Clinical management of Staphylococcus aureus bacteremia – an updated proposal of protocol

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Master's Thesis Internal Medicine
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Abstract

Background: Staphylococcus aureus bacteremia (SAB) is a worldwide frequent life-threatening disease that may cause metastatic infections like infective endocarditis, prosthetic joint infection or infection of an implantable device. Due to its high morbidity and mortality rate, adequate antimicrobial therapy is imperative. We tried to propose a clinical management based on the latest updates.

Methods: We have searched Pubmed, Embase and the Cochrane Library to identify studies addressing the management of SAB written between June 2015 and March 2017. 17 peer-reviewed studies were obtained, all written in English and concentrated on adult patients.

Results: After reviewing all 17 included studies, we managed to compose a clinically usable scheme for management of SAB, especially in terms of empirical antibiotic therapy, foreign bodies and use of echocardiography. For methicillin-sensitive *Staphylococcus aureus* (MSSA) the standard of care remains β-lactam antibiotics, whereas for methicillin-resistant *Staphylococcus aureus* (MRSA) vancomycin is first choice. Catheter-related SAB, cardiac device infections and prosthetic joint infections all demand a bivalent therapy with on one hand removal of the foreign material and on the other hand a thorough antimicrobial therapy with either (flucl)oxacillin for MSSA-infections or vancomycin in case of MRSA-strains. Whether a transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE) is necessary to exclude infective endocarditis still remains a point of discussion. However current guidelines suggest performing a TTE in every patient with SAB. TEE is only necessary in high-risk patients or in case of positive or inconclusive TTE.

Conclusion: SAB is a common serious bacterial infection with a high mortality rate. Optimal clinical practice often remains in the dark since there are still some uncertainties to uncover. We tried to postulate an answer to these questions based on a literature review of the latest updates within this field and to establish a practical protocol for management, specifically for empirical antimicrobial therapy, echocardiography and implantable device infections, which may be possible to implicate in clinical practice.

Introduction

The both commensal and pathogenic bacterium, *Staphylococcus aureus*, is a diagnostically important micro-organism since it is the leading cause of bacteremia and infective endocarditis (IE), as well as other common infections like skin and soft tissue infections (SSTI), osteoarticular infections, device-related and pleuropulmonary infections.[1] *Staphylococcus aureus* bacteremia (SAB) is the most common cause of all bloodstream infections with a high prevalence, morbidity and mortality rate.[2–4] Its complication rate is high and the most common among these pathologies is IE.[5] Numerous studies have tried to establish a uniform way of guidance in the treatment of SAB, with very little success. Nowadays there is still limited evidence how to act properly. Should we perform a transesophageal echocardiography in every patient with SAB, since IE determines the outcome? Which antibiotic therapy do we use and what is the optimal duration of therapy? What about the methicillin-resistant *Staphylococcus aureus* (MRSA) and its decreasing sensitivity to first-line therapy? Do we need to remove an implanted device, prosthesis or catheter when infected? Lots of practical questions rise in regard to SAB and its complications. Our goal is to propose a clinically usable standard protocol, based upon a review of the latest literature updates within this field.

Material and methods

A PubMed search from June 2015 until March 2017 was performed to identify studies addressing the management of SAB. We used the key terms: Staphylococcus aureus bacteremia, Staphylococcus aureus bacteremia review, Staphylococcus aureus bacteremia guidelines, with an additional filter on the date to only select studies ranging from June 2015 until March 2017. A second search was established with the following MESH-terms: Staphylococcus aureus, bacteremia, guidelines, antibiotics, catheter-related bacteremia, echocardiography and management.

An additional search was performed within other databases like EMBASE and Medline from June 2015 until February 2017. We used the exact same search terms and filters to identify studies. All searched studies were limited to peer-reviewed studies written in English and concentrated on adult patients. 17 studies, written about SAB and its management, were included.

An ethical approval for this study by The Supervisory Committee on Medical ethics of the "Master in de geneeskunde (Leuven)" program was obtained the 2nd of November 2016. This study was registered under the code: mp15540.

Results

SAB and its definition

In most studies, SAB was defined as the isolation of *Staphylococcus aureus* in one or more peripheral venous blood cultures collected from a patient with associated clinical signs and symptoms of a bloodstream infection.[2,6] A SAB can be differentiated in two entities, which differ in management, prognosis and outcome. There is a SAB without the detection of a deep focus of infection and a SAB due to a deep focus of infection (e.g. endovascular foci, foci in the joints, bones or central nervous system and intra-abdominal foci).[7] Another important difference to make is the type of acquisition of the infection, as defined by Palraj *et al*.[8] First, *community acquired SAB* was defined as a diagnosis of SAB within 48 hours of admission to the hospital or at the time of hospital admission. Second, *healthcare-associated SAB* was defined as a positive diagnosis of SAB

by culture obtained from a patient at the time of hospital admission or within less than 48 hours after admission if the patient (i) received intravenous therapy at home, received wound care or specialized nursing care through a healthcare agency, or had intravenous medical therapy in the previous 30 days; (ii) attended a hospital or hemodialysis clinic or received intravenous chemotherapy in the previous 30 days; (iii) was hospitalized in an acute care hospital for at least 2 days in the previous 90 days; (iiii) resided in a nursing home or long-term care facility. Third, *nosocomial bacteremia* was defined as a positive blood culture for *Staphylococcus aureus* first obtained more than 48 hours after admission to the hospital. In all studies IE was defined by the modified Duke criteria.[9] Prolonged bacteremia, identified in earlier studies as the strongest predictor of complicated SAB, was defined as persistent positive blood cultures for *Staphylococcus aureus* for ≥72 hours after starting effective antibiotic therapy.[2] Since SAB is a severe disease, in particular when complicated with metastatic infections, the identification of *Staphylococcus aureus* in a blood culture is always clinically significant.[2] The overall prevalence of SAB in industrialized nations, like the USA, ranges from 10 to 30 per 100,000 person-years. The rate of SAB has been relatively stable over the past 20 years, although the specific contribution of methicillin-resistant *Staphylococcus aureus* (MRSA) has fluctuated and augmented. However since 2005, due to increased prevention, improvements in infection control procedures and an increased vigilance, a significant reduction in MRSA bacteremia was observed.[1] There are some important risk factors to consider. A first important determinant of incidence is age, which has a biphasic aspect. Multiple studies show high rates in the first year of life and a gradual increase of incidence with increasing age. Second, there is a gender difference with a male-to-female ratio of 1.5.[1] Other important risk factors are ethnicity, HIV-infection, intravenous drug use or catheters, hemodialysis patients and prostheses or cardiac implantable devices.[1,7] SAB is a clinically important entity since it comes with severe morbidity and mortality. The most important and frequent complication of SAB is IE, with a frequency ranging from 5 to 25%.[1,4,5,7] Overall mortality rates range from 20-40% in industrialized nations.[1,3,6] Identified predictors of mortality from SAB are age; comorbidities; the source, extent and persistence of the bacteremia and failure of removal of foreign devices.[1] For uncomplicated SAB Le Moing *et al* showed in the VIRSTA study an 12 week case-fatality rate of 31.3%, whereas for complicated SAB, more specific SAB with IE, the 12 week case-fatality rate was 39.4% ($p = 0.03$).[7] Therefore, the recognition and diagnosis of IE is important for the patient's prognosis and survival.

Focus identification and removal

Leading management guidelines recommend an appropriate antimicrobial therapy and a drainage or removal of the identified focus of infection.[2] Common known primary foci of SAB are vascular catheter-associated infections, pleuropulmonary or skin and soft tissue infections, osteoarticular infections and IE. All of these primary foci represent an important subgroup of the clinical manifestations of *Staphylococcus aureus* infection (Table 1).[1] Thus, endocarditis can be either a primary focus of *S. aureus* infection or a secondary metastatic complication due to hematogenous spreading to the cardiac valves originating from an extracardiac infection.[8] However, within 20-25% of the patients with SAB the primary focus remains unknown.[1,7] Important predictive risk factors of IE within patients diagnosed with SAB are clinical signs of IE, prolonged bacteremia, intracardiac devices, dialysis, known focus and metastatic infection.[5] Even more, SAB related IE is more frequent in community-acquired and health-care associated SAB than in nosocomial SAB.[1,7] These two most frequent groups account for 20% of all health-care related bacteremias.[8] This implicates a high rate of morbidity and

mortality with rates fluctuating between 20 and 40%, and even higher when complicated with IE (19-65%).[8] A second important focus of infection with *Staphylococcus aureus* is intravenous catheters. This infection poses a difficult clinical challenge since *Staphylococcus aureus* is able to form biofilms. Mortality of catheter-related SAB ranges from 7-21%.[1] Catheter removal is the leading current treatment for catheter-related infections (CRI).[1,4] Remarkably this intervention is not always possible and can result in patient comorbidity and mortality. Therefore, the Infectious Disease Society of America also recommends the use catheter lock solutions with antimicrobial effects.[10] Another source of SAB are implantable cardiac devices. There is a given and stable incidence of cardiac device related SAB of 0,7-2,2%, although the incidence of implantation of cardiac devices still rises. Permanent pacemakers (PPM) and implantable cardiac defibrillators (ICD) can become infected directly during the implantation or indirectly due to hematogenous spreading from another infectious focus. 23 to 46% of all cardiac device infections (CDI) are caused by *Staphylococcus aureus* and 51% of these infections are due to MSRA.[1] Ursan *et al* showed for patients with a cardiac device implanted and SAB a significantly higher rate of CDI in patients with an ICD (60%) than in patients with a PPM (24%).[11] CDI diagnosis requires at least two positive blood cultures. TEE should be performed in case of positive blood cultures or prior use of antibiotics. The recommended therapy, for patients with a CDI with or without clinical evidence or CDI complicated with lead endocarditis or pocket infection, is full extraction of the cardiovascular implantable electronic device (CIED).[1,11] The removed leads and pocket tissue should be obtained for culture. After removal, an antibiotic therapy of 7-10 days is recommended by the American Heart Association (AHA).[1] The fourth most common source of deep focus SAB is prosthetic joint infection (PJI). Similar to catheter-related infections and CDI, *Staphylococcus aureus* can cause prosthetic joint infections due to biofilm production, which implicates a harder management. The majority of PJI occur in the first two years after implantation, although it remains vulnerable to hematogenous spreading throughout the lifespan of the prosthesis.[12] Patients with SAB and a prosthetic joint are at greater risk to have complicated SAB. Almost 30-40% of these patients are complicated with infection of the joint prosthesis. Early PJI are infections within 30 days after implantation, presenting as deep wound infections. Wound infection in the postoperative period is the most important risk factor for early PJI, the odds ratio is 52 (95% CI 21 to 130).[1] Important general risk factors are community-acquired SAB, prosthesis of the knee, methicillin-sensitive *Staphylococcus aureus* (MSSA) bacteremia, diabetes mellitus, prior surgery to the index joint, obesity, rheumatoid arthritis and previous arthroplasty revision.[1,12] Tande *et al* showed a significantly almost two times higher frequency of PJI after knee arthroplasty as compared to hip arthroplasty.[12] A definite diagnosis has become when *Staphylococcus aureus* has been isolated from operative specimens or periprosthetic tissue and/or joint fluids.[1] Management of this type of complicated SAB is hard and includes surgery and antimicrobial therapy. The surgery can be either two-stage joint replacement (first removal of the prosthesis and in second time re-implantation of a new prosthesis) or debridement and implant retention (DAIR). The median duration of intravenous antibiotic therapy was >4 weeks as shown by Tande *et al.*[12] When two-stage joint replacement surgery was performed, the success rate is up to 90%, with DAIR up to 70-80%.[1] Since DAIR is cheaper and more convenient by avoiding multiple operations and prolonged immobilization as is needed with two-stage joint replacement, but has lower success rates, it should only be considered for patients with the following three criteria: (i) the onset of symptoms is less than 3 weeks, (ii) a stable implant and good soft tissue envelope and (iii) an organism susceptible to quinolones and/or rifampin.[1]

Should we perform an echocardiography in all SAB-patients?

IE is a frequent, morbid and often lethal complication of SAB. Bacteremia is a major risk factor of IE, particularly in those patients with abnormal of prosthetic heart valves.[2] The 30-day overall mortality is 23.9% in left-sided IE and 11.8% in right–sided IE.[13] Detection rates of IE by both transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) have been examined in several studies and found to be higher with TEE (14-28%) than with TTE (2-15%).[4] Independent predictors of IE within patients with SAB to withhold in clinic are prolonged bacteremia, the presence of a CIED or prosthetic valve or joint and community onset.[5,8] Heriot *et al* have shown a subset of patients with SAB who have very low risks to develop IE in absence of these three risk factors and demonstrated a higher rate of IE diagnosis in patients who underwent TEE (24%) than patients who underwent only TTE (5%).[12] Similarly, Buitron de la Vega *et al* demonstrated risk factors in patients with MRSA SAB, which in their absence had a low risk of endocarditis and may not standardly require an echocardiography. These risk factors were (i) intravenous drug use, (ii) prolonged bacteremia, (iii) catheter-related infection, (iiii) dialysis dependency, (iiiii) prosthetic valve and/or structural cardiac abnormalities, (iiiiii) previous IE and (iiiiiii) vertebral/non-vertebral osteomyelitis.[13] This study showed that patients with MRSA SAB and ≤ 1 risk factor have a very low risk to develop IE and may be considered not to need a TEE. When this exact same patient group has > 1 of the above risk factors TEE should always be performed since there is a higher risk of developing IE.[13] Tande *et al* showed similar findings for patients with MSSA SAB and their investigated risk factors (Table 2).[12]

Since these studies have their limitations and often little performance rates of TEE, we cannot make definite conclusions and more prospective studies are needed. The European Society of Cardiology (ESC) and the American Heart Association (AHA) recommend within the current guidelines, to perform a TTE in all patients with a suspected IE (following the modified Duke criteria). However cost-effective calculations suggest performing a TEE at first in all adult patients with SAB since they should be considered high-risk patients for IE. Others suggest to perform TEE in patients with a negative TTE and clinical suspicion of IE.[13] Palraj *et al* proposed a 2-day scoring system to determine which patients should be examined for IE with TEE. With daily blood cultures, a score should be obtained on day 1 (day of SAB diagnosis) and on day 5 (when day 3 culture results are known). For the day 1 risk score there is a score to determine for presence of CIED (ICD = 2 points, PPM = 3 points, neither = 0 points) and a score for onset of SAB (community-acquired = 2 points, health-care related = 1 point, nosocomial = 0 points). Screened patients with a day 1 risk score ≥ 4 are patients with a high risk of IE and should undergo a TEE soon after the SAB diagnosis. The highest risk group is patients with a community-acquired SAB and an implantable cardiac device. If initial TEE is negative for IE, these patients need reevaluation in case of prolonged bacteremia (>72h). For patients with a day 1 risk score < 4 TEE should be deferred and they should be reassessed on day 5. The day 5 score is based on the presence of CIED (ICD = 2 points, PPM = 3 points, neither = 0 points), a score for onset of SAB (community-acquired = 2 points, health-care related = 1 point, nosocomial = 0 points) and 2 points for a prolonged bacteremia (≥ 72h). A day 5 risk score ≥ 2 (negative predictive value of 98.5%) is the cut-off to perform a TEE for IE.[8] This manageable score-system could be of clinical use, but needs further and larger prospective studies to be validated. As stated before, the current ESC guidelines recommend performing a TTE in all patients with a clinical suspicion of IE, based on the modified Duke criteria, and only establish a TEE in case of: (i) positive TTE, (ii) presence of prosthetic heart valve(s) or CIED and (iii) inconclusive TTE (Figure 1).[14] If initial TEE is negative in a patient with remaining

high clinical suspicion, repeat TTE and/or TEE within 5-7 days.[14] Newer risk stratification models as given above still have to be validated, so are not yet included in these guidelines.

Profit of infectious disease consultation

Since SAB is a common pathology in clinics, with a high case fatality rate and import morbidity due to its frequent complications as IE and relapse of bacteremia, it is an important burden on the health care system. Vogel *et al* showed in their meta-analysis that the overall 30-day mortality was 19.95% with a significant difference between the arm of patients who had been followed by a infectious disease specialist (12.39%) and the arm who had not (26.07%) with a relative risk (RR) of 0.53 (95% CI 0.43-0.65). Likewise, the 90-day mortality and relapse of bacteremia were significantly reduced with RR of 0.77 (95% CI 0.64-0.92) and 0.62 (95% CI 0.39-0.99) respectively.[6] Other significant differences demonstrated by Vogel *et al* are (i) the appropriateness of the used antimicrobial agent (RR 1.14; 95%CI 1.08-1.20); (ii) the duration of treatment (RR 1.85; 95% CI 1.39-2.46); (iii) obtaining follow-up blood cultures (RR 1.35; 95% CI 1.25-1.46); and (iiii) the frequency of performed echocardiography (RR 1.98; 95% CI 1.66-2.37).[6] Since all of these findings significantly improve the patient's outcome, Tong *et al* concluded that infectious disease consultation for SAB should be the standard of care in facilities where this specialized service is available.[1]

Antimicrobial therapy

MSSA bacteremia versus MRSA bacteremia

Several randomized controlled trials and observational studies showed a significant benefit of β-lactam therapy, specific oxacillin and nafcillin, in comparison with glycopeptides like vancomycin in the treatment of MSSA SAB.[1] The usage of vancomycin for MSSA bacteremia is associated with slower bacterial killing, slower bacterial clearance, poorer tissue penetration and higher relapse frequency, compared with oxacillin and its derivatives.[1,15] Whereas for MRSA SAB vancomycin and daptomycin are the only Food and Drug Administration (FDA)-approved therapeutic options.[1] Together with linezolid and ceftaroline, daptomycin is one of the alternatives to vancomycin for the treatment of MRSA bacteremia. These three alternative agents have been found non-inferior to vancomycin in selected MRSA infections, but have not demonstrated a superiority and are associated with risks of adverse effects and high costs.[15] However, combination of vancomycin with daptomycin or linezolid does not have any synergic effect, whereas in contrary multiple *in vitro* studies showed a beneficial effect of adding β-lactams to the vancomycin treatment of MRSA SAB or vancomycin intermediate sensitive *Staphylococcus Aureus* bacteremia.[15] Davis *et al* showed this beneficial effect of combination therapy with vancomycin in standard dosage and β-lactam (flucloxacillin 2 grams 4 times daily) *in vivo*, but their results were non-significant, lacked mortality benefit and had an increased rate of nephrotoxicity.[15] Other combinations have been studied, but none of them are standardly recommended (e.g. vancomycin + gentamicin, vancomycin + rifampin).[16,17] Although the current recommendations for treatment of MRSA infections remain an antimicrobial therapy with vancomycin, there is a growing concern about the increasing minimal inhibitory concentration (MIC) of MRSA for vancomycin and the rising rates of clinical failures with vancomycin. Therefore the other agents (linezolid for SSTI or daptomycin for SAB or endocarditis or SSTI/bone infections) are intensively studied and showed non-inferiority. Newer agents like ceftaroline, ceftobribole, dalbavacin, ortitavacin and tedizolid are currently investigated.[15,16] Considering the lack of other superior agents, vancomycin remains

nowadays the first-line therapy for MRSA bacteremia and for MSSA bacteremia first-line empirical therapy are β-lactams like oxacillin.[17]

Optimal dosage, administration and duration of antimicrobial therapy

The standard of care in studies and guidelines of SAB therapy for MSSA SAB are intravenous (i.v.) (flucl)oxacilline or nafcillin 2 grams 6 times daily.[15] If the patient has a penicillin allergy, the best option, following a limited amount of observational studies, is cephalosporins like intravenous cefazolin 2 grams 3 times daily.[2] Only cefazolin has been proven as effective as penicillins for the treatment of SAB. Others, like cefonicid (semi-synthetic second-generation cephalosporin) and ceftazidime (third-generation cephalosporin), showed a treatment failure in small observational studies.[2] Likewise, cefotaxime and ceftriaxone (both third-generation cephalosporins) have been studied as SAB-treatment with success rates of >90%, however there is only limited data from small studies.[2] First-line therapy for MRSA bacteremia is intravenous vancomycin (15 mg/kg 2 times daily).[1,15] In case of treatment failure allergies or vancomycin intermediate *Staphylococcus aureus* (VISA) strains (MIC > 8 μg/mL), intravenous daptomycin (6-8 mg/kg once daily) is the second-line treatment. Another second-line treatment option is intravenous linezolid 600 mg 2 times daily.[1,2,15] The optimal duration of therapy depends on the degree of complications. For uncomplicated SAB the recommended duration is at least 2 weeks of intravenous therapy, since a shorter course of antibiotics is associated with a increased relapse rate (8% versus 0%).[1] Complicated SAB (i.e. bacterial bloodstream infection with *Staphylococcus aureus* complicated with metastatic infections or persistent bacteremia) treatment should consist of an intravenous antimicrobial therapy of 4 to 6 weeks.

Infective endocarditis – catheter-related SAB – Cardiac device infection

Infective endocarditis is either a primary focus or a severe complication of SAB. Treatment is necessary for survival. A general line in treatment of IE is the prolonged duration, 6 weeks, of intravenous antimicrobial therapie.[1] Although, in case of uncomplicated or right sided IE, a 2-week course can be sufficient.[18,19] Follow-up blood cultures every 24-48 hours should be obtained to document bacterial clearance. For native valve MSSA IE the current recommendations are the use of antistaphylococcal β-lactams like nafcillin or (flucl)oxacillin in a dosage of 2 grams 6 times daily. In case of penicillin-allergy, cefazolin 2 grams 3 times daily is recommended. If the IE is caused by a MRSA, the standard empirical treatment consists of i.v. vancomycin 15 mg/kg 2 times daily.[18] Intravenous daptomycin is a possible alternative for native valve MRSA IE, in a dosage of 6-8 mg/kg once daily. Higher dosage is currently being studied and appears to be safe.[1] Combination therapy of β-lactams and aminoglycosides (oxacillin + gentamicin) shows to be effective in treatment of uncomplicated native valve MSSA right-sided IE in i.v. drug users.[18] MSSA IE of a prosthetic valve should standardly be treated with a combination therapy of i.v. oxacillin (2 grams 6 times daily), i.v. gentamicin (1.5 mg/kg 2 times daily) and rifampin (300 mg orally 3 times daily).[14] In case of MRSA endocarditis oxacillin needs to be replaced by i.v. vancomycin (15 mg/kg twice daily).[1,15,18] Besides antibiotics, patients with a SAB IE, especially those with heart failure, uncontrolled infection and a high risk of emboli, benefit from early surgery as stated by Tong *et al* and as shown in the ESC guidelines.[1,14]

Catheter-related bacteremia management consists of three major key points: (i) the removal of the infected intravascular catheter, (ii) usage of appropriate antimicrobial therapy and (iii) a classification of the SAB in

complicated or non-complicated.[1] For uncomplicated catheter-related SAB, the duration of therapy should be ≥14 days, since relapse increases if the antibiotic therapy is given <10 days.[1] A complicated catheter-related SAB should be treated for prolonged duration of 4 – 6 weeks.[1] The recommended antimicrobial agent for therapy is vancomycin (15 mg/kg), intravenously administered, twice daily.[1,2,4] In the exceptional case of a patient with limited i.v. access or impossibility of removal, adjunctive antibiotic lock therapy, being the direct instillation of antibiotics into the catheter lumen, should be considered.[1] Newer therapies besides antibiotics are currently tested (e.g. Citrox, ML:8,…).[10]

Cardiac device infections are important to acknowledge since they have an high all-cause 12-week mortality of 25%.[1] Therapy consists of two major acts: (i) complete removal of the CIED and (ii) antimicrobial therapy. The current AHA-guidelines state an empirical use of i.v. vancomycin (15mg/kg 2 times daily) until susceptibility tests are known. In case of methicillin-sensitivity, the patient should be switched to an single antistaphylococcal β-lactam like nafcillin/oxacillin (2 grams 6 times daily) or cefazolin (2 grams 3 times daily) in case of penicillin-allergy.[1] The optimal duration of therapy has still to be established, although the current guidelines recommend 7-10 days of antimicrobial therapy if (i) the removed device shows no inflammatory changes and (ii) the infection is only located in the pocket site. If the CDI does not satisfy these criteria, the duration should be prolonged to 14 days.[20] When the CDI is due to SAB, a course of ≥14 days is recommended; for patients with prolonged bacteremia (positive blood cultures) >24 hours after device removal a course of ≥4 weeks should be established.[20] After removal and antibiotic therapy the patient should be reevaluated whether a re-implantation is warranted, most favorable at the contralateral side.[1]

Prosthetic joint infections need antibiotic treatment in combination and following the removal of the prosthesis. Two approaches have been established in patients treated with DAIR. The first possibility exists of an intravenous administration of 15mg/kg vancomycin two times daily for at least 6 weeks in case of MRSA-infection. For MSSA SAB the use of antistaphylococcal agents like (flucl)oxacillin is recommended in standard dosage (2 grams 6 times daily) for 6 weeks.[1,12] A success rate of 70% at 2 years in early postoperative setting has been reported.[1] The second possible approach, with rising interest, is a combination therapy of i.v. vancomycine 15 mg/kg twice daily (for MRSA) or i.v. oxacillin 1,5-2 g 4-6 times daily (for MSSA) for 2 to 6 weeks along with oral rifampicin 300-450mg twice daily followed by a 3-6 months oral rifampicin-based combination therapy (e.g. rifampicin plus ciprofloxacine/levofloxacine or rifampicin plus fusidic acid).[1,21,22] Although there are limited randomized controlled trials that support this approach, this treatment is the current IDSA recommendation.[22]

Discussion

SAB is a frequent and serious infection. Still, the optimal management and its evidence is poor and little known. First, we tried to establish a practical definition of SAB, with little subcategories. We examined the importance of focus identification and source control. The acquirement of one positive hemoculture for *Staphylococcus aureus* is always clinically significant, considering the pathogenicity and high morbidity and mortality rates of SAB. An identification of *Staphylococcus aureus* bacteremia needs to emerge a profound clinical assessment to identify the primary focus and possible metastatic infections. There is strong evidence that removal of the primary focus is a strong positive prognostic factor which significantly improves the patient's outcome.[1,2,4]

Further we examined the need to use TTE or TEE, which still remains a point of discussion. The current guidelines recommend a TTE in al patients with a high suspicion of IE based on the modified Duke criteria.[14] In case of a low clinical suspicion of IE, an echocardiography is not mandatory, whereas in patients with a predisposing factor (e.g. valve prosthesis, valve malformation and prolonged SAB) TEE is obligatory.[13,14] Newer risk score systems have been established, although they remain clinically unusable since they have a poor sensitivity.[8]

Thirdly, we overviewed the optimal choice, the optimum of duration and administration of antimicrobial therapy for *Staphylococcus aureus* bacteremia. Multiple studies have shown a significant benefit and effectiveness of β-lactam antibiotics in comparison of glycopeptides for treatment of MSSA bacteremia, whereas in case of MRSA bacteremia glycopeptides, more specific vancomycin, still remains the standard of care.[1,2,15] There is limited evidence for the effectiveness of cephalosporins in treatment of MSSA SAB, however they seem to be more effective than vancomycin.[2] With still rising rates of VISA, alternatives for vancomycin have been searched. Therapies with either daptomycin or linezolid have been studied and have been found non-inferior to vancomycin, although resistance emerged shortly after introduction of these agent.[1,2,15] Further studies are needed to determine whether dose-increasing can preserve their activity.[2] 14 days of intravenous antibiotic treatment should be sufficient in most cases of uncomplicated SAB, CRI and CDI. When complicated or in case of PJI or IE, a 6-week course of i.v. antimicrobial therapy is required. Combination of β-lactams with other antimicrobial drugs has not been found significantly beneficial.[1,2] In case of SAB, with or without IE, an aminoglycoside combination has been proposed, although the side-effect of nephrotoxicity outweighs the benefit.[2] However, the patients' clinical outcome is not only determined by the antimicrobial therapy. Studies showed that consultation of a specialist in infectious diseases improved patient's morbidity and mortality.[1,6]

Finally, we tried to assemble a clinically usable protocol based on these latest updates in SAB management (Figure 2). We hope that by using this tool, SAB management becomes less unclear in all day clinical practice and both physician and patient will benefit.

Table 1: The primary foci of infection in *Staphylococcus aureus* bacteremia cohorts[1]

Region (reference)	% of MRSA cases in cohort	% of HCA cases in cohort	No. (%) of cases with focus of infection							Total no. Of cases
			Infective Endocarditis***	Osteoarticular***	SSTI	Pleuropulmonary	Line related	No focus/unknown	Other	
Central Australia	21.6	25.6	9 (7.2)	20 (16)	42 (34)	11 (8.8)	9 (7.2)	30 (24)	4 (3.2)	125
Australia	24.8	79.1	433 (6)	956 (13)	1,415 (20)	519 (7.2)	1,387 (19)	1,100 (15)	1,421 (20)	7,231
Sydney, Australia	100	92	15 (3.8)	37 (9.3)	80 (20)	52 (13)	140 (35)	40 (10)	35(8.8)	399
Calgary, Canada**	11.3	75.3	79 (5.5)	227 (16)	224 (16)	220 (15)		586 (41)	104 (7.2)	1,440
Missouri, USA	100	92.6	0 (0)	0 (0)	39 (24)	0 (0)	37 (23)	70 (43)	17 (10)	163
New York, USA	100	97.9	91 (14)	72 (11)	112 (17)	55 (8.4)	302 (46)	0 (0)	20 (3.1)	652
Birmingham, UK	100	99.5	6 (3.1)	3 (1.5)	37 (19)	0 (0)	73 (37)	68 (35)	8 (4.1)	195
Italy	53.9	85.5	0 (0)	0 (0)	14 (9.3)	7 (4.6)	23 (15)	104 (69)	3 (2)	151
Israel	42.8	100	55 (4.4)	71 (5.6)	294 (23)	144 (11)	172 (14)	298 (24)	227 (18)	1,261
Thailand	27.6	55.1	8 (11)	9 (12)	20 (27)	16 (22)	10 (14)	0 (0)	10 (14)	73
South Korea	100	95.1	9 (3.4)	16 (6)	35 (13)	24 (9)	132 (49)	36 (13)	16 (6)	268
Japan	100	NA	0 (0)	0 (0)	17 (15)	10 (8.7)	27 (23)	23 (20)	38 (33)	115
Multisite	11.7	NA	282 (8.3)	456 (13)	502 (15)	178 (5.2)	942 (28)	641 (19)	394 (12)	3,395
Total										15,468

* The mean percentages of patients for each primary focus of infection from all the studies were as follows:
5% for infective endocarditis, 8% for osteoarticular, 19% for SSTI, 9% for pleuropulmonary, 26% for line-related, 24% for no focus/unknown and 11% for other foci
MRSA, methicillin-resistant Staphylococcus aureus; HCA, Healthcare associated; SSTI, skin and soft tissue infection

** Line-related bacteremia was not reported in this study

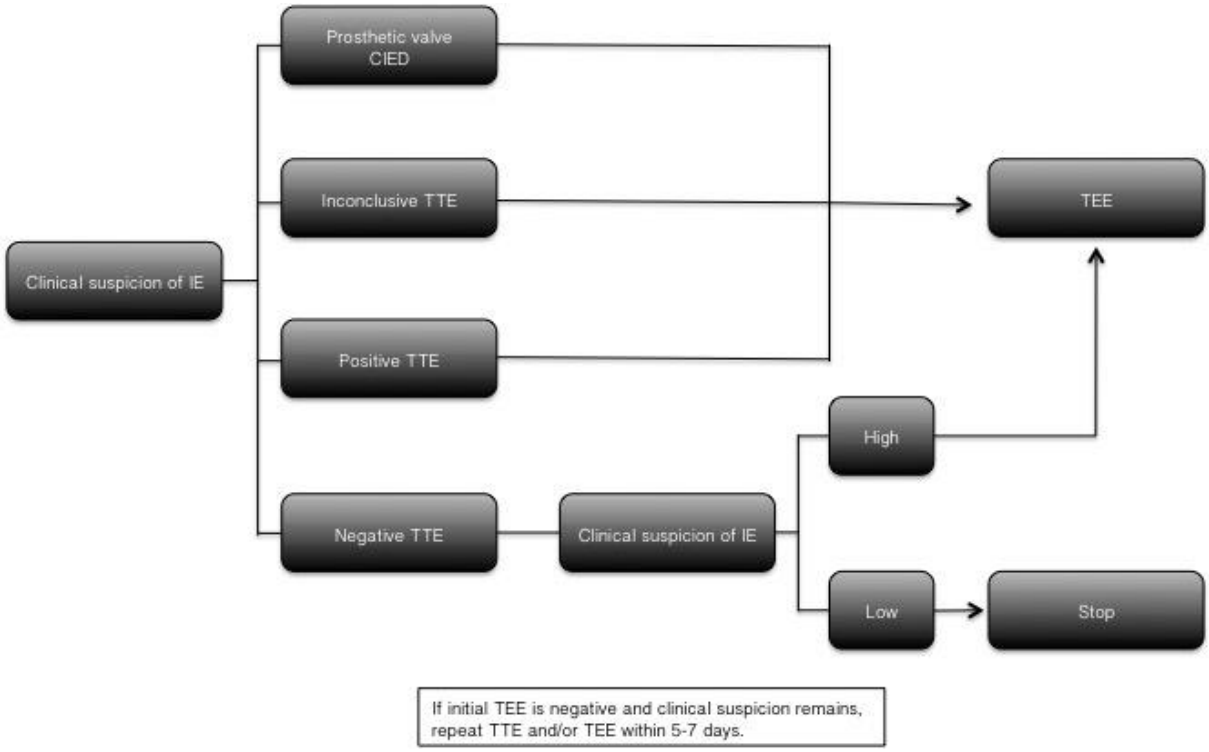
*** Note: Unclear whether IE and osteoarticular infection are a primary focus either than a metastatic complication

Table 2: Predictive risk factor of infective endocarditis with MSSA SAB (Tande *et al*)[12] and MRSA SAB (Buitron de la Vega *et al*)[13]

Tande *et al*	Buitron de la Vega *et al*
Prolonged bacteremia	Intravenous drug use
The presence of an CIED	Prolonged bacteremia
The presence of a prosthetic valve	Catheter-related infection
The presence of a prosthetic joint	Dialysis dependency
Community onset	Prosthetic valve structural cardiac abnormalities
	Structural cardiac abnormalities
	Previous infective endocarditis
	Vertebral/non-vertebral osteomyelitis

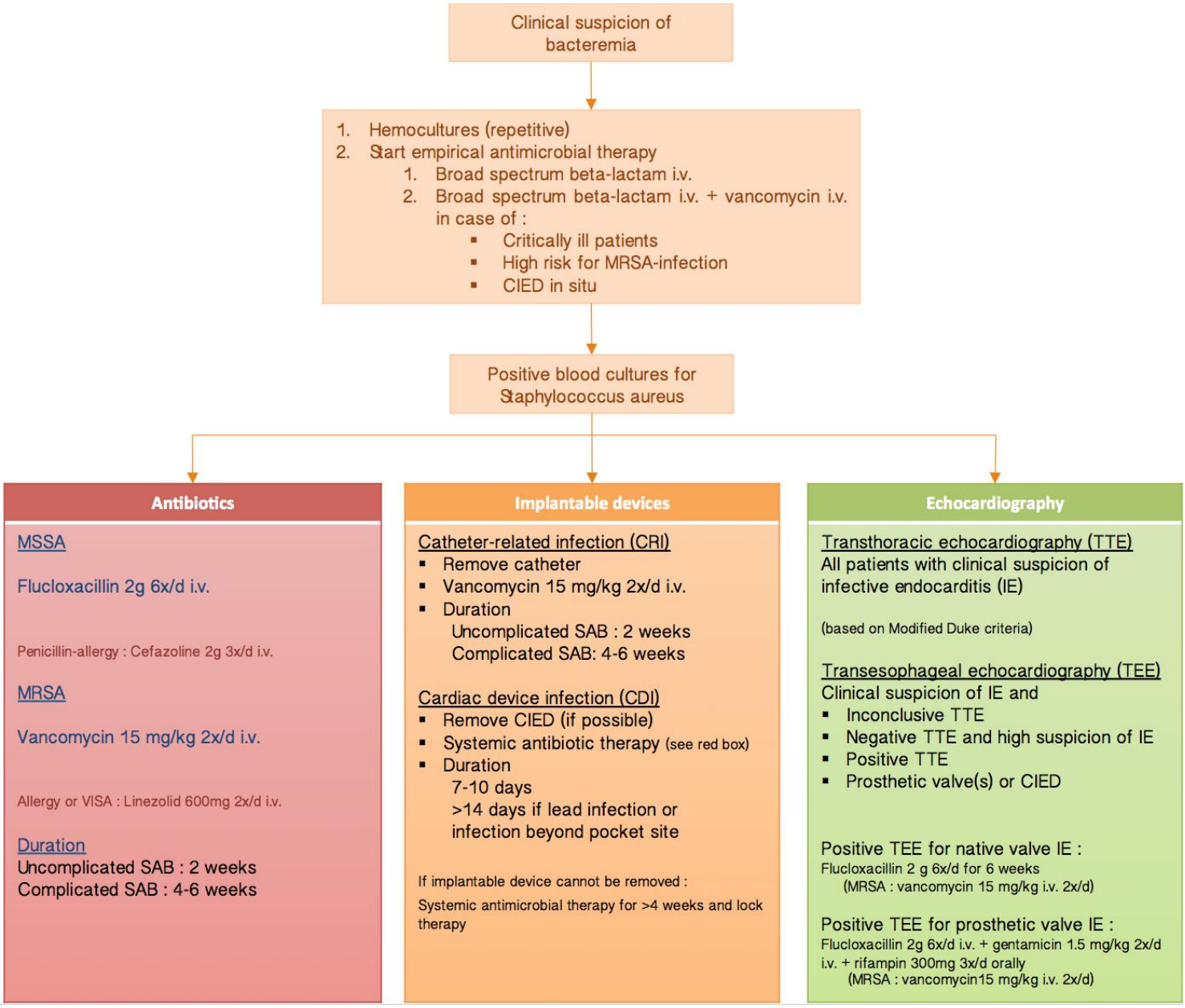
MSSA = methicillin-sensitive Staphylococcus aureus; SAB = Staphylococcus aureus bacteremia; MRSA = methicillin-resistant Staphylococcus aureus; CIED = cardiac implantable electronic device

Figure 1: European Society of Cardiology guidelines and indications for echocardiography in Staphylococcus aureus bacteremia patients.[14]



IE = infective endocarditis; TTE = transthoracic echocardiography; TEE = transesophageal echocardiography; CIED = cardiac implantable electronic device

Figure 2: Practical protocol for *Staphylococcus aureus* bacteremia management



MSSA = methicillin-sensitive *Staphylococcus aureus*; MRSA = methicillin-resistant *Staphylococcus aureus*; VISA = vancomycin intermediate *Staphylococcus aureus*; SAB = *Staphylococcus aureus* bacteremia; CIED = cardiac electronic implantable device; i.v. = intravenous

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