Bacterial infections in hemodialysis patients: Pathogenesis and prevention

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CASE PRESENTATION

A 62-year-old African American man with end-stage renal disease secondary to hypertension who had been treated with hemodialysis for almost 5 years had multiple vascular access problems. After multiple thrombectomies of right and left arm arterio-venous grafts (AVGs), as well as an episode of life-threatening bleeding from the left arm AVG, he underwent insertion of a LifeSite® catheter in the left internal jugular vein 4 years ago. Four months later, he was hospitalized for an episode of chills and rigors, and was found to have methicillin-resistant Staphylococcus aureus (MRSA) bacteremia, which was treated with intravenous vancomycin and oral rifampin. A trans-esophageal echocardiogram revealed no valvular vegetation. Because he was a nasal carrier of MRSA, he was given a 2-week course of mupirocin ointment to his nares for eradication of MRSA colonization.

Extensive discussions ensued with the patient about the future of his vascular access and the likelihood of eradicating the infection with medical therapy alone. Given his history of multiple thrombosed AVGs, and that the implanted catheter might have been his last option for satisfactory dialysis access, the decision was made not to remove the catheter and for him to receive an 8-week course of dual antibiotic therapy. The patient then did well until 13 months later, when erosion of the skin over the arterial port of the LifeSite® catheter required surgical relocation of the port and skin closure.

Seventeen months later, he presented with fever and abdominal pain one day following a dialysis session. Blood cultures from a peripheral vein and from the dialysis catheter grew coagulase-negative staphylococcus species. An abdominal CT scan revealed pneumatosis and air tracking in the superior mesenteric and splenic veins consistent with ischemic bowel disease. Broad-spectrum antibiotics were initiated and he was given intravenous fluids prior to undergoing an emergent exploratory surgery. Laparotomy revealed a gangrenous small bowel from the ligament of Treitz to the ileo-cecal valve. Intraoperative Doppler studies revealed no pulse in the arcade of the mesentery of the small intestine. Because of these findings and the overall poor prognosis, no intestinal resection was attempted, and the abdominal surgical wound was closed. As expected, the patient continued to deteriorate clinically and died due to this devastating complication and overwhelming staphylococcal sepsis. No autopsy was performed.

DISCUSSION

DR. BERTRAND L. JABER (Department of Medicine, Tufts University School of Medicine; and Vice Chairman for Clinical Affairs, Division of Nephrology, Department of Medicine, Caritas St. Elizabeth’s Medical Center, Boston, Massachusetts): Bacterial infections represent a common and important health problem for patients with end-stage renal disease (ESRD) who undergo maintenance hemodialysis (HD), and this patient illustrates the challenges inherent to this problem. Considerable gains have been made in deciphering the pathogenesis of bacterial infections in this high-risk population. These gains
notwithstanding, the therapeutic goal of preventing bacterial infections in HD patients remains unfulfilled. This Forum reviews the magnitude of the problem in the HD patient population, our progress in understanding the pathogenesis of bacterial infections, the use of novel diagnostic tools, and prospects for preventing such occurrences, while outlining areas of uncertainty.

**The clinical problem**

Infection is an important cause of morbidity and mortality among patients with ESRD. According to the United States Renal Data System (USRDS) registry, infection is the second leading cause of death in patients with ESRD (the first is cardiovascular disease), and septicemia accounts for more than 75% of these infectious deaths [1]. Indeed, among ESRD patients undergoing dialysis, the total death rate is 176/1000 patient-years, and septicemia and pulmonary infections combined account for close to 26/1000 patient-years [1]. Annual death rates due to pneumonia and sepsis are markedly higher in dialysis patients compared with the general population; in the 65- to 74-year-old category, the magnitude of difference is on the order of 10- and 100-fold, respectively (Fig. 1) [2, 3]. Whereas the presence of diabetes mellitus confers an additional risk for sepsis-related deaths, this comorbid condition appears to exert little influence on pneumonia-related deaths [2, 3].

Bacterial infections are a major cause of hospitalization. In a recent study on the epidemiology of septicemia in HD patients, hospital admission rates for septicemia during the first year of HD rose by 51% over the 8-year period from 1991 to 1999 [4]. Hospitalization for septicemia also was associated with an increased risk of myocardial infarction, congestive heart failure, stroke, and peripheral vascular disease at 6 months and 5 years after the original hospitalization [4]. These data suggest that septicemia has become more common in dialysis patients in the U.S. and is associated with an increased risk of cardiovascular events and death. Evidence is emerging that HD patients also have a higher incidence of infective endocarditis [5–7]. In one study, the proportion of patients with infective endocarditis who were undergoing HD increased from 7% to more than 20% over a 7-year period [5], and this observation was paralleled by a significant increase of *Staphylococcus aureus*-associated endocarditis from 10% to 68% [5]. In the U.S., the incidence of infective endocarditis in the dialysis population has been estimated at 483 episodes/100,000 patient-years compared with only 7 episodes in the general population [6]. In this study, HD therapy was a strong risk factor for infective endocarditis, which was associated with a 1.5-fold higher risk of death [6].

In a longitudinal cohort study of incident ESRD patients, older age and diabetes were independent risk factors for septicemia in all patients [8]. Among HD patients, low serum albumin level, temporary vascular access, and dialyzer reuse also were associated with increased risk [8], and septicemia carried a markedly increased risk of death. These data suggest that improving nutrition and avoiding temporary vascular access might decrease the incidence of septicemia, and that dialyzer reuse practices might contribute to this risk. In a recent study reporting on a staged program to stop dialyzer reprocessing, conversion to a single-use dialyzer practice was associated with improved survival [9]. This trend lagged by at least 60 days following abandonment of the dialyzer reuse practice and was ascribed to a cumulative decline in exposure to trace industrial products or repeated inflammatory and infectious insults, which only become clinically manifest over time [9].
In the HEMO study, the incidence of infection-related deaths was not reduced by higher dose of dialysis or by high-flux dialyzers, and most infection-related hospitalizations were not attributed to vascular access [10]. However, the frequency of infection-related hospitalizations attributed to vascular access was disproportionately higher among patients with central venous catheters compared with those who had grafts or fistulas [10].

**Pathogenesis**

In the past two decades, major gains have been realized in our understanding of the pathogenesis of bacterial infections in HD patients. I will emphasize the interaction of three pivotal factors: host immunity, bacterial virulence, and the dialysis procedure per se (Fig. 2). The following section reviews the various components of this “access of evil,” with special emphasis on the pathogenesis of bacteremia and bacterial pneumonia.

**Impaired host immunity.** Uremia is associated with alterations in primary host defense mechanisms, which increase the risk of bacterial infections. Indeed, neutrophils exhibit impaired chemotaxis, oxidative metabolism, phagocytic activity, degranulation, and intracellular killing, as well as dysregulated programmed cell death or apoptosis [11–14]. A number of factors have been incriminated in neutrophil dysfunction, including malnutrition, trace element deficiencies, iron overload, impaired glucose metabolism, hyperparathyroidism, dialysis per se, and uremic retention solutes [12, 15–18].

Abundant in vitro and clinical studies have linked iron overload to an increased risk of bacterial infections in HD patients [17, 19–21], including modest iron storage levels (ferritin level of 100–800 ng/mL and transferrin saturation of 10% to 50%) (Fig. 3) [22, 23]. Iron overload modulates this risk by affecting host defense mechanisms and bacterial virulence. Indeed, iron overload has been associated with reduced phagocytic function and oxidative burst, as well as impaired bacterial killing [17, 20, 21].
Iron dextran, at pharmacologically relevant concentrations, attenuates in vitro the function of polymorphonuclear cells harvested from HD patients with normal iron indices [24]. Also, it is possible that the increased availability of iron can stimulate bacterial growth and increase virulence properties [25]. Consequently, the increased use of parenteral iron might be an important contributory factor to the occurrence of bacterial infections.

In recent years, many uremic retention solutes that can adversely affect neutrophil function have been identified, including parathyroid hormone, p-cresol, polyamines, aminoguanidine products, and a series of granulocyte inhibitory proteins, angiogenin and complement factor D [12, 18]. In addition, neutrophil-membrane interactions, mainly with cuprophan membranes, result in transient leukopenia, increased expression of adhesion molecules, degranulation and release of proteolytic enzymes, and release of reactive oxygen species [26]. These interactions might result in cellular “exhaustion” and decreased responsiveness to subsequent stimuli, such as bacteremia.

Other striking abnormalities occur in cell-mediated immunity and primarily involve T-lymphocytes. These include lymphocytopenia, impaired delayed skin reactivity, and decreased in vitro lymphocyte proliferation [26, 27]. Alterations in B-lymphocyte function affect humoral immunity and result in decreased immunoglobulin levels and a depressed antibody response to antigens. Dysregulated cytokine synthesis [28] and impaired macrophage Fc receptor function [29] further impair immune function in uremic patients. In one study, impaired macrophage Fc receptor function was associated with a higher risk of bacterial infection [29]. Finally, impaired ex vivo cytokine production by mononuclear cells in response to IgG, an Fc-mediated response, was associated with an increased risk of hospitalization for bacterial infections in HD patients [30].

Additional susceptibility and risk factors that are specific for pulmonary infections in HD patients include obstructive and central sleep apnea, impaired inspiratory muscle strength, uremic pneumonitis/pleuritis, the hyperhydration syndrome (due to fluid gain during the interdialytic interval), pulmonary metastatic calcification (from an increased calcium × phosphate product), and intradialytic hypoxemia (due to complement activation and transient leukopenia) [2, 31].

**Bacterial virulence and adherence properties.** Bacteria can acquire virulence properties when specific conditions are met. In the normal host, under conditions of low density, bacteria are cleared by primary host-defense mechanisms. However, under conditions of high bacterial density, bacteria can produce extracellular polysaccharides referred to as “quorum sensors” [32, 33]. These molecules are secreted by the bacteria and freely diffuse within the bacterial community, where they interact with transcriptional activators such as LasR and RhlR. This interaction increases expression of virulence genes, thereby facilitating bacterial survival by increased production of proteases, superoxide dismutase, and catalase, which enable the organisms to evade neutrophil killing and the bactericidal or bacteriostatic effects of antimicrobial agents. Bacteria also form a matrix of these extracellular polysaccharides, which is called biofilm or “slime.” This slime renders them less susceptible to antimicrobial agents, as the matrix constitutes a barrier between the antimicrobial agent and the bacterial cell wall. In the presence of foreign surfaces such as central venous catheters, biofilm formation is more likely to develop and can potentiate the pathogenicity of the skin bacterial flora (for example, coagulase-negative staphylococci).

The adherence properties of bacteria are also important determinants of catheter-related infection [34]. For example, *S. aureus* adheres to host proteins that are commonly present on catheters, such as fibronectin, whereas coagulase-negative staphylococci directly adhere to polymer surfaces.

**The hemodialysis procedure.** During the normal course of HD, patients are exposed to several infectious risks. Potential sources of infection include the skin (through repeated disruption of the skin barrier and integrity due to the nature of the vascular access type), the dialysis water treatment system, and dialyzer reuse.

Central venous catheters used for HD include non-tunneled, tunneled, and totally implantable devices, such as the one described in the case presentation. The risk of bacteremia by device type, site of insertion, and duration of use varies widely. In one study of non-tunneled catheters, the incidence of bacteremia was 5% after three weeks of placement in the internal jugular vein, and 11% after one week in the femoral vein [35]. Four pathogenic pathways have been incriminated in the development of catheter-related bloodstream infections, and include, in order of descending frequency: (1) colonization of the cutaneous catheter tract and tip with skin flora; (2) intraluminal colonization due to contamination of the catheter hub; (3) hematogenous seeding to the catheter from another focus of infection; and (4) very rarely, intraluminal contamination of the catheter with solvent/infusate. In addition to intrinsic bacterial virulence factors, another important determinant of catheter-related infection is the type of the device material [34]. For example, catheters made of polyvinyl chloride or polyethylene are less resistant to the adherence of bacteria compared with catheters made of polytetrafluoroethylene (PTFE), silicone elastomer, or polyurethane [36]. Finally, surface irregularities and thrombogenicity of the catheter material are also likely to influence microbial adherence and therefore increase the risk of catheter colonization and catheter-related infection.

Bacteremia also can result from contamination of dialysis fluids or equipment, inadequate dialyzer
reprocessing procedures, or inadequate treatment of muni-
cipal water for use in dialysis [37, 38]. Contaminated
medication vials also are a potential source of bacteremia
[39].

**Novel diagnostic approaches for catheter-related infections**

The confirmation of peripheral bacteremia is paramount in the diagnosis of catheter-related infec-
tions. Unfortunately, for practical purposes often only
one set of blood cultures is collected from the catheter
lumen itself. Although blood culture testing is relatively
inexpensive and easy to process, 24 to 48 hours often
eclipse before a preliminary report is provided to the
clinician. In addition, if a catheter removed on suspicion
of causing infection proves not to be infected, the patient
is exposed unnecessarily to the risks associated with
reinsertion. Consequently, rapid diagnostic approaches
that help confirm a suspected catheter-related infection
in HD patients and that implement the proper use
of antibiotics are needed. Several novel but rather
cumbersome diagnostic approaches include the use of an
endoluminal brush, catheter hub culture, and electron
microscopy [40, 41]. One rapid diagnostic technique, how-
ever, merits discussion. The acridine-orange leuko-
cyte cytospin test (AOLC) is rapid (30 min), inexpensive,
and requires only 100 μL of catheter blood and the use of ultraviolet microscopy [42]. In a study of diagnostic
approaches of catheter-related bloodstream infections in
adult surgical patients, the AOLC provided a diagnostic
sensitivity and specificity of 96% and 92%, respectively,
compared with traditional quantitative peripheral blood
cultures [43]. Although this simple and rapid diagnostic
method compares favorably with traditional blood
culture techniques and might help stratify patients
who require catheter removal and early antimicrobial
therapy, further studies are needed on the sensitivity and
specificity of this assay in the dialysis population.

**Preventive strategies**

Strategies for the prevention of bacterial infections in
HD patients, mainly bacteremia and pneumonia, should
focus on the dialysis procedure with a primary goal of
preventing catheter-related infections and on boosting
host immunity.

**Prevention of catheter-related infections.** In recent
years, numerous studies have attempted to address this
problem, as the prevalence of catheter use in the ESRD
population is on the rise. I will summarize the most
promising approaches.

The LifeSite® HD Access System, a totally implantable
catheter, in one study outperformed a tunneled catheter
in terms of bacteremia and technical device survival [44].
A subsequent study, however, reported a high infection
rate, which was ascribed either to the learning curve asso-
ciated with its use or to its liberal use in a population of
chronically ill patients [45]. These data strongly suggest
that no catheter device can eliminate the infectious risk
that is inherent in the dialysis population.

In the past decade, the topical use of antibiotics
and ointments at catheter sites has gained popularity.
A randomized controlled trial of prophylactic topical
administration of povidone-iodine ointment compared
with sterile gauze dressings alone on the incidence of
subclavian catheter-related infections in HD patients
demonstrated a marked reduction in bacteremia rates
(2% versus 17%) [46]. A subsequent trial comparing
mupirocin ointment with povidone-iodine for preventing
non-tunneled catheter-related infections demonstrated
similar findings [47]. In this study, the use of mupirocin
resulted in fewer episodes of S. aureus-related bacteremia
(1 versus 9 episodes/1000 patient days) and a longer dura-
tion of catheter use (median of 37 versus 20 days). More
recently, a meta-analysis of 10 studies (totaling 2445 pa-
tients) on the use of mupirocin prophylaxis to prevent
S. aureus infection in dialysis patients reported a 78% risk
reduction in bacteremia among HD patients; this percent-
age compared with only a 66% risk reduction in peri toneal
therapy among patients on peritoneal dialysis [48]. Whereas
mupirocin prophylaxis substantially reduces the rate of S. aureus infection in the dialysis population, optimal reg-
imens that minimize the emergence of mupirocin resis-
tance need to be explored.

A multicenter, double-blind, placebo-controlled, ran-
donized controlled trial compared the prophylactic use of
topical Polysporin® Triple formulation with a placebo
ointment on the incidence of tunneled catheter-related
infections in HD patients [49]. This triple agent contains
bacitracin, gramicidin, and polymyxin B, and has strong
topical activity against staphylococci and Gram-negative
bacteria. The study demonstrated a 60% to 65% risk re-
duction in bacteremia over a 6-month period [49]. An un-
expected 78% risk reduction in death also was observed.
This study is relevant as it was contemporaneous with the
well-established catheter care guidelines of the National
Kidney Foundation [50], and the study sample was repre-
sentative of the HD population in the U.S. However, de-
spite the low cost of this prophylactic triple agent and its
lower susceptibility to microbial resistance, an increased
risk of fungal infections, particularly in the immunocom-
promised patient, was a concern raised by these investiga-
tors. These studies on the use of topical agents suffer from
our inability to compare more than two agents. Clearly, a
study should be designed that establishes the superiority
of Polysporin® Triple, mupirocin, or povidone-iodine for
tunneled catheters.

In the new millennium, an effort has been made to
preserve dialysis catheters while combating antimicro-
bial resistance. Catheter lock solutions have emerged as
novel approaches for the primary and secondary prevention of dialysis catheter-related infection (Table 1). A randomized controlled trial for the prevention of tunneled catheter-related infections using a gentamicin-citrate catheter lock solution demonstrated a marked reduction in infections compared with the use of heparin [51]. In addition, the incidence of catheter malfunction did not differ significantly between the two groups. However, predialysis gentamicin levels were significantly higher in patients randomized to the gentamicin-citrate catheter lock solution. The achievement of these systemic levels is the result of instilling a relatively high concentration of gentamicin in the catheter (Table 1) and therefore warrants a note of caution.

Taurolidine, a derivative of the amino acid taurine, is an antimicrobial agent that inhibits and kills a broad range of micro-organisms [52]. Its combination with citrate as an anticoagulant and its use as a catheter lock solution for preventing infections has recently been examined [53, 54]. In two small studies, the taurolidine-citrate catheter lock solution reduced the incidence of non-tunneled and tunneled catheter-related infections. However, in one study [53], unassisted catheter patency was lower among patients who received the taurolidine-citrate catheter lock than among control patients (32% versus 76%). Trisodium citrate, at low concentration (2.2% to 15.0%), has antimicrobial activity against staphylococcal strains; however, higher concentrations (30%) are required for killing Gram-negative bacteria [55]. These data suggest that the optimal concentration of citrate required for antimicrobial effect and anticoagulation remains unknown and warrants further investigation. An additive or synergistic antimicrobial effect between citrate and more traditional antimicrobial agents also requires further inquiry. In one study, the adjunctive use of an antibiotic lock (Table 1) in conjunction with systemic antibiotic therapy eradicated catheter-associated bacteremia while salvaging the catheter in close to 50% of cases [56]. This approach might be advantageous over routine catheter removal but warrants confirmation by further investigation.

Additional experimental agents that have not yet been tested in humans are worthy of mention. In an in vitro model of biofilm formation on polyurethane surfaces, linezolid (2 mg/mL) and eperezolid (4 mg/mL) achieved eradication of Staphylococcus epidermidis biofilms more rapidly than did vancomycin (10 mg/mL) and gentamicin (10 mg/mL) [57]. Other catheter lock agents that have shown promise include recombinant tissue plasminogen activator (rTPA) [58], tetrasodium EDTA [59], and RNAIII-inhibiting peptide (RIP), a molecule that interferes with “quorum-sensing” mechanisms, thereby reducing adherence of S. aureus to catheter polymers [60].

Finally, catheters and cuffs have been impregnated with antimicrobial or antiseptic agents in an effort to reduce catheter-related infections [34]. These include platinum/silver- and silver-impregnated cuffs, and chlorhexidine-silver-, sulfadiazine-, and minocycline-rifampin-impregnated catheters. Among these relatively new and expensive devices, minocycline-rifampin–impregnated catheters are the only catheters that have demonstrated efficacy in reducing catheter-related bloodstream infections in HD patients [61].

**Boosting host immunity.** Strategies for boosting immunity in HD patients include vaccination against common infectious agents such as staphylococcus species, influenza virus, and Pneumococcus pneumoniae, and the experimental use of recombinant human granulocyte colony-stimulating factor (rhG-CSF) to modulate immune responses. Uremic patients, especially those undergoing dialysis, have decreased responses to vaccination. This defect has been ascribed to their inability to achieve and maintain protective antibody levels secondary to impaired macrophage function, T- and B-lymphocyte activation and proliferation, and immunoglobulin production [62–65].

Whereas the administration of the influenza vaccine has been associated with improved outcomes in dialysis patients, less than 50% of the population is vaccinated in the U.S. on a yearly basis [66]. These vaccination rates fall very short of the goal of 90% for the general population, which is targeted for the year 2010 [67].

In a large randomized controlled trial of HD patients, the administration of a capsular polysaccharide-protein conjugate anti-staphylococcal vaccine reduced the incidence of bacteremia secondary to S. aureus [65]. Unfortunately, this vaccine was associated with an unacceptable side effect profile and its cumulative efficacy was short-lived. Protective antibody titers reached a peak by 30 weeks and were followed by a rapid decline.

### Table 1. Antibiotic lock solutions for dialysis catheters

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Final drug concentration</th>
<th>Anticoagulant agent</th>
<th>Final drug concentration</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taurolidine</td>
<td>1.35%</td>
<td>Sodium citrate</td>
<td>4%</td>
<td>[53, 54]</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>40 mg/mL</td>
<td>Tri-sodium citrate</td>
<td>3.13%</td>
<td>[51]</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>2.5 mg/mL</td>
<td>Heparin</td>
<td>2500 units/mL</td>
<td>[56]</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>1 mg/mL</td>
<td>Heparin</td>
<td>2500 units/mL</td>
<td>[56]</td>
</tr>
<tr>
<td>Vancomycin + gentamicin</td>
<td>2.5 mg/mL + 1 mg/mL</td>
<td>Heparin</td>
<td>2500 units/mL</td>
<td>[56]</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>5 mg/mL</td>
<td>Heparin</td>
<td>2500 units/mL</td>
<td>[56]</td>
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<tr>
<td>Cefazolin + gentamicin</td>
<td>5 mg/mL + 1 mg/mL</td>
<td>Heparin</td>
<td>2500 units/mL</td>
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</table>
Nevertheless, these encouraging results await further testing. Finally, administration of the pneumococcal vaccine to dialysis patients has been associated with a suboptimal antibody response by 2 years, warranting a repeat dose [62]. In summary, dialysis patients benefit from influenza vaccination, which is safe, efficacious, and cost effective. Dialysis providers therefore should immunize this high-risk group each year. Similarly, pneumococcal vaccination should be recommended to all dialysis patients, and revaccination is warranted every 3 to 5 years.

The rationale for using immune-modulating strategies such as rhG-CSF in HD patients is the reversal of neutrophil dysfunction. Indeed, in addition to the mobilization of neutrophils from the bone marrow, rhG-CSF directly enhances chemotaxis, phagocytosis, and respiratory burst, while decreasing apoptosis and thereby reversing much of the neutrophil dysfunction of uremia [14, 68]. When assessed as an adjuvant therapy to systemic antibiotics for the treatment of severe diabetic foot infections, rhG-CSF treatment improved neutrophil function, accelerated resolution of the infection, and shortened the hospital length of stay [69]. This drug, as well as other immune-modulating strategies, awaits further investigation in the dialysis population.

Areas of uncertainty

As dialysis providers in the U.S. try to prevent and combat bacterial infections effectively, two emerging problems need to be acknowledged and rapidly contained: bacterial resistance and suboptimal vascular access care.

Emerging bacterial resistance. In the most recent survey of patient care practices and dialysis-associated diseases in the U.S. during the period of 1995 to 2001, the percentage of patients who received dialysis through central catheters increased from 13% to 25% [70]. This trend is worrisome, as infections and antibiotic use—the “breeding ground” for emergence of bacterial resistance—are higher among patients who have dialysis catheters. Indeed, over the same period, the percentage of centers reporting infections or colonization with vancomycin-resistant enterococcus (VRE) and methicillin-resistant Staphylococcus aureus (MRSA) increased from 12% to 31%, and 40% to 72%, respectively (Fig. 4) [70]. Colonization of dialysis patients with VRE is highly correlated with the outpatient use of vancomycin [71]. Of more concern is a recent report on the epidemiology of the 19 patients reported to date who were infected with vancomycin-intermediate S. aureus (VISA) [72]. This analysis suggests that whereas dialysis status was not a risk factor for the emergence of this resistant micro-organism, the use of vancomycin in the previous 1 to 6 months was highly correlated with these infections [72]. All these data point to the importance of the judicious use of antibiotics in the dialysis patient population, and the avoidance of vancomycin whenever possible, in an effort to minimize the emergence of bacterial resistance.

Improving vascular access care. Results from the 2002 ESRD Networks’ Clinical Performance Measures (CPM) reveals that the prevalence of arteriovenous fistulas in the U.S. has not yet reached the goal of 40% put forward by the K/DOQI guidelines [73]. Of more concern is the prevalence of catheter use, which has remained above the target of 10%, reaching close to 25% in 2001 [70, 73]. Data from Europe suggest that for patients in whom arteriovenous fistulas are difficult to achieve, long-term use of tunneled catheters such as the Tesio catheter (a twin-line single-lumen central venous catheter) is an acceptable alternative [74]. Notwithstanding, in the U.S., a national vascular access improvement initiative known as “Fistula First” is aimed at solving the problem by increasing the use of fistulas for Medicare beneficiaries with ESRD, with the hope of reaching a goal of 40% [75]. This rather ambitious initiative will require close multidisciplinary collaboration, but more important, earlier referrals to the nephrologist and to the vascular surgeon for the timely creation of arteriovenous fistulas [76].

QUESTIONS AND ANSWERS

DR. NICOLAOS E. MADIAS (Chairman, Department of Medicine, Caritas St. Elizabeth’s Medical Center, Boston, Massachusetts): What is the impact of the chronic use of antibiotic ointment at the exit site of the dialysis catheter on the risk of bacterial resistance and yeast colonization?

DR. JABER: This is a real long-term concern. For instance, in the study by Lok and colleagues [49], the authors used an ointment that had three active ingredients

![Image](https://example.com/image.png)
to ensure both synergism of action and minimization of bacterial resistance. There is a clear need for long-term studies aimed at examining whether bacterial virulence of the skin flora develops, and whether there is a colonization shift from bacteria to yeast which, in turn, would predispose the patient to more serious catheter-related infections.

**DR. MADIAS:** Do you see a role for rTPA as a fibrinolytic agent for the prevention of both catheter thrombosis and catheter-related infections?

**DR. JABER:** Nephrologists traditionally have used rTPA to maintain catheter patency. This practice has traditionally been driven by a catheter malfunction. However, this fibrinolytic agent also might prevent bacterial biofilm formation in the catheter lumen by stripping the intraluminal fibrin coat, which is one of the first steps in the adherence of micro-organisms to polymers. This hypothesis, which was originally proposed by Dr. Bernard Canaud [58], warrants formal testing in a randomized controlled trial of thrice-weekly rTPA versus heparin as a catheter lock solution.

**DR. ANÍBAL FERREIRA:** (Nephrology Service, Hospital de San António, Porto, Portugal): You briefly reviewed the relationship between iron overload and the risk of bacterial infection. Do you have any recommendations on how to prescribe intravenous iron in terms of frequency and dose?

**DR. JABER:** As you know, iron metabolism is tightly regulated; humans normally absorb 1 mg/day of elemental iron by the gut. A patient undergoing maintenance dialysis who receives a typical intravenous infusion of iron receives on the order of 25 to 100 mg, which is 25- to 100-fold higher than the normal daily intestinal absorption of iron. More important, this dose of iron received intravenously undergoes no first-pass liver clearance and immediately reaches the systemic circulation. Nephrologists have to be mindful about doses of intravenous iron in the context of iron metabolism. There is a need for a clinical trial to examine whether lower doses of intravenous iron, on the order of 10 mg or less per dose, would correct iron deficiency anemia effectively while minimizing iron toxicity. For the time being, using the K/DOQI guidelines, which recommend 25 to 100 mg doses, I would basically err on the side of administering the lower dose. However, in the face of an acute episode of bacteremia, intravenous iron therapy should be temporarily discontinued until the bacteremia has resolved because of the potential effect of iron on bacterial growth.

**DR. ANÍBAL FERREIRA:** (Nephrology Service, Hospital Curry Cabral, Lisboa, Portugal): As you know, vitamin D is an important immunomodulator. Are you aware of any data examining the impact of vitamin D therapy on the risk of infections in dialysis patients?

**DR. JABER:** Vitamin D is used as hormone replacement therapy for vitamin D deficiency, to prevent osteomalacia, and as pharmacotherapy to suppress parathyroid hormone secretion. The immunomodulatory effects of vitamin D at pharmacologic doses remain poorly understood in my opinion. Whereas the recent work by Thadhani's group sheds some light on the differential impact of two vitamin D formulations on all-cause mortality, the study did not address infectious outcomes [77]. I am not aware of any other study that has examined the impact of vitamin D therapy on infectious morbidity.

**DR. GERALD APPEL** (Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons, New York, New York): Many dialysis patients have anticyclodilipin antibodies, and these have been related to a thrombotic tendency. Is there any relation between infection and the presence of anticyclodilipin antibodies in HD patients with either fistulas or grafts?

**DR. JABER:** I am not aware of any published work linking these two entities. But clearly a hypercoagulable state is likely to influence vascular access malfunction and, in the case of a catheter, might predispose to adherence of bacteria to host proteins in the catheter lumen and consequently to colonization and bacteremia. It is possible that the presence of anticyclodilipin antibodies in HD patients is indeed the result of a smoldering infection, which would solicit an immune response; however, this is purely speculative.

**DR. PEDRO PONCE** (Chief of Nephrology, Hospital Garcia de Orta, Almada, Portugal): Is there any rationale for waiting a certain period of time before inserting a tunneled catheter in a patient with bacteremia? We usually wait at least 48 hours after the removal of an infected catheter before reinserting one. Is there any proof that we can colonize the new catheter?

**DR. JABER:** This question has a multifaceted answer, as it merges science and art. Whenever you're dealing with a catheter-related bacteremia, specifically, with *S. aureus*, which is very difficult to eradicate, it is not recommended that a tunneled catheter be reintroduced during the course of bacteremia. Once you have established that at least two surveillance blood cultures are negative following the removal of the catheter, you can proceed with the insertion of a tunneled catheter at a different site; this will minimize the likelihood of introducing the catheter along a previously infected track. The issue of catheter removal versus conservative therapy with antibiotics is a delicate issue often debated by infectious disease consultants and nephrologists. For coagulase-negative staphylococcus species, you might be able to treat with antibiotics alone and not sacrifice the catheter unless there is persistent bacteremia or recurrence after discontinuation of the antimicrobial therapy. Unfortunately, no evidence supports such a recommendation. As I mentioned earlier, Krishnasami and colleagues demonstrated that the adjunctive use of an antibiotic lock in conjunction with systemic antibiotic therapy might be advantageous...
over routine catheter removal [56]. However, this warrants further investigation.

DR. MADIAS: Can you reflect on the potential impact of bacterial infections on future cardiovascular morbidity and mortality?

DR. JABER: This area is gaining momentum in the U.S. Recent work by Foley and colleagues established a strong link between infective morbidity and cardiovascular morbidity and mortality. Indeed, dialysis patients who are hospitalized for septicemia have a four- to tenfold higher risk of subsequent development of myocardial infarction, heart failure, stroke, or cardiovascular death [4]. This is not surprising, as an episode of septicemia is often associated with hypotension, which in turn can lead to hypoperfusion of the coronary arterial bed and, consequently, a non–Q-wave myocardial infarction. Such a scenario in my opinion is not uncommon in clinical practice and is exemplified in today’s case presentation, in which staphylococcal bacteraemia led to septic shock and ischemic bowel disease, and resulted in the death of the patient. In summary, a hemodynamic insult from sepsis renders the patient more vulnerable to a secondary cardiovascular insult, thereby increasing the risk of cardiovascular morbidity and mortality. This emerging concept is in keeping with the new paradigm of inflammation, infection, and cardiovascular mortality.

DR. ANABELA RODRIGUES (Nephrology Service, Hospital de S. António, Porto, Portugal): If you allow me, this is more of a comment than a question. With such a tremendous impact on morbidity and mortality from vascular access–related bacteraemia in HD patients, isn’t it time to demystify peritonitis in PD patients and to offer PD as an excellent alternative in an aging population, a group that presumably has much more vascular access–related complications, as opposed to waiting for access exhaustion?

DR. JABER: I fully agree with you. In the U.S., the challenge we’re facing is that the utilization of PD is declining, while the popularity of HD continues to increase. Some of the concerns include the limited training of nephrologists in management of PD, the lack of physician incentive in recommending this therapy to our patients, lack of patient interest in self-care dialysis, and the fact that renal transplantation is competing with PD, especially pre-emptive renal transplantation.

DR. RODRIGUEZ: The topic is controversial, but certainly PD offers several advantages, even with fewer bactereemic episodes and even pulmonary infections. Clearly it is an option, and a first option in the elderly dialysis population.

DR. JABER: In the U.S., the incident PD patient population is, on average, 10 years younger than its HD counterpart. The provision of PD to the elderly dialysis population is more challenging, as it often requires the active participation of a caregiver, such as a spouse, and these caregivers can become overburdened by this commitment. Nevertheless, I strongly agree with you that PD should be offered to the aging population because of poor vascular access options, especially among those who have some residual renal function and who are not candidates for renal transplantation.

DR. JOÃO CARLOS FERNANDES (Nephrology Service, Centro Hospitalar de Vila Nova de Gaia, Portugal): Would you comment on the incidence of endocarditis among patients with prosthetic cardiac valves, and how their presence can or should influence the choice of vascular access and the treatment plan for infectious complications?

DR. JABER: The presence of prosthetic valves poses a greater risk of endocarditis and metastatic infections among dialysis patients with venous catheter and arteriovenous grafts. The decision should be individualized, and in a patient contemplating dialysis initiation who has limited vascular access options, PD might be a wise approach. Although PD patients are still at risk of developing peritonitis, as you know, this infectious complication is almost never associated with systemic bacteraemia, and PD would offer a lower risk of endocarditis for the patient with a prosthetic valve. In the case of bacteraemia in a patient with a prosthetic valve, transechocardiography to document the presence of valvular vegetation and a prolonged (6- to 8-week) course of dual antibiotic therapy with weekly surveillance blood cultures is likely the best practice. However, in the case of S. aureus bacteraemia or fungemia, it is extremely likely that valvular replacement would be required if medical therapy fails.

DR. MADIAS: What might be the impact of dialyzer reuse on infectious morbidity and mortality?

DR. JABER: As you know, in the U.S. the practice of dialyzer reuse is purely economic in nature, as it has allowed the reuse of high-flux dialyzers, which are more expensive. In recent years, however, high-flux dialyzers have become more affordable in the U.S., and this has prompted dialysis facilities to stop their reuse program. Lowrie and colleagues recently demonstrated that conversion to a single-use dialyzer practice was associated with improved survival [9]. This was ascribed in part to a decline in exposure to repeated infectious insults.

DR. PONCE: Since the early ’90s, we have tried to avoid the outpatient use of vancomycin as the initial empiric treatment of fever in HD patients, although this approach is more practical and less expensive than a hospital admission. What is the risk of avoiding the initial use of vancomycin, especially in the old and frail patient who is febrile, and using instead a first-generation cephalosporin? My concern is that since it takes 48 to 72 hours to obtain the result of a blood culture and antibiotic sensitivities, using the wrong empiric antibiotic regimen might be harmful. By avoiding vancomycin, I
am concerned that lives are being lost in the name of public health.

DR. JABER: I fully agree with your concern that we should consider using the best drug. Although bacteremia in dialysis patients is often due to coagulase-negative staphylococcus species, these bacteria, as well as MRSA, are always resistant to methicillin, and this renders the medical decision regarding the proper antibiotic more challenging. A similar example is the initial choice of antibiotics for peritonitis. A discrepancy exists between the guidelines put forward by the International Society of PD [78] and the microbial flora of these infections, which typically consist of coagulase-negative staphylococcus species [79]. On the other hand, we need to acknowledge that the uncontrolled use of vancomycin in the ambulatory setting is the strongest predictor of bacterial resistance, including the emergence of VRE and VISA.

DR. FERREIRA: Cardiac valvular calcifications are more prevalent than prosthetic valves, reaching 40% in some groups. Do you think that we should adopt a different approach to these patients? Specifically, should we be performing more echocardiograms and providing endocarditis prophylaxis for patients with cardiac valvular calcifications?

DR. JABER: I don’t know. However, a recent study by Eicher and colleagues demonstrated that mitral annular calcification appears to be an underestimated predisposing factor for a particularly severe type of bacterial endocarditis [80]. One can only speculate as to the value of endocarditis prophylaxis prior to dental work in the setting of valvular calcifications among dialysis patients.

DR. PATRICIA MARTINS (Nephrology Service, Hospital de S. João, Porto, Portugal): What is your personal choice for a skin antiseptic agent?

DR. JABER: I would recommend the use of chlorhexidine for skin antisepsis. However, in the case of a catheter, the topical use of an antibiotic/antiseptic ointment warrants further investigation by contacting the catheter manufacturer to ensure that the chemical ingredients of the ointment are compatible with the polymer material of the catheter. There have been cases of catheter erosion due to incompatibility with the antiseptic/antibiotic ointment. Therefore, it is critical that one obtain this information before instituting such a policy in a dialysis facility.

DR. MADIAS: You commented on the role of immune-modulating strategies for the uremic patient, strategies aimed at boosting host defense mechanisms. Specifically, you mentioned vaccinations and G-CSF. What about the potential use of cytokine inhibitors?

DR. JABER: Although the use of cytokine inhibitors appears to be an elegant approach for combating the inflammatory milieu of uremia, it remains unproven. A recent pharmacokinetic study of anakinra (a synthetic interleukin-1 receptor antagonist) in subjects with different levels of renal function demonstrated that little removal occurs by dialysis, which would require a dose or schedule adjustment [81]. Unfortunately, in the rheumatologic literature, this and other cytokine inhibitors have been associated with an increased risk of infection, and this risk might render the dialysis patient population increasingly vulnerable. Although many investigators are intrigued by the use of cytokine inhibitors in dialysis patients, until we have a better understanding of how to assess immune surveillance while a patient is taking such a drug, the potential long-term benefit of cytokine inhibitors remains speculative.

DR. PONCE: I would like to return to the issue of prevention. You reviewed several preventive strategies, including some extremely expensive, some still experimental, and others more practical. Obviously, your own preference is to use topical ointments, such as a polysporin. I am concerned, however, that we are forced into using more expensive prevention strategies because it is an easier approach than the implementation of easier measures, such as standard hygiene precautions. In your opinion, what should we do in terms of prevention?

DR. JABER: I would concentrate on hand hygiene and aseptic techniques for accessing the vascular access. In case of an AV fistula or graft, I would emphasize the need to scrub and rinse the arm prior to cannulation. With venous catheter use, I would use proper catheter site dressing regimens. In terms of antibiotic or antiseptic ointments, I would use the agent that is most biocompatible with the catheter material. Finally, I would discourage the patient from taking a shower as to avoid moisture at the catheter site.

DR. MADIAS: Of the various preventive and therapeutic possibilities, which ones might be the most appealing and promising for future studies?

DR. JABER: I have summarized three preventive studies against catheter-related infections, which examined either the topical use of betadine, mupirocin, or Triple Polysporin ointment. Unfortunately, these studies do not allow us to draw conclusions about the best ointment. A randomized controlled trial comparing these three agents is warranted. With regard to antibiotic-impregnated catheters, they are unlikely to become routinely used because of their exorbitant price. Finally, 40% of dialysis patients have diabetes mellitus, which further compromises host immunity, so I believe that this high-risk group should be the target of these preventive studies.

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