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Staphylococcus aureus bacteremia: Using echocardiography to guide length of therapy

ABSTRACT

Echocardiography can help distinguish simple and uncomplicated bacteremias from true cases of infective endocarditis and guide the type and duration of antibiotic therapy in a more precise and cost-effective manner. Empiric long-term antibiotic therapy is no longer uniformly recommended for all cases of *S aureus* bacteremia, although experts disagree about the optimal length of therapy.

KEY POINTS

Methicillin-resistant *S aureus* (MRSA) may account for up to half of all cases of staphylococcal bacteremia. The proportion of MRSA isolates that are sensitive only to vancomycin has been increasing.

Hematuria in the setting of staphylococcemia is an important clue to coexisting *S aureus* infective endocarditis.

Transesophageal echocardiography (TEE) can visualize much smaller (≤ 8 mm) vegetations and can better detect complications, such as valve perforation and abscesses. Therefore, TEE permits earlier detection and initiation of therapy.

Infectious disease consultation is associated with improved clinical outcomes in patients with *S aureus* bacteremia.

HOW LONG should patients with bacteremia due to *Staphylococcus aureus* receive antibiotic therapy?

Here is the dilemma. *S aureus* bacteremia is serious, but *S aureus* endocarditis is even worse, it can be difficult to detect, and it is often associated with bacteremia. Therefore, 4 to 6 weeks of empiric antibiotic therapy has been standard for patients with *S aureus* bacteremia, with the aim of curing any occult endocarditis.

On the other hand, prolonged antibiotic therapy is expensive and can contribute to microbial resistance, already a major problem with *S aureus*. We now have echocardiography, especially transesophageal echocardiography (TEE), to help diagnose or rule out endocarditis. And in certain clinical situations (eg, if there is a removable focus of infection, such as an intravascular device¹⁻³), the likelihood of endocarditis is low.

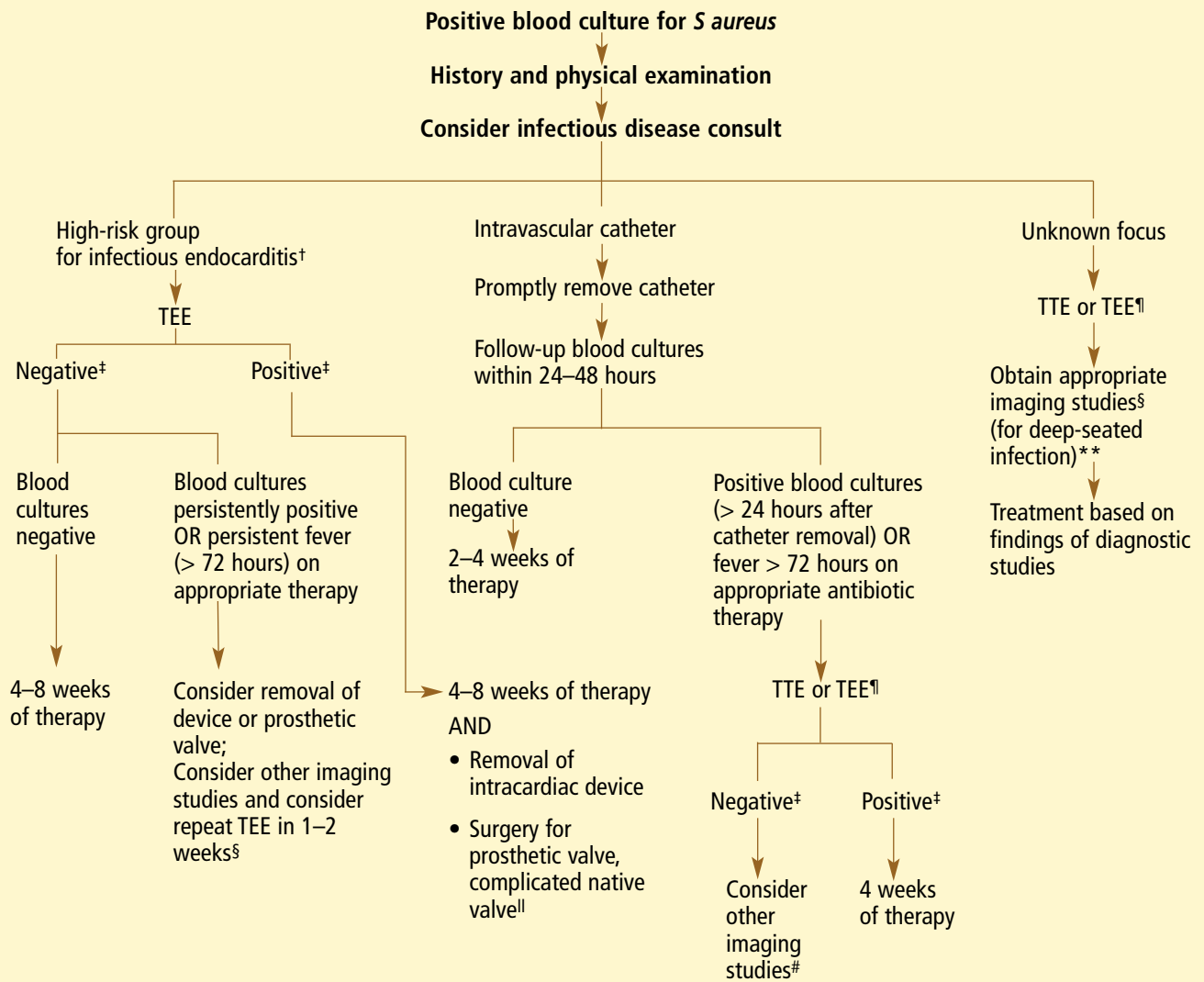
In this article we summarize current knowledge about *S aureus* bacteremia and review the etiology, diagnosis, and treatment of this common infection—including how to assess the risk of endocarditis (FIGURE 1).

S AUREUS INFECTIONS INCREASING

S aureus is a major cause of infections of the skin, soft tissues, respiratory tract, bones, joints, and endovascular system.

The incidence of both community-acquired and nosocomial staphylococcal infections has increased in the past 20 years in the United States and abroad. From 1992 to 1997, *S aureus* was the most common cause of noso-

Algorithm for management of *Staphylococcus aureus* bacteremia*



*Based on existing data and clinical experience of the authors

†Intravenous drug abuser, underlying valvular heart disease, prosthetic heart valve, congenital heart disease, intracardiac device (eg, pacemaker, implantable cardioverter-defibrillator)

‡Echocardiographic findings for vegetation, abscess, paravalvular or valvular leak, perforation, congestive heart failure

§Computed tomography (CT) of the chest, abdomen, and pelvis; magnetic resonance imaging (MRI) of the spine

¶Abscess, paravalvular or hemodynamically significant valvular leak, valvular perforation, congestive heart failure

¶TEE is preferred due to higher sensitivity and specificity

#Venous duplex ultrasonography to rule out catheter-associated deep vein thrombosis in addition to CT and MRI, as indicated

**Eg, osteomyelitis, mediastinitis, abscess (eg, hepatic, splenic)

FIGURE 1

comial pneumonia and the second most common cause of nosocomial bloodstream infections (after coagulase-negative staphylococci), accounting for 24% of these cases.⁴ Since 1980, *S aureus* bacteremia has increased 122%

to 283% in individual hospitals.⁵

Of even more concern is the emergence of increasingly resistant strains of *S aureus*. Methicillin-resistant *S aureus* (MRSA) was first described in 1961 and emerged in the



United States in the 1980s. MRSA may account for up to half of all cases of staphylococcal bacteremia.⁶ Moreover, the proportion of MRSA isolates that are sensitive only to vancomycin has been increasing, from 22% in 1987 to 56% in 1997.⁷

■ EPIDEMIOLOGIC FACTORS

Colonization is common

Humans are a natural reservoir for *S aureus*. Thirty percent to 50% of healthy adults are colonized. Of these, 60% are intermittent carriers, while 10% to 20% are persistently colonized, primarily in the nares but also in the axillae, groin, vagina, pharynx, or damaged skin surfaces.^{8,9} The colonizing organisms can be either methicillin-sensitive or methicillin-resistant.

Rates of *S aureus* colonization are high among intravenous drug abusers and in patients with type 1 diabetes, on hemodialysis, with acquired immunodeficiency syndrome, with dermatologic conditions, and in intensive care.⁹⁻¹²

Risk factors for infection

Colonization. Groups with high rates of colonization are also at high risk for infection and subsequent disease, eg, bacteremia¹³ and endocarditis. For example, the only risk factor identified for infective endocarditis associated with intravenous drug use is carriage of pathogenic staphylococci in the mucous membranes and on the skin.¹⁴ Similarly, surgical and intensive care unit patients with nasal carriage of *S aureus* and patients with central venous catheters (especially hemodialysis catheters) are at significantly higher risk for nosocomial *S aureus* bacteremia.^{15,16}

Other risk factors for nosocomial *S aureus* bacteremia are numerous.⁸ Most notable are:

- Foreign bodies (eg, central and peripheral venous catheters, prosthetic heart valves and joints)
- Immunosuppressive conditions such as cancer and diabetes
- Use of corticosteroids
- Alcohol abuse.

Nonremovable foci. *S aureus* bacteremia can result from a nonremovable focus of infec-

tion, such as cellulitis, osteomyelitis, or pneumonia.

Risks for MRSA bacteremia include advanced age, prolonged hospitalization, prior surgery, severe underlying disease (eg, liver disease, diabetes, renal failure), previous antibiotic therapy, and invasive procedures (eg, catheterization, intubation, or surgery) that result in disruption of mucocutaneous barriers.^{17,18}

Bacteremia can reflect endocarditis

S aureus bacteremia can be a manifestation of underlying endocarditis. Such cases are most commonly community-acquired without an obvious primary source in patients with valvular heart disease.

Vascular catheters as a focus of infection

Most (33%–78%) of the 200,000 cases of nosocomial *S aureus* bacteremia that occur each year in the United States can be attributed to vascular catheters,¹⁹⁻²² which are also implicated in infective endocarditis.

A vascular catheter is considered the primary focus of infection if there is evidence of inflammation at the insertion site, if a culture of the catheter tip is positive for *S aureus*, or both, and if there is no evidence of a source of infection elsewhere.²³

From 20% to 26% of cases of catheter-associated *S aureus* bacteremia are complicated by infective endocarditis or metastatic infection.²⁴⁻²⁶

A recent study²¹ showed that in both nosocomial and community-acquired *S aureus* bacteremia, an intravascular device was the source of infection in half of cases.

S aureus infective endocarditis was a consequence of an infected intravascular catheter placed while the patient was hospitalized for another medical condition in 39% of cases; the remainder of cases were attributed to hemodialysis grafts, surgical wounds, decubitus ulcers, foot ulcers, or no obvious source.

Is a cardiac device the source of infection?

Chamis et al²⁷ found that, in patients with cardiac devices (permanent pacemakers and implantable cardioverter-defibrillators) and *S aureus* bacteremia, the device was more likely to be the source of the bacteremia in cases

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that occurred early on (< 1 year after placement or modification of the device), whereas infected tissue was more likely to be the source of bacteremia in cases occurring later; the tissue infection resulted in hematogenous seeding of the device from a distant or unknown primary source.

***S aureus* endocarditis on the rise**

The incidence of *S aureus* endocarditis has increased and now accounts for 25% to 45% of all cases of infective endocarditis; it is the second leading cause of infective endocarditis and the most common cause of native valve endocarditis among intravenous drug abusers.^{28,29}

Other groups at risk include elderly persons; persons with underlying valvular disease, including those with prosthetic heart valves; hospitalized patients with intravascular devices; patients who were ill before they were hospitalized; and patients undergoing surgical procedures, especially procedures performed via a median sternotomy.²¹

About 20% to 46% of cases of *S aureus* infective endocarditis are nosocomial.^{21,30,31} In a study of patients with prosthetic heart valves who had nosocomial bacteremia, 43% were found to have infective endocarditis, and the second most common pathogen was *S aureus*.³²

Bacteriuria is a clue to bacteremia

Staphylococcal bacteriuria should be a clue to *S aureus* bacteremia or infective endocarditis.

S aureus is rarely isolated from urine; it accounts for only 1% to 1.5% of positive urine cultures.³³ However, it is rarely a contaminant when isolated from the urine.

The most consistent findings in patients with *S aureus* bacteriuria are antecedent urinary tract procedures or abnormalities, such as obstruction or neoplasm. In one study,³³ 73% of cases of nosocomial *S aureus* bacteriuria were related to genitourinary instrumentation (ie, catheters, surgery, or manipulation). If there is no history of manipulation of the urinary tract or an indwelling catheter, the patient should be further evaluated for bacteremia.

In another study,³⁴ 27% of patients with *S aureus* bacteremia had simultaneous *S aureus*

bacteriuria. Most cases of bacteriuria were secondary to the bacteremia (ie, seeding of the urinary tract during bacteremia), as opposed to *S aureus* bacteremia acquired from an *S aureus* urinary tract infection.

Hematuria: A clue to endocarditis

Isolation of *S aureus* from both urine and blood is not more common in endocarditis than in uncomplicated bacteremia.³⁴ However, hematuria in the setting of staphylococemia is an important clue to coexisting *S aureus* infective endocarditis.

Hematuria may arise by two mechanisms: renal infarction by embolization or immunologically mediated glomerulonephritis.

Renal insufficiency, hematuria, and immunologic aberrations often resolve rapidly with appropriate antimicrobial therapy.³⁵

■ ROLE OF ECHOCARDIOGRAPHY

Infective endocarditis is often difficult to diagnose because clinical clues on presentation may be limited. In one study,²⁵ only 7% of patients manifested autoimmune or embolic phenomena, a new murmur, or splenomegaly. In another study,³⁶ no initial focus of infection was detected in one third of cases of *S aureus* bacteremia.

Echocardiography can help detect and guide appropriate treatment of occult endocarditis. Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) are important diagnostic and prognostic tools. They play a crucial role in detecting vegetations on valves and intracardiac devices and in identifying predisposing conditions such as abnormal cardiac valves and congenital heart disease.

Echocardiography also helps detect sequelae of infection such as paravalvular abscesses, valve leaflet perforations or leaks, and congestive heart failure.³⁷

Transthoracic echocardiography or transesophageal echocardiography?

For valvular vegetations, the sensitivity of TTE is 44% to 70%, and the specificity is more than 95%. TEE has both a high sensitivity (87%–100%) and specificity (89%–100%).^{3,38}

For prosthetic valve endocarditis,

***S aureus* causes 25% to 45% of cases of infective endocarditis**

echocardiography has a lower diagnostic yield due to suboptimal precordial windows or interference from prosthetic material. The sensitivity of TTE is only 17% to 36%; for TEE it is 82% to 96%.³⁹⁻⁴² Daniel et al⁴¹ reported that TEE has a significantly greater ability than TTE to detect vegetations on all types of prosthetic valves.

For abscesses caused by endocarditis, TTE has a sensitivity of 28% and a specificity of 98%; TEE has a sensitivity of 87% and a specificity of 94%.⁴³

Prognostic implications

Echocardiographic identification of vegetations in patients with *S aureus* infective endocarditis has prognostic importance as well. Patients with valvular vegetations—particularly those larger than 1 cm by TTE and on the mitral valve—have a substantially worse outcome in terms of systemic embolic events.^{3,44}

TEE can visualize much smaller vegetations (≤ 8 mm) and can better detect complications, such as valve perforation and abscesses. Therefore, TEE permits earlier detection and initiation of therapy.

Echocardiographic screening for endocarditis

In the past, echocardiography was not recommended to screen for nosocomial infective endocarditis in cases of hospital-acquired bacteremia unless the patient had known or suspected valvular heart disease. This recommendation arose from earlier observations that patients with nosocomial *S aureus* bacteremia, particularly from intravascular catheter infections, rarely had occult infective endocarditis.⁴⁵

However, a more recent study by Fowler et al²⁵ showed that 25% of patients with staphylococcal bacteremia and 23% of those with catheters as the primary focus had evidence of endocarditis by TEE in the absence of clinical or transthoracic echocardiographic findings. In a later study by the same group,²¹ TTE and TEE findings contributed to the diagnosis in 91% of patients with definite infective endocarditis.

On the basis of these findings, echocardiography is now a common part of the diag-

nostic evaluation of *S aureus* bacteremia; this is especially the case when intravenous catheters are implicated and not promptly removed, when the focus of infection cannot be identified, and when the patient has other predisposing conditions for endocarditis (eg, known or suspected valvular abnormalities, intracardiac devices). Owing to its increased sensitivity, TEE is preferred to TTE.

CHOOSING THE RIGHT ANTIBIOTIC

Penicillin remains the drug of choice for *S aureus* isolates that are still sensitive to it—but few are anymore (about 1%).

A **semisynthetic penicillin** (ie, nafcillin or oxacillin) is indicated for beta-lactamase-producing strains.

A **first-generation cephalosporin** such as cefazolin is an acceptable alternative in patients with a history of delayed penicillin allergy.

Vancomycin is the drug of choice for methicillin-resistant isolates and can be used in cases of beta-lactam drug allergy. However, in vitro data suggest that vancomycin is a less effective antistaphylococcal drug than the beta-lactams. Use of vancomycin as an antistaphylococcal agent has resulted in a high rate of clinical failure (up to 35%) and relapse due to high protein binding, rapid renal clearance, reduced bactericidal rates, and poor penetration of cardiac vegetations.^{46,47}

Fowler et al²¹ did not find a difference in outcome for patients with infective endocarditis due to MRSA or methicillin-sensitive *S aureus*, but they did recognize a trend toward an increased relapse rate (83%) in patients treated with vancomycin.

A growing concern is the possible emergence of vancomycin-resistant *S aureus* strains. Eight patients with clinical infections caused by vancomycin-intermediate *S aureus* have been confirmed in the United States as of this writing.⁴⁸ In a recent multivariate analysis,⁴⁹ previous MRSA infection in the setting of persistent or recurrent vancomycin exposure was predictive of developing subsequent vancomycin-intermediate *S aureus* infection. In addition, two patients with clinical isolates (from a catheter exit

Few *S aureus* isolates are still sensitive to penicillin

TABLE 1

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site and a foot ulcer) of *S aureus* fully resistant to vancomycin were identified during 2002.⁵⁰ The appearance of such resistant strains of a virulent pathogen such as *S aureus* calls attention to the need for proper infection control practices and appropriate antimicrobial usage.

Antimicrobial combinations have been used to increase bactericidal activity and to prevent antimicrobial resistance. Combinations that exhibit synergistic killing of *S aureus* include:

- Semisynthetic penicillins plus aminoglycosides
- Cephalosporins plus aminoglycosides
- Nafcillin plus rifampin.

In a clinical trial comparing a single drug with combination therapy in *S aureus* endocarditis,^{45,51} combination therapy cleared bacteria from the bloodstream more rapidly but did not affect the mortality rate.

Many physicians use adjunctive therapy with an aminoglycoside for 2 weeks in patients with native valve endocarditis, or longer in cases involving prosthetic valves.

■ LENGTH OF ANTIMICROBIAL THERAPY

The potential for superinfection, the significant rate of occurrence of adverse reactions to antibiotic agents, and the high cost of hospital medical care all dictate that therapy be as brief as possible.⁵²

For simple bacteremia

Recent consensus recommendations for the treatment of *S aureus* bacteremia by Fowler et al⁵³ suggest that simple bacteremia should be treated with intravenous antibiotics for 7 days.

Simple bacteremia is defined as:

- A negative TEE for both vegetations and predisposing valvular abnormalities on day 5 to 7 of therapy
- A negative surveillance blood culture obtained 2 to 4 days after beginning appropriate antibiotic therapy
- A removable focus of infection, and
- Prompt clinical resolution (ie, afebrile and no localizing complaints attributable to metastatic staphylococcal infection within 72 hours of initiating therapy).

For uncomplicated bacteremia

Intravenous antibiotic therapy for 14 days is recommended for uncomplicated bacteremia, defined as meeting one or more of the following criteria:

- Predisposing valvular abnormalities (more than mild regurgitation) but no vegetations shown by TEE
- Positive surveillance blood culture
- Superficial nonremovable focus of infection
- Persistent signs of infection after 72 hours of antibiotic therapy.

For endocarditis

Patients with endocarditis as defined by the Duke criteria (TABLE 1) and patients with extracardiac manifestations (TEE negative for vegetations but positive for a deep-tissue infection such as mediastinitis or osteomyelitis) require 4 to 8 weeks of intravenous antibiotics with or without surgery.⁴⁴

Controversy

These recommendations, however, remain somewhat controversial. Many physicians are uncomfortable with fewer than 14 days of therapy, even for simple bacteremia, given the lack of diagnostic certainty of echocardiography and the lack of data from controlled, randomized studies.

Additional treatment measures

In addition to antimicrobial therapy, drainage of suppurative collections and removal of infected foreign devices are necessary when they are possible. Infected intravascular catheters should be removed or replaced at a new site.

Studies of catheter-associated *S aureus* bacteremia suggest that prompt vascular catheter removal is highly advisable and results in a low risk of endocarditis. Dugdale and Ramsey⁵⁴ noted a cure rate less than 20% with antibiotic therapy when the catheter remained in place in bacteremia. In a recent study,²⁷ patients whose infected cardiac defibrillator was not removed were more likely to die or have therapy fail than patients who had the device removed.

■ OUTCOMES

S aureus bacteremia has an overall mortality rate of 21% to 34%.^{1,2,6,55,56}

**Simple
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Increased morbidity and mortality are more likely in older patients (age > 50 years); in those with serious underlying cardiac, respiratory, or neurologic disease; and in those with unknown or nonremovable foci of infection. Other factors that may lead to an adverse outcome include persistent bacteremia and fever (exceeding 72 hours from removal of the focus and after initiation of antibiotic therapy), inadequate treatment with regard to antibiotic choice and length of therapy, and various laboratory abnormalities, such as leukocytosis, hyperbilirubinemia, elevated serum creatinine, low blood pH, and thrombocytopenia.^{53,57,58}

The mortality rate for nosocomial endocarditis, regardless of the pathogen, is 35% to 56%.^{59,60} Risk factors for in-hospital death are an infected prosthetic valve, systemic embolization, and infection with *S aureus*.^{61,62}

Mortality rates of 23% to 46% have been associated with nosocomial endocarditis due to *S aureus*.^{63–65} However, mortality in one study^{28,66–71} was 70%, with poor outcome correlating with advanced age (> 60 years), nosocomial infection, and presence of heart failure and arterial embolization; the mortality rate is 100% in patients with prosthetic valve *S aureus* endocarditis treated medically.

Harbath et al⁷² found no significant differ-

ences in clinical outcome (eg, infective endocarditis, metastasis, death) in patients with bacteremia due to MRSA compared with methicillin-sensitive *S aureus*. There is also no difference between patients infected with MRSA vs methicillin-sensitive *S aureus* with regard to sex, age, underlying disease, site of entry, or the presence of shock. However, MRSA infections are more frequently hospital-acquired and are more often seen in patients admitted to an intensive care unit and in those who have had surgery or who have received inappropriate therapy.

■ ROLE OF THE INFECTIOUS DISEASE CONSULTANT

Infectious disease consultation leads to a higher cure rate and a lower rate of relapse in cases of *S aureus* bacteremia. This has been attributed to the experience and knowledge of the specialist about the manifestations, complications, and treatment of this disease.

Patients treated by an infectious disease specialist have been found to have a longer hospitalization and receive more days of antibiotic therapy; however, those that followed the physician's recommendations had more acceptable, cost-effective interventions that led to a cure and a lower rate of relapse.^{53,73}

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