2026 Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) on Staphylococcus aureus Bacteremia: Risk Stratification, Diagnostic Evaluation, and Management of Adults and Children

Consensus Statement 1 on the Risk Stratification of Patients with *Staphylococcus aureus* Bacteremia

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Executive Summary

Overview

Risk stratification seeks to identify individuals at low or increased risk for deep-seated or metastatic foci of *Staphylococcus aureus* infection, or relapse of infection, based on the presence or absence of certain risk factors. Risk stratification enables classification of patients into *Staphylococcus aureus* bacteremia (SAB) with and without deep-seated or metastatic foci of infection, and it is crucial for the diagnostic evaluation and tailoring the management plan to each patient's specific SAB-related diagnoses. The primary audience for this consensus statement is clinicians evaluating and treating patients with SAB.

Clinical question 1
In patients with SAB, which risk factors are associated with deep-seated or metastatic foci of infection (e.g., infective endocarditis, osteomyelitis, deep tissue abscess, septic thrombophlebitis, cardiac device-associated infection, septic arthritis,) or relapse of infection?

Consensus statements for the adult population

- The panel suggests stratification based on risk factors associated with deep-seated or metastatic foci of infection or relapse of infection and ongoing clinical assessment to guide the diagnostic evaluation, and treatment plan (Figure 1) (consensus).
- Because individual risk factors lack sufficient negative predictive value to exclude deep-seated or metastatic foci of infection, the panel suggests a risk stratification approach using:
    - Key risk factors consistently associated with deep-seated or metastatic foci of infection or relapse of infection: (1) community-onset SAB (2) positive blood culture obtained ≥48 hours after the first positive blood culture, and (3) presence of an intracardiac device **AND**
    - Other important risk factors: predisposing heart valve conditions, injection drug use, endovascular graft, SAB in prior 90 days, signs or symptoms of a deep-seated or metastatic focus of infection, embolic events, more than one non-contiguous focus of infection, and unknown focus (consensus).

Remarks for the adult population

- Risk stratification promotes appropriate diagnostic evaluation, enabling classification of patients into SAB with and without deep-seated or metastatic foci of infection. This approach guides individualized patient management decisions including source control interventions, antibiotic choice, and duration of therapy. It aims to establish greater precision in diagnosis to avoid both undertreatment and overtreatment.
- The terms "uncomplicated" and "complicated" SAB are subjective, imprecise, and inadequate to guide management. The panel suggests using terms that refer to the risk of a specific adverse outcome, i.e., "low risk" or "increased risk" of deep-seated or metastatic foci of infection or relapse of infection.
- Validation of the risk stratification framework is needed.

Consensus statements for the pediatric population

- The panel suggests that all children with SAB are evaluated for a deep-seated focus of infection (consensus).
- Data are insufficient to define a group of children with SAB who are at low risk of deep-seated or metastatic foci of infection or relapsed bacteremia (consensus).

Remarks for the pediatric population

- There are age-related differences in the epidemiology and pathophysiology of SAB and comorbidities, which make it unclear to what extent outcomes and risk factors identified in studies focusing on adults can be directly applied to pediatric practice.
- Children with SAB usually have a clinically or diagnostically identifiable focus of infection, most commonly a musculoskeletal source in community-onset infections.

- Neonates with SAB are less likely to have a focus of infection while also having a higher rate of endocarditis; such patients should be considered separately from older children. The observed higher risk of endocarditis in neonates/premature infants may be at least partly attributable to other comorbidities and/or the need for invasive procedures.
- In all children with SAB, a symptom- and history-based approach to evaluation for the source of bacteremia is warranted.
- Positive blood cultures obtained ≥48 hours after the first positive blood culture may be associated with the presence of deep-seated or metastatic foci of infection (e.g., osteomyelitis, endocarditis, septic thrombophlebitis).

Introduction

Background

Staphylococcus aureus bacteremia (SAB) has become increasingly complex over the past few decades with increasing rates of comorbidities and device-related infections [1, 2]. It is diagnosed by the presence of at least one blood culture positive for *Staphylococcus aureus (S. aureus*) and clinical signs or symptoms of infection. While *S aureus* is a common colonizer of the skin and mucous membranes, it is rarely considered a contaminant when isolated from blood culture.

Common terminology used to describe aspects of SAB are included here and in the Supplementary Table of definitions. The site of entry into the body is called the "portal of entry." Sometimes, at this site of barrier crossing, a focus of infection is established, such as a skin and soft tissue infection, a respiratory infection, and a venous catheter-related infection. Bacteria can also enter the body through direct inoculation especially when foreign bodies are involved, via accidental trauma, procedural intervention, or injection drug use. In some cases, no infection develops at the portal of entry, but the bacteria enter the bloodstream where they are eliminated by the immune system, or alternatively, spread hematogenously to establish a focus of infection at a distant site. Once an infection is established either at the portal of entry or at the site of initial hematogenous spread, *S. aureus* can disseminate from this focus of infection to distant sites in the body either through direct extension or through the bloodstream (metastatic seeding). Occasionally this dissemination can occur as a result of an embolic event, for example, in the setting of endocarditis.

Infective foci (or "foci of infection") can be superficial or involve deep tissues. Superficial foci are skin and soft tissue infections (SSTIs), including abscesses, and venous catheter-related infections. A deep-seated focus is present when infection involves deeper, sterile tissues or organs or foreign material; examples include endocarditis, osteomyelitis, pneumonia, lung abscess, splenic abscess, psoas abscess, septic thrombophlebitis, and cardiac device infection. During bacteremia, *S. aureus* can be isolated from the urinary tract; however, the urinary tract is rarely considered a focus of infection, especially in the absence of urinary tract instrumentation or structural abnormalities [3-5].

In the case of metastatic seeding, the term "primary focus" (known or unknown) denotes the infective focus that developed first and then hematogenously seeds other sites ("secondary foci"). These terms are often used when several foci are present and a sequence of events is likely (e.g., endocarditis with subsequent splenic metastatic foci). The risk of metastatic foci varies by primary focus; in one study analyzing the clinical course of SAB, multiple foci were diagnosed in 16% of patients with catheter-related SAB compared to 65% of patients with *S. aureus* endocarditis as the primary focus [6]. Deep-seated or metastatic foci of infection are associated with significant morbidity, relapse of infection, and mortality [7-9]. However, SAB is a heterogeneous disease, and foci of infection are potentially numerous, often initially inapparent, and not easily identifiable with a single diagnostic modality [7, 8, 10]. This heterogeneity and complexity highlight the central challenge of determining the optimal diagnostic evaluation and treatment strategy for each individual patient.

The traditional classification of SAB as “uncomplicated” or “complicated” was initially developed to guide management. However, these terms are inconsistently defined in the literature and are neither sensitive nor specific for identifying deep-seated or metastatic foci of infection [6, 11-13]. Additionally, deep-seated or metastatic foci are often inapparent at presentation and become evident only during the clinical course or following diagnostic imaging [12]. Another limitation of this binary classification is that patients labeled as having “complicated SAB” are typically treated with prolonged antibiotic therapy (e.g., ≥ 4 weeks), regardless of whether or not a deep-seated or metastatic focus of infection has been confirmed. This approach may result in overtreatment, with unnecessary antibiotic exposure and adverse effects [12]. Categorizing patients as “uncomplicated” or “complicated” without identifying all the foci of infection, on the other hand, may lead to antibiotic undertreatment and failure to perform necessary source control interventions.

To address these issues, we developed a risk stratification framework to assess each patient’s risk for deep-seated or metastatic foci of infection or relapse, inform diagnostic evaluation, and classify patients by their final diagnosis, ultimately guiding treatment decisions. By integrating evidence across diverse clinical scenarios, this framework aims to support more nuanced, structured, and risk-informed decision-making.

Purpose and objectives

The objective of the panel was to identify risk factors associated with “deep-seated or metastatic foci of infection”, “infective endocarditis”, and “relapse of infection” in order to propose a framework for risk stratification.

Scope

This consensus statement is intended for use by adult and pediatric healthcare professionals including physicians, advanced practice providers, and pharmacists who care for patients with SAB. The target audience includes but is not limited to infectious diseases specialists, hospitalists, emergency care clinicians, intensivists, and health systems research and policymakers.

Methods

Panel composition

The four chairs of the panel were selected by the leadership of IDSA and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID). Twenty-three additional panelists comprised the full panel: Nine from IDSA, 10 from ESCMID, one from the Pediatric Infectious Diseases Society (PIDS), one from the European Society for Paediatric Infectious Diseases (ESPID), one from both IDSA and the Society for Healthcare Epidemiology of America (SHEA), and one from IDSA, the Society of Infectious Diseases Pharmacists (SIDP), and the American Society of Health-System Pharmacists (ASHP). The panel included physicians and pharmacists with expertise in adult and pediatric infectious diseases and microbiology. Panelists were from diverse geographic distributions and years of clinical experience. IDSA staff oversaw all methodological, administrative, and logistical aspects of the guideline. The panel reviewed existing literature and brought in their professional experiences and clinical judgment.

Process

The panel pre-specified ten risk factors (listed below) and evaluated their association with three pre-specified outcomes of interest: (1) any deep-seated or metastatic foci of infection, (2) infective endocarditis, and (3) relapse of infection. These outcomes were selected because they are clinically meaningful, directly relevant to patients and amenable to modification through diagnostic evaluation and therapeutic management. Mortality, by contrast, was not chosen as an outcome, as it is strongly influenced by non-modifiable factors such as age or comorbidities (e.g., active cancer). The ten pre-specified risk factors were selected by the panel using the following criteria: (1) feasibility of assessment early in the course of SAB, (2) clinical plausibility as predictors of the selected outcomes, (3) prior evidence suggesting an association with these outcomes in clinical studies, and (4) historical relevance, with several criteria used in prior definitions of "complicated SAB".

We included studies that reported data from at least 100 patients with SAB and evaluated the association between at least one pre-specified risk factor and one of the outcomes of interest. For studies reporting composite outcomes that included at least one outcome of interest, data were included only if the association between a specific risk factor and the outcome of interest could be extracted and analyzed separately. Because of inconsistent definitions of risk factors, heterogeneous study populations and analytical approaches, we only included studies reporting a statistically significant association between a risk factor and an outcome in multivariate analysis. Studies that examined a risk factor–outcome pair but did not identify a significant association were not included. We acknowledge that approach introduces selection bias and limits our ability to quantify how many studies have evaluated each pair. However, considerable heterogeneity was present in the existing literature, given the variability in which risk factors and outcomes were included in multivariate models as well as in statistical methods applied. Additionally, studies did not consistently report the risk factors in their models that did not show a significant association in their analysis. Within this context, the panel viewed our process as a pragmatic approach to focus on the most relevant evidence, manage study heterogeneity, and navigate the large number of studies that only indirectly examined these associations.

<u>Risk factors</u>

Ten pre-specified risk factors were evaluated for their association with outcomes of interest:

- Positive blood culture obtained ≥48 hours after the first positive blood culture,
- Community-onset SAB,
- Intracardiac device (e.g., prosthetic heart valve, pacemaker, defibrillator, or another implantable cardiac device),
- Injection drug use,
- Chronic renal failure requiring renal replacement therapy,
- Fever for ≥72 hours after starting antibiotics,
- Presence of joint prosthesis, which is deemed not infected at initial clinical evaluation,
- Skin findings consistent with metastatic infection,
- Central Venous Catheter (CVC)-related SAB,
- Skin and soft tissue infection as a source of SAB.

<u>Outcomes</u>

Three pre-specified outcomes were evaluated for their association with each of the 10 pre-specified risk factors:

- Any deep-seated or metastatic foci of infection other than infective endocarditis,
- Infective endocarditis,
- Relapse of infection.

Literature review:
A medical librarian designed the literature searches and Medical Subject Headings (MeSH) terms for Medline (OVID), Embase (OVID), and Cochrane. The formal literature searches were performed in July 2021, July 2023, and January 2025. Searches were limited to studies published in English. We excluded animal studies, conference/meeting abstracts, books/chapters, editorials, or correspondence. Reference lists of related articles and guidelines were reviewed for relevance to supplement the electronic searches Title and abstract screening was done by the methodologist (LAK) and verified by the two panelists (AJK, LS). Full-text screening was done by one panelist (AJK) and verified by another (LS). Search strategies are detailed in the supplementary file.

Consensus statement development
Consensus statements were developed using an iterative, structured process that incorporated input from both topic-specific subgroups and the full multidisciplinary panel. Subgroups drafted preliminary statements based on a comprehensive review of the available literature and expert clinical judgment. The consensus statements were also developed considering the balance of benefits and harms, feasibility, and resource use, while also providing practical advice for implementation and identifying key research gaps. Draft statements were then reviewed and discussed during multiple virtual panel meetings and refined through sequential rounds of asynchronous electronic feedback. Disagreements and areas of limited agreement were systematically identified, documented, and addressed through targeted discussion and revision. Statements were modified iteratively until convergence was achieved. Final consensus for each statement was defined a priori as agreement by >75% of panel members. Consensus statements should be interpreted in the context of evolving evidence and are intended to support, not replace, individualized clinical decision making, while highlighting priorities for future SAB research. Panel members considered whether there was sufficient evidence to support the application of the same guidance to children, or whether available evidence supported development of alternative guidance.

Results

Adults' perspective

Summary of the literature review for the adult population
Among 5,106 titles and abstracts, we identified 28 studies that reported multivariable analyses with odds ratios (ORs) or hazard ratios (HRs) and corresponding confidence intervals (CI) showing a significant association between at least one risk factor and at least one of the outcomes of interest. Table 1 summarizes the statistical findings, while Supplementary Table 1 summarizes the main study characteristics.

The risk factor "**positive blood culture obtained ≥48 hours after the first positive blood culture**" was associated with endocarditis in ten studies [14-23] with metastatic foci in six studies [23-28], and with relapse of infection in one study [29] (Supplementary Table 2). Considerable heterogeneity existed across studies regarding the timing of the follow-up blood cultures. Most assessed blood cultures within 48 to 96 hours after the first positive blood culture, but there was variability in the reference point used to define the timing of the follow-up blood cultures. Some measured timing from the initial blood culture [14, 17, 19-22, 26, 27, 29] , while others reported from initiation of antibiotic therapy [15] or from appropriate or active antibiotic therapy [18, 23-25, 28, 30] .

"Community-onset SAB" was identified as a risk factor for endocarditis in eight studies [14, 18, 20, 22, 31-34], for metastatic infection in six studies [1, 24, 26, 28, 35, 36], and for relapse of infection in one study [29] (Supplementary Table 3). Community-onset was consistently defined by the occurrence of the first positive blood culture prior to or within 48 hours of hospital admission. Some studies included community-onset healthcare-associated infections (i.e., close healthcare contact such as intravenous therapy, wound care, attending hemodialysis clinic within 30 days prior, or more than one day of hospitalization within the prior 3 months, or residence in a nursing home [37]) within the broader category of community-onset SAB whereas other studies analyzed this as a separate category.

The risk factor "**Intracardiac device (e.g., prosthetic heart valve, pacemaker, defibrillator, or other implantable cardiac device)"** was associated with endocarditis in eleven studies [14, 16-22, 31, 38] (Supplementary Table 4). No studies reported an association between intracardiac device and metastatic foci or relapse of infection. Study inclusion criteria varied —some examined all types of intracardiac devices, while others focused on a single type. Among studies including multiple device types, some analyzed device-specific risks separately, whereas others combined them into a single category. All included devices were endovascular; newer leadless pacemakers and extra-vascular cardiac devices were not represented.

The risk factor "**Injection drug use"** was associated with endocarditis in five studies [14, 17, 18, 22, 34] and with metastatic foci in one study [28] (Supplementary Table 5). Right-sided endocarditis is a more common condition in those with injection drug use, and in these studies, many of the endocarditis cases diagnosed were right-sided. No studies reported an association between 'injection drug use' and relapse of infection. Definitions of injection drug use, timing of last injection drug use relative to the SAB episode, and the methodology of data collection varied across studies.

The risk factor "**Chronic renal failure requiring renal replacement therapy"** was associated with relapse of infection in three studies [39-41] (Supplementary Table 6). However, these studies did not clearly distinguish between relapse and re-infection. This is particularly relevant as re-infection, i.e., another infection with *S. aureus* unrelated to the first bacteremia episode, may be more common in this patient group due to indwelling devices, which are frequently accessed, e.g., during hemodialysis. No significant associations were reported with deep-seated or metastatic foci of infection or endocarditis.

The risk factor "**Fever for ≥72 hours after start of antibiotics"** was associated with endocarditis in two studies [16, 38] (Supplementary Table 7). Definitions of fever, data collection methods, and consideration of alternative causes of fever varied. No significant associations were reported with deep-seated or metastatic foci or relapse of infection.

The risk factor "**Presence of joint prosthesis which is deemed not infected at initial clinical evaluation"** was associated with relapse of infection in only one study [42] (Supplementary Table 8). No significant associations were reported with deep-seated or metastatic foci or endocarditis.

The risk factor "**Central venous catheter-related SAB"** was inversely associated (i.e., the risk for the outcome was lower when the risk factor was present) with endocarditis in one study [14] and with metastatic foci in another study [1] (Supplementary Table 9). No significant association was reported with relapse of infection.

We found no studies showing a significant association between **skin findings consistent with metastatic infection** and **skin and soft-tissue infection as the focus of infection** and any of our outcomes of interest.

Risk Stratification Framework for the adult population

The panel developed a risk stratification framework (Figure 1) to guide clinical assessment, diagnostic evaluation, and management of patients with SAB. While this framework has not been validated, it aims to improve clinical consistency and reduce ambiguity in risk assessment.

Considerations in selecting risk factors for inclusion in the framework

Three risk factors were most frequently reported as being associated with increased risk for at least one outcome of interest and thus, were designated as "key" risk factors:

- **Positive blood culture obtained ≥48 hours after the first positive blood culture** was most frequently and consistently identified as the strongest predictor of adverse outcomes. Although the literature varied in whether the 48-hour time point was defined relative to the time of the first positive blood culture or the start of active antibiotic therapy, the panel elected to define as ≥48 hours after the first positive blood culture regardless of when antibiotic therapy was started (Consensus Statement 2).
- **Community-onset SAB** is defined based on the first positive blood culture drawn either prior to hospitalization or within the first 48 hours of hospital admission, regardless of whether the patient meets healthcare-associated criteria [37].
- **Presence of an intracardiac device** (e.g., prosthetic heart valve, pacemaker, defibrillator, or another implantable intravascular cardiac device). The panel grouped all intracardiac devices, despite known differences in endocarditis risk, due to limited data distinguishing risk by device type and the consistently elevated risk observed across all device categories.

Three risk factors from our initial list were excluded from the framework.

- Chronic renal failure requiring renal replacement therapy was recognized as a significant comorbidity but not a strong predictor of SAB-specific risk [12]. The panel noted that many recurrent SAB episodes in this population reflect re-infection rather than relapse [39, 43], a distinction that is challenging to ascertain in observational studies. This uncertainty led to the exclusion of this risk factor.
- Fever ≥72 hours after starting antibiotics was recognized as a notable clinical sign but was excluded due to its low specificity for SAB-related complications. An association was reported in two studies only for the outcome endocarditis [16, 38] and was not observed in a more recent analysis [12]. Since fever can also be absent in patients with SAB and can be suppressed by antipyretic use, the panel determined it was not suitable for inclusion.
- Presence of a joint prosthesis deemed uninfected on clinical evaluation was considered a relevant comorbidity but only 1 study demonstrated an association with the outcome of relapse of infection [42]. Additionally, several studies [44-46] assessed this risk factor but identified a lack of significant association with deep-seated infection, endocarditis, or relapse. Consequently, this risk factor was excluded from the framework.

Few studies have examined the remaining four risk factors from our initial list (injection drug use, skin findings suggestive of metastatic infection, central venous catheter-related SAB, and skin and soft-tissue infection as the focus of infection). Injection drug use is described as a risk factor for endocarditis, with a moderate degree of evidence to support this association and was incorporated as a risk factor [14, 17, 18, 22, 34]. Skin findings suggestive of metastatic infection were not incorporated due to sparse literature, although they may be clinically important in certain scenarios. For example, Janeway lesions are a minor Duke criterion and should prompt investigation for endocarditis [47] . Similarly, skin and soft tissue infection as a focus of infection was not included due to limited evidence. Central venous catheter-related SAB may be protective based on limited evidence and therefore is unsuitable for predicting elevated risk [1, 14].

Recognizing that not all clinically relevant features of SAB risk have been systematically studied, the panel also drew upon clinical expertise to incorporate additional risk factors into the framework. Some of these were included despite limited published evidence, based on their consistent relevance in clinical practice and the difficulty of studying them rigorously. These factors include:

- SAB in the prior 90 days,
- Endovascular graft [48],
- Focal signs or symptoms suggestive of a deep-seated or metastatic focus of infection,
- Embolic events [49],
- Unknown focus of *S. aureus* infection,
- More than one non-contiguous focus of infection,
- Predisposing heart valve conditions [47].

Some of the risk factors are strongly supported by evidence specifically as predictors of endocarditis or are specifically associated with increased risk of endocarditis rather than other outcomes. These are therefore referred to as **endocarditis increased-risk features** and include:

- Presence of an intracardiac device,
- Positive blood culture obtained ≥48 hours after the first positive blood culture,
- Community-onset SAB,
- Injection drug use,
- Embolic events [49],
- More than one non-contiguous focus of infection,
- Predisposing heart valve conditions [47].

Additional factors not pre-specified or systematically reviewed were identified in some studies as potentially associated with increased risk for certain outcomes. However, the panel elected not to include these in the framework for several reasons. In some cases, the relevance or generalizability of the published associations was unclear. In others, the factors were considered difficult to operationalize in routine clinical practice or unlikely to be available across diverse care settings. Examples of these factors include C-reactive protein levels [50], *S. aureus* bacteriuria [51, 52], and blood culture time to positivity which is limited by lack of standardization of blood volume collected and transport time [34, 53]. Patients with rheumatoid arthritis have an increased risk for SAB [54]and for disseminated *S. aureus* infection[29, 35, 55], but comprise a small group of patients. Data in other immunocompromised populations are limited with one study suggesting no significant effect of neutropenia on deep-seated or metastatic foci or relapse [56]. In another study, there was no significant effect of immunosuppressive therapy on risk of SAB-related complications except in the subgroup of patients receiving immunosuppressive therapy other than steroids [57]. In a third study, immunosuppressive therapy was not associated with either osteoarticular infection or metastatic foci of infection [35]. There is little evidence to support risk associated with a non-joint prosthesis orthopedic hardware (e.g., spinal hardware), which is deemed not clinically infected at the time of initial evaluation[58]. Clinicians may choose to integrate some of these parameters and clinical features into their risk stratification approach based on their careful assessment of the primary literature and the characteristics of patients they care for.

Risk stratification

Because no single risk factor had an adequate negative predictive value to rule out deep-seated or metastatic infection, the absence of multiple risk factors—particularly the three key ones—was deemed necessary to identify a population at “low risk” for infective endocarditis, deep-seated or metastatic foci of infection, or infection relapse [12]. Evidence from recent randomized controlled trials [59, 60], observational studies [12, 61-63], and clinical experience supports the existence of such a low-risk population, although the specific criteria used vary. Two recent expert reviews, co-authored by members of this guideline panel, have proposed analogous risk stratification approaches using a more limited set of risk factors [64, 65].

Clinical evaluation of one of these approaches demonstrated a low incidence of deep-seated or metastatic infections in patients meeting comparable low-risk criteria [63]. Another study validated this strategy specifically in a cohort of patients with methicillin resistant *S. aureus* (MRSA) bacteremia [27]. The risk stratification framework presented here differs in several ways: it incorporates additional risk factors to enhance sensitivity, removes others to improve specificity, provides more precise definitions, and includes factors that can be readily assessed in clinical practice, facilitating implementation by frontline clinicians.

It is important to recognize that complications—endocarditis and deep-seated or metastatic infections—are common in patients with SAB, whereas the absence of risk factors is not. For example, one study reported that over 50% of patients with SAB had endocarditis or a metastatic or locally complicated infection [12]. In contrast, only about 10% of SAB cases met the low-risk criteria outlined in another study, defined by the absence of key risk factors [63]. Among those identified as low risk in prior studies, the infective focus was almost always a catheter-related infection (peripheral or central) or a skin and soft-tissue infection. Notably, catheter-related infection was the only factor found to be negatively associated with deep-seated or metastatic infection in our literature review. Low-risk cases were often hospital-acquired, consistent with the observation that community-onset infection is a key risk factor.

The risk of deep-seated or metastatic foci of infection exists on a continuum: the presence of more risk factors increases the likelihood of these complications, whereas the absence of risk factors decreases—but does not eliminate—the risk. A patient's risk profile may also evolve over time, underscoring the dynamic nature of SAB. The panel stresses the importance of ongoing clinical assessment, including repeated physical exams and follow-up blood cultures, to fully evaluate the risk of complications. Consequently, "low risk" should not be interpreted as "no risk". Patients in this category still require recommended evaluations and close monitoring to detect any emerging risk features. Conversely, patients with one or more risk factors, particularly any of the key ones, should be considered at “increased risk,” and warrant ongoing diagnostic investigation until a focus of infection has been identified or confidently excluded.

For the purposes of this framework, the panel defined “**low-risk**” as the absence of risk factors and “**increased-risk**” as the presence of any of the risk factors listed below:

Table 1. Risk factors for deep-seated or metastatic foci of infection or relapse among adult patients with SAB

Key risk factors:
• Community-onset SAB*

- Positive blood culture obtained ≥48 hours after the first positive blood culture*
- Presence of intracardiac device (e.g., prosthetic heart valve, permanent pacemaker automatic implantable cardioverter-defibrillator, left ventricular assist device)*

Other important risk factors:

- Predisposing heart valve conditions*
- Injection drug use*
- Endovascular graft
- SAB in the prior 90 days
- Focal signs or symptoms suggestive of a deep-seated or metastatic focus of infection
- Embolic events*
- More than one non-contiguous focus of infection*
- Unknown focus of infection

**Endocarditis increased-risk features*

Disclaimer: These risk factors are based on a review of the literature and expert opinion and do not represent an exhaustive or comprehensive list of all risk factors associated with increased risk SAB.

Principles underlying the risk stratification framework

- **Tailored diagnostic evaluation**: Patients stratified as increased risk should undergo a diagnostic evaluation tailored to their individual characteristics, clinical findings, and testing resources available locally. Involvement of an infectious diseases' specialist is recommended to support frontline clinicians in determining the most appropriate diagnostic strategy for each clinical scenario.
- **Systematic approach to evaluation for deep-seated or metastatic infection**: For patients at increased risk, further evaluation typically includes additional cardiac imaging (e.g., transesophageal echocardiography; see Consensus Statement 4), repeat blood cultures until clearance is documented (see Consensus Statement 2), and symptom/ exam-directed imaging (e.g., MRI of the spine for suspected spinal infection, venous duplex ultrasound for suspected vascular infection). If targeted investigations do not identify a primary focus, whole-body imaging may be warranted. While [18F]FDG-PET/CT can be highly informative, its availability varies widely and strategies combining different imaging modalities may be used to assess patients with an unknown focus (Consensus Statement 5).
- **Endocarditis-focused evaluation**: Because several risk factors also serve as increased-risk features for endocarditis, their presence should prompt a more intensive diagnostic evaluation aimed specifically at detecting endocarditis (Consensus Statement 4).
- **Risk-guided intensity of evaluation:** The intensity of diagnostic evaluation should be guided by the patient's overall risk profile, taking into account the number and nature of risk factors. When one or more risk factors are present that are strongly associated with deep-seated or metastatic foci (e.g., ongoing bacteremia) a more intense evaluation should be conducted, whereas it may be appropriate to limit the extent of evaluation in patients with fewer or other risk factors.
- **Multiple infectious foci may be present**: Diagnostic evaluation should not stop at the identification of a single focus. This is particularly important when endocarditis-specific risk factors are present—evaluation for endocarditis may need to continue even after another deep-seated focus has been found. Ongoing assessment is warranted if clinical findings or patient-specific risk factors suggest additional, undetected sites of infection.
- **Classification based on the presence or absence of deep-seated or metastatic focus with management tailored accordingly:** The presence of deep-seated or metastatic infection

should guide decisions regarding source control, antibiotic selection, and duration of therapy. If no deep-seated or metastatic foci are identified after appropriate evaluation, the case should be classified as "SAB without a deep-seated focus" and treated with a short duration (two weeks; Consensus Statements 6 and 7). If a deep-seated or metastatic focus of infection is identified, the case should be classified as "SAB with deep-seated or metastatic focus" and treated with an extended course (≥ four weeks), with source control interventions and exact antibiotic duration tailored to the focus identified.

- **Extended duration of therapy for certain risk features.** Longer durations of therapy, guided by the likely focus, may be appropriate in select scenarios (e.g., retained intracardiac device, recently placed endovascular graft, deep venous thrombosis at central venous catheter site), particularly in the setting of prolonged bacteremia, or if diagnostic testing is incomplete or indeterminate. In these situations, reassessment of source control should also be considered (Consensus Statement 7).

Rationale for the consensus statement for the adult population

When considering the balance of benefits and harms, feasibility, and costs, the panel concluded that a structured, systematic approach to risk stratification is preferable to the traditional "complicated/uncomplicated" classification or the absence of a formal strategy. This approach facilitates more accurate, equitable, and consistent management of SAB across diverse clinical settings.

Balance of benefits and harms

- Standardization of risk assessment, reducing subjective interpretation and reliance on imprecise terms such as "complicated" or "uncomplicated"
- Enhanced diagnosis of deep-seated and metastatic foci of infection, facilitating more effective source control and optimized antibiotic therapy which may reduce readmissions, relapse rates, and infection-related mortality
- Reduced overtreatment of patients initially stratified as increased risk but ultimately not found to have deep-seated or metastatic foci of infection on diagnostic evaluation and avoidance of potential harms of extended antibiotic therapy
- Greater equity in care through consistent application of objective criteria, potentially mitigating implicit bias and promoting uniform decision-making across diverse clinical settings
- Feasibility and acceptability to stakeholders, aligning with existing clinical resources, patient characteristics, goals of care, and clinician judgment

Costs and feasibility

- Acceptability to stakeholders is enhanced by providing a systematic approach to risk stratification and diagnostic evaluation of SAB.
- Costs associated with extended durations of therapy may be reduced if risk stratification is appropriately applied.
- Incidental findings from increased diagnostic testing may prompt additional evaluations or interventions unrelated to SAB.
- There is potential for delay in discharge if extended hospital stays are required to await advanced diagnostic results.
- Variability in test availability, such as transesophageal echocardiography (TEE) and [18F]FDG-PET/CT, may limit implementation across geographic regions.

- Local adaptation may be needed according to regional diagnostic capabilities.

Implementation considerations for the adult population

Practical advice

- **Initial Evaluation of SAB:**
    - **Initial Blood Cultures**: All individuals with suspected SAB should have at least two sets of blood cultures drawn (each set includes one aerobic and one anaerobic bottle). A single positive culture for *S. aureus* and clinical signs or symptoms of infection confirms the diagnosis. While contamination is possible, it is rare; therefore, a positive *S. aureus* blood culture should generally be considered a true infection [66].
    - **Clinical evaluation**: All patients with SAB should undergo a thorough history and physical examination. Relevant details include presence of intracardiac device, prosthetic device, or endovascular graft, central venous catheters, history of injection drug use, prior history of SAB and *S. aureus* infections.
    - **Follow-up blood cultures:** At least 2 sets of follow-up blood cultures should be obtained at 48 hours after sampling of the first positive culture and then repeated as either 1 or 2 sets every 24 to 48 hours until negative to document blood culture clearance (Consensus Statement 2).
    - **Transthoracic echocardiography (TTE)**: TTE should be routinely performed in all patients with SAB (Consensus Statement 3).
    - **Central Venous Catheter (CVC) management**: Due to increased risk of hematogenous complications and relapse, central venous catheters should be removed in patients with SAB [67, 68]. Peripheral venous catheters should be removed if identified as a focus of infection.
    - **Infectious Diseases (ID) Consultation**: ID consultation should be obtained when available to assist with risk assessment, further diagnostics, and treatment planning [69, 70].

- **Risk Stratification**: The terms "low-risk" and "increased-risk" SAB should be used rather than "uncomplicated" or "complicated" and patients stratified accordingly based on risk factors. This approach is used to inform further diagnostic evaluation. Most patients with SAB will fall into the "increased risk" category, necessitating further evaluation.
- **Diagnostic Evaluation**: The selection of diagnostic tests should be tailored based on clinical findings and patient-specific risk factors. For example, MRI spine should be performed in a patient with new or worsening back pain while a chest CT should be obtained in a patient with cough or pleuritic chest pain. The intensity of diagnostic evaluation should be guided by the patient's overall risk profile. Certain risk factors—such as ongoing bacteremia beyond 48 hours or the presence of an intravascular cardiac device—indicate a higher likelihood of deep-seated or metastatic infection. As the number of risk factors increases, so does the overall risk, often justifying a more extensive diagnostic evaluation before confidently excluding a deep-seated or metastatic focus. Conversely, in patients with fewer risk factors and with lower clinical suspicion, it may be appropriate to limit the extent of evaluation.
- **Transesophageal echocardiography (TEE)**: Decisions regarding TEE should be guided by presence of endocarditis increased-risk features as well as TTE quality and the anticipated impact on management (Consensus Statement 4).
- **Whole-body imaging**: In patients with SAB and unknown focus following initial and risk-informed diagnostic evaluation, [18F]FDG-PET/CT or combinations of imaging modalities (e.g.,

thoracic/ abdominal CT, duplex venous ultrasound, etc.) that evaluate the most likely sites of infectious foci should be considered to evaluate for deep-seated or metastatic infection(Consensus Statement 5)

- **Ongoing Monitoring**: Patients should be monitored throughout and after antibiotic treatment for new symptoms or signs of metastatic infection. Any change in clinical status should prompt re-evaluation and potential reclassification of the patient's final diagnosis.
- **Classification of final diagnosis**: Management decisions should be based on whether a deep-seated or metastatic focus of infection is identified. Patients without such findings after appropriate evaluation should be classified as "SAB without deep-seated focus of infection," regardless of initial risk category **(Consensus Statements 6 and 7)**. Patients found to have a deep-seated or metastatic focus of infection should have source control interventions as well as treatment choice and duration tailored according to the identified focus.

Barriers

- **Adoption of New Terminology:** Provider reluctance or unfamiliarity with the terms "low-risk"/ "increased-risk" for risk stratification may slow implementation.
- **Diagnostic Limitations:** Access to imaging (e.g., TEE, [18F]FDG PET/CT) may be limited, hindering thorough evaluation in some settings.
- **Resource Constraints**: The scarcity of infectious disease specialists in certain regions may limit the ability to implement and support risk stratification consistently.
- **Evidence Gaps**: Limited published data directly evaluating the new risk stratification framework may pose challenges to widespread adoption.
- **Advocacy and Education:** Successful implementation will require clinical advocates, broader education, and system level interventions to promote uptake and integration into practice.

Research needs for the adult population

Further studies are needed to:

- Define the "low-risk" and "increased-risk" SAB populations more precisely
- Determine the diagnostic accuracy of individual and combined risk factors for identifying deep-seated or metastatic infection
- Clarify the clinical utility of specific diagnostic tests at various stages of the risk stratification process
- Identify when additional interventions or extended antibiotic therapy are warranted, when risk factors are present, but a deep-seated or metastatic focus is not confirmed
- Differentiate between community-onset SAB and community-acquired, healthcare-associated SAB as distinct risk categories
- Better characterize the risk of endocarditis associated with various intravascular cardiac devices
- Expand understanding of risk features for other deep-seated infections (e.g., spinal osteomyelitis, septic arthritis, thrombophlebitis)
- Develop and validate a diagnostic algorithm based on the risk stratification framework

Pediatrics perspective

Summary of the literature review for the pediatric population

The pediatric population encompasses individuals from birth through young adulthood, a period marked by substantial variation in susceptibility to infection and in the prevalence of risk factors.

While some adolescents may have risk factors for adverse outcomes of SAB similar to those observed for adults, younger children and neonates (<28 days of age, particularly those born prematurely) require separate consideration.

There are limited data to guide the identification of children with SAB who are at low risk for deep-seated or metastatic foci of infection or relapse. This is primarily because most children with SAB present with a clinically or diagnostically identifiable infectious focus—often including deep-seated foci—at the time of evaluation [25, 71-75]. Although the site of infection is a key determinant of treatment duration, it remains unclear to what extent the presence of a deep-seated focus should be considered an adverse outcome in children. Notably, a study of 36 children without evidence of deep-seated or metastatic infection (from 631 SAB episodes) reported an 8.3% mortality rate directly attributable to SAB, and one-third required intensive care [73]—rates comparable to or higher than those reported in studies of children with more complex presentations [71, 76-78]. These findings underscore the need for caution in all pediatric SAB cases, even when no deep infection is initially identified.

Outside the neonatal period, only 5–21% of pediatric SAB cases lack an identifiable focus[25, 71-74]. In a three-center observational study of MRSA bacteremia including 232 children [79], the most common foci detected were:

- Musculoskeletal (40.5%; osteomyelitis, septic arthritis, pyomyositis, orthopedic hardware infections),
- Central venous catheters (22.4%),
- Skin and soft tissue infections (15.5%),
- Pneumonia (9%),
- Septic thrombophlebitis (3%).

Infective endocarditis was identified in 1.7% of pediatric cases, although echocardiography was performed inconsistently. Engagement of infectious diseases specialists has been associated with more frequent identification of infection foci and more appropriate management of deep infections in children with SAB [80, 81].

Intrinsic host factors in the pediatric population influence the likelihood of specific foci of infection. For example, a history of congenital or acquired heart disease significantly increases the risk for endocarditis in children with SAB and should be systematically assessed through history and physical exam (Consensus Statements 3 and 4).

Neonates (<28 days of age) represent a distinct population:

- In a large multicenter Australian/New Zealand study [71], a focus was not identified in 43% of neonates with SAB (n=49), compared to a focus being identified in 91% of older children (1-18 years). In this study, osteoarticular infections contributed to 59% of cases among older children (n=416).
- In the setting of SAB, neonates compared to older children have a higher reported risk of endocarditis (10-49% vs 1-6%) [71, 82, 83] and higher mortality (8% vs. 2%) [74]
- S. aureus is a leading cause of late-onset sepsis in hospitalized premature neonates, with risk likely exacerbated by comorbidities such as congenital heart disease and the need for central venous access [84].

The duration of SAB in children likely impacts the risk for complications and deep-seated foci of infection [25, 79]:

- In Hamdy's study [79], each additional day of MRSA bacteremia increased the odds of complications (septic emboli, metastatic infection, or death) by 50%.
- Other studies have demonstrated similar relationships between bacteremia duration and risk of endocarditis and osteomyelitis in children [72, 83, 85].
- In a retrospective study of 298 children with SAB, persistent bacteremia beyond one day was associated with a higher likelihood of clinically unsuspected deep-seated foci of infection (OR 4.99; 95% CI, 1.16–19.8), though such foci were identified in only 11 cases (3.7%) [75].
- In a microbiologic study of pediatric MSSA osteomyelitis across two centers (n=250), SAB occurred in 57% of patients, with a median bacteremia duration of one day [86]. These findings suggest that even brief episodes of SAB are commonly linked to deep-seated infections; however, most children with short-duration bacteremia experience favorable outcomes when treated appropriately.

When SAB is related to a CVC, the timing of its removal impacts the risk of complications:

- In a single-center study of 112 children with CVC-related SAB, delayed catheter removal (≥4 days after the initial positive culture) was associated with a higher rate of complications compared with earlier catheter removal (44% vs. 22%, p=0.02) [87]. Complications included venous thrombosis, metastatic seeding of infection, endocarditis, recurrence, and death. Multivariable analysis demonstrated that complications were more common in those with prolonged bacteremia (≥ 4 days of positive blood cultures, aOR 3.2), delayed or no venous catheter removal (aOR 2.6), and thrombocytopenia (aOR 2.5).
- However, another single-center study of 394 children with SAB (134 (34%) with CVC-related infections) found a reduced risk of complications – including secondary metastatic foci of infection-- when the primary source was CVC-related compared with other sources such as osteomyelitis or pneumonia; multivariable aOR 0.40; 95%CI 0.15-1.03, after adjusting for methicillin-resistance, timing of source control [including catheter removal], and duration of bacteremia [76]. This suggests that aggressive evaluation for metastatic foci in children with *S. aureus* CVC-related bacteremia outside the neonatal period may not always be necessary if the catheter is promptly removed and follow-up blood cultures are negative.
- In the multicenter study of MRSA bacteremia mentioned above, SAB in a patient with a catheter present (n=52) had a lower likelihood of treatment failure when the catheter was considered the only focus [79]. Such a finding likely reflects the nature of this infection being localized to the catheter rather than another focus.

With respect to immunocompromising conditions, a single-center study found that >15% of children with malignancy and SAB had deep-seated infections, and 73% of all SABs were CVC-related [88].

Certain characteristics of *S. aureus* strains may influence the risk of deep-seated or metastatic infection. In some pediatric SAB studies, infections caused by methicillin-resistant *S. aureus* (MRSA) have been more frequently linked to deep foci and poorer outcomes, although these findings are not consistent across all studies[71, 75, 76, 83]. Importantly, adverse outcomes attributed to MRSA may be more reflective of strain-specific virulence factors than of methicillin resistance itself [89].

In a study of 353 SAB isolates from hospitalized children in Australia and New Zealand, whole-genome sequencing revealed a strong association between the presence of Panton-Valentine leukocidin (PVL) genes and deep foci of infection—including osteoarticular, endovascular, pleuropulmonary, and multifocal disease[89]. PVL-positive SAB was also associated with increased odds of composite adverse outcomes in community acquired SAB cases (OR 2.57; 95% CI 1.04–6.22, P=0.038 in multivariable logistic regression analysis). However, as in other studies, most deep infections were suspected clinically at presentation. There is substantial geographic variability in the prevalence of PVL-positive *S. aureus* strains, as well as their association with methicillin-resistance [90, 91]. Consequently, findings from this study may not be generalizable to other settings. Moreover, PVL testing is not routinely available in many healthcare systems, limiting its clinical utility for guiding management decisions [90].

Rationale for the Consensus Statement for the Pediatric Population
Clinicians should maintain a high index of suspicion for deep-seated foci of infection in all children with SAB, given the consistently high rates reported across multiple studies. This consensus statement prioritizes the avoidance of missing deep-seated foci of infection, which may lead to relapse, disease progression, or other serious complications. Although diagnostic evaluation and monitoring carry financial costs, the consequences of missed diagnoses likely exceed these expenses. Diagnostic strategies should be largely guided by clinical history and physical examination—an approach that is both essential and feasible for all pediatric providers. However, access to advanced diagnostic imaging may be limited in certain settings, as discussed below.

Implementation considerations for the pediatric population

Practical advice:

- **Initial Blood Cultures**: All children with suspected SAB should have blood cultures drawn. A single positive culture for *S. aureus* confirms the diagnosis. While contamination is possible, it is rare; therefore, *S. aureus* bacteremia should generally be considered a true infection.
- **Clinical evaluation:** All children with SAB should undergo a thorough history and complete physical examination. Repeat blood cultures should be obtained after the initial positive culture (regardless of whether antibiotic therapy has begun) to assess ongoing bacteremia (Consensus Statement 2).
- **Management and Consultation:** Source control should be considered for deep-seated foci of infection. Central venous catheters should be removed promptly. Infectious diseases consultation should be obtained when available to assist with risk assessment, further diagnostics, and treatment planning.
- **Cardiac Imaging**: A transthoracic echocardiogram is advised for children with congenital heart disease, signs or symptoms of endocarditis, or persistent bacteremia (Consensus Statement 3).
- **Diagnostic Imaging**: The selection of diagnostic tests should be tailored based on clinical findings and patient-specific factors. Tests may include cardiac imaging, cross-sectional imaging, or whole-body imaging to evaluate for deep-seated or metastatic infection.
- **Ongoing Monitoring**: Patients should be monitored throughout and after antibiotic treatment for new symptoms or signs of metastatic infection. Any change in clinical status should prompt re-evaluation.

Barriers:

- Access to Diagnostic Imaging: Advanced imaging in children (e.g., MRI, echocardiography) may be limited in many centers.

- Need for Sedation: Young children may require sedation for MRI or echocardiography, introducing anesthesia-related risks.
- Vascular access challenges: In select cases a CVC may be the only reliable vascular access available for a child, and its removal would leave a child without vascular access.
- Interpretation Challenges: Echocardiography interpretation can be complex, particularly in children with congenital heart disease, requiring experienced personnel.
- Availability of Pediatric Specialists: Limited access to pediatric subspecialists (including pediatric infectious diseases) and pediatric surgeons could impact diagnostic evaluation as well as the potential to achieve source control.

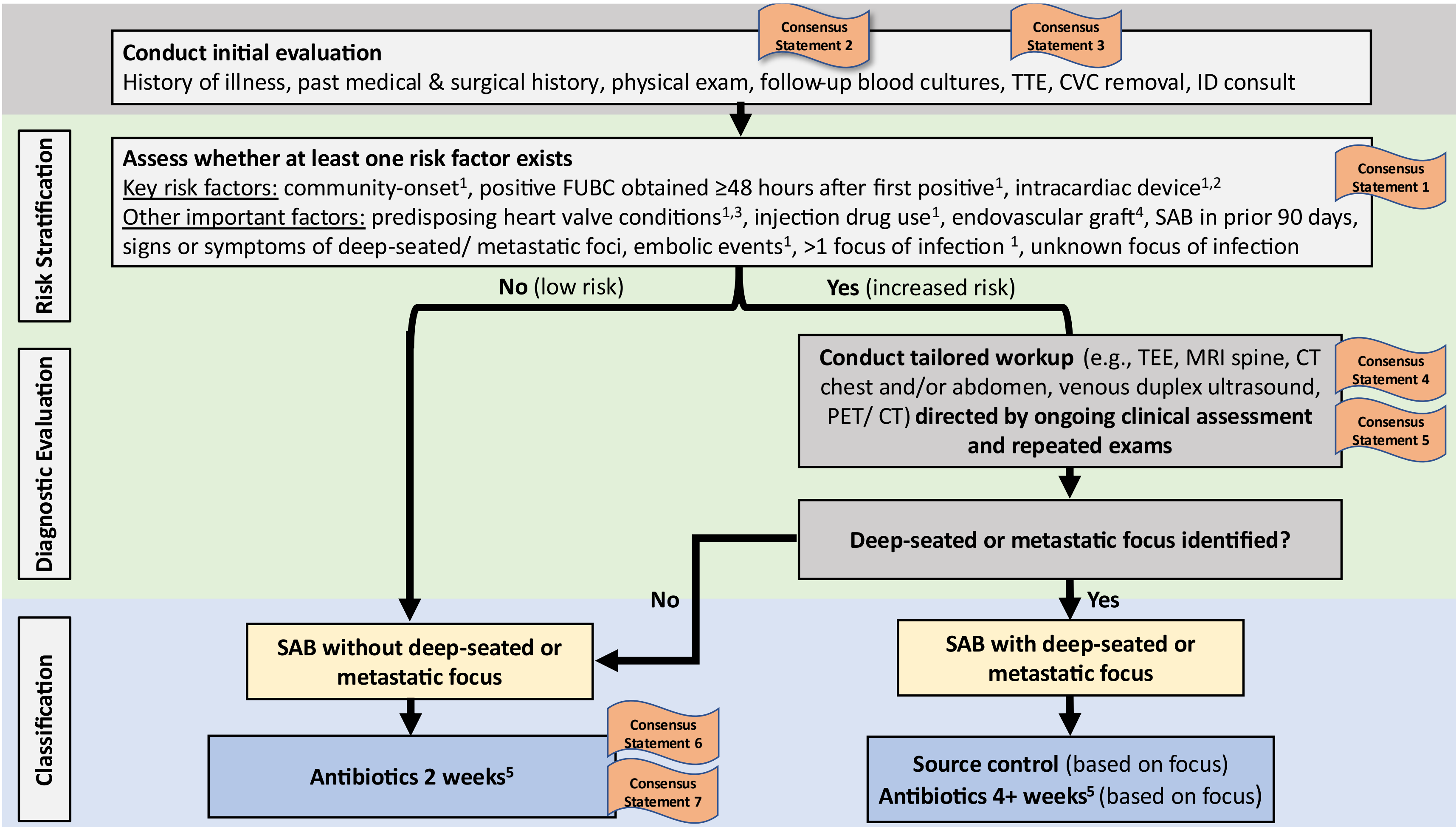
Research needs for the pediatric population

Appropriate, patient-centered outcome measures for SAB must be defined specifically for the pediatric population—and potentially tailored to distinct age groups such as neonates, children, and adolescents. To identify children at low risk for adverse outcomes of SAB, large multicenter studies are needed. Such studies would not only support the development of risk stratification tools but also help inform best practices for diagnostic evaluation in pediatric SAB.

Limitations

This manuscript was developed using a consensus-based methodology rather than a formal clinical practice guideline process. Although a comprehensive literature review was performed, formal systematic review methods and structured evidence grading were not required. Consensus statements reflect a synthesis of available evidence and expert clinical judgment, particularly in areas where high-quality randomized data and systematic reviews are limited. In this SAB guideline project, where clinical presentations are heterogeneous and many management questions lack definitive trial data, this approach allows translation of imperfect but clinically relevant evidence into practical consensus statements. Because of inconsistent definitions of risk factors, heterogeneous study populations, and variable analytic methods across studies, we limited inclusion to studies demonstrating statistically significant associations between risk factors and outcomes in multivariable analyses for the adult consensus statement. This may have excluded studies reporting null associations and could overrepresent positive findings. However, this approach was intended to prioritize factors most likely to represent independent risk in highly heterogeneous evidence base and to limit inclusion of associations potentially driven by confounding or analytic variability.

Figure 1: Framework for Risk Stratification and Diagnostic Evaluation of SAB in Adult Patients



Disclaimer: The listed risk factors are based on a review of the literature and expert opinion and do not represent an exhaustive or comprehensive list of all risk factors associated with increased risk SAB.

Figure 1. Framework for Risk Stratification and Diagnostic Evaluation of *Staphylococcus aureus* bacteremia (SAB) in Adult Patients.
This framework outlines the approach to risk stratification, diagnostic evaluation, and classification of adult patients into a final diagnosis of SAB with or without deep-seated or metastatic foci. It uses a stepwise approach to guide appropriate diagnostic evaluation, minimizing the risk of missed occult infectious foci while avoiding unnecessary prolonged antibiotic exposure in patients without confirmed deep-seated or metastatic foci of infection. An initial evaluation is performed in all patients with SAB that enables patients to be stratified into "low-risk" or "increased-risk" SAB. Patients stratified as "increased risk" will undergo tailored diagnostic evaluation based on clinical findings (e.g., symptom/exam-directed imaging) and individual patient characteristics. Due to the dynamic nature of SAB, ongoing clinical assessment is necessary to guide diagnostic evaluation. This approach ultimately supports appropriate classification of patients into a final diagnosis of SAB with or without a deep-seated or metastatic foci of infection enabling treatment decisions to be tailored accordingly. Please refer to Consensus Statements (indicated by flags) for additional detail.

Footnotes

Abbreviations: *CT: Computed Tomography; CVC: central venous catheter; DVT: deep vein thrombosis; FUBC: follow-up blood cultures; ID: infectious diseases; MRI: magnetic resonance imaging; PET/CT: Positron Emission Tomography/Computed Tomography; SAB: Staphylococcus aureus bacteremia; TEE: transesophageal echocardiography; TTE: transthoracic echocardiography.*

[1]Endocarditis increased-risk features for endocarditis: presence of an intracardiac device[2], predisposing heart valve conditions,[3] positive blood culture obtained ≥48 hours after the first positive blood culture, embolic events, more than one non-contiguous focus of infection, community-onset SAB, injection drug use.

[2]Intracardiac device: prosthetic heart valve, permanent pacemaker, automatic implantable cardioverter-defibrillator, left ventricular assist device.

[3]Predisposing heart valve conditions as defined by 2023 Duke-ISCVID criteria [47].

[4]Endovascular graft: synthetic bypass graft in the vessel wall.

[5]Longer durations of therapy, guided by the likely focus, may be appropriate in select scenarios (e.g., retained intracardiac device, recently placed endovascular graft, DVT at central venous catheter site), particularly in the setting of prolonged bacteremia, or if diagnostic testing is incomplete or indeterminate. In these situations, reassessment of source control should also be considered.

Table 1: Summary of the effect estimates assessing the association of the predefined risk factors with the outcomes of interest. Adjusted Odds Ratios (aOR), adjusted Hazard Ratio (aHR), and confidence intervals (CI) from multivariate analyses are shown.

Risk factor	**Outcome – Infective endocarditis**		**Outcome – Metastatic foci**		**Outcome – Relapse of infection**	
Risk factor	**Number of studies, [range of sample size]**	**Range of aOR (95% CI)**	**Number of studies, [range of sample size]**	**Range of aOR (95% CI)**	**Number of studies, [range of sample size]**	**Range of aHR (95% CI)**
Positive blood culture obtained ≥48 hours after the first positive blood culture	10 studies [198-2,008]	1.3 (1.0-1.7) – 45.6 (6.1-339.7)	6 studies [127-3,147]	2.4 (1.1-5.8) - 6.4 (2.0-19.7)	1 study [18,425]	2.3 (1.9-2.9)
Community-onset SAB	8 studies [274-13,040]	2.1 (1.9-2.4) - 5.0 (2.2 - 11.3)	6 studies [111-3,147]	1.8 (1.3-2.4) – 5.3 (3.3-8.6)	1 study [18,425]	1.1 (1.0-1.3)
Intracardiac device	11 studies [198-2,008]	2.0 (1.3-3.1) - 72.0 (10.2-510.9)	---	---	---	---
Injection drug use	5 studies [205-2,008]	3.1 (1.5-6.4) – 7.6 (3.1 - 18.6)	1 study [3147]	2.3 (1.3-4.1)	---	---
Chronic renal failure requiring renal replacement therapy	---	---	---	---	3 studies [758-80,166]	1.3 (1.1-1.6) – 25.2 (5.9-107.4)
Fever for ≥72 hours after start of antibiotics	2 studies [198-213]	3.1 (1.0-9.0) – 7.0 (2.4-21.0)	---	---	---	---
Presence of a joint prosthesis deemed not infected at the initial clinical evaluation	---	---	---	---	1 study [198]	17.6 (4.9-68.9)
Central venous catheter-related SAB	1 study [574]	0 (*)	1 study [2,348]	0.7 (0.6-0.9)		

* 95% confidence interval not reported.

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