**Staphylococcus aureus** Infections: New Challenges from an Old Pathogen

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*Staphylococcus aureus* is a versatile organism with several virulent characteristics and resistance mechanisms at its disposal. It is also a significant cause of a wide range of infectious diseases in humans. *S. aureus* often causes life-threatening deep seated infections like bacteremia, endocarditis and pneumonia. While traditionally confined mostly to the hospital setting, methicillin-resistant *S. aureus* (MRSA) is now rapidly becoming rampant in the community. Community-acquired MRSA is particularly significant because of its potential for unchecked spread within households and its propensity for causing serious skin and pulmonary infections. Because of the unfavorable outcome of many MRSA infections with the standard glycopeptide therapy, new antimicrobial agents belonging to various classes have been introduced and have been evaluated in clinical trials for their efficacy in treating resistant staphylococcal infections. A number of preventive strategies have also been suggested to contain the spread of such infections. In this review, we address the recent changes in the epidemiology of *S. aureus* and their impact on the clinical manifestations and management of serious infections. We also discuss new treatment modalities for MRSA infections and emphasize the importance of preventive approaches.

**Key words:** *Staphylococcus aureus*. Methicillin resistance. Community-acquired MRSA. Nosocomial infections. Antimicrobial therapy.

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Infections in light of the organism's evolving antimicrobial resistance pattern.

**Microbiology**

*Staphylococcus aureus* belongs to the Micrococccae 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 organism produces catalase and coagulase and grows readily 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 human blood agar plates.

**Epidemiology**

Worldwide epidemics of *S. aureus* disease have been recognized 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 surveillance 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. aureus* 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 894 U.S. hospitals for patients with *S. aureus* infections was $48,634 compared to $14,141 for patients without such infections. In another study, the mean infection-related costs in patients with prosthetic devices and *S. aureus* bacteremia (SAB) amounted to $67,439 for hospital-acquired infections and $57,368 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 mortality rates range between 19% and 34%.

**Community-acquired infections**

*Staphylococcus aureus* infections are commonly acquired outside the hospital, particularly among colonized individuals, and have been reported for several decades. 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 condition is referred to as colonization to distinguish it from actual infection. It should be noted, however, that colonization frequently precedes infection in susceptible patients. The anterior nares are the principal site of colonization 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, hemo-dialysis 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. In turn, colonized health care workers can serve as vehicles for the transmission of *S. aureus* to patients. In fact, nosocomial outbreaks 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 present-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-lactamase-mediated penicillin resistance has been widely described among *S. aureus* isolates, with 90%-95% resistance rates currently reported in the hospital and the community. Penicillinase-stable cephalosporins and semisynthetic penicillins were introduced in the late 1950s. Once again, *S. aureus* was quick to develop resistance and MRSA isolates were described shortly thereafter. Methicillin resistance has been steadily increasing. According to data from the National Nosocomial Infections Surveillance (NNIS) System, the prevalence of MRSA among hospitalized patients rose from 31.9% in 1996 to 60.7% in 2004 (fig. 1). Similar trends have been observed worldwide, although actual MRSA prevalence is subject to wide geographical variation. For instance, in Europe, MRSA rates as high as 58.0% in Italy and 54.0% in Portugal have been recently reported. In Japan, nearly 70% of *S. aureus* bloodstream isolates in 2001 were methicillin-resistant. On the other hand, Scandinavian countries have consistently noted very low rates of MRSA. Several risk factors have been indepen-
S. aureus isolates with intermediate and high-level resistance to glycopeptides have been identified. Different mechanisms account for the two types of resistance. Vancomycin-intermediate S. aureus (VISA) harbors mutations that result in thickening of the peptidoglycan layer. Such resistance might be overcome with high doses of vancomycin.

**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 has a turnaround time of 48-72 hours. Recently developed polymerase chain reaction (PCR) assays provide a more rapid means for identifying MRSA isolates, and especially valuable in detecting nasal colonization and bloodstream 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 plasmid DNA, pulsed-field gel electrophoresis of 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, teichoic acid, S. aureus autolysate, whole 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 endocarditis, chronic osteomyelitis, and septic arthritis, whereas patients with uncomplicated bacteremia, acute os-
We. Nosocomial bacteremia. Higher mortality with MRSA infections with respect to methicillin resistance. Infections: New Challenges from an Old Pathogen. Nosocomial infections. Increased hospital stay with MRSA, no effect on mortality. 85. Various infections. Worse clinical and economic outcomes with MRSA. Bacteremia. No effect on in-hospital mortality. Infective endocarditis. Higher risk of persistent bacteremia and trend towards higher bloodstream infections. Longer hospital stay and higher hospital charges with MRSA. Post-sternotomy mediastinitis. No difference in duration of mechanical ventilation or ICU mortality. Post-sternotomy mediastinitis. Worse clinical outcome and higher overall mortality with MRSA. Bacteremia (meta-analysis). Increased mortality with MRSA. Ventilator-associated pneumonia. No effect on ICU or hospital mortality. Bacteremia. Trend towards increased attributable mortality with MRSA. Bacteremia. Increased length of stay and higher costs of hospitalization. Bacteremia in cancer patients. No effect on outcome. Surgical site infections. Increased mortality and hospital charges with MRSA. Bacteremia in HD patients. Higher mortality, longer hospital stay, higher inpatient costs. Musculoskeletal infections in children. Greater febrile days and hospital days with MRSA, no effect on final outcome. Bacteremia. No effect on outcome. In patients with significant morbidity and mortality and that represent diagnostic and therapeutic challenges for clinical infectious disease specialists. Bacteremia. 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. In addition, hospital-acquired and health-care associated SAB result in significantly greater mortality rates when compared to community-acquired SAB 29%, 29%, and 16%, respectively. All three SAB categories have increased considerably over the last decade. From 1980 to 1989, rates of SAB reported to the NNIS system increased by 283% in non-teaching hospitals and 176% in large teaching hospitals. By 1998, S. aureus had become the second most common bloodstream isolate, contributing to 16% of all hospital-acquired bacteremias. In Finland, Lyytikainen and colleagues documented a 55% increase in the incidence of SAB from 1995 to 2001, primarily in the elderly. Similarly, community-acquired SAB is being encountered more frequently, particularly with the increasing prevalence of pvl-bearing MRSA isolates in individuals without health-care contact. Another notable trend in SAB has been the spread of antimicrobial resistance. MRSA rates have recently witnessed a prominent rise as a result of widespread antibiotic use and poor adherence to infection control precautions; approximately 30% of SAB isolates in the United States are now methicillin-resistant. Resistance is more apparent in hospital-acquired (61%) and health-care associ-

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>
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<tbody>
<tr>
<td>Austin et al' 14</td>
<td>Bacteremia</td>
<td>Trend towards increased attributable mortality with MRSA</td>
</tr>
<tr>
<td>Blot et al' 15</td>
<td>Bacteremia in critically ill patients</td>
<td>Higher attributable mortality with MRSA</td>
</tr>
<tr>
<td>Chang et al' 16</td>
<td>Community-acquired bacteremia</td>
<td>Higher mortality, increased risk of persistent bacteremia and renal insufficiency with MRSA</td>
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<tr>
<td>Combes et al' 17</td>
<td>Post-sternotomy mediastinitis</td>
<td>No difference in duration of mechanical ventilation or ICU mortality</td>
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<tr>
<td>Combes et al' 18</td>
<td>Bacteremia</td>
<td>No effect on in-hospital mortality</td>
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<tr>
<td>Cosgrove et al' 19</td>
<td>Nosocomial infections</td>
<td>Increased hospital stay with MRSA, no effect on mortality</td>
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<tr>
<td>Enneking et al' 20</td>
<td>Surgical site infections</td>
<td>Increased mortality and hospital charges with MRSA</td>
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<tr>
<td>Harbarth et al' 21</td>
<td>Bacteremia</td>
<td>No effect on outcome</td>
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<tr>
<td>Hershow et al' 22</td>
<td>Nosocomial infections</td>
<td>No effect on outcome</td>
</tr>
<tr>
<td>Kopp et al' 23</td>
<td>Various infections</td>
<td>Worse clinical and economic outcomes with MRSA</td>
</tr>
<tr>
<td>Lodew et al' 24</td>
<td>Bacteremia</td>
<td>Increased length of stay and higher costs of hospitalization with MRSA</td>
</tr>
<tr>
<td>Martinez-Aguilar et al' 25</td>
<td>Musculoskeletal infections in children</td>
<td>Greater febrile days and hospital days with MRSA, no effect on outcome</td>
</tr>
<tr>
<td>Marty et al' 26</td>
<td>Bacteremia in cancer patients</td>
<td>No effect on outcome</td>
</tr>
<tr>
<td>Mekontso-Dessap et al' 27</td>
<td>Post-sternotomy mediastinitis</td>
<td>Worse clinical outcome and higher overall mortality with MRSA</td>
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<tr>
<td>Melaner et al' 28</td>
<td>Nosocomial bacteremia</td>
<td>Trend towards increased mortality with MRSA, no effect on risk of dissemination</td>
</tr>
<tr>
<td>Reed et al' 29</td>
<td>Bacteremia in HD patients</td>
<td>Higher mortality, longer hospital stay, higher inpatient costs with MRSA</td>
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<tr>
<td>Romero-Vivas et al' 30</td>
<td>Nosocomial bacteremia</td>
<td>Higher mortality with MRSA</td>
</tr>
<tr>
<td>Selvey et al' 31</td>
<td>Nosocomial bacteremia</td>
<td>No difference in mortality</td>
</tr>
<tr>
<td>Whitby et al' 32</td>
<td>Bacteremia (meta-analysis)</td>
<td>Increased mortality with MRSA</td>
</tr>
<tr>
<td>Yoon et al' 33</td>
<td>Infective endocarditis</td>
<td>Higher risk of persistent bacteremia and trend towards higher mortality with MRSA</td>
</tr>
<tr>
<td>Zahar et al' 34</td>
<td>Ventilator-associated pneumonia</td>
<td>No effect on ICU or hospital mortality</td>
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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.
associated SAB (52%) than in community-acquired SAB (14%) [P = .001] [17].

Approximately one-third of patients with SAB develop one or more complications [13,14]. 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 (18%), intervertebral disk (15%), lungs (15%), liver/spleen (13%), bone (11%), and heart valves (8%). Importantly, more than one metastatic site of infection was present in half of these cases. Distant foci of infection in SAB develop preferentially in populations with certain predisposing conditions: 1) Underlying cardiac disease, such as native valve abnormalities, congenital heart disease, and prior infective endocarditis [10-13]; 2) Prosthetic implants, such as prosthetic valves [14-16], intracardiac devices [17,18], and orthopedic implants [12,17]; 3) Community-acquired SAB, due in part to the typically prolonged disease course and duration of bacteremia prior to detection [19,20]; 4) Old age [19] and comorbid conditions such as hemodialysis [11,14] and infection with the human immunodeficiency virus [11]. 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 [74,14]. In a recent large cohort of patients, S. aureus was the most common cause of native valve endocarditis [4]. Recent years have witnessed a rise in the rates of IE due to S. aureus [140-148] and S. aureus is now the leading cause of IE in many parts of the world. This trend is mostly attributed to the increasing prevalence of healthcare-associated S. aureus IE that has accompanied the growing use of interventional procedures, intravascular catheters, and orthopedic implants [14-17]. For instance, Fernández-Guerrero et al reported a 10-fold increase in the number of cases of hospital-acquired SAB (most of which were due to S. aureus) from 1978 to 1992 compared to the number of cases occurring from 1960 to 1975 [14,19]. 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 [1].

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 [10,11]. In fact, reliance solely upon physical examination findings is likely to result in underdiagnosis of S. aureus IE in a large number of cases [12,13]. Because of the difficulty in clinically identifying S. aureus IE, 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 [15,16]. Conversely, transesophageal echocardiography (TEE) offers significant advantages over TTE, including higher sensitivity in identifying IE (80% vs. 40%, improved identification of IE complications [15,16], and an enhanced ability to exclude IE in patients with native valves (negative predictive value 100%) [17,18].

Whether TTE or TEE should be employed in the initial screening of the patient presenting with SAB remains a controversial issue [19,20]. 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 [14,21] or for patients at higher risk for IE or associated complications [12].

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 19% to 31% [142,143]. Other complications include heart failure (20%-50% [144,145]), paravalvular cardiac abscesses (30%-40%) [144,146], neurological manifestations (50% [146,147]), and systemic embolization (40%) [148].

Pneumonia

Staphylococcus aureus is a significant etiologic agent in lower respiratory tract infections that has become increasingly more common in the hospital setting [21-23]. According to the NNIS System, S. aureus was responsible for 20% of nosocomial pneumonias between 1992 and 1997 [24]. 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 [25]. 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 [24,25]. Nosocomial pneumonia due to MRSA entails significant mortality with rates ranging from 38% to 55% [26,30]. As with other S. aureus infections, whether methicillin resistance by itself contributes to the poor outcome is still a matter of debate [27,28]. 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 [29-34]. 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 [35,173,174]. The mean case fatality rate is noted to be as high as 35% [35,173,174]. 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 [36].

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, caviitation and pneumatoceles may be present [37]. 2) Nosocomial pneumonia usually follows microaspiration and often develops in conjunction with, or following viral pneumonia [38]. 3) Perihilar localized areas of pneumonia are noted with hematogenous seeding of the lungs from septic
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[184,185].

**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[186] and *S. aureus* pneumonia[187] 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[188]. 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[189]. 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[190]. Limited Compassionate Use trials of quinupristin/dalfopristin in patients with cSSSI due to MRSA have resulted in similar success rates as its comparators—semi-synthetic penicillin or vancomycin (71.5% and 71.1%, respectively)[191]. Despite lacking a formal indication, daptomycin is being used considerably in the setting of SAB and *S. aureus* endocarditis[200,201]. 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[192] and proved to be inferior to ceftriaxone in a Phase III trial[211].

**Tigecycline**

Tigecycline is a newly introduced glycyclcline 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 intraabdominal infections[202,203]. In addition, animal models have shown promising results with tigecycline compared to vancomycin in MRSA endocarditis[204].

**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[206] and in a Phase II study in catheter-related bloodstream infections[207]. 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 bacterial 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[212], pneumonia[213], and endocarditis[214]. In Phase II clinical trials, telavancin was compared to stan-
ward 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%; P = 0.45) and in microbiological eradication in the MRSA subgroup (82% vs. 69%; P = 0.043). Phase III trials designed to demonstrate superiority over vancomycin are currently underway 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 adhesin proteins represents an excellent target for the development of novel immunotherapies. Tefazabumab is a humanized IgG monoclonal antibody with high affinity to clumping factor A, an MSCRAMM protein 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 tefazabumab to vancomycin significantly increased bacterial clearance from the bloodstream when compared to vancomycin alone (P < 0.001). The results of a Phase II randomized, double-blind, multi-center clinical study of tefazabumab in patients with SAB were recently presented.

**Prevention**

**Nasal decolonization**

Since MRSA nasal colonization frequently precedes infection, endeavors to contain the transmission of MRSA have targeted the eradication of nasal carriage in susceptible patients. Studies evaluating this strategy have yielded conflicting results. Cardiac surgery patients who received mupirocin prophylaxis had a lower surgical wound infection rate than historical controls (7.3% vs. 2.8%; P < 0.01). More recently, combining results from two randomized trials in surgical patients suggested that the administration of mupirocin in surgical patients reduced postoperative nosocomial S. aureus infections as compared to placebo (RR 0.49, 95% CI 0.29-0.83; number needed to treat 26). mollaret et al found a four- to six-fold reduction in SAB rates in hospitalized patients receiving mupirocin. On the other hand, one study in nonsurgical patients failed to show a benefit from mupirocin prophylaxis with respect to rates of nosocomial S. aureus infections, in-hospital mortality, and duration of hospitalization. Investigators have therefore suggested that a single course of mupirocin may be insufficient in low-risk patients with prolonged exposure. In addition to conflicting messages from clinical trials, the emergence of mupirocin-resistance has also been reported.

**Vaccination**

*Staphylococcus aureus* Polysaccharide Conjugate Vaccine (StaphVax®; Nabi Biopharmaceuticals, Rockville, MD) is an investigational polysaccharide conjugate vaccine that presents a novel approach to the prevention of S. aureus infections. It consists of type 5 and type 8 capsule polysaccharides, the strains accounting for more than 80% of infections. In one double blinded, placebo-controlled Phase III clinical efficacy trial involving 1804 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% reduction 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 development 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 precautions in patients colonized or infected with MRSA. Such precautions include the use of private rooms, protective attire for health care workers, and strict adherence to hand hygiene practices. 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 efforts 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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Staphylococcus aureus bacteraemia in patients who do not abuse intravenous drugs.


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