Staphylococcus aureus Infections: New Challenges from an Old Pathogen

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Introduction

Despite major advances in the medical arena, Staphylococcus aureus remains an important agent of infectious diseases in the human host. Its significance lies in its widespread existence and the broad spectrum of infections it can produce, ranging from inconsequential superficial skin infections to deep-seated life-threatening systemic infections. Indeed, some infections caused by S. aureus, namely bacteremia and endocarditis, are frequently associated with serious complications and high mortality rates. The emergence of antibiotic resistance has brought renewed attention to staphylococci. Methicillin-resistant S. aureus (MRSA) rates both in hospitalized and ambulatory patients have been escalating, and this resistant phenotype is now considered a major public health problem. Reduced susceptibility to other antimicrobials, including glycopeptides, is being increasingly rec-
ogized and further complicates the treatment of staphy-
lococcal infections.

In this review, the authors report on the current trends in the epidemiology, diagnosis, clinical syndromes, and management of *S. aureus* infections in light of the organ-
ism’s evolving antimicrobial resistance pattern.

**Microbiology**

*Staphylococcus aureus* belongs to the Micrococcaeae family. It is a nonmotile, non-spore forming, gram-positive coccus that may occur singly, or in pairs, short chains, or grape-like clusters. It is a facultative anaerobe, but grows better under aerobic than anaerobic conditions. The or-
ganism produces catalase and coagulase and grows readi-
ly on blood and chocolate agar. Colonies measure 1 to 3 mm and typically produce a yellow to golden pigment due to the presence of carotenoids. Most strains produce hemolysis within 24 to 36 hours on horse, sheep, or hu-
man blood agar plates.

**Epidemiology**

Worldwide epidemics of *S. aureus* disease have been rec-
ognized over the years. Outbreaks have been reported in a variety of settings, including hospitals, long-term care facilities and outpatient clinics, as well as in the community.

**Nosocomial Infections**

Staphylococci have been long recognized as a problem on hospital wards, and the policy of routine ongoing surveil-
ance for hospital-acquired staphylococcal disease is well justified. *S. aureus* is the leading cause of postoperative wound infection, and the second most frequent cause of nosocomial pneumonia and bacteremia. Together, *S. au-
reas* and coagulase-negative staphylococci account for 21% of the estimated 4 million infections acquired annually in United States hospitals. *S. aureus* nosocomial infections entail great expenditure. Over a two-year period from 2000 to 2001, the average cost of hospitalization in 984 US hospitals for patients with *S. aureus* infections was $48,654 compared to $14,144 for patients without such in-
fekions. In another study, the mean infection-related costs in patients with prosthetic devices and *S. aureus* bac-
teriaemia (SAB) amounted to $67,439 for hospital-acquired infections and $57,868 for community-acquired infections. In addition to the substantial economic burden, significant morbidity and mortality are associated with staphylococcal infections, particularly with invasive infections where mor-
tality rates range between 19% and 34%.

**Community-acquired infections**

*Staphylococcus aureus* infections are commonly ac-
quired outside the hospital, particularly among colonized individuals, and have been reported for several deca-
des. However, the prevalence of infections caused by MRSA isolates has increased significantly. A Texas-based study in children noted a 14-fold increase in the rate of community-acquired MRSA infections in 2002 compared to previous years. Similarly among adults, the incidence of community-acquired staphylococcal infections varied from 29% in 1997 to 74% in 2002. In addition, recent studies have demonstrated a substantial increase in the rate of nasal colonization with MRSA in the community, from 0.8% in 2001 to 9.2% in 2004.

**Nasal carriage**

*Staphylococcus aureus* may be carried by normal people at various body sites without causing disease. This condi-
tion is referred to as colonization to distinguish it from actual infection. It should be noted, however, that colo-
nization frequently precedes infection in susceptible pa-
tients. The anterior nares are the principal site of colon-
ization with three distinct patterns in the population: persistent carriers (20%), intermittent carriers (60%), or noncarriers (20%). Whereas 10%-20% of healthy adults are persistently colonized with *S. aureus*, populations with higher colonization rates include patients with atopic dermatitis (up to 85%), as well as surgical patients, hem-
modialysis patients, HIV-infected patients, and those with intravascular devices. Health care workers who come in contact with patients colonized or infected with *S. aureus* have higher rates of nasal carriage than providers without such contact, and they may develop clinical disease following colonization. In turn, colonized health care workers can serve as vehicles for the trans-
mission of *S. aureus* to patients. In fact, nosocomial out-
breaaks are frequently attributed to colonization of the nares and hands of health care workers.

**Antimicrobial Resistance Trends**

The propensity of *S. aureus* to develop resistance to virtually all the antimicrobial agents available to date has had a monumental impact on clinical infectious diseases. The pre-
sent day epidemiology of staphylococcal infections has been shaped to a great extent by the rising antibiotic resistance rates commensurate with selective antibiotic pressure.

**Resistance to beta-lactams**

The first report of penicillinase-producing *S. aureus* was published in 1940, almost a year before penicillin was marketed for clinical use. Since then, beta-lacta-
mase mediated penicillin resistance has been widely de-
scribed among *S. aureus* isolates, with 90%-95% resis-
tance rates currently reported in the hospital and the community. Penicillin-stable cephalosporins and semisynthetic penicillins were introduced in the late 1950s. Once again, *S. aureus* was quick to develop resistance and MRSA iso-
lates were described shortly thereafter. Methicillin resis-
tance has been steadily increasing. According to data from the National Nosocomial Infections Surveillance (NNIS) System, the prevalence of MRSA among hospitalized pa-
tients rose from 31.9% in 1996 to 60.7% in 2004 (fig. 1). Similar trends have been observed worldwide, although ac-
tual MRSA prevalence is subject to wide geographical varia-
tion. For instance, in Europe, MRSA rates as high as 58% in Scandinavia and 54% in Portugal have been recently report-
ed. In Japan, nearly 70% of *S. aureus* bloodstream isolates in 2001 were methicillin-resistant. On the other hand, Scandinavian countries have MRSA prevalence rates of over 50%. Several risk factors have been indepen-
S. aureus (VRSA) have acquired the VanA resistance gene from ultrasonicate, whole and other distinct bac-
teremia has 111 isolates Enferm Infecc Microbiol Clin 2006;24(3):182-93 grows on ordinary laboratory infections and various patient 4) have
Temporal trends of MRSA rates according to data from the NNIS epidemic proportions (CA-MRSA) has quickly become a public health problem of healthcare-associated bacteremia that USA300, the most common CA-MRSA clone in the community-acquired MRSA rates vary from 18.0 to 25.7 cases per 100,000 population. In addition, a recent meta-analysis reported a 30.2% rate of community-onset MRSA infections from 27 studies. These figures, however, include outpatients with healthcare-associated infections. When applying strict definitions and excluding patients with healthcare-associated risk factors, CA-MRSA rates have been described. Susceptible populations include children in day care centers, athletic teams, Native American communities, military personnel, and prison inmates. Patients with CA-MRSA commonly present with suppurative skin infections or nontuberculous pneumonia. The ability of the organism to produce such invasive infections has been associated with Panton-Valentine leukocidin (PVL), a hemolysin encoded by a pvl gene in clinical strains. Recent reports document that the epidemiology of CA-MRSA is increasingly blurring with that of hospital-acquired MRSA. A recent report from Atlanta documented that USA300, the most common CA-MRSA clone in the United States, is also a frequent cause of nosocomial and healthcare-associated bacteremia.

The effect of methicillin resistance on patient outcome has been a matter of intense debate. A number of studies addressing this issue have noted conflicting results in the setting of various S. aureus infections and various patient populations (table 1). Whether the deleterious effect of MRSA observed in some of these studies is due to inherent virulence of the resistant strains or rather related to failure of vancomycin therapy must be overcome with high doses of vancomycin. Conversely, vancomycin-resistant S. au-
reus (VISA) have acquired the VanA resistance gene from enterococcal species and therefore do not exhibit a dose-de-
pendent resistance to vancomycin. Although vanco-
mycin resistance rates are still low, the emergence of such strains might be inevitable, especially with the continued pressure posed by intense glycopeptide use.

**Diagnosis**

Sites of staphylococcal infection are usually teeming with organisms. S. aureus grows on ordinary laboratory media and can be readily recognized on Gram stains from most clinical specimens. Definitive identification then relies on the tube or slide coagulase test followed by antibiotic susceptibility testing through disk diffusion or tube-dilution techniques. This method for MRSA identification relies on growing the organism in culture and then performing susceptibility testing; therefore it can be performed within 48-72 hours. Recently developed polymerase chain reaction (PCR) assays can differentiate between methicillin and resistant strains with a more rapid means for identifying MRSA isolates, and are espe-
cially valuable in detecting nasal colonization and blood-
stream infections. Similar assays can now detect the pvl gene in clinical S. aureus isolates.

During outbreaks, phage typing of staphylococci is useful for recognizing the epidemic strain. More recently, molecular typing methods have provided reliable results. These include restriction endonuclease analysis of plas-
mid DNA and polymerase chain reaction amplification of selected DNA sequences.

The serological diagnosis of S. aureus bacteremia has been evaluated. Antibodies to a variety of staphylococcal antigens have been tested including peptidoglycan, te-
ichoic acid, S. aureus zymosanase, white S. aureus cell alpha-toxin, lipase and capsular polysaccharide. Whole cell ELISA has been shown to be the most sensitive assay although all tests lacked specificity. Studies suggest that the presence of antibodies to S. aureus teichoic acid might indicate a chronic deep seated infection, including endo-
carditis, chronic osteomyelitis, and septic arthritis, where-as patients with uncomplicated bacteremia, acute os-
Infections: New Challenges from an Old Pathogen

Community-acquired bacteremia
- Higher mortality, increased risk of persistent bacteremia and renal insufficiency with MRSA

Nosocomial bacteremia
- Higher mortality with MRSA

Bacteremia in cancer patients
- No effect on outcome

Ventilator-associated pneumonia
- No effect on ICU or hospital mortality

Musculoskeletal infections in children
- Greater febrile days and hospital days with MRSA, no effect

Bloodstream infections
- Longer hospital stay and higher costs of hospitalization with MRSA

Bacteremia (meta-analysis)
- Increased mortality with MRSA

Various infections
- Worse clinical and economic outcomes with MRSA

Bacteremia in HD patients
- Higher mortality, longer hospital stay, higher inpatient costs with MRSA

Post-sternotomy mediastinitis
- No difference in duration of mechanical ventilation or ICU mortality

Selection of studies comparing outcomes of patients with bloodstream infections with respect to methicillin resistance

TABLE 1. Selection of studies comparing outcomes of patients with S. aureus infections with respect to methicillin resistance

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Setting</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austin et al117</td>
<td>Bacteremia</td>
<td>Trend towards increased attributable mortality with MRSA</td>
</tr>
<tr>
<td>Blot et al118</td>
<td>Bacteremia in critically ill patients</td>
<td>Higher attributable mortality with MRSA</td>
</tr>
<tr>
<td>Chang et al119</td>
<td>Community-acquired bacteremia</td>
<td>Higher mortality, increased risk of persistent bacteremia and renal insufficiency with MRSA</td>
</tr>
<tr>
<td>Combsa et al120</td>
<td>Post-sternotomy mediastinitis</td>
<td>No difference in duration of mechanical ventilation or ICU mortality</td>
</tr>
<tr>
<td>Corvo et al121</td>
<td>Bloodstream infections</td>
<td>Longer hospital stay and higher hospital charges with MRSA</td>
</tr>
<tr>
<td>Encman et al122</td>
<td>Nosocomial infections</td>
<td>Increased hospital stay with MRSA, no effect on mortality</td>
</tr>
<tr>
<td>Engemann et al123</td>
<td>Surgical site infections</td>
<td>Increased mortality and hospital charges with MRSA</td>
</tr>
<tr>
<td>Hurbarth et al124</td>
<td>Bacteremia</td>
<td>No effect on in-hospital mortality</td>
</tr>
<tr>
<td>Hershow et al125</td>
<td>Nosocomial infections</td>
<td>No effect on outcome</td>
</tr>
<tr>
<td>Kopp et al126</td>
<td>Various infections</td>
<td>Worse clinical and economic outcomes with MRSA</td>
</tr>
<tr>
<td>Lodise et al127</td>
<td>Bacteremia</td>
<td>Increased length of stay and higher costs of hospitalization with MRSA</td>
</tr>
<tr>
<td>Martínez-Aguilar et al128</td>
<td>Musculoskeletal infections in children</td>
<td>Greater febrile days and hospital days with MRSA, no effect on final outcome</td>
</tr>
<tr>
<td>Marty et al129</td>
<td>Bacteremia in cancer patients</td>
<td>No effect on outcome</td>
</tr>
<tr>
<td>Mekontso-Dessap et al130</td>
<td>Post-sternotomy mediastinitis</td>
<td>Worse clinical outcome and higher overall mortality with MRSA</td>
</tr>
<tr>
<td>Melgar et al131</td>
<td>Nosocomial bacteremia</td>
<td>Trend towards increased mortality with MRSA, no effect on risk of dissemination</td>
</tr>
<tr>
<td>Reed et al132</td>
<td>Bacteremia in HD patients</td>
<td>Higher mortality, longer hospital stay, higher inpatient costs with MRSA</td>
</tr>
<tr>
<td>Romero-Vivas et al133</td>
<td>Nosocomial bacteremia</td>
<td>Higher mortality with MRSA</td>
</tr>
<tr>
<td>Selvey et al134</td>
<td>Nosocomial bacteremia</td>
<td>No difference in mortality</td>
</tr>
<tr>
<td>Whitby et al135</td>
<td>Bacteremia (meta-analysis)</td>
<td>Increased mortality with MRSA</td>
</tr>
<tr>
<td>Yoon et al136</td>
<td>Infective endocarditis</td>
<td>Higher risk of persistent bacteremia and trend towards higher mortality with MRSA</td>
</tr>
<tr>
<td>Zahar et al137</td>
<td>Ventilator-associated pneumonia</td>
<td>No effect on ICU or hospital mortality</td>
</tr>
</tbody>
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MRSA: methicillin-resistant S. aureus; HD: hemodialysis; ICU: intensive care unit.

Clinical Syndromes

Virtually any organ system is prone to infection with S. aureus. This review does not present an exhaustive discussion of all the clinical manifestations of staphylococcal infections as these are reviewed elsewhere. We rather focus on systemic infections that have been associated with significant morbidity and mortality and that represent diagnostic and therapeutic challenges for clinical infectious disease specialists.

Bacteremia

Staphylococcus aureus bacteremia is now classified into three categories: hospital-acquired, health-care-associated, and community-acquired SAB. Hospital-acquired and health-care associated infections exhibit similar epidemiological characteristics: both are related to comparable risk factors, such as intravascular devices and comorbid conditions. On the other hand, community-acquired SAB traditionally afflicts intravenous drug users and otherwise healthy patients with infections at various sites. Resistance is more apparent in hospital-acquired (61%) and health-care as-
associated SAB (52%) than in community-acquired SAB (14%) (P < 0.01) [7].

Approximately one-third of patients with SAB develop one or more complications [15,19,21]. Acute systemic complications typically manifest within 48 hours of diagnosis; these include septic shock, acute respiratory distress syndrome, and disseminated intravascular coagulation. On the other hand, metastatic complications of SAB may only become evident several weeks later. In one large retrospective study, common sites of metastatic disease were joints (36%), kidneys (29%), central nervous system (28%), skin (11%), intravascular catheters (9%), heart valve (13%), bone (11%), and heart valves (8%). Importantly, more than one metastatic site of infection was present in half of the cases. Distant foci of infection in SAB develop preferentially in populations with certain predisposing conditions: 1) Underlying cardiac disease, such as native valvular abnormalities, congenital heart disease, and prior infective endocarditis [10,13]; 2) Prosthetic implants, such as prosthetic valves [12], intracardiac devices [14,15], and orthopedic implants [16]; 3) Community-acquired SAB, due in part to the typically prolonged disease course and duration of bacteremia prior to detection [17,18]; 4) Old age [19] and comorbid conditions such as hemodialysis [20] and infection with the human immunodeficiency virus [21]. The absence of the aforementioned risk factors, however, does not exclude the presence of metastatic disease.

Endocarditis

Infective endocarditis (IE) complicates the course of SAB in ~12% of cases [7,14,16]. In a recent large cohort of patients, S. aureus was the most common cause of native valve endocarditis [16]. Recent years have witnessed a rise in the rates of IE due to S. aureus [10,14,16]. S. aureus is now the leading cause of IE in many parts of the world [22]. This trend is mostly attributed to the increasing prevalence of healthcare-associated S. aureus [16] that has accompanied the growing use of interventional procedures, intravascular catheters, and implantable devices [17,18]. For instance, Fernandez-Guerrero et al reported a 10-fold increase in the number of cases of hospital-acquired IE compared to the number of cases occurring from 1960 to 1975 [23]. The increasing frequency of S. aureus IE can also be ascribed to better recognition of the disease through the widespread application of echocardiography in evaluating patients with SAB [19].

Endocarditis in patients with SAB frequently involves normal cardiac valves and is seldom accompanied by the physical stigmata of IE, rendering the diagnosis of the disease difficult [16,17]. In fact, reliance solely upon physical examination findings is likely to result in underдиagno10,13. The use of echocardiography has been advocated to evaluate patients with SAB. Despite its limited sensitivity in detecting vegetations (64%), transthoracic echocardiography (TTE) is a widely available, non-invasive screening modality in the setting of SAB [16]. Conversely, transesophageal echocardiography (TEE) offers significant advantages over TTE, including higher sensitivity in identifying IE (90% [11], improved identification of IE complications [15,17], and an enhanced ability to exclude IE in patients with native valves (negative predictive value 100%) [11].

Whether TTE or TEE should be employed in the initial screening of the patient presenting with SAB remains a controversial issue [15,17]. TEE is currently highly favored at our institution for the evaluation of most patients with SAB. The authors believe that TEE is likely to be cost-effective to guide duration of therapy in patients with intravascular catheter-associated SAB [24] or for patients at higher risk for IE or associated complications [25].

Despite early diagnosis and appropriate therapy, IE following SAB is often associated with devastating and life-threatening sequelae. The overall mortality of S. aureus IE ranges from 15% to 19% [26,27]. Other complications include heart failure (20%-50%) [28,29,30,31], paravalvular cardiac abscesses (30%-40%) [32,33], neurological manifestations (30% [34,35], and systemic embolization (40%) [36].

Pneumonia

Staphylococcus aureus is a significant etiologic agent in lower respiratory tract infections that has become increasingly more common in the hospital setting [37-39]. According to the NNIS System, S. aureus was responsible for 20% of nosocomial pneumonias between 1992 and 1997 [40]. Furthermore, in the European Prevalence of Infection in Intensive Care (EPIC) Study, S. aureus was the predominant infective agent, accounting for 31% of microbiologically proven cases of ventilator-associated pneumonia [41]. Whereas methicillin-susceptible S. aureus (MSSA) is typically encountered in early-onset hospital acquired pneumonia (<5 days after admission), MRSA gains importance in late-onset hospital-acquired pneumonia and particularly in ventilator-associated pneumonia [42,43]. Nosocomial pneumonia due to MRSA entails significant mortality with rates ranging from 38% to 55% [44]. As with other S. aureus infections, whether methicillin resistance by itself contributes to the poor outcome is still a matter of debate [45-47].

In addition to its role as a nosocomially acquired pulmonary pathogen, S. aureus has recently established itself as an emergent threat in the community. Necrotizing pneumonia and sepsis caused by community-acquired MRSA strains carrying pvl genes are being increasingly recognized [48-50]. Afflicted patients are typically healthy individuals without any healthcare contact. These infections are characterized by multifocal involvement of various organs, including lungs, brain, heart, liver, and kidneys. The pathological feature in the lungs is extensive hemorrhagic necrosis of the pulmonary parenchyma [51]. The mean case fatality rate is noted to be as high as 35% [52,53,54,55]. Mortality seems to be tightly linked to the presence of the pvl gene; in a study of S. aureus pneumonia, the mortality rate was 32% in cases with pvl-positive strains, as compared to 6% in those with pvl-negative strains [56].

Staphylococcus aureus pneumonia can present in several different forms, often in parallel with distinct pathophysiological mechanisms: 1) Lobar pneumonia usually occurs as a result of aspiration. Patients are acutely ill with high fevers and productive cough. In severe infections, empyema, abscess formation, cavitation and pneumonia may be present; 2) Late-interstitial pneumonia usually follows microaspiration and often develops in conjunction with, or following viral pneumonia [57].
emboli secondary either to right-sided endocarditis or to soft tissue or joint infection. In this type of *S. aureus* pneumonia, pleuritic chest pain is a hallmark feature whereas cough and sputum production are less likely.

**Novel therapies for MRSA**

The use of beta-lactams in the treatment of *S. aureus* infections has been greatly handicapped by the increasing prevalence of MRSA strains. Although vancomycin, the traditional alternative antimicrobial agent, still maintains in-vitro activity against the majority of MRSA isolates, clinical cure rates in serious infections are disheartening. Treatment failure rates exceeding 40% have been recently quoted for SAB and *S. aureus* pneumonia treated with vancomycin. This has kindled great interest in developing new treatment options for MRSA.

**Quinupristin/dalfopristin**

Quinupristin and dalfopristin belong to the streptogramin class of antibiotics. When combined, these two agents are bactericidal and act in synergy on the 50S ribosomal subunit to inhibit protein synthesis. Quinupristin/dalfopristin is active in-vitro against both MSSA and MRSA. The drug is approved by the Food and Drug Administration (FDA) only for the treatment of complicated skin and skin structure infections (cSSSI) due to MSSA. However, data from a small controlled trial have suggested that quinupristin/dalfopristin is equivalent to vancomycin in the treatment of catheter-related bacteremia caused by *S. aureus* or coagulase-negative staphylococci (50% clinical and bacteriological responses in both groups). Another study compared in a randomized design quinupristin/dalfopristin to vancomycin in the treatment of nosocomial pneumonia. Although both drugs were comparable in clinical efficacy (56% vs. 58%, respectively), the number of episodes of pneumonia caused by *S. aureus* was relatively small in both arms. Quinupristin/dalfopristin has also showed promising results in experimental rat and rabbit models of bacteraemia. The drug is being used considerably in the setting of SAB and endocarditis. Quinupristin is equivalent to vancomycin in the treatment of right-sided endocarditis and has similar clinical efficacy as vancomycin in such infections but was statistically superior to vancomycin with regard to bacterial eradication in patients with confirmed MRSA at baseline. More recently, linezolid obtained FDA approval for the treatment of nosocomial pneumonias. According to a recent pooled analysis of randomized studies, linezolid was not inferior to vancomycin in the treatment of SAB (55% vs. 52%, respectively for overall cure rate). The use of linezolid in MRSA endocarditis has had conflicting results. Although some reports described successful outcomes, there have been recent cases of clinical failure (one of which was fatal) with linezolid despite favorable in-vitro susceptibility results. Consequently, the authors do not recommend the use of linezolid in the setting of MRSA endocarditis regardless of the antimicrobial susceptibility of the isolate.

**Daptomycin**

Daptomycin is a cyclic lipopeptide with rapid bactericidal activity against MRSA. It exerts its action by inserting itself into the bacterial cell membrane. Subsequent events that lead to bacterial cell killing are not fully understood but are thought to involve dissipation of membrane potential. Daptomycin is FDA-approved for the treatment of cSSSI due to *S. aureus* including MRSA. In two distinct Phase III trials in patients with cSSSI, daptomycin resulted in similar success rates as its comparators—semi-synthetic penicillin or vancomycin (71.5% and 71.1%, respectively). Despite lacking a formal indication, daptomycin is used considerably in the setting of SAB and *S. aureus* endocarditis. Currently, Phase III trials are being conducted to evaluate the efficacy of daptomycin in staphylococcal bloodstream infections. Daptomycin is not indicated in the treatment of pneumonia: the drug is inhibited by pulmonary surfactant and proved to be inferior to ceftazidime in a Phase III trial.

**Tigecycline**

Tigecycline is a newly introduced glycycloline derivative with structural homology to tetracyclines. This drug offers broad-spectrum antimicrobial coverage including MRSA through binding to the 30S ribosomal subunit. Tigecycline has received FDA approval for the treatment of complicated intra-abdominal infections. In addition, animal models have shown promising results with tigecycline compared to vancomycin in MRSA endocarditis.

**Dalbavancin**

Dalbavancin is a semisynthetic glycopeptide characterized by a long half-life (9-12 days) that allows once-weekly administration. It exerts its potent activity against MRSA via inhibition of cell wall synthesis. Dalbavancin has shown positive results in Phase III studies in cSSSI and in a Phase II study in catheter-related bloodstream infections. It is currently awaiting FDA approval for these indications.

**Telavancin**

Telavancin is an experimental lipoglycopeptide molecule characterized by two mechanisms of action: inhibition of bacterial peptidoglycan synthesis; and alteration of bacterial cell membrane permeability and depolarization. Telavancin exhibits bactericidal in-vitro activity against *S. aureus* isolates including MSSA, MRSA and VISA isolates. In animal infection models, telavancin was efficacious in the treatment of various MRSA infections including soft tissue infections, pneumonia, and endocarditis. In Phase II clinical trials, telavancin was compared to stan...
dard therapy (semisynthetic penicillin or vancomycin) in patients with cSSSI. Data from this study showed that telavancin was equivalent to standard therapy both in clinical cure in the all treated population (79% vs. 80%) as well as in microbiological eradication in the MRSA subgroup (82% vs. 80%; P=0.43). Phase III trials designed to demonstrate superiority over vancomycin are currently under- way in patients with cSSSI, uncomplicated bacteremia, and hospital-acquired pneumonia.

Immunotherapy

Since microbial adherence is central to the initiation and metastatic spread of *S. aureus*, the MSCRAMM (microbial surface components recognizing adhesive matrix molecules) family of bacterial surface adhesion proteins represents an excellent target for the development of novel immunothera-
pies. Tefibazumab is a humanized IgG monoclonal antibody with high affinity to clumping factor A, an MSCRAMM pro-
tein common to virtually all *S. aureus* strains. It interferes with *S. aureus* adherence to extracellular matrix proteins in vitro and may enhance opsonophagocytosis of *S. aureus* by polymorphonuclear leukocytes. In an animal model of *S. aureus* IE, addition of tefibazumab to vancomycin significa-
tically increased bacterial clearance from the bloodstream when compared to vancomycin alone (P<0.001). The re-
results of a Phase II randomized, double-blind, multi-center clinical study of tefibazumab in patients with SAB were re-
cently presented.

Prevention

Nasal decolonization

Since MRSA nasal colonization frequently precedes in-
feccion, endeavors to contain the transmission of MRSA have targeted the eradication of nasal carriage in suscep-
tible patients. Studies evaluating this strategy have yield-
ed conflicting results. Cardiothoracic surgery patients who received mupirocin prophylaxis had a lower surgical wound infection rate than historical controls (7.3% vs. 2.8%; P<0.001). More recently, combining results from two randomized trials in surgical patients suggested that the administration of mupirocin in surgical patients re-
duced postoperative nosocomial *S. aureus* infections as compared to placebo (RR 0.49, 95% CI 0.29-0.83; number needed to treat 26). Boelaert et al found a four- to six-fold reduction in SAB rates in hemodialysis patients who received mupirocin prophylaxis when compared to placebo (P<0.008). The re-
sults of a Phase II randomized, double-blind, multi-center clinical study of tefibazumab in patients with SAB were re-
cently presented.

Vaccination

*Staphylococcus aureus* Polyvalent Conjugate Vaccine (StaphVax®; Nahi Biopharmaceuticals, Rockville, MD) is an investigational polyvalent polysaccharide conjugate vaccine that presents a novel approach to the prevention of *S. aureus* in-
fections. It consists of type 5 and type 8 capsular polysac-
charides, the strains accounting for more than 80% of infec-
tions. In one double blinded, placebo-controlled Phase III clinical efficacy trial involving 1904 hemodialysis-dependent patients, StaphVax recipients failed to meet the a priori endpoint of reduction in episodes of *S. aureus* bacteremia at 54 weeks. However, post hoc analysis revealed a 57% re-
duction in SAB episodes at 10 months compared to placebo recipients (P=0.015). Based on these findings, a second Phase III confirmatory trial, with modified time points, was undertaken. However, this second trial also failed to meet its primary endpoint. As a result, all clinical trial develop-
ment and further marketing of StaphVax have been held until assessment of the results is completed.

Infection control strategies

Several studies have established that the transmission of MRSA between patients within the hospital setting occurs to a great extent through health care workers. Consequently, the Centers for Disease Control and Prevention (CDC) recommend the implementation of contact precau-
tions in patients colonized or infected with MRSA. Such precautions include the use of private rooms, protectiv-
ve attire for health care workers, and strict adherence to hand hygiene principles. There is abundant evidence to support the efficacy of these infection control programs in reducing the transmission of resistant pathogens within the hospital.

Although active surveillance for MRSA and preemptive isolation of colonized or infected patients remains an integral part of many hospital infection control programs, observance of infection control guidelines has been suboptimal. Hand hygiene practices have been particularly inadequate. Accordingly, continuous ef-
forts should be made to improve compliance with isolation and hand hygiene policies to prevent the dire consequences of nosocomial MRSA transmission.

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