

Staphylococcus aureus Infections in Hemodialysis: What a Nephrologist Should Know

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Staphylococcus aureus is a formidable pathogen that has the ability to colonize approximately half the dialysis population without any sign of disease but is also capable of causing wound and tissue infections; fulminant septicemia; and chronic, difficult-to-eradicate and often foreign body-related infections. *S. aureus* is the main cause of infectious morbidity and mortality in hemodialysis patients. This review highlights the importance of *S. aureus* infections in daily hemodialysis practice from a clinical viewpoint, starting from some key issues in the pathogenesis of staphylococcal infections.

Clin J Am Soc Nephrol 4: 1388–1400, 2009. doi: 10.2215/CJN.01590309

Staphylococcus aureus is a ubiquitous microorganism in both healthy and compromised hosts. It has many faces: It can cause an asymptomatic and long-lasting colonization of human tissues or incorporate in biofilms on inert surfaces; it may also cause a fulminant host invasion with diverse manifestations. *S. aureus* can survive under extreme circumstances in the human host, as well as in the environment and in animals (1). People who undergo hemodialysis are particularly vulnerable to staphylococcal infections, with the vascular access (VA) being a major porte-d'entrée for this "golden" germ.

Pathogenesis

The importance of *S. aureus* infections in hemodialysis is the consequence of the interplay between a well-equipped pathogen and a host with local and systemic predisposing factors.

S. aureus-Related Factors

S. aureus typically appears as Gram stain-positive cocci in grape-like clusters (2). It consists of an environment-resistant cell wall (peptidoglycan) surrounded by a microcapsule that determines the serotype (2). *S. aureus* consists of 13 capsular types, among which type 5 and 8 account for >85% of clinical isolates (3-6). The bacterium produces a battery of surface proteins involved in host colonization, several enzymes engaged in tissue invasion, and a multitude of toxins (2). Taken together, these factors make *S. aureus* one of the most pathogenic germs in humans.

The most important characteristic of *S. aureus* is its marked capacity for swift tissue invasion, multiplication at the nidus of infection, and subsequent rapid dissemination throughout the body (3,7). The major host defense against tissue invasion

seems to be opsonophagocytosis, which is inhibited by the polysaccharide capsule (3).

The second most important characteristic of *S. aureus* is its ability to colonize a broad range of host tissues and to persist intracellularly or in biofilms formed on prosthetic materials or on human tissues (7,8). Such a biofilm is a structural community of staphylococcal cells enclosed in a self-produced matrix, with or without host constituents, that is adherent to a surface (8-10). Biofilm formation determines the persistent character of *S. aureus* foreign body-related infections, endocarditis, and osteoarticular infections. Whereas the metabolism of planktonic staphylococci in sepsis is mainly oriented on rapid dissemination, sessile staphylococci in biofilms behave as organized communities of bacteria with a markedly reduced metabolic activity that are mainly oriented on long-term survival (8,11-15). The most notable clinical characteristic of this biofilm-associated sessile growth mode is the persistent nature of the subsequent infection (9,16). Although antibiotics usually suppress the symptoms of the foreign body-related infection, definite eradication of the infection generally requires (surgical) removal of the foreign body (17). In one report, minimal bactericidal concentration (MBC) for oxacillin, vancomycin, gentamicin, rifampin, and fleroxacin were up to 256 times higher for sessile *S. aureus* than the MBC for the same bacteria growing under planktonic conditions (17).

Host Factors

Patients with uremia demonstrate deficits in cell-mediated immunity, phagocytosis, and antibody production (7), leading to a markedly increased risk for infections, a decreased humoral response after vaccination (18), and an increased incidence of cancer and autoimmune disease (7,19,20). Although the observed immunodeficiency is mainly caused by ESRD *in se*, it is further enhanced by factors such as dialyzer bioincompatibility, diabetes, and the administration of immunosuppressive medication.

Dialysis poses an increased risk for infections as a result of impure dialysate, transient bacteremia caused by the VA, and

Published online ahead of print. Publication date available at www.cjasn.org.

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iron overload (21). Dialysis catheters disrupt the normal skin barrier and form a gateway for bacterial entry into the bloodstream. The presence of a foreign body *in se* also causes a local immune deficiency by activation of the phagocytic functions of polymorphonuclear cells. This leads to “exhausted neutrophils” that display a markedly decreased bactericidal killing activity when they are subsequently exposed to bacteria (22).

***S. aureus* Carriership**

S. aureus Colonization in the Population

Humans are the main natural reservoir of *S. aureus*. Although multiple body sites can be colonized by *S. aureus*, the rate of colonization is highest in the anterior nares (23,24). In cross-sectional population-based surveys, 10 to 50% of adults were colonized with *S. aureus* (2,23,25,26). Longitudinal studies revealed three patterns of *S. aureus* nasal carriage (23,24). Approximately 20% of healthy adults (range 12 to 30%) are persistent carriers and are colonized by a single strain over prolonged periods. Thirty percent (range 16 to 70%) are intermittent carriers that may harbor different strains in their nose over time. Fifty percent (range 16 to 69%) are persistent noncarriers (23,26). The large variation in the number of persistent and intermittent carriers between the available studies is the consequence of nonuniform definitions and methodologic issues (23,24). An attempt to standardize and optimize these definitions was performed (27). The diagnostic accuracy of two quantitative cultures of nasal swabs that were taken within 1 wk and grew ≥ 8 colony-forming units per culture had a positive predictive value of 0.78 and a negative predictive value of 0.96 for the assessment of the persistent carrier state (24,27). Most likely, intermittent carriers carry the staphylococci on the mucosal membranes of the nose, whereas, in persistent carriers, the staphylococci use a special niche, such as an apocrine gland in the keratinized epithelial cells in the anterior nares, to cause long-term persistence (24).

S. aureus Transmission

In addition to the anterior nares, *S. aureus* frequently colonizes the skin, the perineum, and the pharynx and, to a lesser extent, the gastrointestinal tract, the vagina, and the axillae (24). Staphylococci can also survive for months on many types of surfaces and in environmental dust (24,28). Airborne transmission is important in the maintenance of environmental reservoirs, but hands are the main vectors that transmit *S. aureus* from the environment to the nasal niche and from the nasal niche to several body sites, respectively (24,28). A number of large, population-based, retrospective and prospective trials in nondialysis patients demonstrated that in 80 to 85%, the *S. aureus* recovered from the bloodstream during *S. aureus* bacteremia (SAB) is the same strain that the patients carried in their nose (26,29).

Although the presence of *S. aureus* in the nose elicits a subclinical immune response, this host response is ineffective to prevent further colonization once the germ has reached the anterior nares (24). One study demonstrated that *S. aureus* carriers have a three-fold increase in invasive *S. aureus* infection but a 2.5-fold decrease in subsequent mortality (29). This may

indicate that although the subclinical immune response provoked by nasal carriership is inadequate to prevent tissue invasion, it may decrease the devastating consequences of invasive *S. aureus* infection.

S. aureus Carriership in Hemodialysis

Hemodialysis patients—as are patients with diabetes—are at increased risk for intermittent or persistent carriership from the onset of dialysis (24,26,30,31). Moreover, *S. aureus* carriers who are on hemodialysis have a 1.8- to 4.7-fold increase of vascular VA infections and bacteremia compared with noncarriers (24,32,33). The majority of dialysis patients carry the same strain on the hands and in the nose (34). In addition, these strains are frequently the same as those recovered from subsequent infections (35). Similar to those in the general population (26,29), the majority of *S. aureus* infections in hemodialysis patients therefore has to be considered autoinfections (30).

Epidemiology of *S. aureus* Infections in Hemodialysis

Increased Risk for Infection in Dialysis

Hemodialysis patients have a strongly increased absolute risk and relative risk (RR) for morbidity and mortality from infectious diseases. Infection accounts for 12 to 36% of the mortality in patients with ESRD and is second only to cardiovascular disease as a cause of death (36,37). Septicemia is responsible for approximately three quarters of the infectious mortality (36). Infectious mortality is 1.66 times more frequent in peritoneal dialysis than in hemodialysis (38). The annual mortality rate caused by sepsis is 100 to 300 times higher in patients with ESRD than in the general population (39). A large cohort study reported that the increase in risk is not significantly altered by age, gender, or the presence of diabetes (40). Other studies indicated that the risk for infection is linked to age, low Karnovsky index, type of VA, frequency of hospitalization, immunosuppressive therapy, use of a midtreatment heparin bolus, iron overload, and poor hygiene (33,41–45). Forty-eight to 89% of bacteremias in hemodialysis patients are related to a VA infection (36,37,43,46,47). The type of VA is the most important predictor of the infection risk, with native fistulas being safer than grafts (RR 1.47), cuffed catheters (RR 8.49), and noncuffed catheters (RR 9.87) (48). Other studies reported a 10 to 30 times higher risk associated with noncuffed catheters than with native fistulas (49,50). The incidence of bacteremia in hemodialysis patients varies from 7.6 to 14.4 episodes per 100 patient-years (36,43,46,47).

Although the type of VA has a major impact on the risk of bloodstream infections, it hardly affects the outcome of the subsequent infection (51,52). Major complications from VA-related infections in dialysis are severe sepsis, metastatic mainly osteoarticular infections, and infective endocarditis. The risk for infective endocarditis in hemodialysis patients is 17.8 times higher than in the general population (53), mounting to 5.6 per 1000 patient-years (54). Up to 57.9% of these episodes are caused by *S. aureus*, with an in-hospital mortality of approximately 50% (55).

Staphylococcus aureus in Dialysis

There is a strong relation between SAB and dialysis. A total of 14.5 to 66.0% of all SAB episodes occur in patients with ESRD (56–59). *S. aureus* is—as for the general population (60)—the single leading pathogen causing severe infections in dialysis patients, responsible for 27 to 39% of all bacteremias in dialysis patients (43,61). The incidence of SAB in patients who undergo hemodialysis is as high as 1.2 episodes per 100 patient-months, with a complication rate of up to 40 to 44% and infective endocarditis (using the original Duke criteria) in 12% of patients (47). Hemodialysis patients have an 8.1 to 8.6% chance of developing an SAB during their dialysis career (62,63).

The occurrence of SAB in hemodialysis patients is significantly associated with VA site infections (64). In the US dialysis surveillance network of October 1999 through May 2001, *S. aureus* accounted for 32% of the VA-related bacteremia in catheters, 53% of the VA-related bacteremia in fistulas or grafts, and 26.7% of secondary bacteremia (65). Another single-center survey of 210 patients with dialysis-associated SAB demonstrated that 88.1% of the bacteremias originated from the VA (55.7% catheters and 29.5% grafts) (51). Other risk factors for SAB in hemodialysis are diabetes and warfarin use (66).

The total SAB-associated mortality in the dialysis population is 8%, with an endocarditis rate of 4% (62). The mortality of SAB in hemodialysis patients is 20% higher than of other pathogens (61). Mortality tends to be lower when the bacteremia originated from the VA and when the patient was treated for >28 d (62). *S. aureus* bacteremia is associated with a high recurrence rate (14.5 to 44%) (37,47) and the frequent development of metastatic infection such as endocarditis, osteoarticular infection, septic pulmonary embolism, and epidural abscess (37,67). *S. aureus* was involved in up to half of the cases of dialysis-related epidural abscess reported in the literature, which were frequently related to the use of dual-lumen dialysis catheters as VA (67,68).

Methicillin- and Vancomycin-Resistant S. aureus Infections in Dialysis

Methicillin resistance in staphylococci is conferred by the *mecA* gene, which is easily transferred horizontally and encodes for an altered penicillin-binding protein (PBP2a) that has a low binding affinity for all β -lactam antibiotics. The progressive spread of methicillin-resistant *S. aureus* (MRSA) is daunting. Twelve to 30% (2006 through 2007 European data), 33% (1994 through 2001 US data), and up to 65% (most recent US data) of patients on hemodialysis are colonized with MRSA (51,63,69,70). The proportion of infections that are caused by MRSA varies strongly with local epidemiology and according to the year of surveillance. A recent report from Taiwan demonstrated a colonization rate with MRSA as low as 2.4% (71). In North America, conversely, community-acquired MRSA infections are rapidly emerging, accounting for 60 to 75% of all isolates in the community (72,73). The risk for invasive MRSA infections is 100-fold higher in dialysis patients than in the general population (45.2/1000 versus 0.2 to 0.4/1000) (74). Dialysis patients currently account for up to 15.4% of all invasive MRSA infections (74). As for methicillin-sensitive *S. aureus*

(MSSA) infections, molecular typing suggests that colonization of MRSA strains precedes clinical infection (71).

Data regarding the role of methicillin resistance in outcome are conflicting, although most data suggest a higher mortality and recurrence rate. A small, single-center, case-control study found a 38% case fatality rate for the MRSA group versus 28% for the MSSA group, but the difference lost significance after adjustment for major confounders (75). A large cohort study of 908 consecutive SAB episodes did not find an increased adjusted mortality risk in the MRSA group (76). In contrast, a large, single-center cohort study of 385 episodes of SAB reported that methicillin resistance resulted in a 2.59 times higher mortality in the elderly (77). Another case-control study of 184 patients with SAB identified methicillin resistance as an independent risk factor for mortality (odds ratio 3) (57). Despite the use of appropriate antibiotics in the majority of patients, a large (504 episodes of SAB) retrospective cohort study demonstrated a significantly higher mortality rate in the MRSA than in the MSSA group (18.6 versus 12.9%) (78).

A steady increase over time of the minimal inhibitory concentration (MIC) for vancomycin is observed in the staphylococcal population (79). MRSA strains with an increased MIC for vancomycin (>1 to 2 $\mu\text{g}/\text{ml}$) impart a higher risk for death (80–82). MRSA strains with MIC for vancomycin of >2 and <16 $\mu\text{g}/\text{ml}$ are referred to as vancomycin intermediate *S. aureus* (VISA) (83). VISA strains predispose to treatment failure, even when high dosages of vancomycin are used (84). Some patients are infected with heteroresistant MRSA (hVISA), defined by the presence of subpopulations with reduced susceptibility to vancomycin. Heteroresistant MRSA are easily missed by commercial automated tests (85) and predispose to treatment failure (86).

Recently, vancomycin-resistant *S. aureus* (VRSA) was reported in seven patients from the United States. All patients had chronic colonization with MRSA and vancomycin-resistant enterococci, and most of them had received prolonged therapy with vancomycin for MRSA infection. Of note, three of seven patients had ESRD. All VRSA had acquired the *vanA* gene from vancomycin-resistant enterococci, and the median vancomycin MIC was 512 $\mu\text{g}/\text{ml}$. The mechanism of resistance in VRSA is quite different from VISA. The *vanA* gene results in the replacement of D-Ala-D-Ala-ending peptidoglycan precursors with D-alanyl-D-lactate termini, causing a decreased binding affinity for vancomycin and an almost 1000-fold increase in MIC (87).

Vancomycin tolerance refers to an inhibition of growth without bacterial killing (and thus cure) and is defined as a MBC-MIC ratio of >32, or a MBC-MIC ratio of >16 in case of a MIC ≥ 32 $\mu\text{g}/\text{ml}$ (85). Vancomycin tolerance is highly prevalent (74 to 100%) in hVISA, VISA, and VRSA strains and causes clinical treatment failure (85).

Clinical Course and Outcome

Almost all dialysis patients with SAB have fever at presentation. Approximately one fifth have hypotension, and approximately 5% have encephalopathy or present with heart failure (88). Early-onset catheter-related infections generally originate from an extraluminal colonization, whereas late-onset infec-

tions (beyond 10 to 14 d of insertion) frequently have an intraluminal origin (89). Consequently, catheter-related bacteremia in tunneled dialysis catheters is infrequently associated with an exit-site infection (90). Fever associated with VA infections generally occurs well into the dialysis session (after 60 to 90 min) (90).

Complications of SAB are frequent in the population in general and in hemodialysis patients in particular. In a large, prospective, population-based cohort trial, SAB was complicated in 43% by attributable mortality, metastatic or extensive local infections, septic embolism, or early recurrence (59). Twenty-six percent of the study population consisted of hemodialysis patients. Predictors of a complicated course were persistent bacteremia beyond 48 h, persistent fever beyond 72 h, community acquisition, and skin findings suggestive of acute infection (59). A higher APACHE II score, older age, unknown or lung focus, and diabetes were also independent predictors of mortality (56). Mortality of SAB in the general population has varied from 16 to 38% (7,47,51,52,56,59,77,88).

A prospective, single-center cohort study of 210 hemodialysis patients with SAB found complications in 31% (51). Infective endocarditis was present in 17.1%, septic emboli or arthritis in 4.8%, and abscesses in 5.7% (51). Recurrent infections within 12 wk were seen in 12.9% of the patients (51). In-hospital mortality was 9.5%, and 12-wk mortality was as high as 19% (51). SAB resulted in removal of the catheter in the majority of patients and in removal of the graft in up to one third of patients (51). VA loss may also be considered a serious complication of SAB in dialysis, given the limited options for many patients (51).

SAB is associated with considerable additional costs in hemodialysis patients. A retrospective analysis of the US Renal Data System reported an average cost of care of \$20,067 per episode, with an additional increase when the episode was complicated (91). These data were confirmed in a single-center study at Duke University that found a mean cost of \$20,685. The cost was higher for patients with catheters than for patients with fistulas and much higher in complicated SAB (51). A German study revealed a similar cost of €9554 (approximately \$12,651) for community-acquired infections and €20,024 (approximately \$26,516) for nosocomial infections (88). The average treatment cost for MSSA infections was less than half of that of MRSA infections, mainly as a result of a longer hospitalization time and a higher proportion of nosocomial and complicated infections (88).

Management

General Management

Given the high mortality of SAB in dialysis, the rapid institution of a highly efficacious treatment is essential. *S. aureus* bloodstream infections should be treated with adequate doses of bactericidal antibiotics. Antibiotics that permit thrice-weekly dosing after dialysis are preferable (47).

Because of the frequent occurrence of endocarditis, all patients with *S. aureus* sepsis should undergo transesophageal echocardiography (51,86). In addition, any catheter, prosthetic graft, or other infected foreign body should be removed (7,86,92–94). Attempts to salvage the catheter with an antibiotic

lock solution in addition to systemic antibiotics are associated with an unacceptably high rate of complications (95,96).

Vancomycin and β -Lactamase-Resistant Penicillins

Vancomycin has been used in clinical practice since 1958. Vancomycin is a glycopeptide that binds to murein monomers, leading to a terminal chain reaction in peptidoglycan synthesis (97). Vancomycin has a broad anti-Gram-positive spectrum of action (97). Although it is bactericidal, its killing activity is quite slow and further negatively influenced by stationary growth phase, anaerobic growth conditions, and higher inocula (98). Whereas older preparations of vancomycin—also called Mississippi mud—suffered from frequent adverse effects such as nephrotoxicity, infusion-related toxicity, and ototoxicity, newer formulations are generally well tolerated (98). Vancomycin can be dosed intermittently on hemodialysis days, with trough levels being the most practical and accurate method to monitor effectiveness (98,99). A trough level of at least 10 and preferably 15 to 20 mg/L should be obtained to prevent the emergence of resistance during therapy and maximize the therapeutic response (98,99). Vancomycin is partially removed by most currently used hemodialysis filters (99). It should therefore be administered after or during the last hour of dialysis (99). Most studies suggest the administration of a loading dose of 15 mg/kg. Various maintenance schedules have been adopted, with 500 mg after each session being the most frequently used (99). Although good data in hemodialysis are lacking, this schedule may be inadequate to meet the currently recommended trough levels, and loading dose as high as 25 to 30 mg/kg may be required (98–100).

β -Lactam antibiotics inactivate enzymes called PBP that are located in the bacterial cell wall and are involved in cross-linkage of linear peptidoglycan strands, causing a fishnet-like polymer that confers osmotic stability for the bacterium in a hypertonic environment (101). β -Lactam antibiotics mainly—but not exclusively—act on growing staphylococci (101). Almost all staphylococci inactivate penicillin by the presence of a β -lactamase. Semisynthetic penicillinase-resistant penicillins such as methicillin and isoxazolyl penicillins (oxacillin, cloxacillin, and dicloxacillin) as well as (first-generation) cephalosporins resist hydrolysis by the staphylococcal β -lactamase. Isoxazolyl penicillins, administered as sodium salts, impose a significant sodium load. Cephalosporins, especially cephazolin, are validated as a valuable alternative in the treatment of SAB (102,103). Administration of 20 mg/kg cephazolin thrice weekly resulted in a prehemodialysis concentration of ± 70 mg/L in conventional hemodialysis and ± 40 to 45 mg/L in high-flux hemodialysis (104), which is ± 2.5 times above the MIC of cephazolin. Clearance of cephazolin was significantly higher in high-flux hemodialysis than in conventional hemodialysis, but, in both groups, a dose of 15 to 20 mg/kg resulted in trough levels well above the MIC for a 2- to 3-d period (105). Some limited and poorly powered data suggest an increased occurrence of infections with extended-spectrum β -lactamase-producing organisms, when cephazolin is routinely used in the hemodialysis setting (106).

Vancomycin is frequently touted for its favorable pharmaco-

kinetics in dialysis (47,99); however, several *in vitro* and *in vivo* studies suggested that β -lactam antibiotics are superior to vancomycin in the treatment of invasive MSSA infections, with a more rapid killing curve (107) and a higher efficacy (98,108). These findings are supported by multiple clinical trials on bacteremia, endocarditis, and pneumonia (109–114). In a trial of 309 episodes of SAB, patients who were treated with vancomycin had a four times higher risk for a molecularly documented recurrence (96). In accordance, recurrence rate was 19.5% in patients who were treated with vancomycin only *versus* 7.1% in patients who were treated with a regimen that included β -lactamase-resistant penicillins in a single-center study at Duke University (47). Another prospective trial of 123 hemodialysis patients with MSSA bacteremia showed a significantly higher complication rate (31.2 *versus* 13.0%) in patients who were treated with vancomycin compared with patients who were treated with cephazolin, despite a lower severity of disease in the former (92). Consequently, inappropriate use of vancomycin in the treatment of MSSA infections should be avoided.

On the basis of a retrospective, single-center database, the predicted efficacy of empirical therapy in a long-term dialysis population with a low incidence of MRSA is similar for vancomycin and cephazolin (115). One study suggested that inappropriate nonadministration of vancomycin during the first days of empiric therapy of MRSA bacteremia did not result in increased mortality (116). This was not confirmed in another trial of 414 episodes of MRSA bacteremia (117). Certainly, in dialysis populations with high MRSA incidence or in severely ill patients, vancomycin should be included in the empirical treatment of VA-related infections.

Practical Recommendations for the Treatment of SAB in Hemodialysis

A practical approach is the administration of 25-mg/kg vancomycin loading dose with 2 g of cephazolin in case of presumed VA-related SAB. Because Gram-negative rods cause up to 25 to 30% of VA-related sepsis, it may be prudent to include broader Gram-negative coverage such as aminoglycosides or third-generation cephalosporins in the initial empiric treatment of presumed VA-related sepsis (37). In case of MRSA, vanco-

mycin should be continued with a target trough level of 15 to 20 μ g/ml (usually 500 mg after each dialysis session) (11,99,100). When an MSSA infection is confirmed, cephazolin should be continued alone and administered at the end of dialysis with a 2-g dose before a 2-d interdialytic interval and a 3-g dose before a 3-d interdialytic interval (92). Antibiotic treatment options are summarized in Table 1.

The duration of the treatment of SAB in dialysis is not well studied. Typically, a 4- to 6-wk course of intravenous antibiotic therapy is given. Limited data acquired on nondialysis patients suggested that a 2-wk course may be sufficient in selected low-risk patients with catheter-related bacteremia, without metastatic infections, with a negative transesophageal echocardiogram, and with rapid defervescence and negative follow-up cultures at 48 h (86). Pending more trials of hemodialysis patients, it is wise to maintain the 4- to 6-wk regimen for SAB in hemodialysis.

Other Antibiotics in the Treatment of *S. aureus* Infections in Hemodialysis

Other antibiotics that are useful in the treatment of MRSA infections in dialysis are daptomycin, linezolid, clindamycin, quinupristin-dalfopristin, co-trimoxazole, and tigecycline (79). Daptomycin is a bactericidal cyclic lipopeptide with a concentration-dependent killing mechanism that causes depolarization of the cell membrane in Gram-positive infections with consequent disruption of several critical metabolic functions (79). Daptomycin is approved for the treatment of complicated skin and skin-structure infections with MRSA in a dosage of 4 mg/kg per d and for MRSA bacteremia, with or without right-side endocarditis, in a dosage of 6 mg/kg per d (79,118). In stage 4 or 5 renal failure, a similar dosage every 48 h is recommended (119). In MRSA osteoarticular infections, daptomycin also seems to be a valuable alternative to vancomycin (120). Daptomycin has failed to prove value in the treatment of MRSA pneumonia because of its inactivation by surfactant (121). The occasional emergence of subpopulations of staphylococci with reduced susceptibility to daptomycin during therapy is of concern, mainly in patients with severe sepsis and left-sided endo-

Table 1. Treatment of *Staphylococcus aureus* bacteremia in hemodialysis^a

Antibiotic	Dosage	Comment
Empiric combination treatment		
vancomycin	20 to 25 mg/kg	Loading dose
cephazolin	2 g	For a 2-d interval
Maintenance treatment		
vancomycin	500 mg	For MRSA, trough target of 15 to 20 μ g/ml
cephazolin	2 g for 2-d interval, 3 g for 3-d interval	For MSSA
Alternative agents (limited data available)		
daptomycin	6 mg/kg per 48 h	Do not use in MRSA pneumonia
linezolid	600 mg twice a day	Cumulative toxicity after 2 to 3 wk of use

^aMRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*.

carditis (86,118). The main adverse effect of daptomycin is rhabdomyolysis (79,118,120).

Linezolid is a bacteriostatic oxazolidin that has high oral bioavailability and inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit in Gram-positive bacteria and mycobacterial species (122,123). On the basis of several randomized, controlled trials, linezolid has been approved for complicated and noncomplicated skin and skin-structure infections and for community-acquired and nosocomial pneumonia in a dosage of 600 mg twice daily, intravenously or orally (73,122). No dosage adjustment is necessary in chronic kidney disease, but a strict monitoring for adverse effects is recommended (73). Several case reports and smaller series suggested a place for linezolid in the treatment of MRSA osteoarticular infections (73). Only limited data demonstrated activity of linezolid in MRSA sepsis (mainly in secondary bacteremia), and the antibiotic is not approved for this indication (86,124,125). The use of linezolid for a period beyond 2 to 3 wk is associated a dosage- and time-dependent myelosuppression and risk for lactic acidosis that is caused by a depletion of several mitochondrial proteins (122,126).

Co-trimoxazole, clindamycin, and long-acting tetracycline derivatives such as minocycline and doxycycline are increasingly used as oral therapy for the treatment of noncomplicated MRSA skin and skin-structure infections but not in the treatment of SAB or other invasive MRSA infections (73). Well-powered randomized, controlled trials on the use of these agents in the treatment of MRSA infections are lacking. Co-trimoxazole has good *in vitro* activity against staphylococci (127), which has been confirmed in several small studies (128). Co-trimoxazole was inferior to vancomycin in the treatment of SAB (129). The normal dosage of co-trimoxazole is 10 to 15 mg/kg per d in two to three divided doses, with a reduction of 50% when GFR is <30 ml/min (86). Co-trimoxazole is not recommended for dialysis patients. Most community-acquired MRSA strains are susceptible to clindamycin, although resistance is variable and in some cases inducible (73,128). Clindamycin has high oral bioavailability. The dosage of clindamycin is 600 to 900 mg every 6 to 8 h (86). Dosage adjustments are not required in dialysis patients. The dosage of minocycline and doxycycline is 100 mg twice daily. No dosage adjustment is needed, although data on minocycline pharmacokinetics in dialysis are scarce.

Tigecycline is a minocycline derivative and member of the class of the glycylicylines, which inhibits protein synthesis by binding to the 30S ribosomal subunit (123). Tigecycline has good *in vitro* activity against the majority of MRSA strains (130). Tigecycline is approved for complicated skin and skin-structure infections and complicated intra-abdominal infections with a loading dosage of 100 mg, followed by 50 mg/12 h (86,123). No dosage adjustment is required in renal impairment. Tigecycline has a large volume of distribution, and serum levels are rather low (123). Data on the usefulness of tigecycline in the treatment of SAB are lacking.

Quinupristin-dalfopristin is a streptogramin approved for MRSA skin and skin-structure infections in a dosage of 7.5 mg/kg twice daily, with no dosage adjustment in renal impair-

ment (119). Quinupristin-dalfopristin has frequent adverse effects, such as infusion-related thrombophlebitis, myalgia, and arthralgia. Only very limited data support its use in MRSA sepsis (86).

Other agents in the pipeline for the treatment of MRSA infections are the lipoglycopeptides dalbavancin, telavancin, and oritavancin and the broad-spectrum cephalosporins with good activity on PBP2a (and thus on MRSA) ceftobiprole and ceftaroline (86,123,125). Dalbavancin has a long half-life, permitting once-weekly administration in patients with normal kidney function (123). It has proved to be >16 times more potent *in vitro* than vancomycin in a large collection of MRSA strains (131). Preliminary clinical data on dalbavancin, telavancin, and oritavancin are promising, but their role in the treatment of SAB and their place in dialysis have yet to be established. Ceftobiprole has good *in vitro* activity against MRSA strains (132). It will be used in the treatment of MRSA skin and skin-structure infections, MRSA pneumonia, and maybe also in MRSA sepsis (123).

Prevention

S. aureus Vaccine

The high incidence of invasive *S. aureus* infections and the progressive emergence of resistance to numerous antibiotics urged the development of a *S. aureus* vaccine. Capsular polysaccharides 5 and 8 have been linked to a carrier protein (StaphVAX™) and were found to induce protective antibodies in mice and rat models (3). Many people have low-level baseline antibodies against staphylococci. Vaccination with the conjugated vaccine StaphVAX™ induced a 10- to 20-fold and long-lasting increase in antibody levels with a slow decline. Tolerability was acceptable, but clinical efficacy in a large, randomized, controlled trial of 1804 dialysis patients was disappointing. An NS 26% decrease in SAB was observed at 1 yr, with a possibly slightly higher efficacy at earlier time points (3,133). The development of this vaccine has been discontinued.

Catheter Lock Solutions

The type of catheter lock solution used in tunneled and nontunneled hemodialysis catheters plays an important role in the ability of staphylococci to form a biofilm (134). *In vitro* studies demonstrated that concentrations of sodium citrate >0.5% (with or without gentamycin) and EDTA protect against biofilm formation, whereas low molecular weight heparins and concentrations of sodium citrate <0.5% stimulate staphylococcal biofilm formation. Lepirudin and tissue plasminogen activator lock solutions have an indifferent effect on *in vitro* staphylococcal biofilm formation (134).

Several clinical trials have assessed the efficacy of catheter lock solutions in the prevention of dialysis catheter-related infections (135-141). A recent meta-analysis calculated a risk reduction of 7.72 (95% confidence interval [CI] 5.11 to 10.33) for catheter infections when using antimicrobial lock solutions, with no consistent adverse outcome, in particular catheter thrombosis, and no evidence of the emergence of resistance (142). This translates in a number needed to treat of three to prevent one catheter-related infection per 100 catheter-days

(142). Lock solutions with 30% sodium citrate; 1.35% taurolidine with 4% sodium citrate; and various combinations with gentamycin, minocycline, cephazolin, and cefotaxime were included in the analysis (142). Lock solutions that contained gentamycin were the most efficacious, with a rate reduction ratio of 11.8 (95% CI 8.4 to 15.3) (135,136,138,140,142). Lock solutions with higher concentrations of gentamycin (40 mg/ml), however, resulted in a significant systemic exposure with trough levels of 2.8 mg/L, posing a risk for systemic toxicity (138). Even lock solutions that contain concentrations of gentamycin as low as 4 mg/ml may lead to detectable serum levels of 0.2 mg/L (135). Current data support the systematic use of antimicrobial lock solutions in the prevention of catheter-related infections in dialysis, with a slight preference for sodium citrate- and taurolidine]based solutions.

Catheter Handling

Given the importance of dialysis catheters in the occurrence of *S. aureus* infections in dialysis, the number of catheters should be minimized, and a meticulous catheter management is imperative (143). In nondialysis populations, the risk for catheter infection is higher in the femoral position than in the jugular or subclavian position (144–146). In the acute hemodialysis setting, the risk for infection is higher in the jugular position for patients with a low body mass index (<24.2) and in the femoral position for patients with a high body mass index (>28.4) (147). The type of catheter material and the characteristics of the catheter surface influence the probability of biofilm formation and subsequent infection, with Teflon, polyurethane, silicone, and carbothane being the preferred materials (148,149). A rigorous hand hygiene procedure before catheter manipulation is vital (148,150), and the use of maximal sterile barrier precautions during insertion of the catheter may reduce the risk for subsequent infections (151). There seems to be no clear difference in the risk for infection between transparent, semi-permeable polyurethane dressings and standard gauze and tape dressings (152). On the basis of clinical data, 2% chlorhexidine gluconate-based solution seem to be the preferred skin antiseptic (148,153). In contrast, limited *in vitro* data suggest that 0.5% aqueous solutions of chlorhexidine are less effective than povidone-iodine in the eradication of MRSA strains (154). Finally, several data indicate that antiseptic- or antibiotic-impregnated catheters reduce the risk for infections also in dialysis patients (145,148,155).

Aspirin Use

In vitro and *in vivo* experiments indicated that salicylic acid, a major metabolite of aspirin, has an inhibitory effect on the expression of α -toxin and fibronectin-binding adhesin through activation of the σ B stress operon in *S. aureus*. This occurs in concentrations that are easily achieved in patients (156,157). The findings were confirmed in one promising large retrospective analysis of 476 patient-catheter-years, reporting a 54% decrease in the risk for SAB in the aspirin group (0.17 *versus* 0.34 events/patient-catheter-year; $P = 0.002$) (66). The risk reduction was dosage dependent and generally seen with dosages >325 mg/d (66).

Oral Rifampin

Oral rifampin, with or without bacitracin at the exit site, decreases the number of VA-site infections, with an odds ratio in a meta-analysis of 0.16 (95% CI 0.06 to 0.44). Both the emergence of resistance in *S. aureus* (0.0 to 18.2%) and the occurrence of serious drug-related toxicity (6.6%) were frequent in the intervention group. Resistance to rifampin arises as a result of a missense mutation in the *rpoB* gene in one of 10⁵ staphylococci (158). Given this high and predictable frequency of resistance development, rifampin should not be used in monotherapy. The routine use of oral rifampin is not recommended in the prevention of staphylococcal VA-site infections (32,159).

Although many *S. aureus* strains are highly susceptible to rifampin, resistance emerges quickly and the *in vivo* response in combination with β -lactam antibiotics and glycopeptides is highly variable (160). Prospective data failed to demonstrate a clear benefit of the addition of rifampin to vancomycin in the treatment of native valve MRSA endocarditis (160,161). The use of rifampin is not routinely recommended in the treatment of SAB or in the prevention of recurrence, except in the setting of prosthetic valve endocarditis (160,162). Finally, rifampin is also recommended in the treatment of prosthetic joint staphylococcal infections, where it proved to be superior than monotherapy with fluoroquinolones, owing to its activity on adherent and stationary phase staphylococci (163,164).

Local Antibiotic/Antiseptic Ointments

Local povidone-iodine ointment at the exit site resulted in a decreased incidence of exit-site infections (5 *versus* 18%), tip colonization (17 *versus* 36%), and catheter-related bloodstream infections (2 *versus* 17%) in a randomized, controlled trial of 129 patients with a temporary dialysis catheter (165). Thrice-weekly application of topical mupirocin ointment at the exit site of tunneled, cuffed catheters resulted in a five-fold decrease in catheter-related bacteremia in a small, randomized trial (166). Thrice-weekly application of medihoney at the exit site of tunneled, cuffed central venous catheters proved comparable to mupirocin to prevent catheter-related infections in a randomized, controlled trial of 101 patients (that was not powered to prove equivalence of both treatments) (167). The use of nasal mupirocin ointments in *S. aureus* nasal carriers resulted in an eradication of the nasal carriage in the majority of patients and in a four-fold decrease in incidence of SAB (34,168,169). In these studies, an induction scheme of thrice-weekly topical mupirocin during 2 wk was followed by a maintenance scheme of once-weekly application during 9 mo (168,169). Concern exists about the relatively rapid development of resistance and the high recurrence rate of nasal carriage (7).

Conclusions

S. aureus is a major cause of infectious morbidity and mortality around the world, causing a wide variety of clinical manifestations ranging from localized infections; toxin-mediated diseases; and invasive bloodstream infections to biofilm-associated conditions such as infective endocarditis, osteomyelitis, and foreign body-related infections. The success of the germ is a consequence of its large armamentarium of virulence

factors permitting rapid tissue invasion and dissemination throughout the body and its genetic plasticity that permits a constant adaptation to changing environmental conditions. Conversely, *S. aureus* is capable of causing host tissue and foreign body colonization and of surviving and persisting under a wide variety of circumstances.

Dialysis patients are particularly vulnerable to infections caused by *S. aureus*. *S. aureus* accounts for >8% of the mortality in the dialysis population and is the leading cause of mainly VA-site-related infections. Current treatment options clearly reduce the mortality of *S. aureus* infections but do not prevent complications in >40% of patients with SAB. Treatment is further compromised by the widespread emergence of multiresistant *S. aureus* in the population. Although preventive measures against *S. aureus* somewhat reduce the incidence of the infection, the Holy Grail in the prevention and management of *S. aureus* infections in dialysis still has to be discovered.

Disclosures

None.

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