Medical Complications in Hemodialysis Patients Requiring Vascular Access Radiology Procedures

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ABSTRACT

Vascular access maintenance is crucial to providing adequate hemodialysis (HD) and hence preventing signs and symptoms of uremia. The best vascular assess is a permanent arteriovenous fistula (AVF) because it has the longest survival with the least number of complications. However, because of problems with AVF maturation, the majority of HD in the United States is provided via an arteriovenous graft (AVG) or tunneled cuffed central venous catheter. The most common access complications include infection and thrombosis. For these reasons, a patient is often referred to interventional radiology for a procedure such as a catheter placement, change, or a thrombectomy with angioplasty and/or stent placement. Commonly, a HD patient will present after missing a dialysis session. This might predispose the patient to further complications. This review is intended to provide insight into some of the common medical problems (infectious, hematologic, and cardiac) facing a HD patient as a consequence of uremia. Increased awareness to these medical issues provides guidance to prevent unnecessary complications in this difficult patient population.

KEYWORDS: Hemodialysis, vascular access, interventional radiology, bacteremia, coagulation

Objectives: Upon completion of this article, the reader should be able to (1) identify medical complications as a result of uremia common in hemodialysis patients presenting for interventional radiology procedures, and (2) describe treatment options for these medical complications.

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Vascular access for hemodialysis (HD) continues to be a cornerstone to providing adequate HD. The cost of placement and treatment of access complications adds to the complicated care of HD patients. Three types of vascular access currently are available and include central venous catheters, arteriovenous grafts (AVG), and arteriovenous fistulae (AVF). The Kidney Disease Outcomes and Quality Initiative (K/DOQI) practice guidelines

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mandate standards for dialysis access and maintenance.[1] The current K/DOQI guidelines recommend that 50% of all new accesses for HD be natural vein fistulae, with a goal of 40% for the dialysis population of the United States.[1] However, recent data show that on average, 23% of prevalent patients in a HD center dialyze through a cuffed central venous tunneled catheter, 47% with a synthetic graft, and only 27% via an AVF.[2] This review discusses a nephrologist's view of the pertinent medical management of complications that occur in the end-stage renal population (ESRD) referred to the Interventional Radiology department for vascular access procedures. The discussion includes common infectious, coagulation, and cardiac problems.

INFECTION RISK

ESRD causes altered immune regulation that contributes to an increased risk of infection. Altered immune function occurs as the uremic environment leads to the retention of waste products, which are only partially cleared by dialysis. Various defects in immune function can also occur because of the underlying cause of renal failure, such as diabetes or lupus. Altered immune function is caused by ureic toxins, dialysis membrane bio-incompatibility, iron overload, and malnutrition.[3,4] Profound alterations of both humeral and cell-mediated immune responses are hallmarks of uremia.[5] Clinically, cutaneous anergy and poor or absent responses to vaccines are the rule, and bacterial infections are a major cause of morbidity and mortality.[6,7]

Infectious complications are the second leading cause of death in the ESRD population and contribute significantly to morbidity. Bacteremic episodes frequently are caused by vascular access, with indwelling catheters being responsible most often. Noncuffed temporary catheters historically have had the highest incidence of infection, ranging from 1.6 to 7.7 bacteremic episodes per 1000 catheter-days.[8] In some series, tunneled cuffed catheters have a lower rate of infection, ranging from 0.2 to 0.5 bacteremic episodes per 1000 catheter-days.[9] Metastatic complications are more common with cuffed catheters, although patient outcome appears to be much worse when an AV access is the source of metastatic infection.[10]

The pathogenic mechanism of catheter-related bacteremia involves the following: the catheter is placed and a thrombin layer or sheath envelops the intravascular segment, creating a fibrin sheath. Bacteria then enter through the lumen from skin and bind to the thrombin and fibrin on the catheter. Some bacteria such as staphylococci and *Candida* produce a microbial biofilm that helps the organisms adhere to the foreign surface of the catheter.

The most common organism isolated in patients with catheter-related bacteremia is *Staphylococcus aureus*, accounting for 40 to 77% of bacteremic episodes in the HD population.[11] Given that *S. aureus* has a propensity to adhere to valves and bones, a patient is at increased risk of metastatic complications. *Staphylococcus epidermidis*, the second most common organism isolated, is normally present on the skin.[12] Once considered a contaminate, it is now recognized as a clinically significant bloodstream infection. *S. epidermidis* can colonize foreign material such as catheters and is often resistant to multiple antibiotics. It is the most common cause of endocarditis of prosthetic valves. *Enterococci* is the third most common isolate. It is more common in the hospital setting because antibiotic resistance enables survival and proliferation when antibiotic-susceptible organisms are eliminated.[13] Other organisms such as gram-negative rods and fungi are uncommon; when isolated, a thorough search for etiology should be done, including a review of recent dialysate cultures.

Catheter-related bacteremic episodes require careful attention. If the patient is clinically septic, the catheter should be removed immediately. Appropriate cultures should be obtained and the bloodstream cleared for 48 to 72 hours prior to reinserting another central venous catheter. In the interim period a temporary femoral venous catheter can be placed for dialysis. The empiric treatment of patients suspected of a vascular access infection initially involves the administration of intravenous (IV) antibiotics, vancomycin and gentamicin. The advantage of this combination includes a broad spectrum of coverage for gram-positive and gram-negative organisms, along with ease of administration during HD. Once culture results and susceptibilities are known, the patient can be converted to antibiotics with more specific coverage. This conversion helps prevent the incidence of vancomycin-resistant organisms. If not promptly addressed, catheter-related infections can lead to subacute endocarditis, osteomyelitis, and epidural abscess.[10,14] It is well documented that the bloodstream commonly cannot be cleared effectively without the removal of the catheter because the infected biofilm found at the catheter tip cannot be sterilized with antibiotics.[15] Several studies have demonstrated that antibiotic therapy coupled with catheter exchange over a guide wire has limited success.[14,15] If guidewire exchange is chosen as a therapeutic technique to treat catheter-related bacteremia, the patient should be clinically stable and afebrile after 48 hours, with no evidence of tunnel tract infection.[16] In general, whenever possible, catheters should be removed when catheter-associated bacteremia is first recognized.

Medical therapy using antibiotic prophylaxis to prevent catheter-related bacteremia has been shown to have promising results in some clinical trials. These include (1) topical mupirocin, (2) antimicrobial/anticoagulant flush, (3) antibiotic binding to the catheter, and (4) silver-impregnated cuff. Given that *S. aureus* is the

leading cause of catheter-related bacteremic episodes, topical mupirocin has been used as a nasal ointment to decrease nasal carriage. Clearly, nasal carriage of *S. aureus* should be present for this therapy to be effective.[17] The emergence of antibiotic resistance has limited the widespread use of this technique and it is generally reserved for patients with repetitive infections and *S. aureus* nasal carriage.[18] Loading the catheter with antibiotics has also been used to help prevent and treat catheter infections.[19,20] Preliminary data suggest that antibiotic bonding to central venous catheters in an intensive care unit setting can reduce the incidence of catheter infections.[21] Antibiotic bondecl catheters have not yet been studied extensively in the HD population, nor have they been studied as cuffed silastic catheters. Silver in its ionic form has broad-spectrum antimicrobial activity against bacteria and fungi. The use of a silver-impregnated cuff has been shown to decrease the infection rate when compared with conventional catheters.[22]

COAGULATION DISORDERS

Hematologic abnormalities in dialysis patients include both a predisposition to bleeding and a thrombotic proclivity. The coagulation problems encountered are complex. An ESRD patient presenting to interventional radiology for an access procedure has an underlying bleeding tendency that might pose a significant risk. In addition, anticoagulants such as heparin and/or coumadin might be necessary for dialysis and for a thrombectomy of a clotted access. Paradoxically, heparin itself can cause an antibody-mediated mechanism, with resultant platelet aggregation and subsequent thrombosis. This mechanism is referred to as heparin-induced thrombocytopenia (HIT) syndrome.

Bleeding occurs in uremia from platelet dysfunction and anticoagulants used in dialysis procedures. Platelets from a uremic individual have an impaired glycoprotein IIb-IIIa complex receptor function, as demonstrated by defective binding of fibrinogen and von Willebrand factor to stimulated platelets.[23] This defect is partially reversed by HD, suggesting a role of the uremic toxins in platelet dysfunction. Given these problems in platelet function, patients who are to undergo surgery or invasive procedures are always at risk of bleeding. The medical treatment of uremic bleeding secondary to platelet dysfunction includes intensive dialysis and desmopressin.[24]

Thrombosis is the leading cause of AV access failure. In grafts, the primary cause is intimal hyperplasia at the venous anastomosis. However, other factors also contribute. The only definite risk factor for access thrombosis is placement of a synthetic graft rather than a native AV fistula.[25] Other factors that promote thrombosis include heparin therapy, an underlying hypercoaguable state, the presence of diabetes, poor cardiac function associated with hypotension, the location of the access, hypoalbuminemia, and elevated lipoprotein (a) levels.[26,27] In addition, multiple additional factors might contribute to the thrombotic tendency in uremia, including abnormal endothelium, oxidative stress, and alteration in clotting factors and other markers of coagulation.[28] Because heparin is frequently used during radiology procedures to treat access thrombosis, it will be discussed in further detail.

Heparin is used routinely as an anticoagulant during HD. Unfractionated heparin is used the most frequently. HIT is a well-recognized complication of heparin therapy, usually occurring 5 to 10 days after heparin treatment has been initiated.[29] As many as 10 to 20% of patients receiving unfractionated heparin will experience a decrease in platelet count to less than the normal range or a 50% decrease in platelet count within the normal range.

There are two major mechanisms causing thrombocytopenia. Type 1 accounts for majority of the cases and the decrease in platelet count occurs within the first 2 days after heparin initiation, often returns to normal with continued heparin administration, and is of no clinical consequence. The mechanism is nonimmune and appears to be due to a direct effect of heparin on platelet activation. Type 2 occurs in only 0.3 to 3% of patients receiving heparin. These patients develop an immune thrombocytopenia, mediated by antibodies to a heparin-platelet factor 4 complex (PF4/H).[30] Although patients with type 2 HIT develop thrombocytopenia, the platelet count is typically above 20,000/μL and bleeding is unusual. These patients are at high risk for subsequent thrombotic events.[31]

Given that HD patients are continually exposed to heparin, they are at risk of developing PF4/H antibodies. Reports have described the prevalence of these antibodies in HD with frequencies ranging from 0 to 12%.[32,33] It is important to note that the mere presence of PF4/H antibodies does not suggest a diagnosis of HIT in the absence of other clinical events.[34] Several case reports demonstrate a dramatic improvement in access patency after discontinuing heparin with HD and beginning treatment with coumadin. This suggests that heparin antibodies have a role in recurrent vascular access occlusion in some patients.[35]

Therapy for HIT in HD patients involves the use of alternative anticoagulants only if clinical symptoms develop, including thrombocytopenia, systemic thrombosis, excessive clotting of extracorporeal circuit, or vascular thrombosis. Clinical suspicion of HIT should be confirmed by laboratory testing. The assays available for use include the serotonin release assay, heparin-induced platelet aggregation, and solid-phase immunoassay.

The serotonin release assay remains the gold standard among diagnostic tests for HIT.[36] This enzyme-linked immunosorbent assay has been clinically

validated and correlates strongly with thrombocytopenia beginning 5 days or more after heparin exposure. The disadvantages are the high cost and technical demands. The platelet aggregation test is quite specific (> 90%) but lacks sensitivity.[37] The solid-phase immunoassay is not a functional assay. It is very sensitive (91%) but its clinical utility remain to be determined because many antibody-positive patients do not develop clinical HIT.[38] The solid-phase immunoassay is being used along with one of the functional assays because up to 20% of sample results may be discordant between this assay and the other.[39,40] A high index of clinical suspicion is necessary for the accurate diagnosis of HIT, along with appropriate laboratory tests for validation.

Immediate discontinuation of heparin, including heparin flushes and heparin-coated circuits, is now considered mandatory when HIT is suspected. For patients with tunneled cuffed catheters, this includes discontinuing heparin used to lock the dialysis catheter. The use of low-molecular-weight heparin (LMWH) is also contraindicated because both in vitro and in vivo studies have shown a high level of cross-reactivity between PF4/H antibodies and LMWH.[41] While awaiting laboratory confirmation, an alternative anticoagulant should be used. Once HD patients develop HIT, they are usually treated with coumadin. However, because of the risk of coumadin-induced limb gangrene, coumadin therapy should not be initiated until the platelet count has returned to baseline.[42] The current available alternative agents are costly and require close monitoring given the pharmacokinetics associated with renal failure. Hirudin, a direct thrombin inhibitor, has been successfully used in patients requiring HD; however, its half-life is markedly prolonged and dosing protocols are inconclusive.[43] Argatroban, another thrombin inhibitor, also has been successfully used as anticoagulant for ESRD in patients with HIT syndrome.[44] The cost and availability of these alternative agents adds to the challenging care of patients who require long-term dialysis with an alternative agent to heparin.

Hypercoagulable states can also be present in the ESRD population and should be sought if recurrent AV access thrombosis occurs without a specific anatomic reason. Some series have identified a high incidence of antiphospholipid syndrome, protein C deficiency, and other factor defiencies.[35,45] If clinically significant thrombosis occurs, systemic anticoagulation with coumadin should be initiated. However, coumadin use to preserve access patency without an underlying hypercoagulable disorder is controversial.[46,47]

CARDIAC COMPLICATIONS

Cardiac complications in a dialysis patient are numerous and include hypertension, coronary artery disease, calcific valve disease, cardiomyopathy, and resultant high-output failure. Vascular access-related cardiac decompensation is a rare complication, even in patients with underlying cardiac dysfunction. However, patients with cardiomyopathy can develop high-output failure if fistula flow exceeds 20% of the cardiac output.[48] The more common cardiac complications encountered by an interventional radiologist include acute electrolyte abnormalities along with hypertension and/or hypotension.

The patient referred to interventional radiology ideally presents on a nondialysis day for a scheduled outpatient procedure. All too often this schedule is not followed because a patient has missed a dialysis session as a result of a thrombosed graft. The electrolyte abnormalities potentially encountered in this situation include acute hyperkalemia, hypocalcemia, and acidosis. Patients with acute hyperkalemia with electrocardiographic changes (low P waves, peaked T waves, widened QRS, or cardiac standstill) should be treated with IV infusion of calcium chloride, IV glucose plus insulin, or IV sodium bicarbonate, while arrangements for acute HD are made. It is recommended that the patient receive acute hemodialysis prior to a prolonged interventional procedure if severe hyperkalemia is present, especially if general anesthesia is required.

Hypertension is common in chronic renal failure secondary to volume retention and/or pressor mechanisms such as the renin/angiotensin system. Eighty-five percent of HD patients are normotensive or readily controlled with low-dose antihypertensive medication after normalization of extracellular fluid by ultrafiltration.[49] Other mechanisms of hypertension in the ESRD patient include secondary hyperparathyroidism, erythropoietin therapy, abnormal nitric oxide production, uremic toxins, or sympathetic overactivity.[50] The treatment of hypertension in the chronic setting should be achievement of the ideal dry weight. If this is not possible because of a thrombosed access, antihypertensive drugs can be administered. It is rational to choose an antihypertensive medication that causes regression of left ventricular hypertrophy. Calcium channel blockers and angiotensin-converting enzyme inhibitors are generally well tolerated.

Hypotension can be a serious clinical manifestation in a patient with ESRD. Hypotension could be caused by diminished cardiac reserve, too rapid fluid removal with dialysis, underlying autonomic dysfunction, or antihypertensive medications.[51] Autonomic dysfunction occurs as a result of uremia, an underlying disease such as diabetes, or some antihypertensive medications. The impairment occurs as the baroreceptor function minimizes the reflex increase in circulating catecholamines. Infrequently, patients with dialysis-induced hypotension have a serious or life-threatening medical condition requiring immediate attention. These

include pericardial tamponade, arrhythmia, myocardial infarction, sepsis, or pulmonary embolism. If symptomatic hypotension occurs, especially in a patient with ESRD presenting to interventional radiology, a careful physical examination should be performed along with necessary diagnostic work-up, including an electrocardiogram, analysis of cardiac enzymes, and/or an echocardiogram.

In summary, a patient with end-stage renal failure on HD has alterations in multiple organ systems as a result of uremia. Maintenance of vascular access in this population is crucial to adequate dialysis. Inevitably, interventional radiology procedures including central venous catheter placement, thrombectomy procedures, and angioplasty and/or stenting of stenosis, will likely be necessary on most patients to maintain vascular access. The immune, hematologic, and cardiac system might be compromised, contributing to increased morbidity and mortality during interventional radiology procedures. Attention to careful medical management of HD patients will help to prevent complications as patients present to interventional radiology for access procedures.

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