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Future challenges and treatment of *Staphylococcus aureus* bacteremia with emphasis on MRSA

Rasmus V. Rasmussen[1], **Vance G. Fowler Jr.**[2], **Robert Skov**[3], and **Niels E. Bruun**[1]

[1] Department of Cardiology, Copenhagen University Hospital, Gentofte, Copenhagen, Denmark

[2] Division of Infectious Diseases, Duke University Medical Center, Durham, North Carolina, US

[3] Staphylococcal Laboratory, Statens Serum Institut, Copenhagen, Denmark

Summary

Staphylococcus aureus bacteremia (SAB) is an urgent medical problem due to its growing frequency and its poor associated outcome. As healthcare delivery increasingly involves invasive procedures and implantable devices, the number of patients at risk for SAB and its complications is likely to grow. Compounding this problem is the growing prevalence of methicillin resistant *S. aureus* (MRSA) and the dwindling efficacy of vancomycin, long the treatment of choice for this pathogen. Despite the recent availability of several new antibiotics for *S. aureus*, new strategies for treatment and prevention are required for this serious, common cause of human infection.

Keywords

Staphylococcus aureus; bacteremia; MRSA; epidemiology; infective endocarditis; treatment

Introduction

The incidence of *Staphylococcus aureus* bacteremia (SAB) has increased significantly during the past few decades and *S. aureus* has become a leading cause of bloodstream infections (BSI) in most of the industrialized world [1–3]. This is an unfortunate development as BSI due to *S. aureus* is associated with a poor outcome and a high rate of secondary infections such as infective endocarditis (IE), septic arthritis and osteomyelitis [4–6]. In much of the world, bacteremia caused by methicillin resistant *S. aureus* (MRSA) poses a particular clinical challenge, as MRSA infections have been repeatedly associated with a worse patient outcome compared to infections caused by methicillin sensitive *S. aureus* (MSSA) [7]. In addition to the growing incidence of MRSA, clinical reports of

Corresponding author: Niels Eske Bruun, MD, DMSc., Department of Cardiology, Copenhagen University Hospital, Gentofte, Niels Andersens vej 65, 2900 Hellerup, Denmark, Phone: +45 39 97 86 07, Fax: +45 39 77 73 81, nibru@geh.regionh.dk.

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Dr. Fowler has served on speaker's bureau for Cubist

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vancomycin resistance have also emerged adding to the need for new and better antimicrobial agents in the treatment of SAB [8].

Carriage of *S. aureus* with colonization of skin and mucosa is common and often harmless. However, due to the opportunistic nature of *S. aureus*, carriage may evolve into a wide range of infections ranging from skin and soft tissue infections to severe invasive infections such as SAB, IE and meningitis [9,10]. The mechanisms involved in this transition from carriage to infection is partly unknown but has been associated with breakage of the skin or mucosal barrier i.e. due to abrasion, surgery and use of intravascular devices, and a number of host factors such as general or local immunosuppression [11]. Whether some isolates are more invasive than others is still controversial, and the clinical impact of many of the virulence factors known stays largely unexplored.

In this review we will focus on challenges associated with the changing epidemiology, development of secondary infections and treatment of SAB with special emphasis on MRSA. In order to do so, we have chosen four themes: epidemiology, infective endocarditis, genetics, and treatment of MRSA, which we believe deserve special attention.

Epidemiology

The growing incidence of SAB is primarily driven by an increasing number of health care related infections [11,12]. In the period 1980 to 1989 the incidence of nosocomial SAB increased by 283% in non-teaching hospitals and by 176% in large teaching hospitals in the United States (US) [13]. Similarly, in a study by Benfield et al. the incidence of SAB in Denmark increased 1.7-fold during a 20-year period from 1981 to 2000 [4]. Although specific risk factors for SAB vary with the development and structure of the health care system, its diagnosis is linked to such risk factors as intravascular devices, advanced age, diabetes, immunosuppressive treatment, invasive procedures and the emergence of human immunodeficiency virus (HIV) [5,11,14–16]. A growing number of patients are acquiring healthcare-associated SAB outside of the hospital [17]. For example, *S. aureus* is the second most commonly encountered microorganism among outpatients in the US [18]. Hemodialysis-recipients are at particularly high risk for non-nosocomial health care associated *S. aureus* infections [17,19,20]. The problem of non-nosocomial health care associated *S. aureus* infection is still primarilya US phenomenon, and reflects the growing emphasis on outpatient services in that environment [17]. However, as healthcare delivery in other parts of the world increasingly shifts towards the community, this problem is likely to spread.

Another clinical problem of current interest is the continuing growing prevalence of MRSA in many parts of the world. In the US, more than 40% of *S. aureus* BSIs are caused by MRSA [1,18]. The prevalence of MRSA in Europe ranges widely. MRSA prevalence rates in the Mediterranean and United Kingdom (UK) exceed 30%, while rates in the Netherlands and Scandinavian countries are ~ 2% [21]. In these low incidence countries the emergence of livestock-associated MRSA have raised some concerns as it might have the potential to increase the incidence of MRSA infections also in humans. However, the importance of livestock-associated MRSA is so far limited due to a relative small number of human clinical cases. Furthermore, the far majority of livestock-associated cases has been in humans in close contact with animals and not in the general population [22–24]. Interestingly some countries, such as France, UK and Ireland, have been able to reverse the rising trend and lower the number of MRSA due to a dedicated effort to control the number of MRSA infections in inpatients [21]. In contrast to this positive development, it has become evident that S. aureus has emerged as an important cause of sepsis in the developing countries with increasing resistance as a major issue. In certain developing countries MRSA

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now accounts for more than 20% of the cases and is associated with mortality rates double that reported from developed countries. Resistance is also in these areas linked to health-care contact and is fuelled by uncontrolled access to over-the-counter antibiotics combined with a lack of microbiology facilities[25–28].

Traditionally, MRSA infections were confined to the health care environment. Over the past decade, however, the prevalence of community-associated MRSA (CA-MRSA) has increased exponentially. In many parts of North America, MRSA is now the most common identifiable cause of soft tissue infection among persons from the community without healthcare contact [29,30]. Epidemic outbreaks have been reported in several well-defined populations, including prisoners, homosexual males, intravenous-drug users, athletes, indigenous populations of North America, Australia, and New Zealand, and military trainees [31–36]. In a recent population-based study, Gorwitz found that the prevalence of MRSA had doubled to 1.5% from just a few years previously. Interestingly, only 20% of these MRSA carriage isolates were community-associated clones (e.g., USA300 or USA400 Pulsed field gel electrophoresis genotypes), implying that the healthcare environment serves as a continuing reservoir for acquisition of MRSA in the community[37]. Although strains of CA-MRSA primarily cause skin and soft tissue infection, they are emerging causes of bacteremia and necrotizing pneumonia [29,30,38]. Although CA-MRSA is generally more susceptible to antibiotics than strains originating from the healthcare system, its resistance profile in certain populations, such as North American homosexuals, has broadened considerably [36]. CA-MRSA most often harbour the staphylococcal chromosome cassette (SCC) mec type IV which contains the *mecA* gene as the sole resistance determinant. Using pulsed-field gel electrophoresis CA-MRSA have been designated to belong mainly to either the USA300 or USA400 lineage whereas most health-care related MRSA belong to USA100 [19,39]. Furthermore, CA-MRSA infections have been associated with the exotoxin Panton-Valentine leukocidin (PVL) that is believed to causes tissue necrosis and leukocyte destruction [38,40].

As the number of patients with community onset MRSA bacteremia grows the risk of inappropriate initial antimicrobial treatment and subsequently treatment failure and death is likely to increase [41,42]. This development calls for local treatment guidelines taking local resistance into account in order to ensure an effective initial treatment. Simultaneously, clinicians must balance the need for empiric antibiotic therapy that is sufficiently broad as to effectively cover drug-resistant pathogens with the need to limit unnecessary antibiotic administration, which drives the growing problem of antimicrobial resistance in the community.

Infective endocarditis (IE)

SAB is often associated with a poor outcome, and metastatic infections, such as osteomyelitis and IE, develops in up to one-third of the patients [4,6]. These infections are often difficult to treat and associated with increased morbidity, mortality, duration of hospitalization and increased costs [5]. Especially IE is a feared complication of SAB due to the high number of embolic events and high in-hospital mortality[43–45].

Along with the changes previously described in the health-care system the underlying conditions predisposing to IE have changed substantially during the last forty years [46]. The traditional IE risk factor of rheumatic heart disease has been replace in most industrialized countries by degenerative or congenital valvular disease and the presence of cardiac devices. The use of permanent cardiac devices has increased dramatically, with an estimated 300,000 cardiac pacemakers, 85,000 mechanical heart valves and 700 heart assist devices implanted every year in the US [47]. The number of cardiac rhythm management

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devices (CRMD) alone increased by 49% in the period 1996 to 2003 and in the same period the number of CRMD infections increased 3.1-fold [48]. Accordingly, the rates of CRMD infections increase faster than the implant rates, a development mainly driven by a 6-fold increase in ICD (Implantable Cardioverter Defibrillator) infections [48]. This rise in infection rate is due in part to the increasing number of electrodes implanted, an increasing duration of implantation, growing complexity of the medical conditions of the recipient patients, and increases in the number of sites - with a wide range of surgical volume - performing the procedure. With the present high rate of prophylactic biventricular ICD implantations, this problem will only increase further.

The clinical question of device infection arises in every patient with a cardiac prosthesis who develops SAB. Because definitive therapy is usually surgical removal of the device, establishing the presence of cardiac device infection is critical. Approximately half of all patients with CRMDs or prosthetic valves who develop SAB will have cardiac device infection [49,50]. In a recent study by Uslan et al. the rate of cardiac device infection in patients with SAB was 54.6% compared to only 12.0% in patients with BSI due to gram-negative bacilli [47,51,52]. Important in the pathogenesis of device infections is the ability of *S. aureus* to colonise the surface of foreign bodies by the formation of biofilm, making these infections difficult to treat without complete surgical explantation of the device. Device removal is both technically difficult and expensive, but spares the patient from the abysmal prognosis encountered when salvage of the pacemaker or ICD is attempted [53,54]. In order to reduce the number of infections patients should be educated in early signs of infection e.g. fever, fatigue, anorexia, weight loss, muscle aches, dyspnea and edema, whereas there is no scientific basis for the use of additional antibiotic prophylaxis before routine invasive procedures [53]. The value of prophylactic antibiotics to prevent endocarditis in patients at risk is uncertain as carefully controlled studies have never been performed. Although some animal studies support the use of antibiotic prophylaxis it is now recognized that endocarditis more often is the result of exposure to transient bacteremia associated with routine daily activities such as tooth brushing, use of wooden toothpicks, or chewing food than to bacteremia during dental, gastrointestinal(GI) or geni-tourinary(GU) tracts procedures. In addition, antibiotic prophylaxis may prevent only an extremely small number of cases of endocarditis and the risk of antibiotic associated adverse events greatly exceeds the potential beneficial effects. Emphasis on improved oral health in patients with a high risk of the acquisition of endocarditis is therefore much more important to reduce the incidence of transient bacteremia causing endocarditis than the use of prophylactic antibiotics. As a consequence, the American Heart Association and European Society of Cardiology now only recommends prophylaxis to the following high risk patients: 1) prosthetic heart valve; 2) previous endocarditis; 3) congenital heart disease involving an unrepaired cyanotic congenital heart disease, a completely repaired congenital heart disease with prosthetic material in the 6 months after the procedure, or a repaired congenital heart disease with residual defects at the site or adjacent to the site of prosthetic material. In the US but not in Europe cardiac transplantaton recipients who develop heart valve disease are also included in this group. In these patient groups prophylaxis is only recommended before dental procedures where perforation of oral mucosa or manipulation with gengiva or periapical tissue is anticipated, before procedures involving incision of the respiratory tract mucosa, and before GI and GU procedures involving infected tissue. Since these new recommendations represent a radical departure from previous guidelines it is anticipated that some clinicians and patients will feel more comfortable continuing previous practice, and it will take several years before the new recommendations are widely accepted[55,56].

The prevalence of IE in patients with SAB ranges from 11% to 50% depending on the patient population and design of the study [4,6,50,57,58]. In a prospective study by Fowler et al, SAB patients were evaluated by both transthoracic and transesophageal

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echocardiography and 26 (25%) of 103 patients were diagnosed with IE. Clinical evidence of IE in this study was only present in 7 (7%) of the 103 patients and it was not possible, based on clinical findings and predisposing heart valve disease, to distinguish between patients with and without IE [58]. These findings are consistent with another study by Røder et al, in which more than half of the patients with pathologically confirmed *S. aureus* IE had no clinical findings supporting the IE diagnosis [59]. These studies emphasize the difficulties associated with the exclusion of IE solely based on clinical findings and underline the need for screening with echocardiography in high risk patient populations. Accordingly, international guidelines recommend echocardiography in SAB patients in order to exclude IE [55]. Transesophageal echocardiography (TEE) is often used as a supplement to transthoracic echocardiography (TTE) when evaluating IE as the sensitivity of TTE is around 50%, while that for TEE approaches 100%. However, the most recent technologic advances have improved the image quality of TTE and a recent study have reported the sensitivity for detection of native valve IE by TTE to be as much as 82% [60]. The improved ability of TTE to detect vegetations in patients with native valves makes it a valuable screening tool and may eventually reduce the need for TEE, although TEE is still preferred in patients with high suspicion of IE due to the high sensitivity [60].

Despite these recommendations echocardiography is not routinely used in cases of uncomplicated SAB in many institutions [61]. This is a concern as this practise may lead to unrecognized cases of IE and treatment failure as mentioned above. Another concern is that as the quality of the images provided by echocardiography continues to improve smaller mobile structures are seen and the interpretation of significant versus non-significant i.e. degenerative echocardiographic findings become more difficult with the risk of false positive results, which may result in inappropriate treatment.

Blood cultures are together with echocardiography the cornerstones in the diagnosis of IE as expressed by the Duke criteria. Three sets are normally sufficient to identify the causative microorganism in patients with suspected IE. However, whether blood cultures should be used to monitor treatment is still controversial. In the US it is standard care for IE/SAB patients to repeat the blood cultures until they are negative to document resolution of bacteremia whereas blood cultures only are repeated if complications arise in many European countries [5,55,62].

For these reasons it is very important that in patients with SAB the treating physician takes all of the clinical, microbiological, biochemical and echocardiographic findings into consideration when developing a management plan for an individual patient. Furthermore, it is important to emphasize that the information contained within this review represents general guidelines based upon current literature rather than mandates that must be followed for each individual patient with SAB. Some patients with SAB may be appropriately managed by careful clinicians without performing some or all of the tests described above. Thus, these suggestions are not intended to take the place of clinical judgment.

Staphylococcus aureus and genetics

The mechanisms leading to SAB are multifactorial, involving bacterial, host (e.g., diabetes, immunosuppression) and environmental factors (e.g. hospitalization) [11]. While the enhanced ability of specific *S. aureus* strains to become pathogenic is controversial, it is generally accepted that all *S. aureus* clones have the potential to cause invasive infections under the right circumstances [63,64]. *S. aureus* is clonal and can be divided into different clusters or clonal complexes (CC), using either image based typing methods or multi/single locus sequence typing. Population studies using these techniques have identified five major clonal complexes (CC5, CC8, CC22, CC30 and CC45) which covers most of the *S. aureus*

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isolates worldwide [64–66]. This global similarity of *S. aureus* genotypes implies that specific clonal types are particularly suited to colonize and infect humans [67]. A study by Melles et al comparing *S. aureus* strains from healthy carriers with invasive *S. aureus* strains revealed that CC30 and CC45 account for almost half of all carriage isolates whereas invasive strains were more widely distributed across all 5 major clonal complex [64]. These findings are partly consistent with another resent study by Fowler et al showing increasing levels of hematogenous complications associated with strains within CC5 and CC30 [68]. However, other similar studies have failed to show any association between invasive disease and genotype which may be due to differences in methodology used in the various studies or to the epidemiology of the different strains [65]. Taken together, these studies suggest that *S. aureus* by nature is opportunistic and that no hypervirulent lineages have been identified [63,65]. In addition, there is strong evidence that horizontal transfer of virulence genes between strains is common which may result in loss or acquisition of virulence [69]. Accordingly, there is wide disparity in the prevalence of virulence genes in a given clone and the genetic composition in different geographic regions which also may blur the link between invasive disease and overall genotype [70,71].

The clinical impact of any single virulence genes on the ability of individual strains to cause invasive disease is unknown but probably modest due to the enormous redundancy in the virulence gene repertoire of *S. aureus*. One virulence gene family of interest is the Microbial Surface Components Recognizing Adhesive Matrix Molecules (MSCRAMM), e.g. clumping factor (Clf) A and B, fibronectin-binding protein protein A and B (FnBPA and B), and serine-aspartate repeat (Sdr) proteins, which allow *S. aureus* to adhere to host tissue and thereby trigger colonization or infection [72]. This group of virulence genes have also been shown to stimulate platelet activation and aggregation leading to thrombus formation [73]. Platelet aggregation and thrombus formation is important in the formation of vegetations in IE and allow the microorganism to avoid host defences and further colonize the heart valve. *S. aureus* induced platelet aggregation occur in a GP IIb/IIIa-dependent fashion and ClfA, ClfB and SdrE have been recognized to be essential for this process [74]. Furthermore, certain MSCRAMMs also mediate host cell internalization in order to escape host defence and antibacterial agents [75,76]. In addition to the MSCRAMMs a wide range of membrane-damaging toxins and superantigen toxins causing tissue damage and septic shock have been identified [77]. In a study by Peacock et al the authors showed an association between 7 virulence factors (fnbA, cna, sdrE, sej, eta, hlg and ica) and invasive disease [69]. Another recent study by Sabat et al failed to demonstrate a correlation between invasiveness and the SdrE gene but found an association between the SdrD gene and osteomyelitis which is consistent with another study by Trad et al. [78,79]. In yet another study, Xiong et al observed an association between persistent bacteremia and the collagen binding adhesin, cna, as well as toxic shock syndrome toxin-1 (tst) [80]. These findings were not consistent with a study by Lalani et al, as the authors in this study observed an association between persistent bacteremia and seg whereas PVL were associated with a better clinical outcome [81]. PVL belongs to the family of synergohymenotropic toxins, which damage host cell membranes by forming pores in the cellular membranes and thereby causing tissue necrosis and leukocyte destruction [63,82]. PVL has been linked to a number of infections such as skin and soft tissue infections (abscesses), necrotizing pneumonia, arthritis and community-acquired MRSA as previously discussed [64,83–85]. Even though PVL is believed to play an role in a wide range of infections the prevalence of the PVL gene differs significantly in different geographical regions and among different patient populations [70,81].

The importance of virulence genes in disease pathogenesis have only been documented in a limited number of cases e.g. the association between food poisoning caused by enterotoxins, and toxic shock syndrome caused by toxic shock syndrome toxin 1 [86,87]. However, in most cases the pathogenesis of invasive *S. aureus* disease cannot be explained by single or a

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combination of virulence genes and based on current knowledge, it seems likely that none of the single genes described are essential for initiation of human infection. The reason for this is probably that *S. aureus* has multiple mechanisms for initiating invasive disease or that virulence genes essential for this process remains to be identified. Nevertheless, this is an area that calls for more research in the future as a better understanding of the mechanisms leading to infection is essential in order to get new diagnostic tools and help development of future treatment.

Treatment of SAB

In SAB caused by MSSA β-lactams is still considered to be the best treatment and current guidelines recommend penicillinase-stable penicillins as standard treatment. There have been some debate with regard to the length of the therapy but most recent guidelines seems to agree on a minimum of 14 days for uncomplicated bacteremia [62].

Treatment of MRSA

Vancomycin

Vancomycin is currently the gold standard for the treatment of MRSA bacteremia and IE. Despite the great experience and evidence underlying the use of vancomycin this is far from an ideal drug due to poor tissue penetration, slow bactericidal activity, inconvenient administration and a number of side effects [88]. Several studies have shown that the prognosis of invasive MSSA infection treated with vancomycin is worse compared with patients treated with β-lactams [89–91]. The relationship between vancomycin minimum inhibitory concentration (MIC) and patient outcome in infections caused by vancomycin-susceptible strains is controversial, with some, but not all, recent studies finding associations between higher vancomycin MIC values (1.5 or 2.0 μg/ml) and worse prognosis [92–95]. Another concern is the emergence of strains with reduced susceptibility to vancomycin and reports of treatment failure in otherwise susceptible strains. *S. aureus* strains with reduced susceptibility can be divided into three categories; vancomycin resistant strains (VRSA; MIC, ≥16 μg/ml); vancomycin-intermediate strains (VISA; MIC, ≥4 μg/ml); and heterogeneous vancomycin-intermediate strains (hVISA), which have MIC < 4 μg/ml but have subpopulations which grow at higher MICs [96]. Vancomycin resistant strains are still extremely rare whereas VISA strains have been implicated in nosocomial infections and outbreaks of infections and colonisation [18,97,98]. The prevalence of hVISA among MRSA is rising and recent studies have reported a prevalence of 6–11% [97,99,100]. Prevalence of hVISA among cases of MRSA IE is significantly higher, with ~29% of isolates exhibiting this phenotype by population analyses [101]. hVISA strains have been associated with prolonged duration of bacteremia and metastatic infections e.g. IE and osteomyelitis whereas no significant increase in mortality has been observed [101–103]. Another major concern has been reports of increasing MIC that has been observed over time (MIC-creep) [104,105]. However, large surveillance programs have not confirmed these findings and it is speculated that the “MIC-creep” described at some institutions reflects a change in strain types, or potentially even changes in laboratory methods [106]. Nevertheless, recent studies have shown that higher MICs more often are associated with treatment failure and poor outcome even when MICs are below the breakpoint [107,108]. As the prevalence of vancomycin resistance of all kinds increases in MRSA, the need to find new alternatives to vancomycin continues to grow in order to manage future MRSA infections.

Teicoplanin

Teicoplanin is a glycopeptide used in the treatment of gram-positive infections, especially infections caused by *S. aureus*. Several studies have shown that teicoplanin is as effective as

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vancomycin in the treatment of bacteremia, bone and joint infections and is generally better tolerated with fewer adverse events [109–111]. Teicoplanin is available for intravenous or intramuscular administration and has an advantage in terms of its single daily dosing. However, the evidence supporting the use of teicoplanin is based on a wide range of underpowered often retrospective studies making it difficult to evaluate the applicability of this drug and teicoplanin has not yet been approved in the US (Table 1).

Tigecycline

Tigecycline is a glycylcycline antibiotic with a bacteriostatic effect on gram-positive bacteria including *S. aureus*. Tigecycline is FDA-approved for the indications of complicated skin/skin structure infections and complicated intra-abdominal infections, including those due to MRSA and extended spectrum beta lactamase producing enterobacteriaeceae (Table 1) [112–115]. In a recent study by Gardiner et al., comparing the effect of tigecycline in the treatment of patients with secondary bacteremia with standard therapy, the authors showed an overall clinical cure rate of 81.1% versus 78.5% (p=0.702) for Tigecycline and standard therapy, respectively[116]. Tigecycline has not been associated with any organ toxicity or severe adverse events, and does not require dose adjustment for hemodialysis dependence. Nausea and vomiting are common side effects (20–40%), and can be dose limiting [112–115]. Patients taking teicoplanin should also be informed of the risk of photosensitivity. Like Teicoplanin the evidence and clinical experience underlying the use of tigecycline is very sparse and this drug should not be considered for treatment of SAB in most cases.

Linezolid

Linezolid is an oxazolidinone and the first member of this class [117]. Linezolid inhibits bacterial growth by inhibition of ribosomal protein synthesis and is bacteriostatic against staphylococci [117]. Linezolid has the key advantage of high oral bioavailability, and is available for both oral and intravenous administration. A number of clinical trails have compared linezolid with standard antibiotic therapy in the treatment of pneumonia and skin and soft-tissue infections [118–122]. Based on these studies there is a growing body of evidence suggesting that linezolid is comparable to standard antibiotic therapy in the treatment of infections caused by *S. aureus* [118–123]. However, there have been some concerns using linezolid in the treatment of catheter-associated blood-stream infections as a study by Wilcox et al showed a higher mortality associated with linezolid therapy compared to treatment with vancomycin in patients with catheter-associated bloodstream infection [124]. This finding let to a “Black Box” warning from the FDA cautioning clinicians about the use of linezolid in patients with catheter-associated bloodstream infection caused by Gram-negative bacteria [201]. Although one observational Korean study suggested that linezolid had utility in the setting of persistent MRSA bacteremia, rates of myelosuppression (as indicated by thrombocytopenia) were significantly higher in the linezolid recipients [125].

In a recent study by Gandelman et al., rifampin was shown to reduce maximum concentration values for linezolid by 21% when linezolid was coadministered with rifampin. The clinical significance of this finding remains unclear [126]. Another concern is the potential serious adverse events associated with linezolid treatment. In most studies linezolid is well tolerated but linezolid has been associated with reversible myelosuppression, especially thrombocytopenia, in association with prolonged drug use. Accordingly, patients receiving linezolid should be closely monitored with complete blood counts. Other reported adverse events include lactic acidosis, optic and peripheral neuropathy and a serotonin-like syndrome that can be elicited by the simultaneous administration of certain antidepressant medications [127]. Most adverse events are completely or partially reversible when the

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treatment is discontinued but peripheral neuropathy may continue to persist after end of therapy [127]. Finally, resistance to linezolid, including outbreaks of linezolid-resistant *S. aureus* in intensive care units, has been described [128–131]. In summary, linezolid should not be used for treatment of SAB under most circumstances.

Daptomycin

Daptomycin is a cyclic lipopeptide with rapid bactericidal activity against *S. aureus* [132]. In a study by Fowler et al daptomycin was non-inferior to standard therapy in the treatment of SAB with or without IE. This was also the case when the different subgroups e.g. patients with complicated bacteremia, IE, and MRSA were evaluated separately. The overall incidence of adverse events was similar in the two groups, even though standard therapy was associated with a significantly higher rate of renal impairment whereas daptomycin was associated with creatine kinase elevations [133]. As elevated creatine kinase is a known adverse effect of daptomycin and cases of rabdomyolysis have been reported, creatine kinase should be measured on a weekly basis in order to avoid progressive myopathy[134–136]. Other serious adverse events reported include peripheral neuropathies, nephropathy and hepatotoxicity [136]. However, generally daptomycin is a safe and well tolerated antibiotic that has the advantage of only one daily dosing which make it suitable for outpatients. Because it is inactivated by pulmonary surfactant, daptomycin should not be used in the setting of pneumonia [137]. One concern with daptomycin is treatment-emergent resistance. Approximately 5% of S. aureus isolates from daptomycin recipients in the registrational trial developed resistance to daptomycin on therapy[133]. In all of these patients, there was a source of infection that needed, but did not receive surgical debridement. Subsequent works have shown a strong association between the presence and emergence of the VISA phenotype and daptomycin resistance in clinical *S. aureus* isolates [138–140].

Telavancin

Telavancin is a once daily lipoglycopeptide with efficacy against MRSA, VISA, and VRSA strains, attributed to its dual mechanism of action. In a randomized, double-blind study by Stryjewski et al. the authors found that telavancin was at least as effective as vancomycin for the treatment of complicated skin and skin-structure infections caused by MRSA with a clinical cure rate of 90.6% versus 84.4%, respectively [141]. Telavancin was recently approved by the FDA for the treatment of skin and skin structure infections (Table 1). The most common adverse events reported to Telavancin treatment are metallic taste, nausea, vomiting, headache, dizziness, rash and decrease in platelet count. QTc interval prolongation has also been reported [141,142]. Furthermore, animal studies have raise concern about potential teratogenicity, and telavancin should be avoided in pregnant women [117].

Future antibiotics against SAB

Dalbavancin and oritavancin

Dalbavancin and oritavancin are also classified as lipoglycopeptides with bactericidal activity against gram-positive microorganisms including MRSA [117]. In a phase II randomized clinical trail dalbavancin have been reported to be superior to vancomycin in the treatment of cather-related bloodstream infections (87% vs. 50%; $p<0.05$) whereas oritavancin was shown to be noninferior to standard therapy in the treatment of skin and soft-tissue infections and bacteremia, respectively [117,141–143]. Dalbavancin has a very long half-life which allows weekly intravenous administration whereas oritavancin is currently administrated intravenously once a day [144].

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Ceftobiprole and ceftaroline

Ceftobiprole and ceftaroline are cephalosporins with bactericidal activity against gram-positive microorganisms including MRSA [145]. None of these antibiotics have currently been tested for the treatment of SAB. Ceftobiprole has been tested in two unpublished phase III studies evaluating the efficiency of ceftobiprole in the treatment of community-associated and healthcare-associated pneumonia, respectively. In both studies ceftobiprole were noninferior to the comparator treatment whereas ceftobiprole was inferior to the comparator group in the treatment of ventilator-associated pneumonia [117,145,146]. Furthermore, both ceftobiprole and ceftaroline have been demonstrated to be efficient in the treatment of skin and soft-tissue infections caused by *S. aureus* [147,148].

Conclusion and future perspective

SAB continues to be a growing burden for the health-care system due to the poor prognosis and high costs associated with this infection. The latest epidemiological developments suggest that it is a problem that will continue to grow as the number of risk patients rises while problems with resistance now has spread from health-care settings to the community. Of particular concern is the increasing number of patients with prosthetic devices, especially cardiac devices, which contribute substantially the growing prevalence of SAB and secondary infections such as IE. To improve outcome a dedicated effort is needed in the evaluation of SAB patients including a better diagnostic set-up with a higher yield of echocardiography- in particular TEE - in order to rule out IE. The mechanisms leading to SAB involve host factors and environmental factors predisposing to infection, whereas the impact of genotypic features on the ability of different strains to cause infection is still controversial. The clinical impact of genotypic features on the ability of different strains to cause infections as well as the genetic susceptibility of the host to SAB stays largely unexplored and should be a field of great interest in the future.

Of concern is the less than optimal antibiotic effect of vancomycin in general and in particular in MRSA with the emergence of resistance and consequently the risk of treatment failure. Fortunately, several new agents have become available for the treatment of serious MRSA infections during the last years and a number of potential antibiotic agents are in the pipeline. Although the future treatment of SAB therefore seems reassuring randomized clinical controlled trials are needed to establish the role of these promising new antibiotics in SAB and in particular in IE. In addition the efficacy of novel therapeutic strategies like antibacterial antibodies and cell wall-specific enzymes as adjunct to antibiotics is currently explored. Finally, innovative preventive strategies, including vaccines for *S. aureus* infection, are needed to reduce infection rates of this common, serious consequence of medical progress.

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Table 1

Available and investigational antibiotics for treatment of MRSA infections

Agent	Drug class	Killing effect	Marketing authorization EMEA	Marketing authorization FDA	Indications	Route of administration
Vancomycin	Glycopeptide	Bactericidal	Yes	Yes	Standard treatment of MRSA bacteremia	Iv, single daily
Teicoplanin	Glycopeptide	Bactericidal	Yes (Authorization not granted in all EU countries)	No	Bacteremia, joint and bone infections.	Iv., im., single daily
Tigecycline	Glycylcycline	Bacteriostatic	Yes	Yes	cSSTI, cIAI	Iv, twice daily
Linezolid	Oxazolidinone	Bacteriostatic	Yes	Yes	cSSTI, CAP, NP	Iv, po, twice daily
Daptomycin	Cyclic lipopeptide	Bactericidal	Yes	Yes	cSSTI, SAB, rIE	Iv., single daily
Telavancin	Lipoglycopeptide	Bactericidal	No	Yes	cSSTI	Iv., single daily
Dalbavancin	Lipoglycopeptide	Bactericidal	No	No	cSSTI	Iv, once weekly
Oritavencin	Lipoglycopeptide	Bactericidal	No	No	cSSTI	Iv. Single daily
Ceftobiprole	Cephalosporins	Bactericidal	No	No	cSSTI	Iv, three times daily
Ceftaroline	Cephalosporins	Bactericidal	No	No	cSSTI	Iv, single daily

Abbreviations: Iv, intravenous; po, oral; im, intramuscular; cSSTI, complicated skin and soft-tissue infection; cIAI, complicated intra-abdominal infection; NP, nosocomial pneumonia; CAP, community-acquired pneumonia; SAB, Staphylococcus aureus bacteremia; rIE, right-sided infective endocarditis; EMEA, European Medicines Agency; FDA, US Food and Drug Administration.