Hemodialysis Emergencies: Core Curriculum 2021

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Since maintenance hemodialysis (HD) first became available in the United States in 1962, there has been tremendous growth in the population of patients with kidney failure. HD has become a routine treatment carried out in outpatient clinics, hospitals, nursing facilities, and in patients' homes. Although it is a complex procedure, HD is quite safe. Serious complications are uncommon due to the use of modern HD machines and water treatment systems as well as the development of strict protocols to monitor various aspects of the HD treatment. The practicing nephrologist must be knowledgeable about life-threatening complications that can occur during HD and be able to recognize, manage, and prevent them. This installment in the *AJKD* Core Curriculum in Nephrology reviews the pathogenesis, management, and prevention of 9 HD emergencies. The HD emergencies covered include dialyzer reactions, dialysis disequilibrium syndrome, uremic/dialysis-associated pericarditis, air embolism, venous needle dislodgement, vascular access hemorrhage, hemolysis, dialysis water contamination, and arrhythmia episodes.

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Introduction

Hemodialysis (HD) is a life-sustaining treatment for patients with kidney failure and severe acute kidney injury (AKI). In 1945, Dutch physician Willem Kolff successfully used his "artificial kidney" to treat uremia in a patient with AKI who went on to have recovery of her kidney function. Maintenance HD for kidney failure became available in the United States in 1962. For the first decade, HD was only available to a select few patients due to its significant cost. Anonymous committees determined which patients met criteria to receive HD; those who were not selected died. In 1973, the Medicare End-Stage Renal Disease program was established, ensuring nearly universal coverage for dialysis and kidney transplantation in the United States. Since then, the dialysis population has increased well beyond original projections, with nearly 470,000 patients on HD and more than 52,000 patients on peritoneal dialysis at the end of 2017.

Well over 50 million HD treatments are performed in the United States each year. HD has become a routine procedure carried out in outpatient clinics, hospitals, nursing facilities, and patients' homes. It involves the creation and maintenance of a vascular access; generation of water suitable for making dialysate; circulation of blood through an extracorporeal circuit; and administration of medications such as heparin, intravenous iron, erythropoiesis-stimulating agents, and active vitamin D. Complications can occur at any of these steps, which can range from mild to life-threatening. Fortunately, serious complications are uncommon, but some occur as a result of human error and, as such, should be preventable. This review covers 9 HD emergencies and their prevention and management.

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Dialyzer Reactions and Other Allergic Reactions

Case 1: *A 68-year-old woman with hypertension, diabetes, and chronic kidney disease (CKD) stage 5 is initiated on HD due to volume overload refractory to diuretic agents. Ten minutes into her first treatment, she reports generalized pruritus, dyspnea, and chest pain. She is noted to have audible wheezing. Her blood pressure is 86/50 mm Hg (compared to 145/90 mm Hg prior to the start of dialysis). A dialyzer reaction is suspected.*

Question 1: What are the appropriate next steps in the management of this patient?

a) Continue dialysis and administer intravenous antibiotics
b) Continue dialysis and administer albuterol through a nebulizer
c) Continue dialysis and administer intravenous corticosteroids and antihistamines
d) Stop dialysis and return blood in the extracorporeal circuit back to the patient

e) Stop dialysis without returning blood in the extracorporeal circuit back to the patient

For the answer to the question, see the following text.

The dialyzer is composed of many hollow fibers made from a biocompatible membrane across which solutes are cleared through diffusion and convection. Dialyzer reactions are hypersensitivity reactions to the membrane itself or the products used to sterilize the membrane. Reactions have been reported to occur with dialyzers composed of cuprophane, a cellulose membrane used more commonly in the past; acrylonitrile, a synthetic membrane that caused acute reactions among patients taking angiotensin-converting enzyme inhibitors (ACEIs); and polysulfones or polyethersulfones, which are the most commonly used synthetic membranes. Insufficient rinsing of the dialyzer after the use of ethylene oxide, commonly used to sterilize dialysis membranes in the past, and formaldehyde, used to reprocess dialyzers, led to patients being exposed to these substances. Dialyzer reactions were previously called "first use" reactions because they were typically seen when a dialyzer was used for the first time and not when it was reused (dialyzer reuse is uncommon today in the United States). Although they were once fairly common, dialyzer reactions are now rarely seen due to increased use of biocompatible membranes and reduced use of ethylene oxide sterilization.

Dialyzer reactions have been characterized as type A or type B. Type A reactions occur early in the treatment, usually within the first 20 to 30 minutes. They typically occur during the first treatment but can occur after multiple treatments. Signs and symptoms may include pruritus, urticaria, laryngeal edema, bronchospasm, dyspnea, chest pain, vomiting, hypoxia, hypotension, and cardiac arrest. Management of a severe reaction includes stopping dialysis without returning blood from the extracorporeal circuit back into the patient; thus, the correct answer to Question 1 is (e). Fluids, epinephrine, corticosteroids, and antihistamines should be administered as indicated. For future treatments, a dialyzer with a different method of sterilization should be used (eg, switching from a steam- or ethylene oxide–sterilized dialyzer to a gamma ray–sterilized dialyzer). Use of ACEIs with acrylonitrile 69 (AN69) dialyzers should be avoided. Type B reactions occur later in the treatment and are less severe. Symptoms may include chest and back pain, nausea, and vomiting. Dialysis can be continued if symptoms are mild, although switching to a different dialyzer should be considered.

The mechanism varies depending on the causative agent. Most type A reactions have been attributed to ethylene oxide, formaldehyde, and use of ACEIs with acrylonitrile dialyzers, with ethylene oxide accounting for most of these reactions. Ethylene oxide and formaldehyde cause a true, immunoglobulin E (IgE)-mediated anaphylaxis. AN69 membranes appear to stimulate bradykinin production. When AN69 membranes are coupled with ACEIs, which inhibit the degradation of bradykinin, very high plasma levels of bradykinin can occur. This can be prevented if AN69 dialyzers are pretreated with polyethyleneimine, a positively charged polymer that binds to the negatively charged membranes. Cuprophane and polysulfones/polyethersulfones appear to activate complement, which is thought to be the main cause of type B reactions. However, severe reactions with elevated IgE levels have been reported in patients exposed to polysulfone dialyzers. Measuring levels of total IgE and tryptase (a protease released by mast cells during anaphylaxis) may be helpful in determining whether a complication occurring during HD is due to anaphylaxis or other cause.

Hypersensitivity reactions can also be seen with medications administered during dialysis, including heparin, intravenous iron, and erythropoiesis-stimulating agents (ESAs). A subset of patients with heparin-induced thrombocytopenia develop an anaphylactoid reaction immediately after heparin re-exposure that is mediated by IgG antibodies. In 2007-2008, clusters of severe anaphylactoid reactions occurring in patients undergoing HD were traced to lots of heparin contaminated with oversulfated chondroitin sulfate (OSCS). OSCS was found to generate anaphylatoxins C3a and C5a. Intravenous iron has long been associated with hypersensitivity reactions, for which the precise underlying mechanism is unknown. The rate of fatal adverse reactions varies by iron formulation, with high rates for high-molecular-weight dextran and the lowest for iron sucrose, which is currently the most commonly used iron formulation. There have been reported cases of anaphylaxis in reaction to ESAs and additives. In all of those cases, management includes avoidance of the offending agent and use of substitutes where available.

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Dialysis Disequilibrium Syndrome

Case 2: *A 75-year-old man with hypertension, diabetes, CKD, and history of ischemic stroke is initiated on dialysis for nausea, decreased appetite, and hyperkalemia. His predialysis laboratory values are notable for serum creatinine*

(Scr), 10.1 mg/dL; serum urea nitrogen, 170 mg/dL; sodium, 128 mEq/L; potassium, 7.2 mEq/L; bicarbonate, 12 mEq/L; and glucose, 101 mg/dL. The dialysis prescription calls for a treatment duration of 2 hours, a blood flow of 400 mL/min, a dialysate flow of 800 mL/min, a standard sodium dialysate, and a target ultrafiltration of 2 liters. A low-efficiency dialyzer is used. His dialysis is uneventful until the end of his treatment, when he reports new onset of headache. His blood pressure is 145/96 mm Hg, which was stable throughout the treatment. He subsequently develops a seizure. Dialysis is stopped immediately.

Question 2: How could the prescription have been modified to reduce the risk of dialysis disequilibrium syndrome?

a) Reduce ultrafiltration goal
b) Reduce dialysate sodium concentration
c) Reduce blood flow
d) Increase treatment time

For the answer to the question, see the following text.

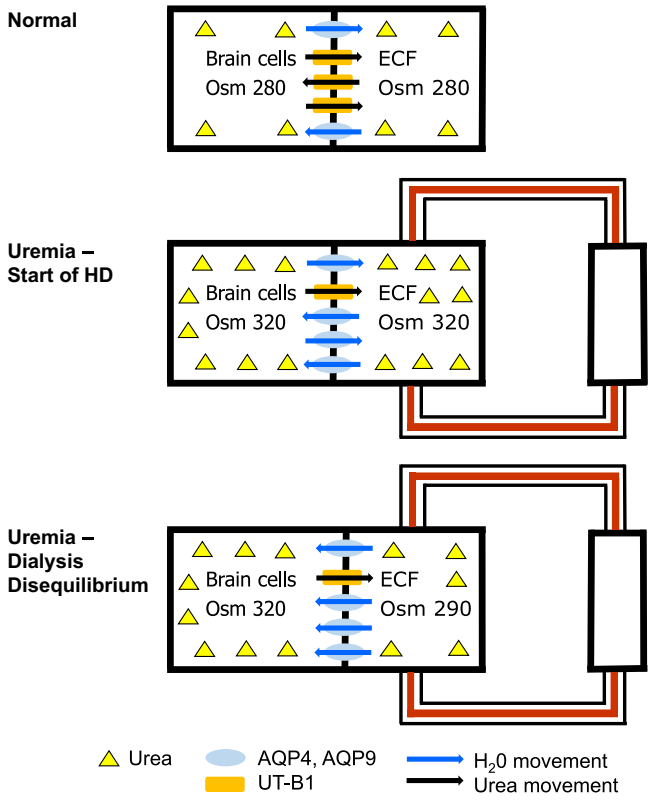

Figure 1. Water movement into brain cells leads to cerebral edema in dialysis disequilibrium syndrome. Based on Tuchman et al 2013 (*Clin Kidney J.* https://doi.org/10.1093/ckj/sft087). Abbreviations: HD, hemodialysis; Osm, osmolality.

Dialysis disequilibrium syndrome (DDS) is characterized by neurologic signs and symptoms occurring during or shortly after an HD session. First described in the 1960s, clinical manifestations can include headache, nausea/vomiting, confusion, agitation, seizures, coma, and even death. Cerebral edema may be seen on computed tomography (CT) and magnetic resonance imaging (MRI). DDS has been typically seen in patients with significantly elevated serum urea nitrogen (SUN) undergoing their first dialysis treatment. Other risk factors include rapid reduction of SUN, extremes of age, metabolic acidosis, hyponatremia/hypernatremia, liver disease, and pre-existing neurologic conditions. The incidence of DDS is believed to have declined in recent decades due to changing practices such as starting dialysis with lower blood flow rates and at lower SUN levels. It is now very rare, although it is possible that it is underrecognized among patients who exhibit milder symptoms.

The cerebral edema seen in DDS is caused by the movement of water into brain cells (Fig 1). The most prevalent theory that has been postulated to explain this occurrence is the "reverse urea effect." This theory states that a rapid reduction of urea with HD lowers serum osmolality significantly relative to the central nervous system (CNS), generating an osmotic gradient that drives water into brain cells. In fact, measurement of urea in the blood and cerebrospinal fluid (CSF) in patients undergoing HD in the 1960s showed significantly higher urea levels in the CSF than in the blood after dialysis. Increased expression of aquaporins AQP4 and AQP9 and decreased expression of urea transporter UT-B1 have been observed in the brain of uremic rats, suggesting that uremia may increase the risk of significant water movement.

Idiogenic osmoles and intracerebral acidosis have also been proposed as possible mechanisms. Idiogenic osmoles are unidentified solutes that are generated in the brain under hyperosmolar conditions such as chronic hyperglycemia and hypernatremia. The generation of idiogenic osmoles during HD was proposed when a study in dogs appeared to show that higher brain osmolality in animals undergoing rapid dialysis could not be accounted for by sodium, potassium, chloride, and urea alone. However, subsequent studies have not provided further evidence to support this theory. The rapid correction of metabolic acidosis may also have a role in increasing osmolality by worsening intracerebral acidosis. In animals, a decrease in CSF pH has been observed with HD; the hydrogen ions that are generated may displace bound sodium and potassium ions, increasing osmolality. Beyond increasing CNS osmolality, rapid correction of acidosis may increase CNS uptake of opioids, causing changes in mental status that could mimic DDS in severely acidemic patients initiating HD.

The treatment of DDS depends on the severity of symptoms. If symptoms concerning for DDS develop during dialysis, the treatment should be stopped. Mild symptoms may be managed supportively. For severe symptoms, measures to reduce intracranial pressure can be used. Administration of hypertonic saline or mannitol and hyperventilation have been used in published cases, but

outcomes have been poor. Prevention of DDS by reducing SUN by no more than 40% over a short period of time is crucial. Initiating HD using a low blood flow of 200 mL/min over 2 hours (or even less depending on the patient's body habitus) is recommended; therefore, the correct answer to Question 2 is (c). DDS has been reported in prevalent maintenance HD patients, so using a lower blood flow when such patients have significantly elevated SUN is also recommended. In patients with very high SUN, slower reduction in SUN using continuous kidney replacement therapy (CKRT) should be considered, although there have been case reports of DDS occurring in patients receiving CKRT. Another approach is to increase the osmolality in the blood or dialysate to reduce the degree of change in osmolality with dialysis. Use of a higher sodium dialysate has been reported to prevent symptoms of DDS. Other agents that have been used include mannitol, glucose, glycerol, and urea.

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Uremic Pericarditis

In 1836, English physician Richard Bright reported the presence of pericarditis in patients with kidney disease at autopsy. Prior to the development of dialysis, the diagnosis of pericarditis in the setting of CKD heralded impending death. More recently, pericarditis in CKD patients has been classified as uremic pericarditis (defined as developing before or within 8 weeks of initiation of dialysis) or dialysis-associated pericarditis (defined as developing after 8 weeks on dialysis). The exact cause of pericarditis is unknown. Uremic pericarditis is thought to be due to the accumulation of uremic toxins, as it improves with dialysis initiation. Dialysis-associated pericarditis frequently occurs in patients with inadequate dialysis and improves with intensified dialysis; it is unclear whether this is an entity that is distinct from uremic pericarditis. Some experts have suggested that viral illness or other stress may trigger the development of this disease. With earlier initiation of dialysis and more efficient dialysis machines, uremic pericarditis is much less common than in the past. Uremic and dialysis-associated pericarditis remain the most common causes of pericardial disease in kidney failure. Other causes of pericarditis in the dialysis population include infections, autoimmune disease, malignancy, trauma, and myocardial infarction. Chronic pericardial inflammation from any cause can result in constrictive pericarditis, which occurs rarely in kidney failure.

The clinical presentation of uremic/dialysis-associated pericarditis may differ from pericarditis due to other causes or pericarditis occurring in patients without kidney failure. Pleuritic chest pain is common, but improvement by leaning forward is not commonly reported. Uremic/dialysis-associated pericarditis may be accompanied by fever, chills, dyspnea, cough, or malaise. A pericardial friction rub is heard in most patients. The rub is typically triphasic with the components corresponding to atrial systole, ventricular systole, and rapid ventricular filling during diastole. On electrocardiography, the diffuse ST-segment elevations classically associated with pericarditis in nondialysis patients are seen in less than 10% of dialysis patients; this has been attributed to the high prevalence of left ventricular hypertrophy by some but thought by others to indicate lack of epicardial involvement. An echocardiogram is most commonly used to evaluate for pericardial effusion and signs of tamponade. Laboratory studies commonly show elevated erythrocyte sedimentation rate and C-reactive protein; leukocytosis may be seen in approximately 50% of cases. Pericardial fluid is exudative, and mononuclear cells are seen.

Cardiac tamponade is a life-threatening complication of pericarditis that has been reported to occur in approximately 10%-20% of patients with uremic/dialysis-associated pericarditis. Patients may present with hypotension, tachycardia, muffled heart sounds, and elevated jugular venous pressure. Pulsus paradoxus, defined as an inspiratory decrease in systolic blood pressure of more than 10 mm Hg during normal breathing, is suggestive of tamponade and should lead to urgent further evaluation. Signs of tamponade on echocardiogram include collapse of the right atrium and right ventricle during early diastole and increased variation in tricuspid and mitral valve blood flow velocity with respiration. The mechanism of the latter is that during inspiration, the drop in pleural pressure reduces right atrial pressure, which increases venous return, blood flow velocity through the tricuspid valve, and right ventricular volume. This increase in right ventricular volume reduces left ventricular volume (referred to as ventricular interdependence) and increases left ventricular diastolic pressure and reduces blood flow velocity through the mitral valve. A diagnosis of tamponade requires urgent pericardiocentesis to avoid cardiogenic shock and cardiac arrest.

Management of uremic pericarditis in patients not already receiving dialysis is initiation of HD. These patients respond well to HD and rarely require further intervention. Intensification of dialysis is recommended for dialysis-associated pericarditis, with daily HD for 10-14 days. Patients with dialysis-associated pericarditis frequently do improve with intensification of dialysis,

but fewer respond than is the case for patients with uremic pericarditis who are initiated on HD. In 1 study, 87% of uremic pericarditis patients improved with HD initiation whereas only 53% with dialysis-associated pericarditis responded to HD intensification. Avoiding heparin during dialysis is recommended due to concern for hemorrhagic pericarditis. Fluid removal by ultrafiltration should be attempted very cautiously as it can precipitate cardiac tamponade. Medications such as indomethacin, colchicine, and oral and intrapericardial corticosteroids have been evaluated in small studies without evidence of benefit. Significant pericardial effusions that do not improve with intensified dialysis usually require further intervention. Treatment options include pericardiocentesis with or without drain placement and pericardial window. If pericardiocentesis is performed without placement of a drain, monitoring for reaccumulation of the effusion is required. Management of constrictive pericarditis requires complete pericardiectomy.

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Air Embolism

Case 3: *A 70-year-old man starts HD with a nontunneled catheter for acute kidney injury occurring after coronary artery bypass surgery. He suddenly develops cough, hypoxia, and hypotension. Cardiac examination reveals a continuous murmur in systole and diastole.*

Question 3: What is the most appropriate management step in addition to stopping HD?

a) Place patient on 100% oxygen
b) Start intravenous thrombolytic therapy
c) Start intravenous corticosteroids and antihistamines
d) Obtain echocardiogram
e) Place patient in reverse Trendelenburg position

For the answer to the question, see the following text.

Air embolism is a potential complication of every HD treatment. There are multiple potential causes of air entry into a patient's bloodstream. Air can be pulled into the arterial portion of the extracorporeal circuit (from the patient to the blood pump) due to negative pressure if the connection between the arterial needle and the circuit is poor or if there are any defects in the tubing. Improper administration of normal saline or medications, as well as inadequate priming of the dialyzer, may result in the introduction of air into the circuit. If a significant volume of air enters the circuit by these mechanisms; however, it is detected by the air-foam detector. Air entering the air trap lowers the blood level, which is detected by a sensor that triggers an alarm and stops the blood pump. HD can be resumed after assessing the patient and the venous line and then taking any necessary steps to remove blood from the circuit. Because of this safety mechanism, life-threatening air embolism is very rare. Cases reported in recent years have been attributed to failure to clamp tubing or a catheter, or other human error.

The clinical manifestations of air embolism depend on the volume and rate of air entry and the end organ(s) affected. Very small air bubbles, termed microbubbles or microemboli, do not trigger the air-foam detector and enter the patient's bloodstream. These do not appear to cause any immediate effects but could be responsible for chronic injury to the lungs and brain seen in patients on HD. The entry of a significant amount of air into the right heart and pulmonary artery can cause increased pulmonary arterial pressure, pulmonary edema, hypoxia, hypotension, and cardiac arrest. Air can enter the systemic circulation from the right heart in the presence of a patent foramen ovale, or in the setting of a large volume of air entering the pulmonary circulation; all of the air cannot be eliminated by the pulmonary capillaries, and some ends up in the arterial circulation. Once in the systemic circulation, air emboli can occlude blood vessels and cause ischemic injury. The cerebral arteries are most commonly involved, and patients may develop altered mental status, neurologic deficits, seizures, strokes, and death. Cerebral air emboli may be seen on CT or MRI. Air can also enter the CNS by ascending the internal jugular vein into the cortical veins and cavernous sinuses in the seated patient. In an adult, 100-300 mL of air is likely to be lethal.

Management of a possible air embolism includes administration of supplemental oxygen to treat hypoxia and reduce the size of air emboli by increasing the rate of nitrogen removal; therefore (a) is the correct answer to Question 3. Fluids and vasopressors should also be administered where needed. HD should be stopped without returning blood from the extracorporeal circuit to the patient. A patient with suspected or known venous air embolism should be placed in the left lateral recumbent position to prevent any air in the right ventricle from entering the pulmonary circulation. For arterial air embolism, the recommendations are to position the patient in the supine position, as left lateral recumbent positioning is insufficient to prevent arterial air emboli from entering the systemic circulation. Head down positioning

may exacerbate cerebral edema in patients who sustain cerebral air embolism. Other possible interventions are limited to attempted removal of air for patients with catheters and use of hyperbaric oxygen therapy. Given limited treatments and poor outcomes, prevention of air embolism is paramount. Avoiding very high blood flow rates, maintaining high blood level in the air trap, and training staff and patients/caregivers (for home HD) to avoid scenarios that increase risk of air embolism are recommended. Preventing air embolism during placement and removal of central catheters is also crucial. Measures such as correcting hypovolemia and other causes of reduced central venous pressure, placing the patient in Trendelenburg position, priming the catheter, inserting needle during expiration, and keeping needle hubs and lumens occluded may help to prevent air embolism during catheter placement. Trendelenburg positioning, catheter removal during Valsalva maneuver or with breath held after full inspiration, and placement of an occlusive dressing for 24 hours are recommended for catheter removal.

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Venous Needle Dislodgement

The needles used to cannulate an arteriovenous fistula (AVF) or arteriovenous graft (AVG) can rarely become dislodged during dialysis. If the venous needle is completely dislodged, blood flowing through the extracorporeal circuit is lost at 300-450 mL/min (the blood flow rate) until the pump is stopped. Severe hemorrhage and even death can occur within minutes. Causes of needle dislodgement include improper needle taping, suboptimal cannulation technique, failure to secure blood lines appropriately, and patient movement/needle removal. Other factors such as covering needles and/or blood lines with blankets or other items and setting the lower limit of the venous pressure alarm too low, can make it more difficult to detect venous needle dislodgement when it occurs.

Dialysis machines include pressure monitors that measure arterial and venous pressure. Each monitor has high and low limit alarms, as significant changes in arterial or venous pressure could indicate a problem with the patient's access or the extracorporeal circuit. The high and low limits are usually set approximately 50 mm Hg above and below the actual pressure, as pressures vary during HD due to patient positioning and movement. Setting alarm limits very close to the actual pressure will result in many false alarms. The venous pressure monitor measures the pressure in the circuit between the venous air trap and the patient's venous access. The venous pressure is positive, reflecting the resistance in the circuit and venous access. If a venous needle becomes dislodged, the venous pressure will decrease, but the drop in venous pressure may not be sufficient to trigger a low limit alarm. This occurs when the intra-access pressure is fairly low, as seen with many AVFs (AVGs tend to have higher intra-access pressures). If a patient with an AVF with an intra-access pressure of 20 mm Hg has a venous needle dislodgement, the venous pressure will decrease by 20 mm Hg. If the low alarm limit is set to less than 20 mm Hg below the baseline venous pressure, no alarm will be triggered. Therefore, it is possible for a patient to lose a significant amount of blood before an alarm is triggered.

Blood loss following venous needle dislodgement can range from minimal to life-threatening or fatal. Management of significant blood loss includes intravenous fluids and vasopressor support as needed and blood transfusion. Prevention and early detection of venous needle dislodgement is key. Recommended measures include using consistent procedures for needle/blood line taping, keeping the access and blood line connections visible at all times, regular monitoring of the vascular access during HD (particularly for patients who are at high risk), prohibiting staff from adjusting alarm limits, educating staff and patients about venous needle dislodgement and its consequences. Certain groups of patients may be at higher risk for venous needle dislodgement or severe blood loss if needle dislodgement does occur—aside from those who do solo or nocturnal home HD, these may include patients who are restless, have dementia or altered mental status, have a difficult access, or have allergies to tape. Keeping such patients close to the nurses' station and maintaining access visibility are of utmost importance. The use of an additional device to detect blood loss can be considered but should never replace preventive measures. Enuresis monitors have been occasionally used to detect blood loss. More recently, some centers have begun to use the Redsense venous sensor patch (Redsense Medical), which is applied directly over the venous needle site and has an optical sensor that detects blood loss.

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Vascular Access Hemorrhage

Vascular access hemorrhage is a rare but life-threatening complication of HD access. It was reported as the cause of death for 1,654 HD patients in the United States during 2000-2006, representing about 0.4% of deaths among HD patients. Approximately 80% of deaths caused by vascular access hemorrhage occur outside the dialysis unit, most commonly in the patient's home. Most of these events occur due to rupture of an AVF or AVG. A smaller number result from a central venous catheter (CVC)-associated complication, such as perforation, uncapped ports, disconnection from the extracorporeal circuit, and accidental removal. Venous needle dislodgement during HD accounts for a very small fraction of fatalities.

Rupture of AVFs and AVGs occur at sites where the vessel wall has weakened. Aneurysms and pseudoaneurysms are such sites; they most commonly develop after repeated cannulations in the same location. Aneurysms are focal dilations of the vessel wall. Pseudoaneurysms are hematomas that communicate with the AVF/AVG through a defect in the vessel wall. Both can occur in AVFs, whereas only pseudoaneurysms can develop in AVGs. AVGs are more likely to develop pseudoaneurysms than AVFs due to higher intra-access pressure and limited capacity to repair defects at cannulation sites. Because of this, AVGs are associated with higher risk of vascular access hemorrhage. Other factors that may increase the formation of aneurysms and pseudoaneurysms include high blood flow, repeated dilation of recurrent stenosis, infections, and venous stenosis. In published series, more than half of the patients who experienced fatal vascular access hemorrhage had had an infection, clotting, hemorrhage or other vascular access complication in the weeks or months prior to their death.

Vascular access hemorrhage should be managed by applying direct continuous pressure to the site until emergency medical personnel arrive. Use of tourniquets, blood pressure cuffs, or bandages on the affected extremity should be avoided. Education of patients and caregivers is crucial as most events occur at home. Ruptured AVFs/AVGs require ligation, resulting in the loss of access. In order to prevent aneurysm/pseudoaneurysm formation, proper cannulation technique is important. The rope ladder technique, where cannulation sites are rotated along the length of the AVF/AVG, should be used. Cannulation of any aneurysmal portions of the access should be avoided. In addition, every vascular access should be examined regularly and aneurysms/pseudoaneurysms monitored. Not every aneurysm warrants concern; many patients have large AVFs that are stable for years. However, a rapid increase in size, thinning of overlying skin (skin becomes shiny and translucent) (Fig 2), necrotic skin, pain, and infection require prompt evaluation by a vascular surgeon. Signs of imminent rupture or infection may require access ligation. Aneurysm repair or pseudoaneurysm resection may be appropriate in other cases. For small, stable aneurysms/pseudoaneurysms, evaluation for venous outflow stenosis is warranted. Signs of outflow stenosis include failure of the draining vein to collapse on arm elevation and presence of a high-pitched bruit. These warrant referral to vascular surgery. Treatment of any significant lesions should reduce intra-access pressure and limit aneurysm/pseudoaneurysm expansion.

Additional Readings

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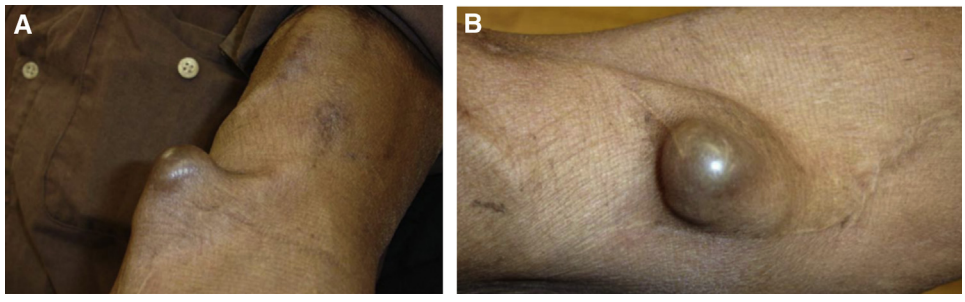

Figure 2. Brachiocephalic arteriovenous fistula with aneurysm that has tight, shiny skin. From Vachharajani, *Atlas of Dialysis Vascular Access,* accessed from https://ukidney.com/nephrology-publications/atlas-of-dialysis-vascular-access. Original images ©2010 T.J. Vachharajani; reproduced with permission from Dr Vachharajani.

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Hemolysis

Case 4: *During a shift at a dialysis clinic, multiple patients develop abdominal pain, nausea, vomiting, and hypertension during their dialysis treatment. Examination of the extracorporeal circuit is notable for the blood having a cherry red color that is brighter than usual. The affected patients are transported to a local hospital where laboratory testing reveals hemoglobin levels ranging from 5-8 g/dL (compared to 10-11 g/dL previously) and mild to moderate hyperkalemia.*

Question 4: Which of the following could have caused hemolysis in these patients?

a) Hypotonic dialysate
b) Kinked blood tubing
c) Chloramine exposure
d) All of the above

For the answer to the question, see the following text.

Red blood cells are subjected to shear stress when traveling through the extracorporeal circuit, as the blood flow in the center of the tubing is higher than at the wall. This causes low-grade hemolysis during dialysis that is clinically undetectable. In the presence of other factors that increase red blood cell fragility, significant hemolysis can result (Fig 3). Mechanical causes of red blood cell fragmentation include high rates of blood flow through smaller gauge needles, excessively negative arterial pressures, needle malposition, and obstructed or kinked tubing. This was exemplified by a 1998 outbreak of hemolysis in HD units in 3 states; the cause was determined to be a faulty lot of tubing that contained an area of narrowing. Inadequate water treatment resulting in contamination of dialysate with oxidizing agents such as chloramine, copper, and nitrates has also caused outbreaks of hemolysis. Although now rare, there have been several reports of chloramine-associated hemolysis in the past, including one in which the hemolysis manifested only as erythropoietin resistance. Formaldehyde has also been associated with hemolysis, but its use has decreased significantly with reduction of dialyzer reprocessing. High dialysate temperature has been reported to cause thermal injury to red blood cells resulting in hemolysis. Inadvertent use of hypotonic dialysate has led to fatal hemolysis due to osmotic injury. Option (d) is therefore the correct answer to Question 4. In addition, there are patient-related factors that can increase the risk of hemolysis. These include disorders such as sickle cell anemia, electrolyte abnormalities such as hypophosphatemia, and certain medications.

Clinical manifestations vary depending on the severity of hemolysis. Mild hemolysis may be not be associated with any symptoms. Severe hemolysis may present with nausea, vomiting, diarrhea, abdominal/back/chest pain, dyspnea, chills, and hypertension. Time to symptom onset can vary depending on the cause of hemolysis. The blood in the extracorporeal circuit may appear brighter and more translucent; the color has been described as cherry red. When hemolysis is suspected, dialysis should be stopped immediately. The blood in the extracorporeal circuit should not be returned to the patient, as this may result in severe hyperkalemia due to potassium release from hemolyzed cells. Patients should be referred to an emergency department for urgent medical evaluation. Laboratory findings include decreased hemoglobin and haptoglobin, and increased lactate dehydrogenase and bilirubin. The patient's serum may be pink due to the presence of free hemoglobin. Hemoglobin and markers of hemolysis, as well as potassium levels, should be monitored. Blood transfusion should be considered when appropriate. HD may be required for hyperkalemia. Massive hemolysis can be complicated by arrhythmias, acute coronary syndromes, respiratory distress, severe necrotizing pancreatitis (thought to be due to release of proinflammatory cytokines), and death.

Once the patient has been stabilized and referred for appropriate medical care, then an assessment of possible causes should be undertaken. The dialysate temperature and osmolality should be measured and checked for contaminants. The tubing should be inspected for kinks or obstruction and saved for further testing. A systematic evaluation is essential for preventing further events. Other general measures to minimize the risk of hemolysis include strict adherence to protocols for testing water, dialysis machines, and extracorporeal circuits; using appropriate blood flow rates for needle size; avoiding very negative arterial pressures; and avoiding compression of tubing.

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Dialysis Water Contamination

Dialysate is produced by adding dialysate concentrates to processed water. During dialysis, HD patients are exposed

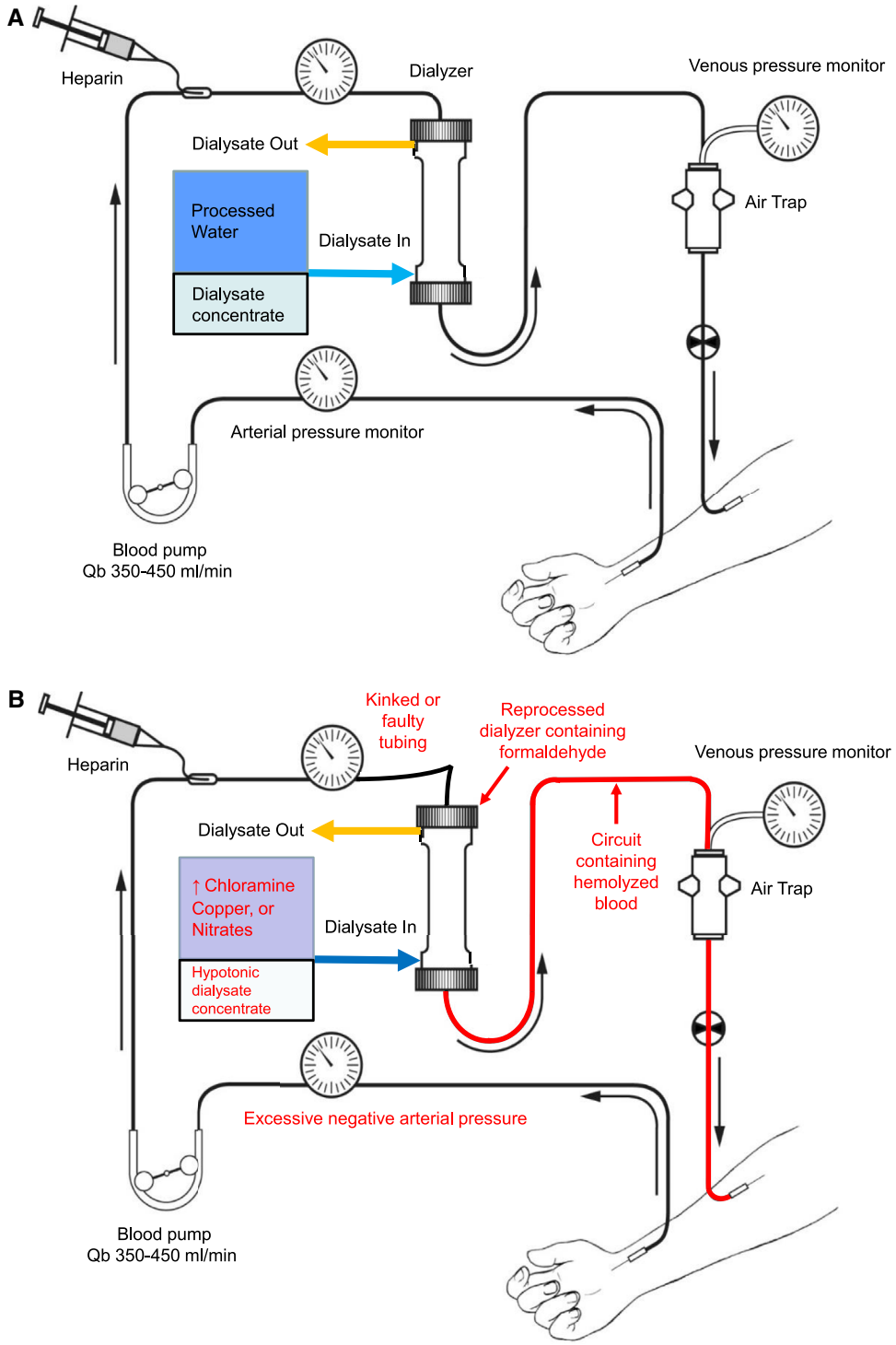

Figure 3. Normal dialysis circuit (top panel) and possible causes of hemolysis (bottom panel). Drawing of dialysis circuit from the National Institute of Diabetes and Digestive and Kidney Disease, US National Institutes of Health.

to large amounts of dialysate and, therefore, water. The typical HD patient is exposed to more than 400 L of dialysate per week. Since the dialysis membrane is permeable to many potentially toxic substances, removal of all such substances is crucial for providing safe dialysis. Water treatment systems consist of a series of components that each remove contaminants by a different mechanism (Table 1). When 1 or more components of the water treatment system fail, or there is significant contamination of the water supply, the product water may be unsuitable for dialysis. If water contamination goes undetected, patients may experience life-threatening complications.

Table 1. Components of Water Treatment Systems

Component[a]	Purpose/Mechanism
Pretreatment	
Temperature-blending valve	Control water temperature to ensure optimal function of reverse osmosis unit(s) by blending heated water with cold water
Multimedia depth filtration	Remove solid materials through filters that contain sand and/or coal
Activated carbon filter	Remove organic matter and chlorine/chloramine by adsorption
Softener	Remove calcium and magnesium ions by resin exchange
Water treatment	
Reverse osmosis	Remove organic and inorganic solutes by forcing water through a very tight membrane
Deionization	Remove inorganic ions by ion exchange using cationic and anionic resins
Ultraviolet	Kill bacteria through ultraviolet radiation
Endotoxin-retentive filter	Remove bacteria and endotoxin

Based on information in Coulliette and Arduino 2013 (*Semin Dial.*, https://doi.org/10.1111/sdi.12113) and Ahmad 2005 (*Hemodial Int.*, https://doi.org/10.1111/j.1492-7535.2005.01124.x).
[a]Not every water treatment system will have all of these components.

Fortunately, with current protocols for monitoring and maintaining water system components, complications related to water quality are rare.

Chloramine (chlorine bound to ammonia) is frequently added to drinking water as a disinfectant to kill microbes. It is removed by carbon tanks that contain activated granular carbon. Elevated chloramine levels can occur if the carbon tanks are exhausted or the chloramine level in the water supply exceeds the filtering capacity. Monitoring of chloramine levels is done by checking total chlorine levels multiple times a day. As discussed previously, chloramine exposure has caused multiple outbreaks of hemolysis in HD centers. Chloramine has also been reported to cause methemoglobinemia, which presents as dyspnea and cyanosis. It is suggested by chocolate brown–colored venous blood and confirmed by direct measurement of methemoglobin levels. For mild cases, monitoring of methemoglobin levels may be sufficient. For severe cases, methylene blue is the first-line therapy (except in patients with glucose-6-phosphate dehydrogenase deficiency). Similarly, hydrogen peroxide is used to disinfect water in storage tanks in hospitals. It has caused hemolysis and methemoglobinemia when amounts exceeding the filtering capacity of the carbon tanks were added.

Fluoride is also widely added to the water supply to prevent tooth decay. It is removed by reverse osmosis and deionization. In reverse osmosis, mechanical pressure is applied to force water across a membrane containing pores that only allow water to pass through, generating water that is nearly devoid of solutes. Deionization removes ions by ion exchange—a cationic resin exchanges cations for hydrogen ions, while an anionic resin exchanges anions for hydroxide ions. Hydrogen and hydroxide ions then form water. Fluoride toxicity in HD patients has occurred due to exhausted deionization resins and accidental overfluoridation of water at a water treatment plant. Signs and symptoms of fluoride toxicity include pruritus, chest pain, nausea, vomiting, diarrhea, syncope, tetany, and ventricular fibrillation leading to cardiac arrest. Fluoride binds to calcium and magnesium, causing hypocalcemia and hypomagnesemia. It also causes hyperkalemia, oxidative stress, cell cycle arrest, and apoptosis; the exact mechanisms are unknown.

Other notable chemical intoxications have occurred. Aluminum toxicity has occurred due to exhausted deionization tanks, use of pumps with aluminum casing to transfer acid concentrate from storage tanks to treatment areas, and use of a water pipe lined with cement. Acute aluminum exposure causes severe neurotoxicity, which can manifest as seizures, myoclonus, and encephalopathy. Treatment includes HD and chelation with deferoxamine. Copper intoxication manifesting as myalgias, abdominal pain, diarrhea, acidosis, pancreatitis, hemolysis, and methemoglobinemia was reported in the 1960s due to partially exhausted deionization resins. Currently, deionization is infrequently used as the primary water treatment method, therefore intoxication with the above chemicals is much less likely to occur.

Contamination of dialysate with microorganisms can also cause serious complications. Water treatment systems and HD machines are susceptible to growth of Gram-negative bacteria and nontuberculous mycobacteria. Gram-negative bacteria also produce endotoxins that can cause pyrogenic reactions, which are characterized by fever, chills, hypotension, headache, and muscle ache occurring during dialysis or within a few hours after dialysis. Disinfection of water treatment and HD equipment keeps bacterial/mycobacterial counts low. Endotoxin is removed by reverse osmosis and by endotoxin filters. Outbreaks of bacteremia or pyogenic reactions have occurred in the setting of dialyzer reuse, contaminated water/dialysate, contaminated dialysis machines, and central catheter use. Pyrogenic reactions are usually mild to moderate in severity, but bacteremia has led to severe systemic infections and death. Adherence to protocols for monitoring water treatment systems, which include regular water cultures and measurement of endotoxin levels, are key to preventing complications.

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Arrhythmia

Cardiac arrest and arrhythmia are the most common causes of death in kidney failure, accounting for 29% of deaths among dialysis patients in 2015. Sudden cardiac death has been defined as unexpected, sudden death within an hour of symptom onset, or unexpected death without obvious noncardiac cause in patients known to be well within the previous 24 hours; no universally accepted definition has been developed. Sudden cardiac death is likely common in kidney failure due to the high prevalence of coronary artery disease and structural heart disease combined with frequent exposure to proarrhythmic triggers. In the nondialysis population, reduced left ventricular ejection fraction (LVEF) is common among patients who have sudden cardiac death. Among HD patients, reduced LVEF is less common. Instead, left ventricular hypertrophy, which can be eccentric instead of concentric, is observed more frequently, reported to be present in more than 70% of HD patients with sudden cardiac death in some case series.

It is well known that HD patients have a higher risk of sudden cardiac death following the long interdialytic period (ie, on Mondays and Tuesdays). Hyperkalemia, which has been associated with sudden cardiac death, may be one of the reasons for this trend. Fluid and electrolyte shifts that occur during HD may also play a role. Use of dialysate potassium of less than 2 mEq/L has been associated with higher rates of sudden cardiac death. Rapid changes in the serum potassium concentration and therefore the potassium gradient across cardiac myocytes and the conduction system are thought to increase the risk of arrhythmia. Dialysate calcium less than 2.5 mEq/L and higher serum-dialysate calcium gradient have also been associated with increased risk of cardiac arrest. Metabolic alkalosis has been associated with QT prolongation, which could be a risk factor for sudden cardiac death.

In the general population, ventricular fibrillation is the most common cause of sudden cardiac death. Recent studies using implantable loop recorders have shown that bradyarrhythmias appear to be more common than ventricular arrhythmias in patients undergoing dialysis. In the Monitoring in Dialysis Study, 1,678 clinically significant episodes of arrhythmia were noted in 66 patients with a loop recorder. Most of these were bradyarrhythmias. Clinically significant arrhythmias were seen to occur most commonly during the first dialysis session of the week and were also common in the last 12 hours of the long interdialytic period. Bradyarrhythmias were fairly common in the last 12 hours of the other interdialytic periods as well.

Table 2. Possible Strategies for Preventing Arrythmias in HD Patients

Strategy	Intervention
Manage cardiomyopathy	
Systolic dysfunction	Use carvedilol in dilated cardiomyopathy
Diastolic dysfunction/LVH	Consider more frequent HD to reduce left ventricular mass; consider use of spironolactone, ACEIs, or ARBs
Minimize arrhythmic triggers	
Potassium shifts	Monitor predialysis potassium frequently and change dialysate bath accordingly; avoid low (<2 mEq/L) potassium baths
Calcium shifts	Avoid low (<2.5 mEq/L) calcium baths, especially with concurrent use of QT interval–prolonging drugs
Metabolic alkalosis	Avoid high dialysisate bicarbonate concentrations in alkalotic patients; account for all sources of base in dialysate, including acetate
Rapid ultrafiltration	Encourage patient to adhere to salt and fluid restrictions; extend dialysis time so that UFR does not exceed 10 mL/kg/h
HD-induced myocardial ischemia	Lower dialysate temperature to 0.5-2 °C below patient temperature to reduce intradialytic hypotension
Medications	Avoid QT interval–prolonging medications when possible and reconcile medication list regularly
Weigh risks/benefits of devices	
Pacemakers	Consider permanent pacemaker if bradycardia noted
ICDs	Consider ICDs for secondary prevention; increase communication between nephrologists and cardiologists to consider risks and benefits of primary prevention ICDs; consider leadless defibrillators to reduce vascular and infectious risks
Improve response to cardiac arrest	Increase dialysis clinic staff awareness of cardiac arrest risk and readiness to provide basic life support; encourage awareness and CPR training among patients and families

Adapted with permission of the copyright holder (National Kidney Foundation) from Pun 2014 (*Adv Chronic Kidney Dis.*, https://doi.org/10.1053/j.ackd.2014.06.007).
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARBs, angiotensin receptor blockers; CPR, cardiopulmonary resuscitation; HD, hemodialysis; ICD, implantable cardioverter-defibrillator; LVH, left ventricular hypertrophy; SCD, sudden cardiac death; UFR, ultrafiltration rate.

Management of symptomatic arrhythmias and cardiac arrest is cardiopulmonary resuscitation (CPR). Dialysis staff should be trained to provide basic life support, and CPR training should be encouraged for patients and families. Cardiac arrest is associated with very high mortality; therefore, prevention is crucial. There are no interventions that have been demonstrated to prevent sudden cardiac death in HD patients, but there are several measures that

Table 3. HD Emergencies

Emergency	Pathogenesis	Clinical Presentation	Management/Prevention
Dialyzer reaction	Hypersensitivity reaction to dialyzer membrane or membrane sterilization method Type A: IgE-mediated anaphylaxis to ethylene oxide, formaldehyde, or polysulfone dialyzer; or high bradykinin levels from ACEI use with AN69 membrane; Type B: complement activation by cuporphane or polysulfone/ polyethersulfone membrane	Type A: pruritus, urticaria, laryngeal edema, bronchospasm, dyspnea, chest pain, vomiting, hypoxia, hypotension, or cardiac arrest usually occurring within first 20-30 min of HD session Type B: chest pain, back pain, nausea, or vomiting; symptoms less severe than in Type A and occur later in HD session	Type A: stop dialysis without returning blood from circuit to patient; fluids, epinephrine, corticosteroids, antihistamines if indicated; use different dialyzer and avoid ethylene oxide sterilization; avoid ACEI with AN69 dialyzers Type B: switch to a different dialyzer
Dialysis disequilibrium syndrome	Thought to be due to rapid reduction of serum osmolality relative to the CNS, which drives water into brain cells and results in cerebral edema; urea is thought to be the predominant solute involved but idiogenic osmoles and intracerebral acidosis may also contribute	Signs/symptoms: headache, nausea/vomiting, confusion, agitation, seizures, coma, or death occurring during or soon after HD session; possible cerebral edema on imaging Risk factors: very high SUN, first HD treatment, rapid SUN reduction, extremes of age, metabolic acidosis, hyponatremia, liver disease, pre-existing neurologic conditions	Management: stop HD, provide supportive care Prevention: avoid reducing SUN by more than 40% during a short period; initiate dialysis using low blood flow; consider using higher sodium dialysate; consider CKRT
Uremic pericarditis/ dialysis-associated pericarditis	Exact cause unknown, thought to be due to accumulation of uremic toxins	Symptoms: pleuritic chest pain, fever, chills, dyspnea, cough, malaise Signs: pericardial friction rub heard in most patients; diffuse ST-segment elevations rarely seen; echocardiogram with pericardial effusion; hypotension, tachycardia, pulsus paradoxus if tamponade present	Initiate HD for uremic pericarditis, intensify HD (daily for up to 10-14 d) for dialysis-associated pericarditis, avoid heparin with HD; do not dialyze if signs of tamponade—this requires urgent intervention with pericardiocentesis (usually with drain placement) or pericardial window
Air embolism	Air enters bloodstream through dialysis circuit or through vascular access; causes include poor connection between arterial needle and circuit, defects in tubing in arterial portion of circuit, inadequate priming of dialyzer, improper medication administration, uncapped dialysis catheter, dialysis catheter placement/ removal	Air entering right heart/ pulmonary artery can cause pulmonary edema, hypoxia, cardiac arrest; a air in CNS can cause altered mental status, neurologic deficits, seizures, stroke, death	Management: stop HD without returning blood from extracorporeal circuit, position patient supine, administer oxygen and (if needed) fluids and vasopressors Prevention: avoid very high blood flow rates, maintain high blood level in air trap, train staff to avoid risky scenarios
Venous needle dislodgement	Dislodgement of venous needle due to improper needle, poor cannulation technique, failure to secure blood lines, patient movement/needle removal; may go undetected if needles/blood lines are covered by blankets or other items or venous pressure alarm lower limit is too low	Blood loss, fatigue, pale skin, lightheadedness, shortness of breath, hypotension, cardiac arrest	Management: transfuse blood, administer IV fluids and vasopressors as needed Prevention: secure needles and blood lines well and keep them visible at all times, monitor vascular access regularly, avoid adjusting venous alarm limits, consider blood leak detector

(Continued)

Table 3 (Cont'd). HD Emergencies

Emergency	Pathogenesis	Clinical Presentation	Management/Prevention
Vascular access hemorrhage	Rupture of AVF or AVG at aneurysm or pseudoaneurysm, CVC perforation, uncapped ports, disconnection from extracorporeal circuit, or accidental removal	Rapid blood loss, exsanguination	Management: apply direct continuous pressure to site; avoid tourniquets, blood pressure cuffs, and bandages; ligate ruptured AVFs/AVGs Prevention: use proper cannulation technique (rope ladder); examine access regularly; refer promptly to vascular surgeon if concerning findings seen
Hemolysis	Red blood cell fragmentation due to high blood flow in smaller gauge needles, excessively negative arterial pressures, needle malposition, obstructed or kinked tubing, contamination of dialysate with chloramine, copper, or nitrates; exposure to formaldehyde, high dialysate temperature, hypotonic dialysate	Signs/symptoms: nausea, vomiting, diarrhea, abdominal/back/chest pain, dyspnea, chills, hypertension, arrhythmias, acute coronary syndromes, respiratory distress, severe necrotizing pancreatitis, death Key features: cherry red blood in extracorporeal circuit, pink serum due to free hemoglobin Laboratory findings: decreased hemoglobin and haptoglobin; increased LDH, bilirubin, and potassium	Management: stop HD without returning blood to patient, transfuse blood, dialyze for hyperkalemia Prevention: follow protocols for monitoring water, HD machines, and HD circuit; use appropriate blood flow rates, avoid compression of tubing; if hemolysis occurs, thorough evaluation to identify cause
Dialysis water contamination: chloramine, hydrogen peroxide	Exhaustion of carbon tanks, high levels in water supply	Hemolysis (see above); methemoglobinemia—dyspnea, cyanosis, chocolate brown venous blood, high methemoglobin levels	Hemolysis (see above); treat severe cases with methylene blue
Dialysis water contamination: fluoride	Exhausted deionization resins, high levels in water supply	Pruritus, chest pain, nausea, vomiting, diarrhea, syncope, tetany, ventricular fibrillation, cardiac arrest	HD to remove fluoride and manage hyperkalemia, correct hypocalcemia and hypomagnesemia
Dialysis water contamination: aluminum	Exhausted deionization resins, high levels in water supply	Seizures, myoclonus, encephalopathy	HD, chelation with deferoxamine
Dialysis water contamination: copper	Exhausted deionization resins, high levels in water supply (copper pipes)	Myalgia, abdominal pain, diarrhea, acidosis, pancreatitis, hemolysis, methemoglobinemia	Supportive care, possible chelation
Dialysis water contamination: bacteria/endotoxin	Improper disinfection of water treatment components and HD machines	Bacteremia, pyrogenic reactions	Antibiotics, supportive care
Arrhythmia	Frequent exposure to proarrhythmic triggers, including rapid changes in serum potassium, changes in serum calcium, and metabolic alkalosis, occurring in the setting of coronary artery disease and structural heart disease	Bradycardia, asystole, atrial fibrillation, ventricular tachycardia/fibrillation	Management: CPR; Prevention: avoid low potassium and low calcium dialysate, avoid metabolic alkalosis, limit UFR, lower dialysate temperature, consider frequent HD; consider pacemaker/ICD if indicated

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; AN69, acrylonitrile 69; AVF, arteriovenous fistula; AVG, arteriovenous graft; CKRT, continuous kidney replacement therapy; CNS, central nervous system; CPR, cardiopulmonary resuscitation; CVC, central venous catheter; HD, hemodialysis; ICD, implantable cardioverter-defibrillator; IgE, immunoglobulin E; LDH, lactate dehydrogenase; SUN, serum urea nitrogen; UFR, ultrafiltration rate.

could potentially be beneficial. Use of low potassium and calcium dialysate should be avoided whenever possible. Dialysate bicarbonate concentrations should be adjusted to avoid metabolic alkalosis. As high ultrafiltration rates have been associated with increased mortality (although not specifically sudden cardiac death), limiting ultrafiltration

rates also seems reasonable. More frequent dialysis (only feasible in the home HD setting) has been shown to reduce left ventricular hypertrophy; more frequent dialysis also likely reduces significant fluid and electrolyte shifts by eliminating the long interdialytic period. Given the recently identified prevalence of bradyarrhythmias, pacemakers may have a role, although kidney failure patients have higher complication rates following pacemaker or implantable cardioverter defibrillator (ICD) implantation compared to nondialysis patients. Similarly, the role of ICDs in kidney failure is uncertain, even for secondary prevention in patients with a history of ventricular fibrillation. Possible strategies for prevention of sudden cardiac death are listed in Table 2.

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Root Cause Analysis

The HD emergencies discussed in this article are summarized in Table 3. Should any HD complication occur, a thorough evaluation should be conducted to prevent further events. Root cause analysis is a process that is widely used for quality improvement. It provides a structured framework for identifying one or more root causes that led to an adverse outcome and determine changes that can be implemented improve performance. Many institutions, including the Centers for Medicare & Medicaid Services, have provided guidance for conducting root cause analysis.

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