**Staphylococcus aureus** Bacteremia: Epidemiology, Pathophysiology, and Management Strategies

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*Staphylococcus aureus* is a major cause of bacteremia, and *S. aureus* bacteremia is associated with higher morbidity and mortality, compared with bacteremia caused by other pathogens. The burden of *S. aureus* bacteremia, particularly methicillin-resistant *S. aureus* bacteremia, in terms of cost and resource use is high. The risk of infective endocarditis and of seeding to other metastatic foci increases the risk of mortality and raises the stakes for early, appropriate treatment. The incidence of *S. aureus* bacteremia and its complications has increased sharply in recent years because of the increased frequency of invasive procedures, increased numbers of immunocompromised patients, and increased resistance of *S. aureus* strains to available antibiotics. This changing epidemiology of *S. aureus* bacteremia, in combination with the inherent virulence of the pathogen, is driving an urgent need for improved strategies and better antibiotics to prevent and treat *S. aureus* bacteremia and its complications.

Effective treatment of gram-positive bloodstream infections (bacteremia), including those caused by *Staphylococcus*, *Streptococcus*, and *Enterococcus* species, represents a major clinical challenge. *Staphylococcus aureus* bloodstream infections are among the most prevalent and difficult to treat [1]. The incidence of *S. aureus* bacteremia (SAB), particularly bacteremia caused by methicillin-resistant *S. aureus* (MRSA) strains, has increased dramatically in recent years in the United States and in some European countries [2, 3].

SAB is associated with a high mortality rate and places a substantial cost and resource burden on health care systems [2, 4]. This burden is increased by the high likelihood that life-threatening complications of SAB will occur, including infective endocarditis (IE) and metastatic infections [5, 6]. *S. aureus* IE (SAIE) is associated with significantly higher mortality, compared with IE caused by other bacteria [7].

Resistance of *S. aureus* strains to antibiotics has been increasing; thus, the ability of these pathogens to spread in both hospital and community settings has increased [8]. Increased antibiotic resistance, in addition to the increased frequency of invasive surgery, increased use of intravascular devices, and increased numbers of patients with immunocompromised status because of HIV infection or immunosuppression after transplantation or cancer treatment, has led to sharp increases in the incidence of SAB and SAIE over the past 30 years [6].

This article addresses the epidemiology, burden, and pathogenicity of SAB, SAIE, and metastatic infections and summarizes current management strategies.

**Epidemiology**

**SAB.** *S. aureus* is the most frequently occurring bacterial pathogen among clinical isolates from hospital inpatients in the United States and is the second most prevalent bacterial pathogen among clinical isolates from outpatients (figure 1) [9]. According to the SENTRY Antimicrobial Surveillance Program, which ex-
Figure 1. The 5 most frequently occurring bacteria (*Escherichia coli*, *Staphylococcus aureus*, enterococci, *Pseudomonas aeruginosa*, and coagulase-negative staphylococci [CoNS]) identified in 3,209,413 clinical isolates from hospital inpatients (top) and outpatients (bottom) in the United States from 1988 through March 2005. Figure adapted from Styers et al. [9].

...amined >81,000 isolates during the period 1997–2002, *S. aureus* was the most common cause of nosocomial bacteremia in North America (prevalence, 26.0%) and Latin America (prevalence, 21.6%) and was the second most common cause of nosocomial bacteremia in Europe (prevalence, 19.5%) [10]. Furthermore, *S. aureus* was found to be the most common cause of early-onset bacteremia in a study involving 6697 patients with bloodstream infections who were identified in 59 US hospitals during 2002–2003 [11].

MRSA can be classified as nosocomial or community acquired (or community associated [CA-MRSA]). The incidence of nosocomial MRSA has increased greatly in recent years in both the United States and Europe. In a US study by the Surveillance Network, annual rates of MRSA were shown to have increased steadily during 1998–2005, with rates of up to 59.2% among *S. aureus* isolates in clinical specimens from non-intensive care unit patients. In the same study, MRSA constituted 49.1% of bloodstream *S. aureus* isolates from inpatients and 41.4% of such isolates from outpatients [9]. Annual rates of methicillin resistance among *S. aureus* isolates also continued to increase in several European countries during 1999–2006, as reported by the European Antimicrobial Resistance Surveillance System [3]. However, in contrast to the general upward trend, rates of MRSA infection decreased significantly in France and Slovenia. This decrease over the past 5–6 years reflects concerted long-term efforts in these 2 countries to control MRSA levels in hospitals. The percentage of *S. aureus* bloodstream isolates that are resistant to methicillin in 30 European countries, according to the latest available European Antimicrobial Resistance Surveillance System data (from 2007), is shown in figure 2 [12]. The highest rates of methicillin resistance among *S. aureus* isolates occur in southern Europe, reaching up to 52.4% in Malta.

CA-MRSA was first reported in the early 1990s in Western Australia [13]. Multidrug-resistant CA-MRSA clones have subsequently spread rapidly in the United States, where they have now reached epidemic proportions and constitute a major public health concern [14]. Although outbreaks of CA-MRSA infection are typically associated with skin diseases, they can result in invasive infections [15]. This was demonstrated in a recent US study of the incidence and distribution of invasive MRSA infections (75.2% of which were bacteremias) in which 13.7% of invasive MRSA infections were community associated [14].

Evidence suggests that CA-MRSA isolates are distinct strains that emerge de novo from community-associated methicillin-susceptible *S. aureus* (MSSA) isolates, rather than from nosocomial MRSA isolates that originate from the hospital setting [16]. Compared with nosocomial MRSA strains, CA-MRSA strains are more susceptible to non–β-lactam antimicrobials (e.g., clindamycin), trimethoprim-sulfamethoxazole, and tetracyclines (e.g., doxycycline) [17]. CA-MRSA strains frequently contain the staphylococcal chromosome cassette (SCC) mec type IV, which contains *meca*, the resistance gene against β-lactam agents [17]. SCCmec type IV is smaller than the cassettes usually found in hospital strains of MRSA, primarily because of the omission of non–β-lactam resistance genes; this omission may make SCCmec type IV particularly efficient at transferring resistance between bacteria [17]. CA-MRSA strains are also associated with greater toxin production, compared with nosocomial MRSA strains; many CA-MRSA strains carry the Panton-Valentine leukocidin genes [17], which encode cytotoxins that can cause tissue necrosis and leukocyte destruction [18]. Nosocomial and CA-MRSA strains can typically be distin-
Figure 2. Prevalence of methicillin-resistant *Staphylococcus aureus* among patients with bacteremia in Europe in 2007, as reported by the European Antimicrobial Resistance Surveillance System [12]. AT, Austria; BE, Belgium; BG, Bulgaria; CY, Cyprus; CZ, Czech Republic; DE, Germany; DK, Denmark; EE, Estonia; ES, Spain; FI, Finland; FR, France; GR, Greece; HR, Croatia; HU, Hungary; IE, Ireland; IL, Israel; IS, Iceland; IT, Italy; LT, Lithuania; LU, Luxembourg; LV, Latvia; MT, Malta; NL, The Netherlands; NO, Norway; PL, Poland; PT, Portugal; RO, Romania; SE, Sweden; SI, Slovenia; TR, Turkey; UK, United Kingdom.

Distinguished by molecular typing methods, because CA-MRSA is predominantly of USA300 or USA400 lineage, whereas nosocomial MRSA is predominantly of USA100 or USA200 lineage [17]. However, there is evidence that the distinction between nosocomial and CA-MRSA strains is becoming blurred: CA-MRSA clones are emerging as major causes of nosocomial infections in patients with traditional risk factors for community-acquired infection [19, 20]. Klevens et al. [14] identified the USA300 strain in 67% of invasive CA-MRSA infections and in 22% of nosocomial MRSA infections. The USA100 strain was identified in 23% of CA-MRSA infections and in 62% of nosocomial MRSA infections. These findings may indicate important factors for the treatment of MRSA infections.

IE. *S. aureus* is one of the only causes of endocarditis in structurally normal heart valves [21], and it is the leading cause of IE in several countries [6]. Many patients acquire SAIE in the hospital, and an intravascular device is often the source of infection [22]. Patients with SAIE, particularly SAIE due to MRSA, tend to have worse outcomes than do patients with IE caused by other bacterial pathogens [6]. In a large international study involving 1779 patients with IE, SAIE accounted for 31.4% of identified cases and was associated with significantly higher rates of stroke, systemic embolization, persistent bacteremia, and death, compared with IE caused by other bacteria (*P* < .001) [6]. Mortality rates were 29.4% among patients with nosocomial infection, 27.7% among patients with cardiac devices, 29.8% among patients infected with MRSA, and 23.3% among patients infected with MSSA.

Rates of IE that is a complication of SAB can be even higher in at-risk patient groups. In a study that involved patients with prosthetic cardiac valves, the incidence of IE among patients with SAB was 43% (the incidence was 33% at the time when bacteremia was discovered and 11% at a mean of 45 days after diagnosis) [23]. In a study that involved 430 adults with SAB, although the overall rate of IE was 17%, the rate was significantly higher among injection drug users than among patients who did not use injection drugs (46% vs. 14%; *P* < .001) [24]. Right-sided IE occurred significantly more frequently among injection drug users than it did among patients who did not use injection drugs (60% vs. 7%; *P* < .001), whereas the vast majority of patients with IE who did not use injection drugs had left-sided involvement (93% vs. 30%; *P* < .001). Complication rates were high among all patients with SAB and IE in this study (85%–89% of patients had deep-seated extracardial infections, 21%–50% experienced thromboembolic events, and 45%–52% had severe sepsis).

At-risk groups. Colonized patients are the primary source of infection in hospitals. According to US studies, 10%–20% of the general population are persistent carriers of *S. aureus*, and up to 50% are intermittent carriers [25]. Furthermore, carrier rates of 25% have been found among hospital staff [26]. A significant proportion of cases of SAB originate from colonization in the nasal mucosa [27].

Several factors associated with an increased risk of developing SAB have been identified, including previous MRSA infection or colonization, skin ulcers or cellulitis at hospital admission, presence of central venous catheters [28], urinary catheter insertion, surgical site infection [29], injection drug use, presence of immunosuppressive conditions, use of corticosteroids, and liver disease [30].

SAIE occurs frequently among injection drug users (typically right-sided infection) and in patients with prosthetic heart valves and intravascular devices [22, 24]. In addition, the following patient groups are at increased risk of SAIE: those with...
type I diabetes mellitus, those who are receiving renal hemodialysis, those who have received vancomycin treatment, and those with intravascular devices, MRSA infection, or persistent bacteremia [6]. The following clinical variables can be used to identify patients at risk of complicated bacteremia: a positive result of follow-up blood culture at 48–96 h after the initial blood culture positive for S. aureus, community-acquired infection, persistent fever at 72 h after presentation, and skin lesions suggestive of acute systemic infection [31].

DISEASE BURDEN

SAB represents a significant burden on health care systems. According to an analysis of a large US database, SAB was associated with a longer median duration of hospital stay, higher median total treatment cost, and greater risk of mortality, compared with bacteremia caused by any other pathogen [2]. There is substantial variation in the mortality rates (range, 0%–83%) reported for SAB [32]. The wide variation in these mortality rates is likely attributable to differences in patient groups, settings, and the mortality measurements used. Mortality rates associated with SAB due to methicillin-resistant strains are particularly high among intensive care unit patients. In a Belgian study that consisted of a subset of critically ill patients, the MRSA bacteremia–associated mortality rate was 23.4%, which was significantly higher than the corresponding MSSA bacteremia–associated mortality rate of 1.3% [33]. Meta-analyses have demonstrated a significantly higher risk of mortality associated with MRSA bacteremia, compared with MSSA bacteremia, with an OR of 1.93 (95% CI, 1.54–2.42; \( P < .001 \)) [32] and a relative risk of 2.12 (95% CI, 1.76–2.57; \( P < .001 \)) [34].

An analysis of ~1000 US hospitals revealed that inpatients with SAB had a 3-fold longer mean duration of hospital stay than did inpatients without SAB (14.3 vs. 4.5 days; \( P < .001 \)), and this resulted in a 3-fold increase in treatment costs [35]. In another study that involved community-dwelling patients receiving hemodialysis, MRSA bacteremia was associated with significantly higher treatment costs, compared with MSSA bacteremia, at both initial hospitalization (mean cost, US$21,251 vs. US$13,978; \( P = .012 \)) and after 12 weeks of hospitalization (mean cost, US$25,518 vs. US$17,354; \( P = .015 \)) [36]. Complications associated with S. aureus also increase disease burden. For example, among patients with end-stage renal failure, the cost of treatment increased significantly for patients with S. aureus infection who had \( \geq 1 \) complication, compared with those who had no complications (mean cost, US$25,804 vs. US$18,476; \( P < .05 \)) [37]. Inappropriate initial antibiotic therapy also contributes to higher costs and mortality rates [38].

MECHANISM OF PATHOGENICITY

The ability to up-regulate virulence factors under stressful stimuli (e.g., host immune response or circulating antibiotics) is a key factor in the enabling of S. aureus to persist in the bloodstream, to seed deep tissues, and to form secondary foci of infection. S. aureus strains have been effectively able to adhere to and colonize the skin and mucosa of nares, to invade the bloodstream, to evade host immunological responses, to form protective biofilms, and to develop resistance to several antibiotics. Consequently, despite the availability of many antibiotics with activity against wild-type strains, S. aureus is a highly successful and increasingly clinically important gram-positive pathogen.

Adhesion and colonization. S. aureus can up-regulate a variety of virulence factors, enabling it to adhere to and colonize the nares and damaged skin or the surfaces of implanted devices or prostheses and to cause serious bloodstream infections. Teichoic acid, a polymer on the surface of S. aureus, is essential for this purpose [39].

Invasion. S. aureus can disrupt the skin barrier by secreting exfoliative toxins [40], hemolysins (including α-hemolysin [α-toxin], which forms pores in skin cell membranes), and various enzymes that destroy tissue [25]. Invasion may be triggered when the immune system is compromised, when there is a break in the physical integument, and/or when localized inflammation occurs [41].

Evasion. S. aureus evades the host immune response by secreting anti-opsonizing proteins (e.g., chemotaxis inhibitory protein), which prevent phagocytosis by neutrophils [42]. Protein A, located on the surface of S. aureus cells, also has antiphagocytic properties. Furthermore, S. aureus secretes leukotoxins (e.g., Panton-Valentine leukocidin), which lyse leukocytes [25], and expresses superantigens (e.g., enterotoxins and toxic shock syndrome toxin 1 [43]), which subvert the normal immune response by inducing strong, polyclonal stimulation and expansion of T cell receptor Vβ-specific T cells (followed by the deletion or suppression of these T cells to an anergic state) [44].

Biofilms. S. aureus quorum sensing may regulate gene expression to form slimy biofilms on damaged skin, fitted medical devices, and healthy or damaged heart valves. The depletion of nutrients and oxygen causes bacteria to enter a nongrowing state in which they are less susceptible to some antibiotics. In particular, small-colony variants of S. aureus, when adherent and in the stationary phase, demonstrate almost complete resistance to antimicrobial agents [45]. The biofilm matrix provides protection against immune cells and may restrict the penetration of some antibiotics [46].

Antibiotic resistance. Strains of S. aureus have developed resistance to antibiotics, including penicillin, cephalosporins, methicillin, vancomycin, and linezolid. S. aureus abrogates the effects of penicillin by producing β-lactamase, and MRSA strains have acquired the mec gene, which encodes penicillin-binding protein 2a, and the fem gene, which confers resistance...
to methicillin, penicillinase-resistant penicillins, and cephalosporins [47]. True vancomycin resistance in *S. aureus* appears to rely on acquisition of the *vanA* gene [48], whereas reduced vancomycin susceptibility in vancomycin-intermediate *S. aureus* and heteroresistant vancomycin-intermediate *S. aureus* has been linked to a different mechanism: mutations in structural or regulatory genes associated with the accessory gene regulator pathway [49]. Linezolid resistance is conferred by a mutation in *S. aureus* ribosomal RNA [50]. In addition to clear resistance, there is the phenomenon of “MIC creep,” which is best recognized with respect to the glycopeptide class of antibiotics and refers to insidious, numerically small increases in MICs over time that, nevertheless, appear to reflect a clinically significant reduction in susceptibility [51].

**S. AUREUS BACTEREMIA MANAGEMENT**

Numerous guidelines for the prevention and management of SAB exist, but these are not uniform in their recommendations. Many cases of SAB originate from colonization of the nasal mucosa; thus, elimination of nasal carriage by locally applied or systemic antibiotics is a useful prevention strategy [27]. Although guidelines suggest that antibiotics should be used prophylactically when patients undergo medical procedures associated with bacteremia, these guidelines are aimed at pathogens such as streptococci and enterococci, depending on the procedure [52]. A combination of aggressive antibiotic therapy and removal of the source of infection are central to the management of SAB. The appropriate antibiotic for SAB is determined by numerous factors, including the antibiotic susceptibility of the infecting organism, the source of infection, the presence of endocarditis and/or other metastatic sites of infection, and patient factors, including underlying comorbidities, concurrent medication, and antibiotic allergies [30]. Empirical therapy is of critical importance in the treatment of SAB, because delaying antibiotic treatment, even by only 45 h, has been shown to increase the risk of infection-related mortality and to increase the duration of hospitalization [53]. However, the use of an inappropriate empirical treatment regimen can also have detrimental effects, because it is associated with high in-hospital mortality [38]. The need for early initiation of appropriate empirical therapy is of particular importance with respect to combating the increasing rates of MRSA infection. The repeated demonstration that vancomycin (the current “gold standard” for the treatment of MRSA infection) is associated with a significantly worse outcome when used for patients with MSSA infection [54–56] emphasizes the need for drugs that are equally effective for the treatment of MSSA and MRSA infections.

**CONCLUSIONS**

*S. aureus* is a particularly complex, virulent, and successful pathogen. The increasing incidence of SAB is paradoxically associated with advancements in medicine that require more frequent use of catheters and implanted devices. The mortality rates associated with SAB remain high, particularly among vulnerable patient groups, and the duration of hospital stay and the treatment costs that are associated with this infection are a significant economic burden on health care systems. The emergence of MRSA, including strains with reduced susceptibility or with resistance to vancomycin and linezolid, and the spread of genetically distinct CA-MRSA strains with increased virulence and a different pattern of necrotizing infection add to the present concern. Early and aggressive antibiotic therapy and the removal of intravascular devices are important for optimal management.

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