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Staphylococcus aureus bacteremia and endocarditis

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Staphylococcus aureus bacteremia is a serious and common disease often associated with infective endocarditis. It occurs in both healthy, immunologically competent people in the community and compromised patients in the hospitals. For *S. aureus* bacteremia, questions on clinical issues such as antimicrobial treatment are raised. Is nafcillin/oxacillin superior to vancomycin? Does the addition of rifampin improve outcome? Does addition of aminoglycoside improve the outcome? Does increasing duration of therapy (> 4 weeks versus < 2 weeks) improve outcome? How many cases of community-acquired *S. aureus* bacteremia have endocarditis on admission? What are the risk factors that would separate bacteremia from endocarditis? What is the role of echocardiography? What are the indications for routine echocardiography? Are methicillin-resistant *S. aureus* (MRSA) more virulent than methicillin-susceptible *S. aureus* (MSSA)? What factors predict mortality in *S. aureus* bacteremia? Herein, the above important issues on *S. aureus* bacteremia and endocarditis are critically reviewed.

Key words: *Staphylococcus aureus* bacteremia, endocarditis, methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-susceptible *Staphylococcus aureus* (MSSA)

Staphylococcus aureus is a gram-positive coccal bacterium. One-fourth to one-third of normal individuals carries it in the anterior nares and skin. It can colonize and infect both healthy, immunologically competent people in the community and hospitalized patients with decreased host defenses [1]. *S. aureus* is the most common and important cause of gram-positive hospital-acquired organism. Once *S. aureus* invades deeper structures, it often spreads hematogenously to other organ systems, leading to metastatic infection. *S. aureus* accounts for 11% to 38% of cases of bacteremia in large, recent published series of both community-acquired and hospital-acquired bacteremia [2,3]. Endocarditis and septicemia often have significant mortality despite aggressive antimicrobial therapy. Some important clinical issues on *S. aureus* bacteremia and endocarditis are reviewed in this article.

Issues on Antimicrobial Treatment

Nafcillin/oxacillin versus vancomycin

Penicillinase-resistant penicillins are the preferred drugs for all *S. aureus* infections caused by penicillin-resistant, methicillin-susceptible *S. aureus* (MSSA) strains [1]. These agents have gained wide acceptance because they are bactericidal and, like other penicillins, have a low incidence of adverse reactions. Cephalosporins, particularly those of the first generation, have proven useful alternatives to penicillinase-resistant penicillins, since they are relatively stable to staphylococcal ß-lactamase [1].

Vancomycin is the drug of choice for infections caused by *S. aureus* strains that are resistant to ß-lactam antibiotics and for patients who are allergic to the latter drugs. However, several anecdotal reports have questioned the efficacy of vancomycin for both MSSA and methicillin-resistant *S. aureus* (MRSA) [4-6]. Relapse and treatment failure of *S. aureus* bacteremia and endocarditis were associated with vancomycin therapy [7-11]. Chambers demonstrated that the cure rate of right-sided endocarditis in intravenous drug abusers was 33% (1/3) versus 100% (47/47) as compared to the therapy of vancomycin plus tobramycin versus nafcillin plus tobramycin for 2 weeks [7]. Prolonged bacteremia of more than 6 days was often demonstrated in patients receiving vancomycin therapy [5,6,12,13]. In contrast, almost all the blood cultures of the patients receiving nafcillin or other ß-lactams became sterile within 6 days [14-16].

The slower bactericidal rate has been suggested as a possible reason for the higher failure rate seen with

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vancomycin therapy in patients with MSSA endocarditis [6]. Moreover, sporadic cases of infection due to organisms with intermediate resistance to vancomycin reported in Japan and the United States have been met with great apprehension [17].

Rifampin combination

The *in vitro* effect of rifampin in combination with semisynthetic penicillins, vancomycin, and aminoglycosides is highly variable. Some suggest that the combination may be antagonistic [18-20]. Some reports of the studies *in vitro*, animal models and clinical response favor the addition of rifampin [21-24]. Rifampin combinations might be considered in situations such as prosthetic valve endocarditis, other prosthetic device infections or osteomyelitis caused by *S. aureus*. Moreover, a combination of rifampin and ciprofloxacin cured 100% (10/10) intravenous drug abusers with right-sided *S. aureus* endocarditis [25]. It is practical to use these drugs in combination to prevent the emergence of quinolone resistance during therapy of *S. aureus* infection, provided that a MRSA strain is susceptible to both fluoroquinolone and rifampin [1].

Aminoglycoside combination

The addition of gentamicin to nafcillin produces an enhanced bactericidal effect *in vitro* and in experimental staphylococcal endocarditis in rabbits [26,27]. The combinations of vancomycin-gentamicin and vancomycin-tobramycin were synergistic against a majority of MSSA and MRSA strains [19]. If synergism was defined as a decrease in colony counts of at least 100-fold at 24 h with the combination compared with that of the most active single drug, vancomycin-gentamicin synergism was not predictable for strains of MRSA with a gentamicin minimum inhibitory concentration (MIC) of 0.5 to 128 μg/mL [28]. Moreover, a gentamicin MIC of more than 500 μg/mL predicted a lack of vancomycin-gentamicin synergism for strains of MRSA [28]. However, three patients studies failed to show an improved cure rates of combination therapy compared with single-drug therapy for *S. aureus* endocarditis when the total length of therapy was 4 to 6 weeks [16,29,30]. Among the three studies, only one study examined the rate of clearance of bacteremia and this study showed that eradication of bacteremia in nonaddicts was significantly faster in the nafcillin plus gentamicin group (2.8 days versus 4.1 days, $p < 0.05$) [16]. Of patients treated with nafcillin plus gentamicin, 50% (8/16) had sterile blood cultures on day 2 compared with only 11% (1/9) patients treated with nafcillin. However, the more rapid clearance of bacteremia in the nafcillin plus gentamicin group did not correlate with a more rapid clinical response, as patients in both groups were febrile for approximately the same period of time [16]. An increased incidence of renal dysfunction was associated with addition of gentamicin for the first 2 weeks [16]. Of the patients, 94% (47/50) experienced clinical and bacteriological cures in a short-course (2-week) therapy of nafcillin plus tobramycin for patients with uncomplicated right-sided *S. aureus* endocarditis [7].

It is biologically plausible to infer that more rapid control of bacteremia would be accompanied by a lower incidence of metastatic infection and accelerated sterilization of heart valves that should have a salutary impact on the outcome of the disease. Thus, it seems reasonable to add gentamicin for the first 3 to 5 days of therapy in the hope of more rapid clearing of bacteremia and minimizing damage to the heart valve while avoiding toxic reactions associated with more prolonged courses of aminoglycosides [31,32].

Duration of therapy (> 4 weeks versus < 2 weeks)

For uncomplicated *S. aureus* bacteremia, 2 to 3 weeks of antibiotic therapy appears to be sufficient for those patients who have no underlying cardiac valvular disease and who respond rapidly to antibiotic treatment [33-37]. The presence of a prosthetic valve, diabetes mellitus with a primary focus of infection or prolonged bacteremia for several days is more likely to have endocarditis and deep-seated infection [13,36,38,39]. The risk of endocarditis appears to be high in patients with community-acquired *S. aureus* bacteremia without a definable focus, so antibiotic treatment for 4 to 6 weeks is usually recommended [37]. Of 20 patients with *S. aureus* endocarditis receiving complete 4 weeks or more of treatment, all were cured at 1-month follow-up [40]. On the other hand, of 12 patients with *S. aureus* bacteremia associated with intravenous catheter infection, three out of eight patients received 2-week treatment were considered failures: one each developed endocarditis 3 days and 7 weeks later, respectively; one developed epidural abscess and meningitis after first week of therapy and underwent 6 weeks of antibiotic therapy [40].

In a comprehensive review, an average complication rate for 11 studies of short-course therapy for catheter-related *S. aureus* bacteremia was 6.1% [41]. A study of *S. aureus* bacteremia in patients on chronic hemodialysis showed that less than 4 weeks of treatment was associated with a higher occurrence of primary treatment failure, as compared with treatment for more than 4 weeks [42].

In patients with *S. aureus* endocarditis or septicemia complicated by metastatic infections, a full 4-week course of antibiotic therapy has been recommended [43]. In case of endocarditis occurring on prosthetic devices, a 6-week course of an adequately chosen penicillin with an aminoglycoside has been recommended [43]. However, a combination of nafcillin and tobramycin treatment for 2 weeks cured 94% (47/50) of right-sided endocarditis in intravenous drug abusers [7].

Although short-course treatment of uncomplicated *S. aureus* bacteremia may be appropriate, these issues remain contentious and unresolved. For catheter-related *S. aureus* bacteremia, the accumulated data regarding the safety of short-course therapy are flawed both by bias and by statistical imprecision [41]. The available data do not tell us what the optimal duration of therapy should be [40,41,44].

Issues on Endocarditis

Incidence and risk factors for endocarditis

The incidence of infective endocarditis in patients with community-acquired *S. aureus* bacteremia has ranged from 6% to 64% [3,32,45-50]. A high frequency of endocarditis have been observed in populations with a large preponderance of patients with intravenous drug abuse or had underlying valvular heart disease [46,47, 49,50]. In reports featuring predominantly nonaddict-related, hospital-acquired *S. aureus* bacteremia, the incidence of infective endocarditis was much lower (ranged from 0 to 17%) [3,37,44,48,50-54]. However, one recent study highlighted 51% (30/59) of the source of *S. aureus* endocarditis was intravascular catheter [55].

The clinical differentiation of uncomplicated *S. aureus* bacteremia from infective endocarditis has obvious therapeutic and prognostic implications. In the absence of typical Oslerian manifestations (such as changing murmur, splenomegaly, embolic lesions), the clinical diagnosis of infective endocarditis among patients with *S. aureus* bacteremia is difficult [32].

Nolan and Beaty reported that three simple bedside criteria proved useful for predicting the subsequent occurrence of infective endocarditis among bacteremic patients: 1. community-acquired *S. aureus* bacteremia, 2. inapparent primary focus, and 3. metastatic sequelae [33]. Risk factors for endocarditis in *S. aureus* bacteremia have been well-studied. Mitral valve prolapse and audible regurgitant murmur, degenerative valvular lesions, cyanotic congenital heart disease, bicuspid aortic valves, rheumatic heart disease, and prosthetic heart valves are well-documented pre-existing cardiac risk factors for endocarditis [56]. Community-acquired *S. aureus* bacteremia, intravenous drug users, the absence of primary foci correlated with a significant increased incidence of endocarditis [3,33, 47]. Diabetic patients with *S. aureus* bacteremia associated with primary focus of infection were more likely than nondiabetics to develop endocarditis [39]. Advanced age and male gender are significant risk factors for endocarditis [56].

Among 10% to 29% of all cases of infective endocarditis in some series have been attributed to a nosocomial source [36,57,58]. Of patients with catheter-related *S. aureus* bacteremia, 8% to 9% may develop endocarditis or metastatic abscess after intravenous antibiotic treatment for 2 weeks [52].

The role of echocardiography

Since the differentiation of infective endocarditis from uncomplicated *S. aureus* bacteremia is not possible by clinical criteria, investigators have attempted to use the echocardiogram to increase the diagnostic efficiency in this regard. Transthoracic two-dimensional echocardiogram (TTE) identified typical valvular vegetations in approximately 60% to 70% of unselected patients with clinically overt infective endocarditis [59, 60]. Routine use of TTE in all cases of community-acquired *S. aureus* bacteremia was important in identifying occult endocarditis in patients without classic stigmata of disease. In 18% (6/33) of patients with *S. aureus* bacteremia without stigmata of endocarditis, echocardiography provided information that led to a diagnosis of endocarditis and a subsequent change in the therapy [47]. However, patients in this study were already at high risk of infective endocarditis [e.g., 38.5% (25/65) were drug addicts] [47].

The routine use of TTE in patients with nosocomial *S. aureus* bacteremia is not recommended unless patients have previously known or current clinical evidence of valvular heart disease [32]. Indications for TTE have included patients with suspected endocarditis, community-acquired *S. aureus* bacteremia, especially diabetic patients [32,61].

The transesophageal echocardiogram (TEE) is more sensitive than TTE for the detection of vegetations and is safe [61,62]. TEE has been recommended whenever endocarditis is strongly suspected and the results of the TTE are negative or equivocal, and is especially valuable in patients with prosthetic valves [61]. TEE is also more sensitive for the detection of two important complications of endocarditis: abscesses and valve perforations [63,64].

Three echocardiographic findings have been cited

as major criteria for the diagnosis of endocarditis: 1. an oscillating intracardiac mass located at sites where vegetations typically occur, such as on valves, chordae, or in the path of turbulent jets of blood passing through incompetent valves or septal defects. Ruptured chordae and stable healed vegetations from previous episodes of infective endocarditis should be excluded, 2. an intracardiac abscess, and 3. new partial dehiscence of a prosthetic valve [65]. Given the widespread use of TEE, elimination of the minor criterion "echocardiogram consistent with infective endocarditis but not meeting major criterion" was strongly recommended recently [66].

For right-sided *S. aureus* endocarditis, patients with TTE-confirmed vegetations experienced prolonged febrile morbidity (mean = 12.3 days) as compared to that of patients without vegetations (mean = 6.8 days) ($p < 0.005$) [67]. Furthermore, 91% (20/22) of patients with prolonged fever (fever for more than 10 days while receiving appropriate therapy without identifiable causes) had tricuspid vegetations versus 58% (18/31) with fever response had tricuspid vegetations ($p = 0.009$) [67]. Patients with vegetations larger than 2 cm on TTE fared significantly worse than their counterparts with smaller vegetations; six of 18 patients with vegetations larger than 2 cm died, as opposed to only two of 80 patients with smaller vegetations ($p < 0.0005$) [68]. The echocardiographic-clinical correlation has not been specifically examined in a large subset of patients with left-sided *S. aureus* endocarditis.

MRSA versus MSSA

Although a plethora of clinical studies have demonstrated the virulence of MRSA strains, it has been shown that many MRSA strains are neither highly contagious nor possessing virulence determinants. Collopy has suggested that MRSA organisms are somewhat more likely to be colonizing bacteria, while MSSA organisms are more likely to be associated with infection [69]. On the other hand, persistent MRSA nasal carriage in patients in a long-term-care facility was significantly more likely to result in serious staphylococcal infection than MSSA carriage [70]. An important confounding factor is the fact that MRSA strains are more likely to be found in sicker patients with more severe underlying disease receiving multiple prior antibiotics.

MRSA strains did not differ from MSSA strains in intraleukocyte survival or phagocytic destruction, animal lethality studies, or production of extracellular hemolysins, enzymes, or toxins [71,72]. The morbidity and mortality of bacteremic infection due to MSSA and MRSA seem to be similar in most studies, regardless of antibiotic treatment [37,73]. Although the mortality of MRSA endocarditis was significantly higher than MSSA endocarditis, higher apache III score was the independent risk factor for mortality [50].

Factors predict mortality

S. aureus bacteremia is still associated with a high mortality, ranging from 17% to 43% [33,35,37,46,48]. Complicated bacteremia, such as endocarditis, shock, and secondary foci, i.e., central nervous system and pulmonary infection have been shown to affect adversely survival from *S. aureus* bacteremia [3,29,33, 46,48]. Old age, rapidly fatal underlying diseases, and pre-existing cardiovascular disease were shown to have a poor prognosis in both *S. aureus* bacteremia and endocarditis [33,35,37,48]. *S. aureus* bacteremia and/ or endocarditis acquired in the hospital or prior hospitalization within 30 days of onset of illness and delay in treatment was associated with high mortality [46]. Primary *S. aureus* bacteremia as well as phage type 95 were also considered as poor prognostic factors in individual studies [3,74]. Treatment with vancomycin (as opposed to ß-lactams) has also been suggested as a poor prognostic factor for MSSA bacteremia [6].

Conclusion

Although there are evidences that suggests vancomycin may not be as effective as nafcillin/oxacillin for treatment of *S. aureus* bacteremia and endocarditis, the observations are retrospective and the numbers are too small to draw firm conclusions. Evaluation of antibiotic therapy requires a large number of patients to be enrolled, because subgroup analyses must also control for therapeutic variables including combination of gentamicin and rifampin and duration of antibiotic therapy. Recently, three echocardiographic findings have been cited as the major criteria for the diagnosis of endocarditis (i.e., Duke criteria). Echocardiogram will provide valuable information for the decision of both surgical intervention and duration of antibiotic therapy. Therefore, if the TTE is negative or equivocal, the application of TEE is encouraged. Since bacteremia and endocarditis caused by *S. aureus* will continue to be an important infectious disease in the 2000s, more prospective studies to address the issues highlighted in this article are required.

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