NOVA Score to Predict Endocarditis in Patients With Enterococcal Bacteremia: Sticking to Valves or to Scores?

Martin E. Stryjewski¹ and G. Ralph Corey²,³

¹Department of Medicine and Division of Infectious Diseases, Centro de Educación Médica e Investigaciones Clínicas “Norberto Quirino,” Buenos Aires, Argentina; ²Division of Infectious Diseases, Duke Clinical Research Institute, and ³Duke University Medical Center, Durham, North Carolina

(See the Major Article by Bouza et al on pages 528–35.)

Keywords. Enterococcus; bacteremia; endocarditis; score; model.

Managing patients with enterococcal bacteremia or endocarditis is a significant challenge in clinical practice [1–6]. Studies indicate that 3%–9% of patients with enterococcal bacteremia have infective endocarditis [1–3]. Enterococcal endocarditis represents 10% of all cases of infective endocarditis, making it the third most common pathogen after staphylococci and streptococci [7]. Although several species have been described, Enterococcus faecalis is responsible for approximately 90% of cases of enterococcal endocarditis [8]. Given the changes in patient characteristics (eg, older, more comorbidities) and medical practice (eg, more invasive procedures, prolonged outpatient intravenous therapy), enterococci have also become an important cause of both healthcare-related and nosocomial endocarditis [9].

Evidence indicates that enterococcal bacteremia without endocarditis does not increase the risk of death when compared to similar patients without bacteremia [6]. In contrast, mortality in patients with enterococcal endocarditis is high, reaching 29% at 1 year for all patients and 39% for patients with prosthetic valves [8]. Patients with uncomplicated enterococcal bacteremia are usually treated for ≤2 weeks; however, patients with enterococcal endocarditis require longer and more complex treatments [10], particularly those patients infected with vancomycin-resistant enterococci [11]. Therefore, differentiating patients with enterococcal bacteremia from those with enterococcal endocarditis has critical implications in both the treatment and prognosis of such patients.

Variables selected from clinical trials and large prospectively collected databases of patients diagnosed with Staphylococcus aureus bacteremia have led to the creation of bedside scores to assist clinicians in the differentiation between patients with uncomplicated S. aureus bacteremia vs those with complicated infection [12] and/or endocarditis [13].

Similarly, several clinical variables are intuitively utilized by clinicians to differentiate enterococcal bacteremia from enterococcal endocarditis. These variables include presence of a prosthetic valve [2], preexisting valvular heart disease [1], bacteremia due to E. faecalis [2], bacteremia from an unknown source [1], and persistent bacteremia (eg, ≥3 positive blood cultures). In addition, although older studies pointed out community acquisition of the infection as a factor associated with endocarditis [1, 4], this was not confirmed in more recent investigations [2]. Unfortunately, clinical variables used to risk-stratify possible endocarditis in patients with enterococcal bacteremia have been extracted from separate, and often dissimilar studies [1–4]. Therefore, a simple prediction tool to weight and stratify the risk of endocarditis in a particular patient with enterococcal bacteremia is lacking.

In this issue of Clinical Infectious Diseases, Bouza and colleagues provide a simple clinical score to rule out endocarditis among patients with enterococcal bacteremia. In this large single-site study, investigators prospectively identified and followed patients with enterococcal bacteremia and endocarditis (modified Duke criteria). During a 9-year period, 1515 episodes of enterococcal bacteremia, including 65 episodes of enterococcal endocarditis (4.3%), were analyzed. Transeosophageal echocardiography (TEE) was performed in 26% of all patients and in 72% of patients with a final diagnosis of endocarditis. In response to specialist advice, TEE was obtained more frequently (15% vs 34%) during the second half of the study period. To identify variables potentially associated with enterococcal
endocarditis, a group of 65 patients with enterococcal bacteremia and negative TEE were randomly selected for a case/control study. These variables were further analyzed in a logistic regression model (multivariable analysis) validated with bootstrapping. Three clinical variables were identified as independently associated with endocarditis: (1) presence of continuous bacteremia (3/3 positive blood cultures or the majority if >3), (2) unknown source of infection, and (3) history of cardiac valve disease. Using these variables along with the auscultation of a heart murmur, the authors created a second logistic regression model to predict endocarditis using a 12-point scoring system (Number of positive blood cultures, unknown Origin of bacteremia, prior Valve disease, Auscultation of heart murmur [NOVA] score). This score, which was also validated with bootstrapping, performed well (receiver operating characteristic, 0.83). An important finding was that no patients with a NOVA score <4 had enterococcal endocarditis. This score and cutoff worked well also when applied to a sample of study patients with endocarditis in whom TEE had not been performed. Bouza and colleagues should be congratulated for their efforts in developing a clinical tool to assist direct patient care. However, although the NOVA score can be offered and tested in clinical practice, important questions remain.

Is the NOVA score truly validated? We consider a score (or model) validated when such a score is able to predict an outcome in subjects who did not participate in the original dataset (from which the model was created). Bootstrapping is a data-based simulation method [14] that can be used for model validation [15]. It re-creates a large number of random samples from the original dataset to retest a proposed model. Using random sampling with replacements, a single patient may be chosen more than once, and other patients may not be included at all in each sample. By iterating the model in up to thousands of re-created samples of the same size, bootstrapping can provide very accurate estimates on how the model works with different distribution of study subjects, thus providing an internal validation. However, a model developed from a selected sample of patients may not work when applied to a different sample of patients. Therefore, we agree that to be externally validated and eventually generalized, the NOVA score needs to be retested in unselected patients with enterococcal bacteremia from different settings/cohorts.

Will this score save TEEs? Similar to other studies [16, 17], TEEs performed better than transthoracic echocardiography in the diagnosis of endocarditis in the Bouza et al study. However, TEE can be costly or unavailable in certain settings. Clearly, the NOVA score (especially when combined with clinical judgment) can be helpful in avoiding TEEs in a significant proportion of patients without compromising their care. That certainly translates into better use of resources and lower medical costs. This potential advantage is related to the negative predictive value of the score to rule out endocarditis. In this study, no patients with score <4 points (low risk) had endocarditis (all true negatives), reaching a maximal negative predictive value (100%). However, because predictive values are influenced by the prevalence of the disease, the authors have correctly addressed the limitation that the real prevalence of endocarditis in their cohort is unknown. More than 1000 patients in the cohort did not undergo TEE. Assuming a population with enterococcal bacteremia and 5% prevalence of endocarditis, Bouza et al estimated that 27% of patients could have TEE safely obviated. As a key message for clinicians, no patients with continuous bacteremia (5 points) or with unknown origin of bacteremia (4 points) would be classified as low risk (<4 points), and all of them would deserve further investigation. Based on the high negative predictive value, we believe this score will be particularly useful to avoid unnecessary TEEs in a setting where these procedures are commonly used in patients without recognized risk factor(s) for endocarditis.

More importantly, will the NOVA score save lives? Perhaps. Relying on the TEE as the gold standard in the diagnosis of endocarditis is hazardous, especially in patients with prosthetic valves or cardiovascular implantable electronic devices. A recent prospective study has shown that 27% of patients with cardiovascular implantable electronic devices and endocarditis (as defined by the modified Duke criteria) had a negative TEE [18]. Although intracardiac echocardiography [18] or positron emission tomography [19] can be helpful in such cases, these tests are not widely available. As a result, the NOVA score could, along with clinical judgment, provide the clinician with the tools necessary to proceed with prolonged double therapy. For example, a patient with a pacemaker and fever but only 1 positive blood culture for enterococci and a nondiagnostic TEE (eg, unknown source) may be best treated for endocarditis.

Ultimately, the question is, should we “stick” to the NOVA score if our clinical judgment disagrees with the estimated risk? We agree with the authors that the short answer is no. For example, regardless of a low NOVA score (<4 points), we would strongly recommend an active search for endocarditis in any patient with fever and enterococcal bacteremia who suffered a stroke or who has other embolic phenomena. When uncomfortable with the results of scores or diagnostic tests, clinicians should always rely on their experience and judgment [20]. Scores, models, and tests should be used to assist such judgment rather than replace it.

In conclusion, the NOVA score can be helpful to avoid unnecessary TEEs among patients with enterococcal bacteremia, particularly in settings with a low prevalence of endocarditis and high TEE use. The NOVA score may also be helpful when the physician suspects complicated
infection but the imaging fails to demonstrate valvular or device abnormalities. Until this score is validated in other settings, however, clinical judgment will continue to tell us if we should stick closely to this score, our experience, or both.

**Note**

**Potential conflict of interest.** Both authors: No reported conflicts.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**References**