dialysis is similar to that in patients without dialysis. It consists of volume and blood replacement, identification of the bleeding sites, and appropriate definitive therapy, which depends on the severity and site of bleeding. The administration of desmopressin acetate (DDAVP), cryoprecipitate, and conjugated estrogens may be beneficial.[30,48]

Repetitive thrombosis of the extracorporeal circuit and hemofilter is a common consequence of inadequate anticoagulation. The hemofilter's life span is correlated directly to the activated partial thromboplastin time (APTT). The likelihood of hemofilter plugging decreases by 25% with every 10 second increase in APTT.[11,49] It appears that polyamide membranes are less thrombogenic than acrylonitrile membranes.[50]

Hypoxemia

During dialysis treatment, arterial partial pressure of oxygen (PaO_2) falls by about 10 to 20 mm Hg. The clinical implication of the dialysis-induced hypoxemia is of immediate importance to the patient whose cardiopulmonary function is already compromised. Hypoxemia is multifactorial in cause, but it is related principally to the use of acetate dialysate (rarely used) and bioincompatible membranes. Acetate causes hypoxemia by at least two mechanisms, increased oxygen consumption resulting from acetate metabolism and hypoventilation secondary to carbon dioxide loss across the dialyzer membrane.[51,52] Hypoxemia is observed particularly with use of unmodified cellulose membranes. The interaction between blood and cellulosic membranes activates the alternate complement pathway, leading to intrapulmonary leukostasis, which in turn causes ventilation-perfusion mismatch and hypoxemia. This is decreased significantly if biocompatible noncellulosic membranes such as polyacrylonitrile and polysulfone are used.[53–56]

In critically ill patients, who already may have some predialysis hypoxia, it is necessary to increase the ventilated volume and/or the fraction of inspired oxygen (FiO_2) during dialysis. The use of bioincompatible membranes and acetate dialysis should be avoided.[30]

Hypotension

Although hypotension is common with hemodialysis, it becomes all the more significant in the ICU setting, owing to a much sicker patient population with multiple comorbidities. Hypotension is common in patients receiving intensive care. It may be a special problem in kidneys with acute tubular necrosis, which appear to be particularly sensitive to diminished perfusion. Normal kidneys vasodilate in the presence of ischemia as part of the autoregulatory response to keep renal blood flow and glomerular filtration rate near

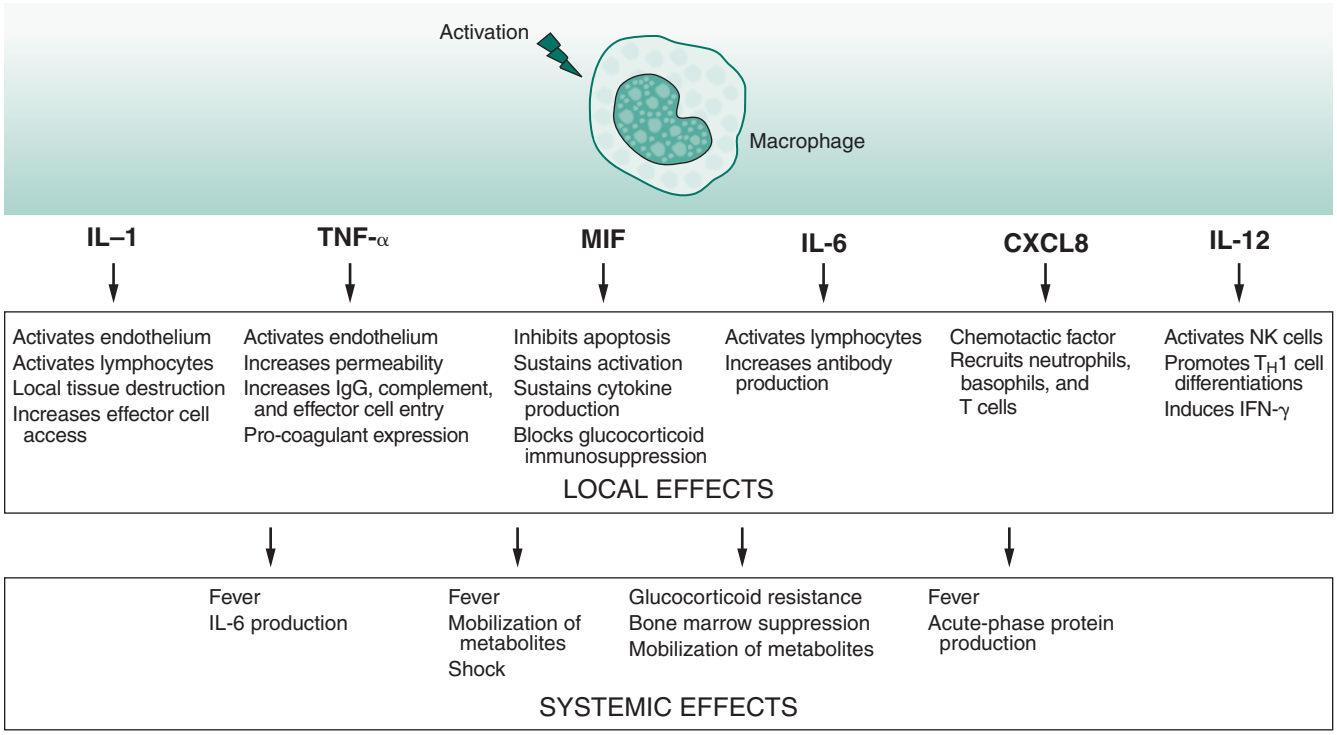

FIGURE 154.1 Causes of intradialytic hypotension. *CXCL-8,* C-X-C motif chemokine ligand 8 (also known as interleukin 8, IL-8); *IL-1,* interleukin-1; *IL-6,* interleukin-6; *IL-12,* interleukin 12; *MIF,* macrophage migration inhibitory factor; *TNF-α,* tumor necrosis factor-alpha.

baseline levels. Autoregulation is impaired in acute tubular necrosis, perhaps because ischemic endothelial injury reduces the release of vasodilating substances such as prostacyclin and nitric oxide.[57,58] Hemodynamic instability experienced by patients with such problems can be enhanced further by initiation of RRT. The mechanisms of dialysis-related hypotension are complex (Fig. 154.1). In addition, hypovolemia secondary to blood loss or third spacing of fluids may contribute to hypotension in this patient group.

The most important factors causing hemodynamic instability seem to be aggressive reduction of circulating blood volume owing to ultrafiltration, rapid decrease in extracellular osmolality associated with sodium removal, and coexisting imbalance between ultrafiltration and plasma refilling.[59] The rate-limiting step for removal of fluid from the body is the transport rate between the extravascular and the intravascular compartments. In many patients in the ICU, the fluid transport between the intravascular and extravascular fluid compartments is altered by changes in the permeability of the capillaries resulting from inflammation and by alterations in plasma colloid or crystalloid osmolarity resulting from hypoalbuminemia and/or electrolyte disturbances. The fluid removal rate thus often is limited because of inadequate "refilling" of the vascular bed.[60] If ultrafiltration takes place at a rate exceeding the capacity of the interstitial fluid to migrate into the intravascular compartment, a rapid fall in plasma volume with consequent hypotension will result.[61] The usual response to a reduction in circulating plasma volume consists of increases in cardiac output, peripheral vascular resistance, and venoconstriction. Hypotension can occur when one or more compensatory responses are defective. Several factors, including autonomic dysfunction, dialysate temperature, membrane biocompatibility, splanchnic fluid sequestration, and tissue ischemia, could impair the normal compensatory response of patients to intravascular volume depletion.

The situation may be compounded by a reduction in venous capacitance reactivity, which is in part related to the cardiopulmonary redistribution of blood flow that may occur if patients undergo dialysis through an arteriovenous fistula or arteriovenous graft. The combined effect is a further reduction in cardiac filling pressures. Initially the reduction is compensated by increased sympathetic nervous and neuroendocrine activity. However, in some patients, these compensatory mechanisms fail for a variety of causes (autonomic dysfunction, dialysate temperature, membrane biocompatibility, splanchnic fluid sequestration, and tissue ischemia). This failure may lead to the Bezold-Jarisch reflex, a cardiodepressant reflex typified by a relative bradycardia and hypotension. Clinically, patients experience muscle cramps resulting from reduced muscle blood flow, abdominal pain resulting from mesenteric angina and/or ischemic pancreatitis, cardiac angina, transient ischemic brain damage, and, in severe cases, unconsciousness and even a full-blown stroke or myocardial infarction. Repetitive hypotension may result in numerous small cerebral infarcts.

The composition of the dialysate also may influence blood pressure in several ways. Sodium and calcium concentrations, the nature of the buffer (i.e., bicarbonate or acetate), and the temperature of the dialysis fluid are among the factors that influence the frequency of hypotension during dialysis. Acetate, a peripheral vasodilator, also may predispose to hypotension by reducing myocardial contractility. Hypoxemia during dialysis is exacerbated by acetate-buffered dialysate and contributes to hypotension. Patients undergoing dialysis often are receiving antihypertensive agents or other medications that can interfere with the normal hemodynamic response to ultrafiltration. Beta blockers reduce myocardial contractility and also exert a negative chronotropic effect. Such agents, by preventing a compensatory increase in the heart rate, interfere with a major defense supporting blood pressure during

dialysis. Verapamil can be expected to exert a similar effect. Vasodilators can prevent the vasoconstriction response to ultrafiltration.[62]

Hypotension also can be a major problem in patients with liver failure. RRT in these patients often is complicated by severe intradialytic hypotension despite the use of pressors and cooled/high sodium dialysate. As a result, achieving ultrafiltration in these patients can be challenging. Thus SLED (or continuous renal replacement therapy) may be preferable in this patient population to maintain cardiovascular stability as well as achieve better solute clearance/fluid removal.[63]

There is concern that hypotensive episodes during RRT may impede renal recovery.[64] Conversely, reduction of hypotensive episodes should have a positive effect on the recovery of renal function. On the basis of the premise that SLED is hemodynamically "gentler" and thus less prone to cause hypotension, it also has been studied in this regard.[65–68] The first randomized, prospective, controlled trial, performed by Kielstein et al.,[66] compared cardiovascular tolerability of extended dialysis with that of continuous venovenous hemofiltration in severely ill patients with AKI in the ICU. The results of the study showed no difference in mean arterial blood pressure or use of catecholamines between the treatment groups.[66] Some other studies also have shown cardiovascular tolerability associated with SLED to be similar to that associated with continuous RRT, even in severely ill patients.[67–69]

SLED is an increasingly used mode of RRT that may have a favorable hemodynamic profile, even in critically ill patients with AKI in the ICU.[70]

Preventive measures to avoid hypotension consist of using cool dialysate (35°C) and use of selective α agonists such as midodrine. Treatment of intradialytic hypotension depends on its mechanism. Hypovolemia-induced hypotension (low cardiac output, low preload) should be managed with either isolated or sequential ultrafiltration or SLED. Patients with cardiogenic shock (low cardiac output, high filling pressures) requiring RRT may benefit from inotropic support, reduction of afterload, and a higher dialysate calcium concentration. Finally, if vasodilatory shock is present (high cardiac output, low systemic vascular resistance), the use of vasopressors (norepinephrine, phenylnorepinephrine, vasopressin) and/or corticosteroids may be required. Dosage of vasopressors may have to be increased at the start of RRT for patients already receiving vasopressors. In general, measures such as reducing or stopping ultrafiltration and performing volume replacement with normal saline commonly are used.

Biocompatibility

Several studies in experimental animals with AKI have shown that complement activation during the blood-dialyzer interaction with cuprophane membranes (but not with more compatible membranes) can lead to neutrophilic infiltration into the kidney (and other tissues) and prolonged AKI. Animal studies have shown the adverse effects of infiltrating leukocytes on recovery of renal function[71] and on whole-kidney glomerular filtration rate when activated neutrophils are infused into a mildly ischemic kidney.[72] In studies of rats with AKI, dialysis using a membrane that activated complement and neutrophils was found to lead to a slower resolution of renal failure and to be associated with a threefold rise in the number of neutrophils per glomerulus in histologic sections in comparison with dialysis using a membrane that did not activate complement.[73,74]

These findings may be applicable to humans, because some prospective randomized trials have shown that survival rate and rate of recovery from AKI in critically ill patients were significantly higher and that the recovery occurred earlier when dialysis was performed with biocompatible rather than bioincompatible cuprophane membranes.[75–77] Other studies, however, have not detected a difference in survival with use of these different membranes.[78–80] Several meta-analyses have been performed, with inconsistent results.[81–83] In a meta-analysis of the Cochrane database, 10 studies were reviewed, involving a total of 1100 patients with AKI requiring IHD. The values for relative risk of death and rate of recovery of renal function were similar for biocompatible and bioincompatible membranes.[84]

Another important issue in this context is the choice of membranes for dialysis of patients with concomitant hepatic failure. Because these patients may be particularly prone to harmful effects of elevated intracranial pressure, owing to their tendency for development of cerebral edema, the choice of membranes becomes important. In this regard, polyacrylonitrile and polyamide membranes are preferable to cuprophane membranes. The former, being more biocompatible (polyacrylonitrile more than polyamide), has a lesser tendency to affect intracranial pressure.[85]

Hypersensitivity Reactions

Hypersensitivity reactions are observed occasionally during dialysis therapy for AKI. There are two types of first-use reactions, a hypersensitivity type (type A) and a nonspecific type (type B).

Type A reactions usually occur in the first few minutes of dialysis, immediately after the return of blood from the dialysis circuit to the patient; however, the onset may be delayed up to 30 minutes into treatment. The symptoms may be mild to moderate, consisting of itching, urticaria, flushing, rhinorrhea or lacrimation, cough, sneezing, wheezing, abdominal cramping, diarrhea, and dyspnea. However, severe reactions—bronchospasm, bradycardia, hypotension, cardiac and/or respiratory arrest, and death—have been described. Several mechanisms have been suggested to explain these reactions. Among these, pretreatment with ethylene oxide and use of polyacrylonitrile membranes, especially AN69 (in patients treated with angiotensin-converting enzyme [ACE] inhibitors) are well-defined causes of anaphylactoid reactions. Reactions to ethylene oxide are uncommon with improved degassing techniques, thorough rinsing of new dialyzers and tubing, and replacement of ethylene oxide by steam or gamma radiation to sterilize dialyzers.[86,87]

Since 1990, a number of clinical studies have shown a strong correlation of use of synthetic AN69 polyacrylonitrile membrane with induced anaphylactoid reactions. Most of the reactions were observed in patients treated with ACE inhibitors,[88–91] although a few episodes have been reported that were not associated with ACE inhibition,[89,92] or in the presence of angiotensin II receptor antagonist therapy.[93,94] The pathogenesis of these anaphylactoid reactions is not clear, but the involvement of ACE inhibitors in the vast majority of cases suggests a role for bradykinin.[92] Bradykinin is generated via contact activation, so contact of blood with negative charges on the surface of an AN69 membrane could cause release of bradykinin. Normally, the released bradykinin is degraded effectively by the activation of ACD (which is identical to kininase II), but in the presence of an ACE inhibitor, the degradation is inhibited and bradykinin can accumulate, allowing the full development of the clinical picture.[92,95] If the reaction occurs, dialysis

should be stopped immediately and the tubing should be clamped. The dialyzer and tubing, along with the blood contained therein, should be discarded. The patient should be treated, depending on the severity of the symptoms, with antihistamines, corticosteroids, epinephrine, bronchodilators, and/or vasopressors.[96]

Type B reactions are less severe than type A reactions. The most common symptoms are chest and back pain, dyspnea, cramps, nausea, vomiting, and hypotension. Symptoms of type B first-use reactions usually are observed during the first hour of dialysis and disappear or lessen dramatically during subsequent hours.[96] The pathogenesis of type B reactions is not clear. It is thought that they may be related to complement activation. Treatment with oxygen and analgesics is sufficient.

Cardiac Arrhythmias

Arrhythmias are one of the major cardiovascular complications of dialysis, because their occurrence may result in severe cardiovascular collapse and sudden death. Both patient- and treatment-related factors are involved in their occurrence. Patient-related factors include age, heart and/or lung failure, rapid reduction of extracellular fluid volume, electrolyte and acid-base derangements, cardiac and major vascular surgery, digoxin therapy, and sympathetic dysfunction. Treatment-related factors include changes in serum potassium or calcium concentrations as well as in acid-base balance produced by dialysis.[30] Hypokalemia increases the vulnerability of the heart to arrhythmias because of a higher ratio between intracellular and extracellular potassium concentrations, which results in a negative membrane potential. Dialysis leads to rapid changes in serum potassium level, especially when a low-potassium bath is used. The concomitant use of digoxin increases the sensitivity of the heart to rapid changes in serum potassium and may augment the risk for arrhythmias in patients undergoing dialysis.[27,97,98] Acetate in the dialysate also has been implicated in the pathogenesis of arrhythmias during dialysis, and a reduction in the incidence has been demonstrated with a switch to bicarbonate-buffered dialysis fluid[99,100]; however, these findings have not been universal.[101]

Dialysate calcium level also can influence the incidence of arrhythmias. Use of a dialysate with high calcium concentration raises the serum calcium concentration and may induce life-threatening arrhythmias during dialysis through an increase in reentry or triggered activity.[102] If arrhythmia develops in a patient undergoing dialysis, blood samples should be drawn immediately for measurement of sodium, potassium, calcium, magnesium, bicarbonate, and glucose levels. An electrocardiogram should be obtained and evaluated for supraventricular or ventricular arrhythmias. Treatment is based on the same principles as for arrhythmias in patients not receiving dialysis.

Febrile Reactions

Febrile reactions can be observed after bacterial contamination of the circuit or the contamination of water or bicarbonate dialysate. These exposures result in bloodstream infections, which are related to exposure of the patient's blood to bacterial endotoxins or lipopolysaccharides. Another important cause of febrile reactions during dialysis is vascular access infection. Such an infection usually is caused by *Staphylococcus aureus*, and treatment requires removal of the infected catheter.

Dialysis Dysequilibrium Syndrome

Dialysis dysequilibrium syndrome is a neurologic disorder that occurs in patients starting on IHD, especially if they have a high predialysis blood urea nitrogen (BUN) value. Early clinical manifestations include nausea, vomiting, and headache. In more severe cases, hypertension, confusion, disorientation, seizures, coma, and sometimes death are observed. The cause of this syndrome is controversial. Most authorities believe it to be related to an acute rise in brain water content. When the plasma solute level is lowered rapidly during dialysis, the plasma becomes hypotonic with respect to the brain cells, and water shifts from the plasma into brain tissue. Other researchers incriminate acute changes in the pH of the cerebrospinal fluid during dialysis.[103] Dialysis dysequilibrium syndrome is generally a self-limited condition. For severe cases, dialysis should be discontinued. Seizures can be treated with intravenous diazepam. In several studies, the syndrome has been treated with the addition of osmotically active solutes (mannitol, glucose, fructose, glycerol, sodium chloride) to the dialysate. Because dialysate sodium levels can be changed easily in modern dialysis machines, the use of high-sodium dialysate may be the most convenient approach.[30]

Also, in patients with acute brain injury requiring HD, a rapid fall in plasma osmolality may worsen preexisting cerebral edema. Cerebral hypoperfusion in such situation also may result in case of excessive ultrafiltration volume or if the rate of ultrafiltration rate is too rapid (>10–15 mL/kg/hr). As a result, continuous or extended therapies are preferred in these patients. Care should be taken to use a smaller dialyzer, higher dialysate sodium, and slower blood/dialysate flow rates to minimize the initial fall in serum osmolality. In addition, these patients may benefit from daily treatments if intermittent RRT is used to minimize the fluctuations in serum urea concentration.[104]

MISCELLANEOUS COMPLICATIONS

Nutritional and Metabolic Problems

Dialysis (SLED or IHD) may affect nutrition and metabolism in a multitude of ways in a patient with AKI. Besides substrate losses affecting protein and amino acid metabolism, the treatment also may inhibit protein synthesis. Dialysis also may result in loss of low-molecular-weight nutrients (vitamins and amino acids) with small volume of distribution and sieving coefficients less than 1. Amino acid losses may amount to 5 to 10 g/day. Although there is an obligatory loss of amino acids with dialysis, nutritional amino acid infusions (1 to 1.5 g/kg/day) do not increase this elimination (or plasma concentrations) substantially, because the endogenous clearance of amino acids is several times higher. The other possible ways in which dialysis could remove clinically relevant molecules are convection (peptides/hormones) and adsorption (e.g., hormones, interleukins, complement factors). However, the clinical relevance of such removal is minimal.

Prolongation of Renal Recovery

There are several putative mechanisms by which recovery of renal function may be adversely affected by hemodialysis (Table 154.2). Of these, hemodynamic compromise and inflammatory burden–induced injury (secondary

TABLE 154.2

Mechanisms by Which Recovery of Renal Function May Be Adversely Affected by Hemodialysis

	IMPACT ON RENAL FUNCTION		
FREQUENCY	**HIGH**	**UNCERTAIN**	**LOW**
High	Hemodynamic compromise Catheter-associated infection		Access malfunction Anticoagulation-associated complications Membrane bioincompatibility
Unknown	Human error	Vitamin and micronutrient depletion Hormone depletion Amino acid depletion Hyperglycemia Impaired thermal balance	Electrolyte complications
Low	Catheter-associated hemorrhage Catheter-associated vascular/visceral organ injury Membrane-associated bradykinin activation	Microbiologic contamination Acid-base disturbances	Catheter-associated thrombosis Mechanical dysfunction Chemical contamination

predominantly to microbiologic infections) are the most important.

The kidney in AKI is vulnerable to further insult owing to impairment in renal autoregulation.[59] Thus repeated episodes of hypotension with hemodialysis may prolong or worsen renal ischemic injury and delay recovery.[105] Whether "gentler" therapies such as continuous venovenous hemodialysis, which conventionally use lower blood flow rates over a longer period, may be less injurious in this respect is yet to be proven.[106] Similar evidence in favor of SLED is also lacking. A systematic review of 15 studies (1550 patients) comparing the use of CRRT and IRRT in AKI showed no difference in renal recovery (number of surviving patients not requiring RRT).[107] Whenever blood is exposed to an extracorporeal circuit, blood-membrane interaction results in activation of several important biologic pathways. Blood-membrane interactions are important in humans with biocompatible membranes because they lead to a higher rate of renal recovery and patient survival.[76,77] Although this issue is still not settled completely,[84] the use of bioincompatible membranes in patients with AKI generally is not recommended.

Dialysis Dosing and Recovery of Renal Function in Acute Renal Failure

There is some evidence that time to recovery of renal function is shorter in patients receiving IHD than in those receiving daily dialysis. Thus daily dialysis may mitigate ongoing renal injury by decreasing the ultrafiltration requirements per treatment in addition to causing fewer hypotensive episodes.[108] Last, the decrease in the amount of urine produced over a 24-hour period usually falls with the institution of dialysis. Ultrafiltration (convective) and urea (diffusive) removal may contribute to this effect. However, whether the decrease in urine output affects the overall renal recovery from AKI is not clear.

Issues With the Dose of Dialysis in the Intensive Care Unit

ICU patients requiring dialysis are usually hypercatabolic. Consequently, the dosing parameters derived for maintenance hemodialysis may not be applicable in this circumstance and may even pose a risk of underdialysis. Computer models show that for a 50-kg man in AKI, 4.4 dialyses per week will maintain a steady-state BUN of 60 mg/dL; however, even daily 4-hour hemodialysis may be insufficient to maintain the same steady-state BUN for a 90-kg man.[109] Although solute removal is only one of the goals of RRT in AKI, data do support aiming for higher clearances with RRT to improve patient survival, at least in patients with AKI of intermediate severity.[110] Efforts to achieve a steady-state BUN of 60 to 70 mg/dL or an equilibrated efficacy value (eKt/V) of 1.0 (single-pooled Kt/V 1.2), as an index of providing intensive hemodialysis in AKI, may be hampered by the fact that the prescribed dose may not match the delivered dose.[111,112]

Poor blood flow, hypercatabolic state, difficulties with anticoagulation leading to frequent filter clotting and increase in down time, and increased body water (higher V) are some factors that may be responsible for failure to achieve dosing targets in AKI. Dialysis dosing in AKI is a controversial issue, and the recent Veterans Affairs (VA)/National Institutes of Health (NIH) Acute Renal Failure Trial Network (ATN) study has shown no benefit of a more intensive dialysis regimen.[113] This study compared the effects of intensive versus less intense dialysis dosing on mortality and renal recovery. Patients in the intensive therapy group were treated with hemodialysis and prolonged intermittent RRT (PIRRT) six times per week with a target Kt/V of 1.2 to 1.4 per treatment (median delivered dose of 1.3 per treatment), while CRRT was provided with an effluent flow rate of 35 mL/kg per hour. Patients in the less intensive therapy group were treated with hemodialysis and PIRRT three times per week with a target Kt/V of 1.2 to 1.4 per treatment (median delivered dose of 1.3 per treatment), whereas CRRT was provided with a flow rate of 20 mL/kg per hour. The authors found no difference in the death rate at day 60 or the duration of RRT and rate of renal recovery.[113] Similar findings were noted in the Randomized Evaluation of Normal Versus Augmented Level of RRT (RENAL) study, which included 1508 patients with AKI randomly assigned to continuous venovenous hemodiafiltration (CVVHDF) at an effluent flow of either 25 or 40 mL/kg per hour. There was no difference between the two groups in mortality at 90 days or the rate of renal recovery (incidence of patients who continued to receive RRT at 90 days).[114]

Key Points

1. Sustained low-efficiency dialysis and intermittent hemodialysis are successful in managing acute renal failure in the intensive care unit.
2. Both therapies can have technical as well as clinical complications.
3. Poorly functioning vascular access is often a cause of treatment down time.
4. Bleeding/thrombosis and hypotension are major clinical problems that require prompt recognition and management.
5. Intermittent hemodialysis and sustained low-efficiency dialysis provide viable alternatives to continuous therapies in managing acute renal failure in the intensive care unit.

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