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
ognized and further complicates the treatment of staphylococcal infections\(^\text{17,18}\).

In this review, the authors report on the current trends in the epidemiology, diagnosis, clinical syndromes, and management of \textit{S. aureus} infections in light of the organism’s evolving antimicrobial resistance pattern.

**Microbiology**

\textit{Staphylococcus aureus} belongs to the \textit{Micrococccaeae} family. It is a nonmotile, non-sporing, 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\(^\text{19}\).

**Epidemiology**

Worldwide epidemics of \textit{S. aureus} disease have been recognized over the years\(^\text{9-11}\). Outbreaks have been reported in a variety of settings, including hospitals\(^\text{22}\), long-term care facilities\(^\text{23}\) and outpatient clinics\(^\text{24}\), as well as in the community\(^\text{25}\).

**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\(^\text{25,26}\). \textit{S. aureus} is the leading cause of postoperative wound infection, and the second-most frequent cause of nosocomial pneumonia\(^\text{27}\) and bacteremia\(^\text{28}\). Together, \textit{S. aureus} and coagulase-negative staphylococci account for 21% of the estimated 4 million infections acquired annually in United States hospitals\(^\text{29}\). \textit{S. aureus} nosocomial infections entail great expenditure. Over a two-year period from 2000 to 2003, the average cost of hospitalization in 994 US hospitals for patients with \textit{S. aureus} infections was $48,634 compared to $14,141 for patients without such infections\(^\text{30}\). In another study, the mean infection-related costs in patients with prosthetic devices and \textit{S. aureus} bacteremia (SAB) amounted to $67,439 for hospital-acquired infections and $37,868 for community-acquired infections\(^\text{31}\). 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%\(^\text{32,33}\).

**Community-acquired infections**

\textit{Staphylococcus aureus} infections are commonly acquired outside the hospital, particularly among colonized individuals, and have been reported for several decades\(^\text{34,35}\). 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\(^\text{36}\). Similarly among adults, the incidence of community-acquired staphylococcal infections varied from 29% in 1997 to 74% in 2002\(^\text{37}\). 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\(^\text{38}\).

**Nasal carriage**

\textit{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\(^\text{39}\). 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%)\(^\text{40}\). Whereas 10%-20% of healthy adults are persistently colonized with \textit{S. aureus}, populations with higher colonization rates include patients with atopic dermatitis (up to 85%)\(^\text{41}\), as well as surgical patients\(^\text{42}\), hemodialysis patients\(^\text{43}\), HIV-infected patients\(^\text{44}\), and those with intravascular devices\(^\text{45}\). Health care workers who come in contact with patients colonized or infected with \textit{S. aureus} have higher rates of nasal carriage than providers without such contact\(^\text{46,47}\), and they may develop clinical disease following colonization\(^\text{48}\). In turn, colonized health care workers can serve as vehicles for the transmission of \textit{S. aureus} to patients. In fact, nosocomial outbreaks are frequently attributed to colonization of the nares and hands of health care workers\(^\text{49,50}\).

**Antimicrobial Resistance Trends**

The propensity of \textit{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 \textit{S. aureus} was published in 1940, almost a year before penicillin was marketed for clinical use\(^\text{51}\). Since then, beta-lactamase-mediated penicillin resistance has been widely described among \textit{S. aureus} isolates, with 80%-93% resistance rates currently reported in the hospital and the community\(^\text{52,53}\).

Penicillinase-stable cephalosporins and semisynthetic penicillins were introduced in the late 1950s. Once again, \textit{S. aureus} was quick to develop resistance and MRSA isolates were described shortly thereafter\(^\text{54}\). 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)\(^\text{55}\). 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\(^\text{56}\). In Japan, nearly 70% of \textit{S. aureus} bloodstream isolates in 2001 were methicillin-resistant\(^\text{57}\). On the other hand, Scandinavian countries have reported noted very low rates of MRSA\(^\text{58}\). Several risk factors have been independen...
S. aureus teichoic acid might have acquired the VanA resistance gene from a mobile phage that can be transmitted through nosocomial infections and various patient isolates. Over the past decade, community-acquired MRSA has been a matter of intense debate. A number of studies have been associated with nosocomial MRSA colonization and infection, particularly in patients admitted to an intensive care unit (ICU). These include old age, severity of illness, length of ICU stay, multiple antibiotic use, mechanical ventilation, and the use of invasive medical devices (central venous catheters, urinary catheters, feeding tubes).

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. Vancomycin-resistant (VRSA) and VanA- strains might be inevitable, especially with the continued pressure posed by intense glycopeptide use.

### Resistance to glycopeptides

*Staphylococcus aureus* isolates with intermediate and high-level resistance to glycopeptides have been reported. 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. 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 clinical specimens. Antibodies to a variety of staphylococcal antigens have been tested including peptidoglycan, teichoic acid, *S. aureus* adsorbrates, whole-cell extracts, and septic arthritis, where patients with uncomplicated bacteremia, acute os-
tempyelitis, cellulitis, and meningitis frequently have negative titers\textsuperscript{112}.

### Clinical Syndromes

Virtually any organ system is prone to infection with \textit{S. aureus}. This review does not present an exhaustive discussion of all the clinical manifestations of staphylococcal infections as these are reviewed elsewhere\textsuperscript{113,114}. 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

\textit{Staphylococcus aureus} bacteremia is now classified into three categories: hospital-acquired, health-care-associated, and community-acquired SAB\textsuperscript{117}. 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\textsuperscript{115,116}. In addition, hospital-acquired and health-care associated SAB result in significantly greater mortality rates when compared to community-acquired SAB (39%, 29%, and 16%, respectively\textsuperscript{117}). All three SAB categories have increased considerably over the last decade\textsuperscript{117}. 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\textsuperscript{118,119}. By 1998, \textit{S. aureus} had become the second most common bloodstream isolate, contributing to 16% of all hospital-acquired bacteremias\textsuperscript{117}. In Finland, Lyytikainen and colleagues documented a 55% increase in the incidence of SAB from 1995 to 2001, primarily in the elderly\textsuperscript{120}. Similarly, community-acquired SAB is being encountered more frequently, particularly with the increasing prevalence of \textit{pvl}-bearing MRSA isolates in individuals without health-care contact\textsuperscript{121,122}. 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\textsuperscript{123}; approximately 30% of SAB isolates in the United States are now methicillin-resistant\textsuperscript{124}. Resistance is more apparent in hospital-acquired (61%) and health-care ass-

### Table 1. Selection of studies comparing outcomes of patients with \textit{S. aureus} infections with respect to methicillin resistance

<table>
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<tr>
<th>Author (reference)</th>
<th>Setting</th>
<th>Findings</th>
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<tr>
<td>Austin et al\textsuperscript{13}</td>
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<td>Trend towards increased attributable mortality with MRSA</td>
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<tr>
<td>Blot et al\textsuperscript{17}</td>
<td>Bacteremia in critically ill patients</td>
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<tr>
<td>Chang et al\textsuperscript{18}</td>
<td>Community-acquired bacteremia</td>
<td>Higher mortality, increased risk of persistent bacteremia and renal insufficiency with MRSA</td>
</tr>
<tr>
<td>Comba et al\textsuperscript{19}</td>
<td>Post-sternotomy mediastinitis</td>
<td>No difference in duration of mechanical ventilation or ICU mortality</td>
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<tr>
<td>Cougrove et al\textsuperscript{20}</td>
<td>Bloodstream infections</td>
<td>Longer hospital stay and higher hospital charges with MRSA</td>
</tr>
<tr>
<td>Cowie et al\textsuperscript{21}</td>
<td>Nosocomial infections</td>
<td>Increased hospital stay with MRSA, no effect on mortality</td>
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<tr>
<td>Engemann et al\textsuperscript{22}</td>
<td>Surgical site infections</td>
<td>Increased mortality and hospital charges with MRSA</td>
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<td>Harbarth et al\textsuperscript{23}</td>
<td>Bacteremia</td>
<td>No effect on in-hospital mortality</td>
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<tr>
<td>Hershow et al\textsuperscript{24}</td>
<td>Nosocomial infections</td>
<td>No effect on outcome</td>
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<tr>
<td>Kopp et al\textsuperscript{25}</td>
<td>Various infections</td>
<td>Worse clinical and economic outcomes with MRSA</td>
</tr>
<tr>
<td>Lodise et al\textsuperscript{26}</td>
<td>Bacteremia</td>
<td>Increased length of stay and higher costs of hospitalization with MRSA</td>
</tr>
<tr>
<td>Martinez-Aguilar et al\textsuperscript{27}</td>
<td>Musculoskeletal infections in children</td>
<td>Greater febrile days and hospital days with MRSA, no effect on final outcome</td>
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<td>Marty et al\textsuperscript{28}</td>
<td>Bacteremia in cancer patients</td>
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<td>Mekontso-Dessap et al\textsuperscript{29}</td>
<td>Post-sternotomy mediastinitis</td>
<td>Worse clinical outcome and higher overall mortality with MRSA</td>
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<tr>
<td>Meurman et al\textsuperscript{30}</td>
<td>Nosocomial bacteremia</td>
<td>Trend towards increased mortality with MRSA, no effect on risk of dissemination</td>
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<tr>
<td>Reed et al\textsuperscript{31}</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\textsuperscript{32}</td>
<td>Nosocomial bacteremia</td>
<td>Higher mortality with MRSA</td>
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<tr>
<td>Selvey et al\textsuperscript{33}</td>
<td>Nosocomial bacteremia</td>
<td>No difference in mortality</td>
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<td>Whitey et al\textsuperscript{34}</td>
<td>Bacteremia (meta-analysis)</td>
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<tr>
<td>Youn et al\textsuperscript{35}</td>
<td>Infective endocarditis</td>
<td>Higher risk of persistent bacteremia and trend towards higher mortality with MRSA</td>
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<tr>
<td>Zahr et al\textsuperscript{36}</td>
<td>Ventilator-associated pneumonia</td>
<td>No effect on ICU or hospital mortality</td>
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associated SAB (52%) than in community-acquired SAB (14%) ([P = 0.01]).

Approximately one-third of patients with SAB develop one or more complications.[146-148] Acute systemic complications typically manifest within 48 hours of diagnosis; these include septic shock, acute respiratory distress syn-

drome, and disseminated intravascular coagulation. On the other hand, metastatic complications of SAB may only become evident several weeks later. In one large retrospec-
tive study, common sites of metastatic disease were joints (36%), kidneys (29%), central nervous system (28%), skin (16%), intracranial (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[146-148]; 2) Prosthetic implants, such as prosthetic valves[170], intracardiac devices[171], and ortho-

edic implants[172]; 3) Community-acquired SAB, due in part to the typically prolonged disease course and duration of bacteremia prior to detection[173,174]; 4) Old age[175] and co-

morbidity conditions such as hemodialysis[176] and infection with the human immunodeficiency virus[177]. 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.[7,8,149] In a recent large cohort of patients, S. aureus was the most common cause of native valve endo-
carditis.[146] Recent years have witnessed a rise in the rates of IE due to S. aureus[149-150]. S. aureus is now the leading cause of IE in many parts of the world.[4] This trend is mostly at-

tributed to the increasing prevalence of healthcare-associated S. aureus IE that has accompanied the growing use of in-

terventional procedures, intravascular catheters, and implantable devices.[149-150]. For example, Fernández-Guerrero et al reported a 10-fold increase in the number of cases of hospital-acquired IE (most of which were due to S. au-

reus) from 1976 to 1992 compared to the number of cases oc-

curring from 1960 to 1975.[150] The increasing frequency of S. aureus IE can also be ascribed to better recognition of the disease through the widespread application of echocardiog-

raphy in evaluating patients with SAB.[8]

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.[151,152] In fact, reliance solely upon physical examination findings is likely to result in underdiagnosis of S. aureus IE in a large number of cases.[152,153] Because of the difficulty in clinically identifying S. aureus IE, the use of echocardiography has been advocated to evaluate pa-

tients with SAB. Despite its limited sensitivity in detect-
ing vegetations (64%), transesophageal echocardiography (TEE) is a widely available, non-invasive screening modal-

ity in the setting of SAB.[153] Conversely, transesophageal echocardiography (TEE) offers significant advantages over TTE, including higher sensitivity in identifying IE (90%)[154], improved identification of IE complications[155-157], and an enhanced ability to exclude IE in patients with native valves (negative predictive value 100%)[158,159].

Whether TTE or TEE should be employed in the initial screening of the patient presenting with SAB remains a controversial issue.[159-161]. 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 in-

travascular catheter-associated SAB[162] for patients at higher risk for IE or associated complications[163].

Despite early diagnosis and appropriate therapy, IE fol-

lowing SAB is often associated with devastating and life-threatening sequelae. The overall mortality of S. aureus IE ranges from 19% to 30%.[164,165] Other complications include heart failure (20-50%),[147,148,150,152] paravalvular cardiac abscesses (30-49%),[147,150] neurological manifestations (10-100%),[150,151,152] and systemic embolization (40-90%).[150]

Pneumonia

Staphylococcus aureus is a significant etiologic agent in lower respiratory tract infections that has become increas-
ingly more common in the hospital setting[166,167]. According to the NNIS System, S. aureus was responsible for 20% of nosocomial pneumonias between 1992 and 1997[168]. Fur-

thermore, in the European Prevalence of Infection in Intensive Care (EPIC) Study, S. aureus was the predomi-
nant infective agent, accounting for 31% of microbiologi-
cally proven cases of ventilator-associated pneumonia.[169]

Whereas methicillin-susceptible S. aureus (MSSA) is typi-
cally encountered in early-onset hospital acquired pneumo-

nia (< 5 days after admission), MRSA gains importance in late-onset hospital-acquired pneumonia and particularly in ventilator-associated pneumonia[170,171]. Nosocomial pneu-

monia due to MRSA entails significant mortality with rates ranging from 38% to 55%.[172,173]. As with other S. au-

reus infections, whether methicillin resistance by itself con-

tributes to the poor outcome is still a matter of debate[168,169].

In addition to its role as a nosocomially acquired pul-

monary pathogen, S. aureus has recently established it-
self as an emergent threat in the community. Necrotizing pneumonia and sepsis caused by community-acquired MRSA strains carrying pvl genes are being increasingly recognized[72,175-179]. Afflicted patients are typically healthy individuals without any healthcare contact. These infections are characterized by multifocal involve-
ment of various organs, including lungs, brain, heart, liv-

er, and kidneys. The pathological feature in the lungs is an extensive hemorrhagic necrosis of the pulmonary parenchyma[72,175,176,178,179]. The mean case fatality rate is noted to be as high as 35%.[72,175,176,178,179]. 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[177].

Staphylococcus aureus pneumonia can present in sever-

al different forms, often in parallel with distinct patho-

tophysiological mechanisms: 1) Lobar pneumonia usually oc-
curs as a result of aspiration. Patients are acutely ill with high fevers and productive cough. In severe infec-
tions, empyema, abscess formation, cavitation and pneu-
matoceles may be present; 2) Ventilator-associated pneumonia usually follows microaspiration and often de-

velops in conjunction with, or following viral pneumo-

nia[118]. 3) Peripheral localized areas of pneumonia are not-

ed 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.

**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. Its clinical and bacteriological responses in both groups are comparable. 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 shown promising results in experimental rat and rabbit models of *S. aureus* endocarditis alone or in combination with various antimicrobial agents such as beta-lactams, aminoglycosides, rifampin, and vancomycin. Limited Compassionate Use Registry data are available regarding the use of quinupristin/dalfopristin as a treatment option in patients with serious MRSA infections who are failing or are intolerant of traditional therapy. However, the cost, the requirement for administration by central catheter, and the side effects profile have all limited the use of this agent.

**Linezolid**

Linezolid is an oxazolidinone antimicrobial agent that binds reversibly to the bacterial 23S ribosome, thereby inhibiting protein synthesis. As a result of reversible inhibition, linezolid exhibits bacteriostatic activity against *S. aureus*. A major advantage offered by this new drug is an oral bioavailability of approximately 100%. Linezolid is indicated for the treatment of MRSA in the setting of cSSSI including diabetic foot infections without osteomyelitis. It 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 pneumonia. 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 MRS 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 being 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 glyucycline 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 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 a Phase II clinical trials, telavancin was compared to stan-
dard therapy (semisynthetic penicillin or vancomycin) in patients with cSSSI[221]. Data from this study showed that telavancin was equivalent to standard therapy both in clinical cure in the all treated population (79.2% vs. 80%) as well as in microbiological eradication in the MRSA subgroup (87% 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 component recognizing adhesive matrix molecules) family of bacterial surface adhesion 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[222]. 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)[223]. The results of a Phase II randomized, double-blind, multi-center clinical study of tefibazumab in patients with SAB were recently presented[224].

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 (7.5% vs. 2.8%; P < 0.011)[225]. 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)[226,227]. Boelaert et al found a four- to six-fold reduction in SAB rates in hemodialysis patients when compared to vancomycin alone (P < 0.008)[228]. The results of a Phase II randomized, double-blind, multi-center clinical study of tefibazumab in patients with SAB were recently presented[229].

Vaccination

Staphylococcus aureus Poly saccharide 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 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)[230]. 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[231,232]. Consequently, the Centers for Disease Control and Prevention (CDC) recommend the implementation of contact precautions in patients colonized or infected with MRSA[233]. Such precautions include the use of private rooms, protective 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[20,234-236]. 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[237,238]. Hand hygiene practices have been particularly inadequate[239,240]. Accordingly, continuous efforts should be made to improve compliance with isolation and hand hygiene policies to prevent the dire consequences of nosocomial MRSA transmission.

References

Staphylococcus aureus


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