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Staphylococcus aureus Bacteremia and Infective Endocarditis: Old Questions, New Answers?

In a recent population-based surveillance study in Olmsted County, MN, between 2003 and 2005, *Staphylococcus aureus* was the most common cause of nosocomial bacteremia and the second most common cause of community-acquired bacteremia.[1] *S aureus* bacteremia (SAB) can be complicated by infective endocarditis (IE), a syndrome associated with high morbidity and mortality rates.[2]

Tremendous gains have been achieved recently in our understanding of the pathogenesis of IE due to *S aureus*. In the setting of SAB, at least 2 different host (ie, patient) components[2] are required for the bacterium to attach to the endocardial surface, a required step in the development of IE. Among patients with underlying predisposing valvular conditions, current dogma suggests that abnormal turbulent blood flow within the heart is associated with endothelial sites of injury. Platelets and fibrin deposit at the injury sites, and these deposits form a nidus where the bacteria can adhere. Whether infection is established in this setting depends somewhat on the multidimensional behavior of the platelet: On one hand, the deposited platelet serves as a site for bacterial binding; on the other, it elaborates antimicrobial proteins that can impact staphylococcal survival if the organism is susceptible to the proteins. In patients with structurally normal valves, infection can occur by a different mechanism. Staphylococci adhere to the endocardial surface and are then phagocytized by endothelial cells. The intracellular environment protects staphylococci from both host defense mechanisms and the bactericidal effects of antibiotics. The engulfment of *S aureus* by endothelial cells could initiate cellular alterations, including tissue factor expression, that promote formation of vegetations.[2]

The reported incidence of IE in patients with SAB has markedly varied among different investigations and has ranged from less than 5%[3] to more than 30%.[4] These wide-ranging rates are due in part to several factors and include the type of population examined, presence of selection bias, and occurrence of measurement bias that is linked to use of transesophageal echocardiography (TEE).

The clinical presentation of IE in patients with SAB is as wide ranging as its incidence calculations. The clinical diagnosis is obvious in some patients when the presentation is florid and both cardiac and peripheral stigmas are present. The diagnosis is extremely difficult in other patients in whom physical examination findings are lacking. Perhaps the most telling example of the difficulties with diagnosis was demonstrated in a pivotal nationwide surveillance study of SAB among nondrug addicts from Denmark.[5] Between 1982 and 1991, 260 cases of *S aureus* IE were identified. In 83 cases (32%), IE was not suspected clinically and was proven only at postmortem examination. Given the paucity of clinical findings in IE due to SAB in some cases and the high associated morbidity and mortality with this syndrome, physicians have been keenly interested in clinical tools to help identify a subgroup of patients with SAB and IE who potentially would benefit from a longer duration of antibiotic therapy.

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The topic of risk factors for the development of IE among patients with SAB has garnered interest for decades. Several studies[3,6-8] have identified risks such as the presence of community-acquired SAB, an occult primary focus, metastatic infection, persistent fever or bacteremia, prosthetic heart valve, history of IE, and injection drug use.

With the advent of TEE, do we need to continue to pursue the identification of risk factors for IE? Current guidelines from the Infectious Diseases Society of America[9] recommend the use of TEE in all patients with SAB. This recommendation was supported by a cost-effectiveness analysis for use of TEE in defining the duration of therapy for SAB.[10] Nevertheless, TEE is not readily available at all institutions, and more importantly, compliance with this recommendation has been low. In 1 of the initial investigations that examined the utility of this tool in SAB management, physicians failed to obtain TEE in 100 (41%) of 244 consecutive patients with SAB despite the recommendation to perform TEE by the infectious diseases consultant.[11] More recently, investigators from the same in-

Address correspondence to Imad M. Tleyjeh, MD, MSc, Division of Infectious Diseases, Department of Medicine, 4th Floor, Main Hospital, King Fahd Medical City, PO Box 59046, Riyadh, 11525, Saudi Arabia (itleyjeh@kfmc.med.sa).

stitution[7] and others have either described or at least acknowledged that use of TEE in patients with SAB was less than desired and was a limitation in some studies. Thus, the availability of TEE has not resolved the decades-old quest to identify risk factors for IE developing in patients with SAB.

In this issue of *Mayo Clinic Proceedings*, Hill et al[12] report on a novel approach, ie, a nested case-control study design in a contemporary cohort of patients with SAB, to identify risk factors for the development of IE. This study design has similar strengths to a cohort study but has the primary advantage of minimizing both data collection and expensive laboratory procedures. In a cohort of 1107 patients with SAB, 66 patients (6%) had IE. Cases with IE were matched to non-IE controls from the same SAB cohort (nested within the cohort). Rather than collecting data on 1107 patients, the authors restricted data collection to 66 cases and 132 controls. In a multivariate regression analysis, they found that unknown origin of SAB, presence of a valvular prosthesis, persistent fever, and persistent bacteremia were independent predictors of IE in patients with SAB. Although the presence of a permanent pacemaker was associated with IE in univariate analysis, this association was not statistically significant in the model, probably due to the low number of IE cases. This prompts an important concept that is often misinterpreted in the medical literature: the appropriate meaning of a statistically nonsignificant *P* value. Failing to reject the null hypothesis that there is no association between 2 variables should not lead one to accept the null hypothesis. In other words, "absence of evidence is not evidence of absence."[13] Hill et al also investigated purported risk factors for mortality among patients with SAB. However, the wrong study design was used to address this topic. A case-control design to determine risk factors of a particular outcome should only be used for the outcome from which cases were sampled; in this study, the sampling of cases was based on the presence or absence of IE and not on the vital status. An appropriate approach would have been to study the total cohort of SAB and look for risk factors of mortality or to use a nested case-control design in which the cases are patients who died and the controls, selected randomly from the total cohort, are patients who lived.

The report by Hill et al confirms the findings of previous investigations conducted during the past 3 decades that have examined the risk of IE in SAB. All studies published to date, including the current study, have one important limitation that has not been acknowledged, the so-called diagnostic suspicion bias. Accepting that a large proportion of patients with SAB do not undergo TEE, the following question should be asked when the validity of these studies is appraised: Who are the patients undergoing TEE? In clinical practice, physicians are more likely to suspect IE (and therefore to perform TEE) in patients with cardiovascular devices, including permanent pacemakers and prosthetic valves, persistent fever or bacteremia suggesting an endovascular focus, or an unknown source of bacteremia. Thus, these variables could have led to a diagnosis of IE and may not have been risk factors because of diagnostic suspicion bias. To avoid this bias, outcome (IE) should be measured systematically and equally in both the exposed (patients with a purported risk factor) and unexposed groups (those without the same risk factor).

Currently, we have 2 options: comply with guidelines and perform TEE in all patients with SAB or develop a rigorous prediction rule to identify those at high risk of IE. Until TEE is used to evaluate a prospective cohort of patients with SAB, and all (or virtually all) patients in the series are thoroughly studied, the same uncertainties that plagued the study by Nolan and Beaty[3] more than 3 decades ago will persist.

Imad M. Tleyjeh, MD, MSc
Divison of Infectious Diseases
King Fahd Medical City
Riyadh, Saudi Arabia

Larry M. Baddour, MD
Division of Infectious Diseases
Mayo Clinic
Rochester, MN

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