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

Microbiology

*Staphylococcus aureus* belongs to the *Micrococaceae* 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 years18-21. Outbreaks have been reported in a variety of settings, including hospitals17, long-term care facilities15, and outpatient clinics17, as well as in the community15.

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 justified17-21. *S. aureus* is the leading cause of postoperative wound infection, and the second-most frequent cause of nosocomial pneumonia22 and bacteremia23. Together, *S. aureus* and coagulase-negative staphylococci account for 21% of the estimated 4 million infections acquired annually in United States hospitals24. *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 $14,141 for patients without such infections18. 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 $57,868 for community-acquired infections45. 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%26,27.

Community-acquired infections

*Staphylococcus aureus* infections are commonly acquired outside the hospital, particularly among colonized individuals, and have been reported for several decades28. 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 years31. Similarly among adults, the incidence of community-acquired staphylococcal infections varied from 2% in 1997 to 74% in 200222. 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 200442.

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.4 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%)43. 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%),44 as well as surgical patients45, hemodialysis patients46, and those with intravascular devices46. 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 contact45,46, and they may develop clinical disease following colonization41. 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 workers44,45.

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.

Resistances to beta-lactams

The first report of penicillinase-producing *S. aureus* was published in 1940, almost a year before penicillin was marketed for clinical use47. Since then, beta-lactamase-mediated penicillin resistance has been widely described among *S. aureus* isolates, with 80%-90% resistance rates currently reported in the hospital and the community48-50. 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 thereafter51. 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)52,53. 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 reported52. In Japan, nearly 70% of *S. aureus* bloodstream isolates in 2001 were methicillin-resistant54. On the other hand, Scandinavian countries have reported noted very low rates of MRSA54. Several risk factors have been independent...
S. aureus (VRSA) have acquired the VanA resistance gene from a mobile phage that can be transmitted among various patient populations (table 1). The VanA resistance gene located on a mobile phage that can be transmitted can be found in various patient populations (table 1).


Although initially confined to the hospital setting, MRSA isolates are now increasingly encountered in the community. Over the past decade, community-acquired MRSA (CA-MRSA) has quickly become a public health problem of epidemic proportions. Different mechanisms account for the two types of resistance. Vancomycin-resistant S. aureus (VISA) harbors mutations that result in thickening of the peptidoglycan layer (1). Such resistance might be overcome with high dosages of vancomycin. Conversely, vancomycin-resistant S. aureus (VRSA) have acquired the VanA resistance gene from enterococcal species and therefore do not exhibit a dose-dependent resistance to vancomycin. Although vancomycin 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 has a turnaround time of 48-72 hours. Recently developed polymerase chain reaction (PCR) assays provide a much faster means for identifying MRSA isolates, and especially valuable in detecting nasal colonization and bloodstream infections. Similar assays can now detect the plg 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 enterotoxin, and S. aureus cytolysin. Antibodies to these antigens have been found in patients with uncomplicated bacteremia, acute os-
Bacteremia in cancer patients No effect on outcome

Nosocomial bacteremia Trend towards increased mortality with MRSA, no effect on risk

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

Ventilator-associated pneumonia No effect on ICU or hospital mortality

Nosocomial infections Increased hospital stay with MRSA, no effect on mortality

Post-sternotomy mediastinitis Worse clinical outcome and higher overall mortality with MRSA

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

Surgical site infections Increased mortality and hospital charges with MRSA

Various infections Worse clinical and economic outcomes with MRSA

Bacteremia Increased length of stay and higher costs of hospitalisation with MRSA

Musculoskeletal infections in children Greater febrile days and hospital days with MRSA, no effect on final outcome

Bacteremia in cancer patients No effect on outcome

Post-sternotomy mediastinitis Worse clinical outcome and higher overall mortality with MRSA

Bacteremia in HD patients Trend towards increased mortality with MRSA, no effect on risk of dissemination

Nosocomial bacteremia Higher mortality, longer hospital stay, higher inpatient costs with MRSA

Nosocomial bacteremia Higher mortality with MRSA

Bacteremia Trend towards increased attributable mortality with MRSA

Bacteremia No effect on in-hospital mortality

Bacteremia No effect on outcome

Bacteremia No difference in duration of mechanical ventilation or ICU mortality

Bacteremia No difference in mortality

Bacteremia No effect on ICU or hospital mortality

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 al 175</td>
<td>Bacteremia</td>
<td>Trend towards increased attributable mortality with MRSA</td>
</tr>
<tr>
<td>Bilot et al 176</td>
<td>Bacteremia in critically ill patients</td>
<td>Higher attributable mortality with MRSA</td>
</tr>
<tr>
<td>Chang et al 177</td>
<td>Community-acquired bacteremia</td>
<td>Higher mortality, increased risk of persistent bacteremia and renal insufficiency with MRSA</td>
</tr>
<tr>
<td>Combos et al 178</td>
<td>Post-sternotomy mediastinitis</td>
<td>No difference in duration of mechanical ventilation or ICU mortality</td>
</tr>
<tr>
<td>Coagrovo et al 179</td>
<td>Bloodstream infections</td>
<td>Longer hospital stay and higher hospital charges with MRSA</td>
</tr>
<tr>
<td>Cowie et al 180</td>
<td>Nosocomial infections</td>
<td>Increased hospital stay with MRSA, no effect on mortality</td>
</tr>
<tr>
<td>Enzmann et al 181</td>
<td>Surgical site infections</td>
<td>Increased mortality and hospital charges with MRSA</td>
</tr>
<tr>
<td>Hurbarth et al 182</td>
<td>Bacteremia</td>
<td>No effect on in-hospital mortality</td>
</tr>
<tr>
<td>Hershow et al 183</td>
<td>Nosocomial infections</td>
<td>No effect on outcome</td>
</tr>
<tr>
<td>Kopp et al 184</td>
<td>Various infections</td>
<td>Worse clinical and economic outcomes with MRSA</td>
</tr>
<tr>
<td>Lodise et al 185</td>
<td>Bacteremia</td>
<td>Increased length of stay and higher costs of hospitalisation with MRSA</td>
</tr>
<tr>
<td>Martinez-Aguilar et al 186</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 al 187</td>
<td>Bacteremia in cancer patients</td>
<td>No effect on outcome</td>
</tr>
<tr>
<td>Mekontso-Dessap et al 188</td>
<td>Post-sternotomy mediastinitis</td>
<td>Worse clinical outcome and higher overall mortality with MRSA</td>
</tr>
<tr>
<td>Melner et al 189</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 190</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 al 191</td>
<td>Nosocomial bacteremia</td>
<td>Higher mortality with MRSA</td>
</tr>
<tr>
<td>Selvey et al 192</td>
<td>Nosocomial bacteremia</td>
<td>No difference in mortality</td>
</tr>
<tr>
<td>Whitby et al 193</td>
<td>Bacteremia (meta-analysis)</td>
<td>Increased mortality with MRSA</td>
</tr>
<tr>
<td>Yoon et al 194</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 195</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 affects 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) [127].

Approximately one-third of patients with SAB develop one or more complications [126-128]. 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 (13%), liver (10%), lungs (9%), bone (9%), 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 valvular abnormalities, congenital heart disease, and prior infective endocarditis [129-131]; 2) Prosthetic implants, such as prosthetic valves [132], intravascular devices [133], and orthopedic implants [134]; 3) Community-acquired SAB, due in part to the typically prolonged disease course and duration of bacteremia prior to detection [135,136]; 4) Old age [137] and co-morbid conditions such as hemodialysis [138] and infection with the human immunodeficiency virus [139]. 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 [74,141]. In a recent large cohort of patients, S. aureus was the most common cause of native valve endocarditis [142]. Recent years have witnessed a rise in the rates of IE due to S. aureus [140,143-145]. S. aureus is now the leading cause of IE in many parts of the world [74]. 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 implantable devices [146-148]. For instance, Fernandez-Guerrero et al reported a 10-fold increase in the number of cases of hospital-acquired IE (most of which were due to S. aureus) from 1976 to 1992 compared to the number of cases occurring from 1960 to 1975 [149]. 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 [143].

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 [143-145]. In fact, reliance solely upon physical examination findings is likely to result in underdiagnosis of S. aureus IE in a large number of cases [146,147]. 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%), transesophageal echocardiography (TEE) is a widely available, non-invasive screening modality in the setting of SAB [148]. Conversely, transesophageal echocardiography (TEE) offers significant advantages over TTE, including higher sensitivity in identifying IE (80% [149], improved identification of IE complications [150-153], and an enhanced ability to exclude IE in patients with native valves (negative predictive value 100%) [154,155].

Whether TTE or TEE should be employed in the initial screening of the patient presenting with SAB remains a controversial issue [156,157]. 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 [158,159] or for patients at higher risk for IE or associated complications [160].

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 55% [161-163]. Other complications include heart failure (20-50%) [164-166], paravalvular cardiac abscesses (30-40%) [167,168], neurological manifestations (30%) [169-171], and systemic embolization (40%) [172].

Pneumonia

Staphylococcus aureus is a significant etiologic agent in lower respiratory tract infections that has become increasingly more common in the hospital setting [173-175]. According to the NNIS System, S. aureus was responsible for 20% of nosocomial pneumonias between 1992 and 1997 [176]. 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 [177]. 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 [178,179]. Nosocomial pneumonia due to MRSA entails significant mortality with rates ranging from 38% to 55% [180,181]. As with other S. aureus infections, whether methicillin resistance by itself contributes to the poor outcome is still a matter of debate [182,183].

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 [184-186]. 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 [187-189]. The mean case fatality rate is noted to be as high as 35% [190,191]. Mortality seems to be tightly linked to the presence of the pvl gene; in a study of S. aureus pneumonia, the mortality rate was 52% in cases with pvl positive strains, as compared to 6% in those with pvl-negative strains [192].

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, cavitary and pneumatocles may be present. 2) Post-interstitial pneumonia usually follows microaspiration and often develops in conjunction with, or following viral pneumonia [193]. 3) Peripheral 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 common in the case of pneumonia or in combination with various antimicrobial agents such as beta-lactams, aminoglycosides, or coagu-

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 in synergy against 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 MRSA. 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 endocarditis. A Phase II study in catheter-related bloodstream infections compared to vancomycin showed 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 ceftaroline in a Phase III trial.

Tigecycline

Tigecycline is a newly introduced glycyccline 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. 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 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 (87% vs. 89%; 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 adhesive proteins represents an excellent target for the development of novel immunotherapies. Tefibazumab 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 tefibazumab to vancomycin significantly increased bacterial clearance from the bloodstream when compared to vancomycin alone (P < 0.008). The results of a Phase II randomized, double-blind, multi-center clinical study of tefibazumab 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. Cardiothoracic surgery patients who received mupirocin prophylaxis had a lower surgical wound infection rate than historical controls (7.5% 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 (OR 0.49, 95% CI 0.28-0.83; number needed to treat 26) [219,220]. Boelaert et al found a four- to six-fold reduction in SAB rates in hospitalization 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 [221]. Investigators have therefore suggested that a single course of mupirocin may be insufficient in low-risk patients with prolonged exposure [222]. In addition to conflicting messages from clinical trials, the emergence of mupirocin-resistance has also been reported [223,224].

**Vaccination**

*Staphylococcus aureus* Polyvalent 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 capsular polysaccharides, the strains accounting for more than 80% of infections. In one double blinded, placebo-controlled Phase III clinical efficacy trial involving 1804 hematogenous-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) [225]. 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 [226,227]. Consequently, the Centers for Disease Control and Prevention (CDC) recommend the implementation of contact precautions in patients colonized or infected with MRSA [228]. 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 [229-231]. 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 [232,233]. Hand hygiene practices have been particularly inadequate [234,235]. 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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