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PERSPECTIVES IN RENAL MEDICINE

Infectious complications of the hemodialysis access

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Infectious complications of the hemodialysis access. Infectious complications of the vascular access are a major source of morbidity and mortality among hemodialysis (HD) patients. Numerous reports implicate the vascular access in up to 48 to 73% of all bacteremias in HD patients. The incidence of vascular access-related infection is highest when central venous dialysis catheters are employed. Native arteriovenous fistulas carry the lowest risk of infection. Unfortunately, prosthetic arteriovenous grafts, which represent the most common type of HD access in the United States, have been repeatedly shown to be a risk factor for bacteremic and nonbacteremic infections. Silent infection in old nonfunctional clotted prosthetic arteriovenous grafts has recently been recognized as a frequent cause of bacteremia and morbidity among HD patients. High proportions of infections related to the vascular access are caused by staphylococcal organisms, which carry high rates of mortality, recurrence, and metastatic complications. Management of vascular access-related infection has two aspects: The first relates to the choice, duration, and mode of administration of antibiotic therapy. Empiric antibiotic therapy, guided by demographic data and severity of illness, should be employed when the causative organisms are unknown. Prolonged administration of specific parenteral antibiotics is crucial in decreasing complications of infection, especially in cases of staphylococcal bacteremia. The second aspect relates to management of the vascular access. Efforts directed toward bacteriological cure should be concurrent with efforts to preserve native venous access sites whenever possible. Efforts to prevent vascular access-related infection should focus on increasing placement of arteriovenous fistulas and minimizing insertion of central venous dialysis catheters. Careful inspection and monitoring of the vascular access is of paramount importance in early detection of vascular access site-related infections. Several new approaches aimed at preventing catheter and prosthetic graft-related infection are being explored.

Infectious complications continue to be among the foremost causes of morbidity and mortality in hemodialysis (HD) patients. The United States Renal Data System (USRDS) showed that for the years 1991 and 1992, infection accounted for 12% of all deaths among HD patients in the United States [1]. In a subsequent report for the years 1993 to 1995, the USRDS showed that infection accounted for 15.5% of adult end-stage renal disease (ESRD) causes of death [2]. Mortality among the HD population may even be of larger magnitude than what has traditionally been appreciated from the USRDS. For example, in a large cohort study of 532 patients starting HD and followed-up for 16 years, Mailloux et al showed that death caused by infection accounted for 36% of all-cause mortality [3]. In a retrospective autopsy-based analysis of causes of mortality in 63 insulin-dependent diabetic patients on HD, Zander et al found that infection accounted for 20.6% of all deaths [4]. Perhaps the gigantic risk of death caused by infection in ESRD patients is best highlighted by Sarnak and Jaber, who compared annual mortality rates caused by sepsis in patients with ESRD with that in the general population [5]. In their comparative analysis, which relied on data from the USRDS for the years 1994 to 1996, they found 100- to 300-fold higher risk of death caused by sepsis in ESRD patients. Stratification for age, sex, gender, and the presence of diabetes did not significantly alter the magnitude of such risk posed by the ESRD status.

Of particular concern is that the HD vascular access has emerged as a major risk factor for infection and bacteremia [1, 6–20]. Numerous reports implicate the vascular access in up to 48 to 73% of all bacteremias in the HD population (Table 1) [1, 8–10, 13, 18]. Furthermore, the majority of these bacteremias are caused by staphylococcal organisms that are associated with high rates of mortality (8 to 25%), recurrence (14.5 to 44%), and serious metastatic complications (14.5 to 44%) [7–20]. Among the most common complications are infectious endocarditis, septic arthritis, epidural abscess, septic pulmonary emboli, and osteomyelitis [8–10, 14–17].

The incidence of infection caused by the HD vascular access is highest when it is a central venous catheter and lowest when it is a native arteriovenous fistula [6, 7, 9, 13, 14, 18–21]. Unfortunately, the prosthetic arteriovenous graft composed of polytetrafluoroethylene (PTFE), which has become an acceptable alternative to the native arteriovenous fistula, when the latter is not surgically feasible, is very often plagued by infection [19, 22, 23]. In the

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Table 1. Incidence of bacteremia in hemodialysis patients

Source [reference]	Country	Year	*N*	Incidence of bacteremia per 100 patient-years	Bacteremia due to vascular access	% bacteremia due to gram-positive cocci
Dobkin et al. [13]	USA	1978	N/A	15	73%	70%[a]
Kessler et al. [8]	France	1993	1455	8.4	51%	69.80%
USRDS [1]	USA	1996	USRDS	7.6	48%	N/A
Marr et al. [9][b]	USA	1998	445	14.4	89%	100%
Kaplowitz et al. [18]	USA	1988	71	8.4	27%	50%[c]
Hoen et al. [20]	France	1998	988	11.2	N/A	68%

N denotes number of hemodialysis patients during the study period. N/A denotes data not available.
[a] Rate applies if bacteremia is vascular access-related
[b] A study on *staphylococcal aureus* bacteremia
[c] Percent of combined bacteremic and nonbacteremic infections related to vascular access

Table 2. Incidence of catheter-related bacteremia (CRB) in hemodialysis patients

Source [reference]	Country	Year	*N*	Incidence of CRB per 1000 catheter-days	% CRB due to gram-positive cocci
Moss et al. [28]	USA	1990	131	0.7	N/A
Marr et al. [29]	USA	1997	102	3.9	63%
Kairaitis and Gottlieb [21]	Australia	1999	105	6.5	100%
Beathard [30]	USA	1999	387	3.4	84.5%[b]
Saad [31]	USA	1999	101	5.5	67.4%[c]
Cuevas et al (abstract)[a]	Spain	1999	189	1.54	84%
Cuevas et al (abstract)	Spain	1999	45	1	84%

N denotes number of patients with hemodialysis catheters; N/A denotes data not available.
[a] A study on temporary dialysis catheters
[b] Includes 9.8% of cultures due to mixed gram-positive and gram-negative infections
[c] Includes 12.8% cultures with mixed gram-positive and gram-negative infections

United States, the increasing use of dialysis catheters [24] and the widespread placement of PTFE grafts [25] place HD patients at high risk of serious vascular access-related infections [1–22, 24].

INFECTIONS RELATED TO DIALYSIS CATHETERS

Incidence

Numerous reports implicate tunneled (permcath) and nontunneled (temporary) dialysis catheters as important causes of serious infections in HD patients (Table 2). In a large seven-year longitudinal study of 4005 incident ESRD patients in the case-mix study of the USRDS, Powe et al found temporary vascular access as an independent risk factor for septicemia [7]. Hung et al studied 168 temporary dialysis catheters for an average of 27.8 (9 to 73) days. Catheter-related bacteremia (CRB) developed in 21.4% of cases. The cumulative probability of patients remaining free from CRB was 75% by the end of four weeks and less than 50% near the end of the second month [26]. A similar increase in the risk of developing CRB with longer duration of catheterization was also reported by Kairaitis and Gottlieb [21]. In their prospective study of 105 temporary dialysis catheters, CRB developed in 16% and exit site infections in 8% of cases.

Earlier reports described lower infection rates with tunneled cuffed catheters as opposed to nontunneled double lumen catheters [27, 28]; however, this has not been subjected to confirmation by large randomized trials. In 1988, Schwab et al observed one CRB among 80 tunneled catheters with a median follow-up of eight weeks (3 weeks to 5.4 months) [27]. In 1990, Moss et al followed 168 tunneled dialysis catheters over a four-year period (median catheter survival 18.5 months) and reported 0.7 CRB per 1000 catheter-days [28]. More recent studies show less optimistic results. In Marr et al's recent prospective study of 102 tunneled catheters, the incidence of CRB was found to be 3.9 episodes per 1000 catheter-days [29]. Similar rates of tunneled CRB ranging between 3.4 and 5.5 per 1000 catheter-days were reported by other investigators (Table 2) [30, 31].

A recent prospective study involving 234 HD catheters (45 of which were tunneled), presented by investigators from Spain (abstract; Cuevas et al, *J Am Soc Nephrol* 10:204, 1999), found CRB to occur at similar rates among tunneled and nontunneled catheters (1 per 1000 catheter-days with tunneled catheters vs. 1.54 per 1000 catheter-days with nontunneled catheters, $P = 0.98$). However, the average time from catheter placement to infection was longer with tunneled catheters (66.2 $\pm$ 84.5 days vs. 20.6 $\pm$ 29.4 days).

Risk factors

Several studies have attempted to define the risk factors involved in CRB. Both the site of insertion and the duration of use influence the rate of infection. Femoral catheters are more susceptible to infections than thoracic catheters [11]. This may relate to accumulation of sweat and moisture around the exit site. Kairaitis and Gottlieb found temporary HD catheters placed in the internal jugular vein to be associated with higher infection rates than those placed in the subclavian vein [21]. However, these results should not justify routine use of subclavian veins for HD catheters for two reasons. First, these findings may not apply to tunneled catheters. Second, the subclavian location carries the highest rate of catheter associated central venous stenosis [24]. The duration of catheter use is also important as the risk of infection increases linearly with time [21, 26].

Among local factors, poor personal hygiene, use of occlusive transparent dressing, and accumulation of moisture around the exit site have been described as risk factors for CRB [18, 24]. Nasal and skin colonization with S*taphylococcus aureus*, as well as bacterial colonization of HD catheters, has been reported as a risk factor for systemic infection [12, 32–35]. Systemic factors such as immunosuppression [20], diabetes mellitus [21, 28], low albumin [6, 7, 36], and high ferritin [24] have been found to be associated with increased risk of CRB.

In addition to bacteremia, catheter-related exit site infections are common complications of HD catheter use (8 to 21% of cases) and are important causes of catheter loss [21, 28, 30]. With tunneled catheters, infections external to the cuff are classified as exit site infections, whereas infections that extend in the tunnel proximal to the cuff are labeled as tunnel infections [24, 30]. Tunnel infections are more serious because of their frequent association with bacteremia [24, 30]. Several reports have identified poor patient hygiene and diabetes mellitus as risk factors for exit-site infections [21, 24, 28].

Diagnosis and management

Catheter-related bacteremia may have various clinical presentations. The acute onset of fever and chills in a patient with a HD catheter and no localizing signs is easily recognized and is generally considered to be a CRB until proven otherwise. Such an explosive presentation is often observed during the hemodialytic procedure, but could occur at any time during the interdialytic period. Less acute presentations of CRB are also frequent, especially in the older population and the immunocompromised. These may include any of the following: the insidious onset of low-grade fever, hypothermia, lethargy, confusion, hypotension, hypoglycemia, or diabetic ketoacidosis. Such insidious presentations may cause delay in the diagnosis, and a metastatic infectious complication may on occasion be the first clue to CRB. HD patients with suspicion of CRB must have blood cultures done immediately and should be promptly initiated on empiric antimicrobial therapy.

Management of CRB in the HD patient has two aspects. The first relates to antimicrobial therapy. Initial empiric antibiotic therapy should take into consideration the frequency of the bacterial isolates in such settings. Staphylococcal species have repeatedly been demonstrated to be the most prevalent (60 to 100%) bacterial isolates in HD patients with CRB [12–14, 20, 21, 24, 26, 30]. The prevalence of *S. aureus* and coagulase negative staphylococci bacteremia is similar in most series [20, 24, 26, 30, 31, 37]. Enterococci have been found in 11 to 19% of CRB [26, 30, 31]. Gram-negative rods are reported in up to 33% of cases [30, 31]. In some patients, both gram-positive and gram-negative organisms have been isolated from the blood stream, indicating mixed bacteremia [30, 31]. These data mandate that empiric antibiotic therapy should target both gram-positive and gram-negative organisms. Empiric therapy that ignores the possibility of gram-negative rods as mediators of CRB places a considerable number of patients at unwarranted risk and should not be a consideration. Specific antimicrobial therapy should replace empiric therapy as soon as the identity of the bacterial isolate is determined.

The other aspect of management is related to removal of the HD catheter, which is the source of the bacteremia (Fig. 1). While this approach is scientifically the most correct, it poses certain practical problems, especially in HD patients whose vascular access sites have been exhausted. In an attempt to preserve venotomy sites, Beathard prospectively evaluated a more conservative approach in a series of 114 patients with CRB [22, 30]. While all of his patients were appropriately treated with antibiotics, catheter management depended on the clinical picture. Patients with severe clinical symptoms had catheter removal with delayed replacement after defervescence (86.5% cure rate). Patients with minimal symptoms but with tunnel or exit site infection had a catheter exchange over a guide wire with creation of new tunnel (75% cure rate). Patients with minimal symptoms and a normal-appearing tunnel and exit site had a catheter exchange over a guide wire within 48 hours of antibiotic initiation (87.8% cure rate). Cure rates were defined as a 45-day, symptom-free interval after antibiotic therapy was complete [30]. In keeping with these results, Tanriover et al conducted a retrospective study in which they compared the outcomes of two treatment strategies for CRB in HD patients: catheter exchange over a guide wire (31 catheters) versus catheter removal with delayed replacement (38 catheters). The infection-free survival was similar with both strategies that included three weeks of systemic antibiotic therapy [36].

Treatment of CRB with antibiotics while the catheter

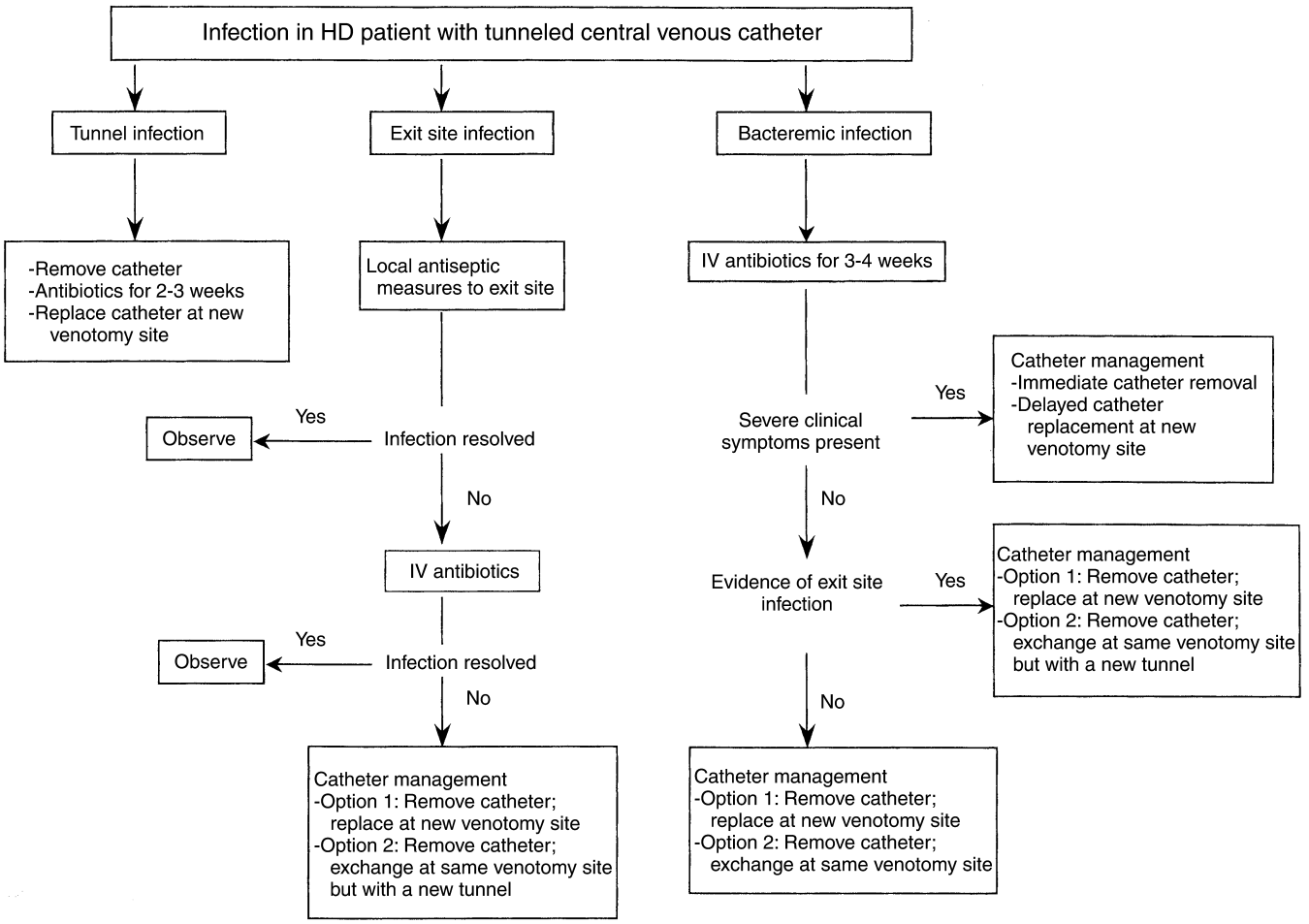

Fig. 1. Management of infection in hemodialysis (HD) patients whose vascular access is a tunneled central venous dialysis catheter.

remains in place has been advocated by some authors; however, Marr et al observed a failure rate of 68% with this approach [29]. Most authorities do not consider this approach a treatment option and advocate catheter removal or exchange [24, 29–31]. Bacteria adherent to a biofilm on the inner or outer surfaces of the catheter are unlikely to be eradicated by antibiotic administration and are suspected to be the cause of recurrent bacteremia when the catheter is not exchanged [37].

Exit site infections are common and are recognized by redness, exudation, and crusting. Unless associated with bacteremia or tunnel infection, exit site infections should be treated conservatively [24, 28, 30]. Topical antiseptics and local application of antimicrobials may be sufficient in milder cases. Systemic antibiotics should be used in cases that fail to respond to topical therapy. Catheter removal may become necessary if the previously mentioned measures fail to eradicate the exit site infection. Tunnel infection is best treated by catheter removal and the replacement at a new venotomy site [24, 30].

Newer strategies to prevent catheter-related infection

A gentamycin/sodium citrate mixture has been used with preliminary success as an antibiotic-lock technique for salvage and prevention of catheter-related infections. Sodemann et al described near elimination of catheter related infections with this mixture when installed in the HD catheter lumen at the end of dialysis instead of heparin (abstract; Sodemann et al, *J Am Soc Nephrol* 8:173, 1997). Similar favorable results were observed by Ash et al, who described a decrease in the incidence of CRB from 4.5 to 1.6 episodes per 100 patient-months following the use of a catheter lock solution (abstract; Ash et al, *J Am Soc Nephrol* 10:272, 1999). The latter consisted of 10 or 20% sodium citrate mixed with gentamycin at 2.3 mg/mL. In the same meeting, Ash et al reported that concentrated sodium citrate (47%), without gentamycin, was also successful in preventing catheter-related infection when used as a catheter lock solution by virtue of its bactericidal and sporicidal activity in vitro. However, the Food and Drug Administration (FDA) has recently cautioned against the use of 47% sodium citrate (but not

4% solution) as a dialysis catheter lock solution for fear of adverse events (for example, hypocalcemia) should concentrated citrate accidentally enter the blood stream.

An antibiotic heparin lock may prove to be useful in central venous catheters. Preliminary studies by Vercaigne et al tested the in vitro stability of antibiotic heparin combinations [38]. While ciprofloxacin produced immediate precipitation with heparin, cefazolin, vancomycin, and ceftazidime at 10 mg/mL and gentamycin at 5 mg/mL were successfully incubated with heparin (5000 U/mL) for 72 hours in the central venous catheter lumen. Despite progressive reductions in free antibiotic levels, largely caused by adherence to the inner luminal surface of the catheter, sufficient bactericidal antibiotic concentrations persisted at 72 hours [38]. These encouraging results provide the basis for further investigation of the usefulness of the antibiotic heparin catheter lock in preventing CRB.

In an attempt to minimize central venous catheter-related infection in intensive care units, Maki et al studied the usefulness of a subcutaneous silver-impregnated attachable cuff in a prospective randomized multicenter trial, which involved 234 catheters (not for dialysis) [39]. The results demonstrated nearly fourfold less bacteremia with this cuffed catheter (1.0 vs. 3.7%). In addition, catheters with the cuff were threefold less likely to be colonized on removal (9.1 vs. 28.9%). Similar results were obtained with central venous catheters impregnated with chlorhexidine and silver sulfadiazine [40].

In keeping with the same concept, catheters impregnated with minocycline and rifampin were developed. In vitro and animal studies suggest that these catheters resist infection more effectively than catheters impregnated with chlorhexidine and silver sulfadiazine [41, 42]. Darouiche et al recently published the results of a prospective, randomized clinical trial with 865 central venous catheters (not for dialysis) and showed that catheters impregnated with minocycline and rifampin are associated with lower rates of colonization (7.9 vs. 22.8%) and CRB (0.3 vs. 3.4%) in comparison with catheters impregnated with chlorhexidine and silver sulfadiazine [43]. Such catheters are not yet commercially available to the HD community; however, an initial trial with minocycline/rifampin-impregnated HD catheters is being conducted in the University of Texas in Houston (personal communication with Dr. Darouiche).

To eliminate the external location of dialysis catheters, a totally implantable port-system has been developed as a dialysis access (Biolink Corp., Middleboro, MA, USA). It consists of a subcutaneously implanted metallic chamber connected to permanent silicone twin catheters. The chamber is implanted subcutaneously in the chest area below the clavicle, and the twin catheters end in the right atrium (Biolink Corp.). This system is referred to as Dialock and is accessed percutaneously at each dialysis session with special needle cannulas that convert it to a conventional twin catheter system. While this system is not totally free of the mechanical complications that affect dialysis catheters, preliminary reports describe lower rates of bacteremia (0 to 3 per 1000 catheter days) [44–46].

INFECTIONS OF THE ARTERIOVENOUS ACCESS

Arteriovenous fistula versus graft

The arteriovenous HD access includes the native arteriovenous fistula and the synthetic arteriovenous graft. In 1995, a large U.S. national survey, conducted by the Centers of Disease Control (CDC) and involving 224,954 HD patients, showed that only 22% of patients were dialyzed through a native arteriovenous fistula [25]. This is unfortunate because the probability of dialysis access-related infection is considerably less for patients with native arteriovenous fistula than for those with synthetic grafts [6, 9, 14, 19, 47]. Postoperative wound infection as well as poor aseptic technique at dialysis may cause infection of the fistula. In most instances, such infections are successfully managed by systemic antibiotics and conservative surgery, but can lead to loss of the fistula [47].

In the United States, the majority of current arteriovenous grafts are of PTFE material. PTFE arteriovenous grafts have gained widespread popularity because of ease of placement at sites where it is surgically unfeasible to create a native arteriovenous fistula. This surgical success has created two untoward consequences: high rates of arteriovenous access thrombosis and infection [22, 23, 48–50]. In the United States, the vast majority of arteriovenous access-related infections are associated with PTFE grafts.

Incidence and risk factors

The risk of PTFE infection starts at the time of surgical placement. Zibari et al reported an initial 30-day graft infection rate of 6% in 208 patients undergoing PTFE placement [49]. The femoral location (thigh graft) of PTFE grafts is associated with higher postoperative wound infection rates caused by sweat and moisture accumulation in between the overlying skin folds [47]. This is of particular concern in obese patients, diabetics, and those with poor hygiene. While the incidence of postoperative PTFE infection can be reduced with prophylactic antimicrobial therapy [49], a persistent risk of infection continues to haunt the PTFE graft through out its lifetime.

A considerable risk of PTFE graft infection is posed by the need for repetitive cannulation of the graft for dialytic purposes [50]. Difficulty in cannulation of the PTFE graft, perigraft hematoma formation, prolonged postdialysis bleeding from the graft, and a break in the sterile technique further increase the likelihood of PTFE graft infection at needle puncture sites. Bonomo et al found surgical manipulation to be a risk factor for graft infection [19]. In their study of 51 graft infections in 31 patients, the risk of graft infection increased linearly with the number

of surgical revisions. Curi et al studied the outcome of arteriovenous access in 42 HIV-positive patients and found HIV-positive status to be a risk factor for PTFE graft infection but not for native arteriovenous fistula [51]. PTFE graft infection occurred in 30% of their HIV positive versus 7% of their HIV negative HD patients. Poor patient hygiene has been recognized as a risk factor for graft infection [18], whereas diabetes mellitus [7], hypoalbuminemia [7, 35], advanced age [7, 18], and high serum ferritin [8] have been recognized as general risk factors for infection in HD patients.

Infection of PTFE graft material may also develop as a result of a transient bacteremia caused by an infection at a distant site [19]. Central venous catheters are notorious for causing bacteremia and should be regarded as a risk factor for bacterial infection of the PTFE graft. Once infected, the PTFE graft may in turn act as a source of bacteremia at a subsequent date when the original source of infection had been eliminated and forgotten.

Diagnosis and management

Infection of the arteriovenous graft is often recognized clinically. Signs and symptoms of local infection may include any of the following: pain, irritation, tenderness, redness, warmth, diffuse or localized swelling, serous or purulent discharge, and skin breakdown. The lack of such signs and symptoms does not exclude the possibility of clinically silent graft infection, especially in cases of unexplained sepsis, leukocytosis, or fever of unknown origin.

Management of PTFE graft infection has to strike a balance between an attempt for bacteriological cure and preservation of venous access sites (Fig. 2). In doing so, it is extremely important to recognize signs and symptoms of graft-related infection very early when it may be amenable to therapy with systemic antibiotics and local measures. Many local infections of the arteriovenous graft site can be cured with early aggressive medical therapy without resorting to graft excision [52]. However, abscess formation in the immediate proximity to the graft, purulent drainage from infection that dissects onto the graft material, and infected aneurysmal dilations of the graft require surgical excision of the graft or a segment of it. This is especially true when the source of bacteremia is an obvious PTFE graft infection. It is our personal experience that conservative excision of infected segments of PTFE grafts is associated with high rates of recurrent infection necessitating total graft excision. Therefore, careful observation and follow-up are necessary when conservative surgical measures are employed.

When bacteremia occurs in the absence of clinical signs of graft infection, silent arteriovenous graft infection may go undetected. Such episodes may be more common than what is generally appreciated and may explain the high rates of recurrent bacteremia in patients with synthetic grafts [9, 53]. A high index of suspicion is required to diagnose silent infection in functional PTFE grafts. In such instances, indium scanning of prosthetic grafts is an extremely helpful tool in diagnosing clinically silent infection, as discussed later in this article.

Newer strategies to prevent arteriovenous access-related infection

A recent development in the area of the HD access is the availability of cryopreserved human femoral veins for use as arteriovenous access grafts (CryoLife, Inc., Kennesaw, GA, USA). These cryoveins have the ability to revascularize, thus allowing the patient to fight and resist infection. Since 1996, over 500 cryopreserved superficial femoral vein allografts have been implanted for HD access. In many of these cases, these vein allografts were placed in the setting of systemic or local infection. Initial experience by Matsuura et al shows a remarkable absence of cryovein-related infection (abstract; Matsuura et al, *24th Annual Meeting of the Peripheral Vascular Surgery Society*, 1999). The rarity of cryovein-related infection in these preliminary reports is promising for patients with history of repeated PTFE graft infections and exhaustion of dialysis arteriovenous access sites. In these patients, cryovein arteriovenous grafts may be placed at new sites, but their placement at old graft sites seems possible despite the presence of intercurrent PTFE graft infection (personal communication with Dr. Matsuura). In such clinical scenarios, Matsuura et al advocate one operation in which cryovein graft is created at the same site while the infected PTFE graft is being removed. This leads to salvage of angioaccess sites that would have otherwise been abandoned. In keeping with the same concept, lower rates of arteriovenous access-related infection were also observed with the use of denatured homologous vein grafts, as opposed to PTFE grafts, in a prospective randomized multicenter trial [54].

INFECTIONS OF OLD CLOTTED ARTERIOVENOUS GRAFTS

Incidence and diagnosis

The risk of PTFE graft infection in the HD patient does not end when the graft is no longer in use. Such grafts are typically nonfunctioning with a thrombosed lumen. It is common practice to leave these clotted grafts in place, and thus, many HD patients have one or more old clotted grafts in their extremities. Even though these old clotted grafts tend to be considered innocuous by most health care practitioners, it has recently been recognized that they may harbor occult bacterial infection that can lead to serious infectious complications [55–57].

It is difficult to diagnose infection in old clotted grafts largely because of the fact that such infections tend to be silent. Clinical recognition of PTFE-related infection is easy when there is tenderness, erythema, warmth, in-

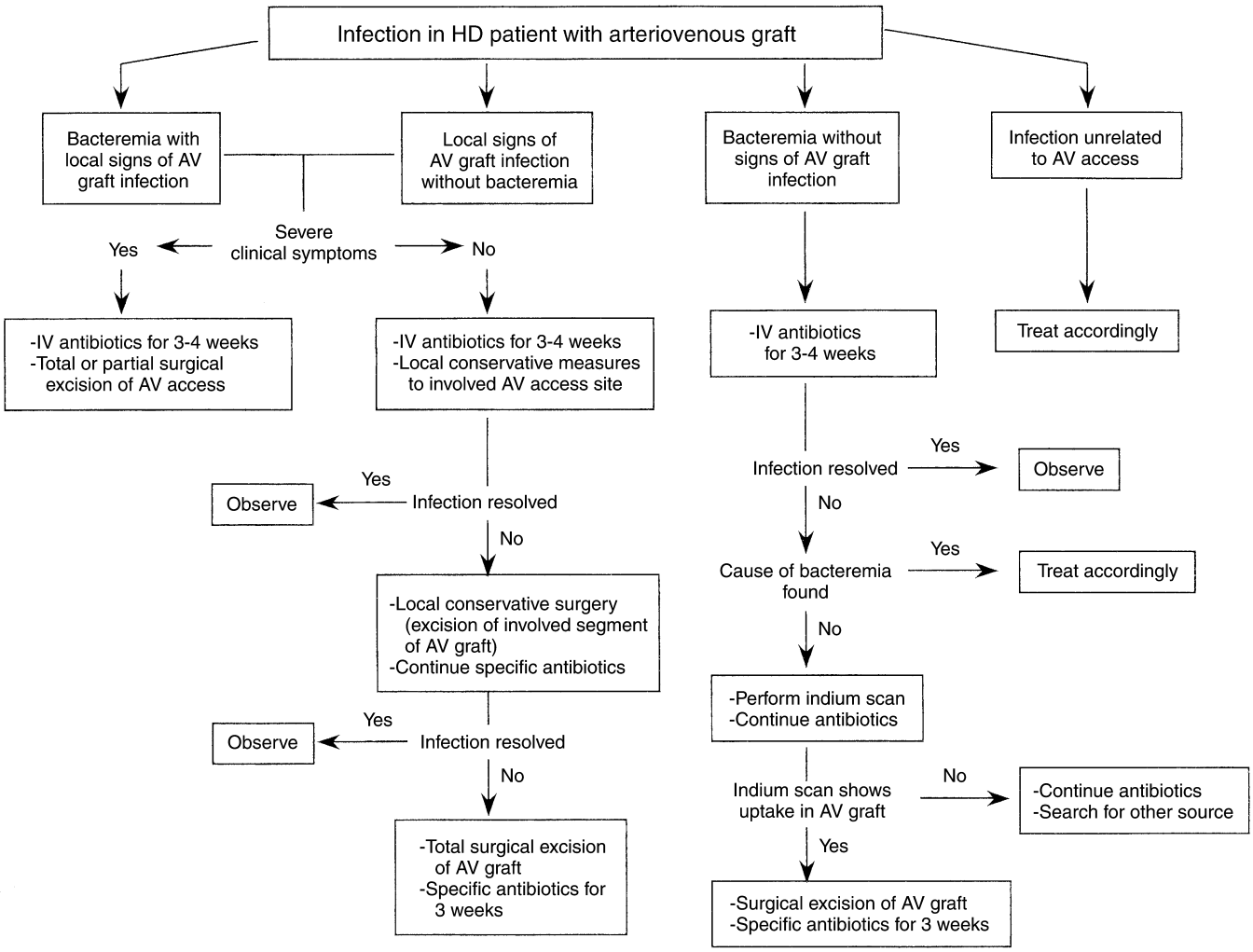

Fig. 2. Management of infection in hemodialysis (HD) patients whose vascular access is a synthetic arteriovenous (AV) graft.

duration, or local drainage around the graft. In patent grafts, these localizing signs of infection are often noted at the sites of previous graft punctures or surgical manipulation. In old clotted grafts, these signs are frequently absent. Thus, the diagnosis of clinically silent graft infection requires a high index of suspicion and is frequently missed [55–57].

To evaluate the prevalence and clinical relevance of silent infection in clotted grafts, we studied a series of 20 HD patients with old clotted PTFE grafts who presented with fever (15 patients) or fever and clinical signs of sepsis (5 patients) in whom the source of infection was not immediately localized to any organ system [55]. A comparison was made with 21 asymptomatic HD patients with clotted PTFE grafts who served as control subjects. Both febrile patients and control subjects were evaluated with indium scans and then subjected to surgical removal of the graft. Bacterial cultures of the recovered surgical material and blood were done simultaneously in all study participants.

Blood cultures were positive for bacterial pathogens in 15 of the 20 febrile patients, indicating that serious illness was present. In contrast, all of the asymptomatic control subjects had negative blood cultures. Indium uptake in or around the clotted grafts was present on scanning in all 20 patients and in 15 of the control subjects. The importance of the indium scan findings was verified when purulent infected material was recovered from graft material in all 20 patients and in 13 of 15 indium scan-positive control subjects. The pathogens recovered from blood culture were identical to those cultured from the graft material in all patients, strongly indicating a causal relationship. By far the most frequent pathogens recovered from the graft material were *S. aureus*, followed by *Staphylococcus epidermidis.* Other less frequent pathogens were *Escherichia coli*, *Serratia marcescens*, and *Streptococcus pneumonia.*

Indium scan is a well-established and accepted method for localization of infection in general [58, 59]. This tech-

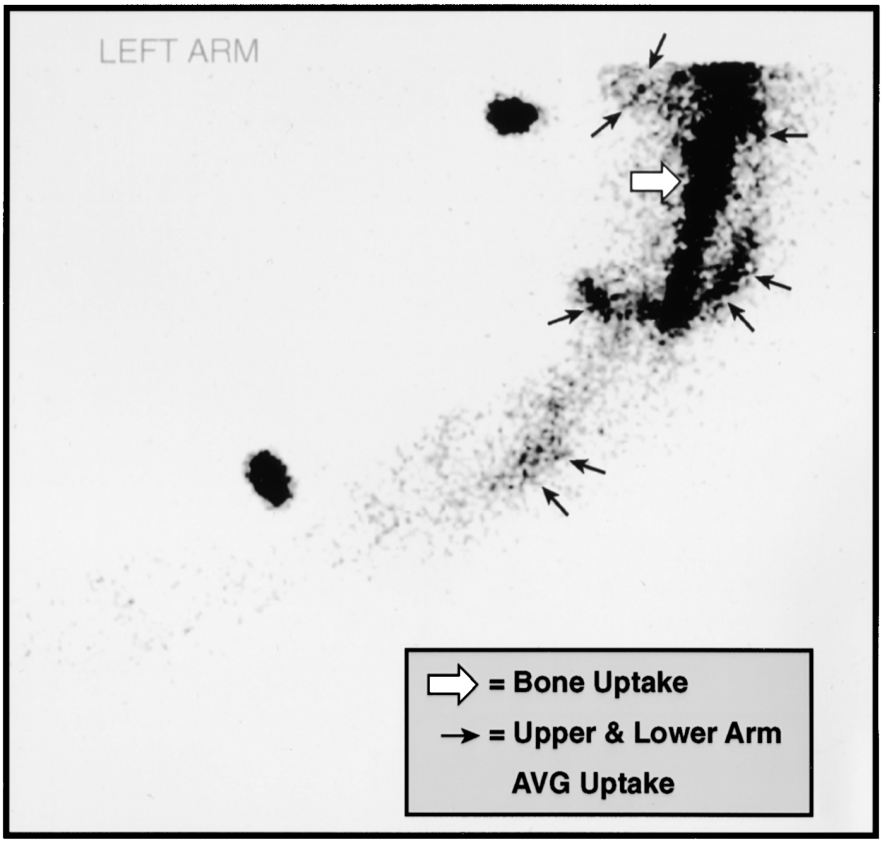

Fig. 3. Indium 111-labeled leukocyte scan showing diffuse and intense tracer uptake in a prosthetic upper arm arteriovenous graft indicating high likelihood of infection. The scan also shows mild tracer uptake in a prosthetic forearm arteriovenous graft also suspicious for infection. These grafts were old, clotted, and nonfunctional accesses in a 63-year-old woman on HD suffering from hypoalbuminemia and anemia resistant to erythropoietin. Surgical excision of these grafts uncovered purulent material, from which *S. aureus* organisms were recovered. Following graft excision and treatment with antimicrobials, serum albumin increased and erythropoietin resistance resolved. Note that tracer uptake by bone, as seen on the scan, is not of pathologic significance.

nique requires administration of autologous indium-111–labeled leukocytes and subsequent (24 h later) total body scanning with a gamma camera (Fig. 3). It has been shown to be useful in vascular graft infection, with overall satisfactory sensitivity and specificity [60, 61]. A variety of lesions other than foci of bacterial infection can produce positive results, but an intense focal uptake is uncommon in lesions other than abscesses and hematomas. In our experience, the indium scan demonstrated a sensitivity of 100% and a specificity of 75% for graft infection [55]. We therefore advocate indium scanning as a diagnostic tool to investigate the possibility of graft infection when such suspicion exits in the absence of clinically obvious signs.

Management and risk factors

The natural history of silent PTFE infection has not been studied prospectively, but spontaneous resolution is unlikely. We also doubt reliable resolution of infection with antimicrobial therapy since it involves foreign material. Two concerns emerge. The first is obvious and relates to acute dissemination of bacterial infection into the blood stream or other organ systems. The second concern is less obvious but equally grave; it evokes the possibility that silent graft infection may be a contributor to the "chronic inflammatory state" that afflicts HD patients. In support of the latter concern is a recent report by Fishbane et al, who found high rates of occult bacterial infection in nonfunctioning arteriovenous grafts among their HD patients with refractory anemia and low serum albumin (abstract; Fishbane et al, *J Am Soc Nephrol*, 10:1402, 1999). Excision of the graft led to a decline in serum C-reactive protein (CRP) levels and total serum ferritin, along with a rise in serum albumin and improved responsiveness to erythropoietin. Preliminary data from our HD patients also show improvement of serum albumin following excision of PTFE grafts harboring occult infection (unpublished observations). While the link between occult PTFE graft infection and chronic inflammation has not been adequately studied, it is worthy to mention that serum CRP levels, which are markers of chronic inflammation, are significantly higher in asymptomatic HD patients in comparison with those on peritoneal dialysis [62, 63].

Infected old clotted PTFE grafts should be surgically excised without any delay, and systemic antibiotics should be administered. It is tempting to conclude that old PTFE grafts should be routinely excised because they frequently are sites of infection [55–57]. At present, there are no prospective data to address this question appropriately. However, the common practice of routinely leaving clotted nonfunctioning grafts in place pre-

Table 3. Risk factors for arteriovenous graft infection

Diabetes mellitus
Immuno-incompetency
Renal transplantation
Indwelling central venous catheter
History of bacteremia
Previous major infection in any organ system
Previous arteriovenous graft-related infection
Previous arteriovenous graft-related surgery
Fever of unknown origin

disposes many HD patients to the risk of developing serious infectious complications [57]. If we are not in a position to advocate removal of all nonfunctioning PTFE grafts, then we need to identify a subgroup of patients who are at added risk of PTFE infection. It is our personal experience that the following factors identify patients at such risk: diabetes mellitus, immunoincompetency, renal transplantation, indwelling central venous catheter, previous bacteremia, previous infection in any organ system, previous PTFE graft-related infection, and fever of unknown origin (Table 3) [57]. In these patients, evidence of infection in their old clotted PTFE grafts should be actively investigated and managed.

GENERAL CONSIDERATIONS IN ANTIMICROBIAL THERAPY

Empiric antimicrobial therapy

Fever in the HD patient may have various etiologies, and antimicrobial therapy should be tailored accordingly [64]. When the source of fever is suspected to be due to the HD access (catheter or graft), antimicrobial therapy must reliably cover gram-positive species (including methicillin-sensitive *S. aureus*), since these organisms account for about two thirds of HD access-related bacteremias [8–10, 12–18, 20, 21, 24, 26–31, 55–57]. Enterococci and gram-negative organisms account for the majority of the remaining bacteremias, and antimicrobial therapy should target these organisms as well [18, 25, 30, 31, 55–57].

Based on the previously mentioned data, it has become a common practice to treat the febrile HD patient empirically with a combination of parenteral vancomycin plus gentamycin. The popularity of this combination is due to two reasons: (*1*) It provides broad spectrum antimicrobial coverage, which includes methicillin-resistant *S. aureus* (MRSA) and enterococci, and (*2*) based on the pharmacokinetics of vancomycin and gentamycin, it allows convenient in-center dosing, once or three times weekly, respectively. The empiric use of this combination (or vancomycin plus a third generation cephalosporin) is medically justified in HD patients when bacteremia is suspected (Fig. 4).

Emergence of vancomycin resistant enterococci

With the emergence of vancomycin-resistant enterococci (VRE) and the recognition of HD and peritoneal dialysis as independent risk factors for VRE bacteremia [65–68], the empiric use of vancomycin in the febrile patient on HD has recently been challenged by several authorities [69, 70]. Among these are the CDC, which published guidelines for the prudent use of vancomycin in an attempt to prevent the spread of vancomycin resistance [70]. In accordance with these guidelines, empiric treatment with vancomycin is appropriate in patients with β-lactam allergy or in instances when serious infections with β-lactam-resistant gram-positive bacteria (MRSA, *S. epidermidis*) are likely. In a given dialysis facility, the likelihood of such infections can be determined by knowing the percentage of MRSA isolates and the percentage of serious infections caused by *S. epidermidis.* Continuing treatment, however, depends on culture results. If the patient is allergic to β-lactam antibiotics or if β-lactam-resistant bacteria are isolated, vancomycin is appropriate.

Alternatives to vancomycin

The use of parenteral cefazolin, as an alternative to vancomycin, either singly or in combination with gentamycin, has recently been explored in HD patients. In a retrospective review of blood and wound culture results from a 217-patient, non–hospital-based outpatient HD center, Fogel et al found cefazolin to be equivalent to vancomycin for empiric treatment of clinically significant infections in a population with a low rate of MRSA [71]. In the same report, a prospective pharmacokinetic analysis in anuric HD patients demonstrated safe and effective peak and trough cefazolin levels with 1 g postdialysis dosing. Similarly, Marx et al were successful in using empiric postdialysis cefazolin (20 mg/kg) to treat 15 consecutive HD patients suffering from various infections [72]. Collectively, these data support two conclusions. First, for infections with documented sensitivity to cefazolin in anuric HD patients, intravenous postdialysis dosing of cefazolin is both safe and effective, and second, empiric treatment of non–life-threatening infections with cefazolin alone or in combination with gentamycin may be appropriate in HD patients in a facility with low MRSA infection rates, pending culture results (Fig. 4).

Complications of bacteremia

Infectious complications of bacteremia are a frequent occurrence in HD patients. Death, recurrence of bacteremia, endocarditis, epidural abscess, purulent pericarditis, septic arthritis, septic pulmonary emboli, liver abscess, and endophthalmia have all been reported as complications of bacteremia [8, 14–16]. By far, the leading bacterial isolate in HD patients with metastatic complications is *S. aureus* [8, 14–16]. Infectious endocarditis

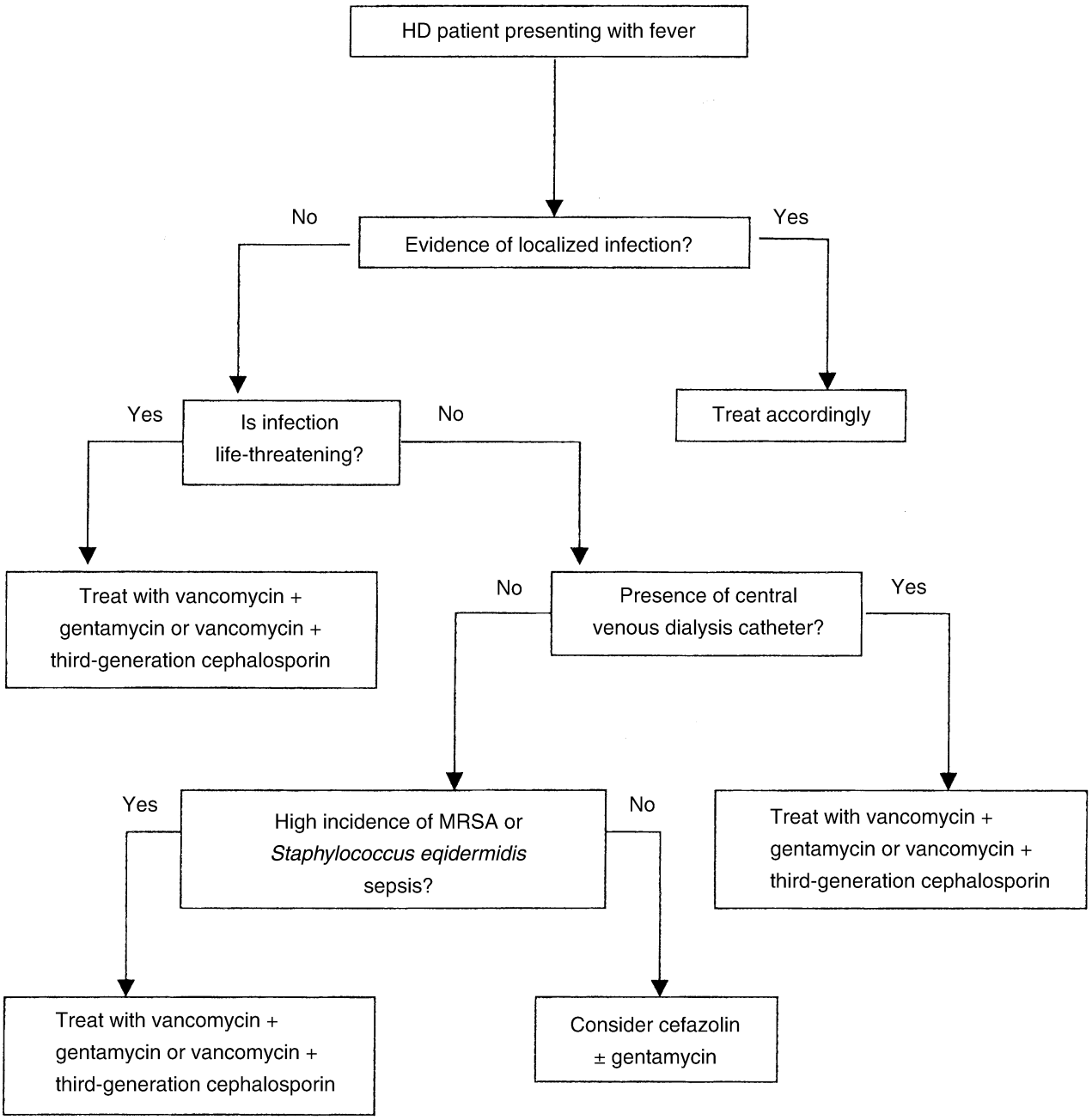

Fig. 4. Initial management and empiric use of antimicrobials in hemodialysis (HD) patients with fever. MRSA denotes methicillin-resistant *S. aureus.*

is the most dreaded of these complications. Robinson et al reported a 30% mortality rate in a series of 20 HD patients with infectious endocarditis [14]. In addition, 25% required heart valve replacement. Transthoracic echocardiography is likely to miss the majority of infectious endocarditis cases; therefore, establishing the diagnosis requires a high index of suspicion coupled with transesophageal echocardiography [14]. Another serious complication is the occurrence of spinal epidural abscess, which can evolve to severe permanent neurologic deficit or death if the diagnosis is delayed. Obrador and Levenson summarized data on 12 HD patients with spinal epidural abscess and found back pain and radicular pain to be the most common signs at presentation [15]. *S. aureus* was implicated in all of these cases. Magnetic resonance imaging with gadolinium or myelography is the best available tools for establishing the diagnosis of epidural abscess. Early recognition and treatment with antibiotics and decompressive laminectomy is associated with better outcome.

Duration of antibiotic therapy

When bacteremia is documented by positive blood cultures, the duration of antimicrobial treatment should be sufficiently prolonged so as to minimize recurrence of bacteremia and prevent the occurrence of the previously mentioned infectious complications. These complications are more common with short (two weeks or less) courses of antimicrobial therapy, and several authorities advocate at least four weeks of adequate antibiotic therapy for *S. aureus* bacteremia [73]. For all other organisms, a minimum of three weeks of adequate antimicrobial therapy is advocated [30].

Nasal mupirocin

Nasal carriage of *S. aureus* is a risk factor for the development of *S. aureus* bacteremia in HD patients [33, 34]. Nasal mupirocin ointment has been successfully used to eradicate nasal carriage of *S. aureus* [33–35]. Boelaert et al found fourfold reduction in the incidence of *S. aureus* bacteremia with intranasal mupirocin during 167.7 patient years of HD [33]. Nasal mupirocin did not lead to the development of bacterial resistance or overgrowth of other microorganisms [33, 34]. Hence, chemoprophylaxis with intranasal mupirocin in HD patients who are nasal carriers of *S. aureus* seems cost-effective [33].

COST CONSIDERATIONS

It is well known that morbidity of the dialysis vascular access is one of the most important causes of hospitalization in the U.S. ESRD population [74]. In 1986, approximately 17% of all-cause hospitalization among the U.S. ESRD population was vascular access-related, and the number of vascular access-related hospital days was approximately 40,000. By 1991, over 20% of all-cause hospitalization was vascular access related, representing 70,000 hospital days. In 1996, Feldman, Kobrin, Wasserstein estimated the total annual cost of vascular access morbidity to be approximately 10% of the total U.S. ESRD budget and projected that this cost will likely exceed $1 billion in the ensuing years [74]. Unfortunately, the percentage of this total annual cost that is due infection is not known, but we believe it is substantial.

CONCLUDING REMARKS

The vascular access imposes a serious risk of life-threatening infections that lead to significant morbidity and mortality among the HD population. While central venous catheters provide immediate vascular access, they carry the highest risk of bacteremia. Arteriovenous PTFE grafts, the most common type of arteriovenous access for HD in the United States, are also frequent causes of bacteremic and nonbacteremic infections. Several steps should be carried out at various levels of care to minimize the global impact of vascular access-related infection.

The first step in minimizing the frequency of vascular access-related infection should be a serious attempt to increase the percentage of HD patients whose vascular access is an arteriovenous fistula. These accesses are associated with the least risk of infectious complications.

The second step is recognition of risk factors for HD vascular access infection. Some of these factors, such as the presence of diabetes mellitus, immunosuppression, and low serum albumin, may not be amenable to modification. However, other risk factors such as nasal *S. aureus* carrier status, poor personal hygiene, and improper cannulation techniques at dialysis are important to recognize and modify. Prophylactic antibiotics are useful in certain situations such as patients undergoing surgical procedures on their PTFE grafts.

The third step is early recognition and treatment of vascular access-related infection. Careful monitoring of the vascular access is essential, and prompt treatment of suspected infection may be life saving. In many instances, recognition of infection requires a high index of suspicion. For example, occult infection in old clotted arteriovenous grafts may not be associated with overt signs of local infection. In such instances, a leukocyte-labeled indium scan is likely to demonstrate evidence of graft infection. Empiric antimicrobial therapy of vascular access-related infection should target both gram-positive as well as gram-negative bacteria. Specific antimicrobial therapy should replace empiric therapy whenever the identity of the bacterial isolates mediating infection is known. Prolonged systemic antimicrobial therapy is essential to prevent recurrence of infection as well as serious metastatic infectious complications. In addition to antimicrobial therapy, proper management of vascular access-related infection requires a plan of management of the vascular access itself, which in turns depends on the clinical scenario. For example, bacteremia in association with a HD catheter mandates removal of the catheter, and purulent drainage in proximity to PTFE graft material requires a minimum of segmental graft excision.

The fourth step relates to exploring novel approaches directed at decreasing the risk of vascular access-related infection. The use of antibiotic-lock techniques in the HD catheter lumen during the interdialytic period has been initially successful in decreasing catheter-associated infections. The use of HD catheters impregnated with antimicrobial agents is being investigated in HD patients. Preliminary experience with human cryoveins suggests a significant reduction in arteriovenous access-related infections.

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REFERENCES

1. Bloembergen WE, Port FK: Epidemiological perspective on infections in chronic dialysis patients. *Adv Ren Replace Ther* 3:201–207, 1996
2. Causes of death: USRDS: United States Renal Data System. *Am J Kidney Dis* 30(Suppl 1):S107–S117, 1997
3. Mailloux LU, Bellucci AG, Wilkes BM, *et al:* Mortality in dialysis patients: Analysis of the causes of death. *Am J Kidney Dis* 18:326–335, 1991
4. Zander E, Schultz B, Gums G, *et al:* Causes of death in insulin-dependent diabetic patients treated with hemodialysis. *J Diabetes Complications* 3:163–166, 1989
5. Sarnak MJ, Jaber BL: Mortality caused by sepsis in patients with end-stage renal disease compared with the general population. *Kidney Int* 58:1758–1764, 2000
6. Churchill DN, Taylor DW, Cook RJ, *et al:* Canadian Hemodialysis Morbidity Study. *Am J Kidney Dis* 19:214–234, 1992
7. Powe NR, Jaar B, Furth SL, *et al:* Septicemia in dialysis patients: Incidence, risk factors, and prognosis. *Kidney Int* 55:1081–1090, 1999
8. Kessler M, Hoen B, Mayeux D, *et al:* Bacteremia in patients on chronic hemodialysis: A multicenter prospective survey. *Nephron* 64:95–100, 1993
9. Marr Ka, Kong L, Fowler VG, *et al:* Incidence and outcome of *Staphylococcus aureus* bacteremia in hemodialysis patients. *Kidney Int* 54:1684–1689, 1998
10. Quarles LD, Rutsky EA, Rostand SG: *Staphylococcus aureus* bacteremia in patients on chronic hemodialysis. *Am J Kidney Dis* 6:412–419, 1985
11. Zaleski GX, Funaki B, Lorenz JM, *et al:* Experience with tunneled femoral hemodialysis catheters. *Am J Roentgenol* 172:493–496, 1999
12. Nielsen J, Ladefoged SD, Kolmos HJ: Dialysis catheter-related septicaemia: Focus on *Staphylococcus aureus* septicaemia. *Nephrol Dial Transplant* 13:2847–2852, 1998
13. Dobkin JF, Miller MH, Steigbigel NH: Septicemia in patients on chronic hemodialysis. *Ann Intern Med* 88:28–33, 1978
14. Robinson DL, Fowler VG, Sexton DJ, *et al:* Bacterial endocarditis in hemodialysis patients. *Am J Kidney Dis* 30:521–524, 1997
15. Obrador GT, Levenson DJ: Spinal epidural abscess in hemodialysis patients: Report of three cases and review of the literature. *Am J Kidney Dis* 27:75–83, 1996
16. Peacock SJ, Curtis N, Berendt AR, *et al:* Outcome following haemodialysis catheter-related *Staphylococcus aureus* bacteraemia. *J Hosp Infect* 41:223–228, 1999
17. Kovalik E, Albers F, Raymond J, Conlon P: A clustering of cases of spinal epidural abscess in hemodialysis patients. *J Am Soc Nephrol* 7:2264–2267, 1996
18. Kaplowitz LG, Comstock JA, Landwehr DM, *et al:* A prospective study of infections in hemodialysis patients: Patient hygiene and other risk factors for infection. *Infect Control Hosp Epidemiol* 9:534–541, 1988
19. Bonomo RA, Rice D, Whalen C, *et al:* Risk factors associated with permanent access-site infections in chronic hemodialysis patients. *Infect Control Hosp Epidemiol* 18:757–761, 1997
20. Hoen B, Paul-Dauphin A, Hestin D, Kessler M: EPIBACDIAL: A multicenter prospective study of risk factors for bacteremia in chronic hemodialysis patients. *J Am Soc Nephrol* 9:869–876, 1998
21. Kairaitis LK, Gottlieb T: Outcome and complications of temporary haemodialysis catheters. *Nephrol Dial Transplant* 14:1710–1704, 1999
22. Connoly JE, Brownell DA, Levine EF, McCart MP: Complications of renal dialysis access procedures. *Arch Surg* 119:1325–1328, 1984
23. Munda R, First MR, Alexander JW, *et al:* Polytetrafluoroethylene graft survival in hemodialysis. *JAMA* 249:219–222, 1983
24. Schwab SJ, Beathard G: The hemodialysis catheter conundrum: Hate living with them, but can't live without them. *Kidney Int* 56:1–17, 1999
25. Tokars JI, Miller ER, Alter MJ, Arduino MJ: National surveillance of dialysis associated diseases in the United States, 1995. *ASAIO J* 44:98–107, 1998
26. Hung KY, Tsai TJ, Yen CJ, Yen TS: Infection associated with double lumen catheterization for temporary haemodialysis: Experience of 168 cases. *Nephrol Dial Transplant* 10:247–251, 1995
27. Schwab SJ, Buller GL, McCann RL, *et al:* Prospective evaluation of a Dacron cuffed hemodialysis catheter for prolonged use. *Am J Kidney Dis* 11:166–169, 1988
28. Moss AH, Vasilakis C, Holley JL, *et al:* Use of a silicone dual-lumen catheter with a Dacron cuff as a long-term vascular access for hemodialysis patients. *Am J Kidney Dis* 16:211–215, 1990
29. Marr KA, Sexton D, Conlon P, *et al:* Catheter-related bacteremia and outcome of attempted catheter salvage in patients undergoing hemodialysis. *Ann Intern Med* 127:275–280, 1997
30. Beathard GA: Management of bacteremia associated with tunneled-cuffed hemodialysis catheters. *J Am Soc Nephrol* 10:1045–1049, 1999
31. Saad TF: Bacteremia associated with tunneled, cuffed hemodialysis catheters. *Am J Kidney Dis* 34:1114–1124, 1999
32. Dittmer ID, Sharp D, McNulty CA, *et al:* A prospective study of central venous hemodialysis catheter colonization and peripheral bacteremia. *Clin Nephrol* 51:34–39, 1999
33. Boelaert JR, Van Landuyt HW, Godard CA, *et al:* Nasal mupirocin ointment decreases the incidence of *Staphylococcus aureus* bacteraemias in haemodialysis patients. *Nephrol Dial Transplant* 8:235–239, 1993
34. Boelaert JR, De Baere YA, Geernaert MA, *et al:* The use of nasal mupirocin ointment to prevent *Staphylococcus aureus* bacteraemias in haemodialysis patients: An analysis of cost-effectiveness. *J Hosp Infect* 19(Suppl B):41–46, 1991
35. Boelaert JR, Van Landuyt HW, Gordts BZ, *et al:* Nasal and cutaneous carriage of *Staphylococcus aureus* in hemodialysis patients: The effect of nasal mupirocin. *Infect Control Hosp Epidemiol* 17:809–811, 1996
36. Tanriover B, Carlton D, Saddekni S, *et al:* Bacteremia associated with tunneled dialysis catheters: Comparison of two treatment strategies. *Kidney Int* 57:2151–2155, 2000
37. Passerini L, Lam K, Costerton JW, King EG: Biofilms on indwelling vascular catheters. *Crit Care Med* 20:665–673, 1992
38. Vercaigne LM, Sitar DS, Penner SB, *et al:* Antibiotic-heparin lock: In vitro antibiotic stability combined with heparin in a central venous catheter. *Pharmacotherapy* 20:394–399, 2000
39. Maki DG, Cobb L, Garman JK, *et al:* Attachable silver-impregnated cuff for prevention of infection with central venous catheters: A prospective randomized multicenter trial. *Am J Med* 85:307–314, 1998
40. Maki DG, Stolz SM, Wheeler S, Mermel LA: Prevention of central venous catheter-related bloodstream infection by use of an antiseptic-impregnated catheter: A randomized, controlled trial. *Ann Intern Med* 127:257–266, 1997
41. Raad I, Darouiche R, Hachem R, *et al:* Antibiotics and prevention of microbial colonization of catheters. *Antimicrob Agents Chemother* 39:2397–2400, 1995
42. Raad I, Darouiche R, Hachem R, *et al:* The broad-spectrum activity and efficacy of catheters coated with minocycline and rifampin. *J Infect Dis* 173:418–424, 1996
43. Darouiche RO, Raad II, Heard SO, *et al:* A comparison of two antimicrobial-impregnated central venous catheters. *N Engl J Med* 340:1–8, 1999
44. Levin NW, Yang PM, Hatch DA, *et al:* Initial results of a new access device for hemodialysis. *Kidney Int* 54:1739–1745, 1998
45. Canaud B, Levin N, Ing T, *et al:* Dialock: Pilot trial of a new vascular port access device for hemodialysis. *Semin Dial* 12:382–388, 1999

46. Canaud B, My H, Morena M, *et al:* Dialock: A new vascular access device for extracorporeal renal replacement therapy. Preliminary clinical results. *Nephrol Dial Transplant* 14:692–698, 1999
47. Fong IW, Capellan JM, Simbul M, Angel J: Infection of arteriovenous fistulas created for chronic haemodialysis. *Scand J Infect Dis* 25:215–220, 1993
48. Taylor SM, Eaves GL, Weatherford DA, *et al:* Results and complications of arteriovenous access dialysis grafts in the lower extremity: A five year review. *Am Surg* 62:188–191, 1996
49. Zibari GB, Gadallah MR, Landreneau M, *et al:* Preoperative vancomycin prophylaxis decreases incidence of postoperative hemodialysis vascular access infections. *Am J Kidney Dis* 30:343–348, 1997
50. Raju S: PTFE grafts for hemodialysis access: Techniques for insertion manage complications. *Ann Surg* 206:666–673, 1987
51. Curi MA, Pappas PJ, Silva MB Jr, *et al:* Hemodialysis access: Influence of the human immunodeficiency virus on patency and infection rates. *J Vasc Surg* 29:608–616, 1999
52. Alpers FJ: Clinical considerations in hemodialysis access infection. *Adv Ren Replace Ther* 3:208–217, 1996
53. Fowler VG Jr, Kong LK, Corey GR, *et al:* Recurrent *Staphylococcus aureus* bacteremia: Pulsed-field gel electrophoresis findings in 29 patients. *J Infect Dis* 179:1157–1161, 1999
54. Bosman PJ, Blankestijn PJ, van der Graaf Y, *et al:* A comparison between PTFE and denatured homologous vein grafts for haemodialysis access: A prospective randomized multicentre trial. The SMASH study group. Study of graft materials in access for haemodialysis. *Eur J Vasc Endovasc Surg* 16:126–132, 1998
55. Ayus JC, Sheikh-Hamad D: Silent infection in clotted hemodialysis access grafts. *J Am Soc Nephrol* 9:1314–1317, 1998
56. Sheikh-Hamad D, Ayus JC: The patient with a clotted PTFE graft developing fever. *Nephrol Dial Transplant* 13:2392–2393, 1998
57. Nassar GM, Ayus JC: Clotted arteriovenous grafts: A silent source of infection. *Semin Dial* 13:1–3, 2000
58. Syrjala MT, Valtonin V, Liewendahl K, Myllyla G: Diagnostic significance of indium-111 granulocyte scintigraphy in febrile patients. *J Nucl Med* 28:155–160, 1987
59. Schmidt KG, Rasmussen JW, Sorensen PG, Wedebye IM: Indium-111 granulocyte scintigraphy in the evaluation of patients with fever of undetermined origin. *Scand J Infect Dis* 19:339–345, 1987
60. Lawrence PR, Dries DJ, Alazraki N, Albo D Jr: Indium-111-labeled leukocyte scanning for detection of prosthetic vascular graft infection. *J Vasc Surg* 2:165–1173, 1985
61. Palestro CJ, Vega A, Kim CK, *et al:* Indium-111-labeled leukocyte scintigraphy in hemodialysis access-site infection. *J Nucl Med* 31:319–324, 1990
62. McIntyre C, Harper I, Macdougall IC, *et al:* Serum C-reactive protein as a marker for infection and inflammation in regular dialysis patients. *Clin Nephrol* 48:371–374, 1997
63. Haubitz M, Brunkhorst R, Wrenger E, *et al:* Chronic induction of C-reactive protein by hemodialysis, but not by peritoneal dialysis therapy. *Perit Dial Int* 16:158–162, 1996
64. Nassar GM, Ayus JC: Choosing antimicrobial therapy for a febrile patient on hemodialysis. *J Crit Illness* 9:8–9, 1999
65. Uttley AHC, George RC, Naidoo J, *et al:* High-level vancomycin-resistant entercococci causing hospital infections. *Epidemiol Infect* 103:173–181, 1989
66. Shay DK, Maloney SA, Montecalvo M, *et al:* Epidemiology and mortality risk of vancomycin-resistant enterococcal bloodstream infections. *J Infect Dis* 172:993–1000, 1995
67. Singer DA, Jochimsen EM, Gielerak P, Jarvis WR: Pseudoutbreak of enterococcus durans infections and colonization associated with introduction of an automated identification system software update. *J Clin Microbiol* 34:2685–2687, 1996
68. Grayson ML, Grabsch EA, Hohnson PD, *et al:* Outcome of a screening program for vancomyin-resistant enterococci in a hospital in Victoria. *Med J Aust* 171:133–136, 1999
69. Keane WF, Alexander SR, Bailie GR, *et al:* Peritoneal dialysis-related peritonitis treatment recommendations: 1996 update. *Perit Dial Int* 16:557–573, 1996
70. Centers for Disease Control and Prevention: Recommendations for preventing the spread of vancomycin resistance. *MMWR Morb Mortal Wkly Rep* 44:1–13, 1995
71. Fogel MA, Nussbaum PB, Feintzeig ID, *et al:* Cefazolin in chronic hemodialysis patients: A safe and effective alternative to vancomycin. *Am J Kidney Dis* 32:401–409, 1998
72. Marx MA, Frye RF, Matzke GR, Golper TA: Cefazolin as empiric therapy in hemodialysis-related infections: Efficacy and blood concentrations. *Am J Kidney Dis* 32:410–414, 1998
73. Musher DM, Lamm N, Darouiche RO, *et al:* The current spectrum of *Staphylococcus aureus* infection in a tertiary care hospital. *Medicine (Baltimore)* 73:186–208, 1994
74. Feldman HI, Kobrin S, Wasserstein A: Hemodialysis vascular access morbidity. *J Am Soc Nephrol* 7:523–535, 1996