Proposed Modifications to the Duke Criteria for the Diagnosis of Infective Endocarditis

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Although the sensitivity and specificity of the Duke criteria for the diagnosis of infective endocarditis (IE) have been validated by investigators from Europe and the United States, several shortcomings of this schema remain. The Duke IE database contains records collected prospectively on >800 cases of definite and possible IE since 1984. Databases on echocardiograms and on patients with Staphylococcus aureus bacteremia at Duke University Medical Center are also maintained. Analyses of these databases, our experience with the Duke criteria in clinical practice, and analysis of the work of others have led us to propose the following modifications of the Duke schema. The category “possible IE” should be defined as having at least 1 major criterion and 1 minor criterion or 3 minor criteria. The minor criterion “echocardiogram consistent with IE but not meeting major criterion” should be eliminated, given the widespread use of transesophageal echocardiography (TEE). Bacteremia due to S. aureus should be considered a major criterion, regardless of whether the infection is nosocomially acquired or whether a removable source of infection is present. Positive Q-fever serology should be changed to a major criterion.

Infective endocarditis (IE) is typically a syndrome diagnosis that is determined on the basis of the presence of multiple findings rather than a single definitive test result. Although the presence of IE may be obvious when a patient with predisposing cardiac lesions has bacteremia without an obvious source, it is often a difficult diagnosis to establish in other patients who are seen in routine clinical practice. When the features of IE are atypical or masked by coexisting diseases, misdiagnosis may lead to clinical catastrophe. On the other hand, overdiagnosis of IE may lead to numerous iatrogenic problems arising from antimicrobial therapy or its concurrent vascular access.

Practical and logical case definitions for IE are important for both clinicians and researchers who study this complex disease. In 1994, Durack et al. [1] proposed a new set of diagnostic criteria for the diagnosis of IE that subsequently came to be known as the Duke criteria. These criteria have been validated by the authors of reports of numerous studies during the past 4 years in a wide spectrum of patients, including children, adults, the elderly, prosthetic valve recipients, injection drug users, nondrug users, patients in tertiary care settings, patients in primary hospitals, and patients treated outside of the United States. When pathologically confirmed cases were considered to be the gold standard for assessing the Duke criteria, the collective sensitivity of the Duke criteria in numerous studies was >80% [2–9]. In addition, the high specificity [10] and negative predictive value [11] of the Duke criteria have been confirmed.

Despite these data, the Duke criteria have shortcomings. An often-heard criticism of the Duke criteria is the overly broad categorization of the group “possible IE.” For example, in the original Duke criteria, an individual patient could be classified as having “possible IE” if only 1 minor criterion was present and if the patient did not meet requirements for “rejected IE.” To “reduce the size of this possible group and to amplify the size of the rejected group,” Bayer [12] recently called for a “diagnostic floor” for the group of patients listed as “possible IE.” Other critics have suggested the modification of current [13] or the inclusion of additional minor criteria [14] to increase the sensitivity of the Duke criteria. Finally, issues such as the relative risk of IE in cases of Staphylococcus aureus bacteremia [15, 16], the poor diagnostic sensitivity in suspected cases of Q-fever IE [17], and the relative role of transesophageal echocardiography (TEE) in the diagnosis of IE [18–20] remain unresolved.
In response to these criticisms, we have sought to re-evaluate the Duke criteria. The Duke University database currently contains detailed clinical records on >800 cases of definite and possible IE hospitalized at Duke University Medical Center (DUMC) since 1984. In addition, the Duke Endocarditis Service also maintains prospective databases on all echocardiograms performed at DUMC and on all patients with S. aureus bacteremia seen in our institution from 1994 to the present. Analyses of these databases, our growing experience with the Duke criteria in clinical practice, and the analysis of the work of other groups have led us to propose the following modifications of the Duke schema.

Redefinition of “Possible IE”

The original Duke criteria classified any case of suspected IE as “possible,” if it fell short of qualifying as a “definite” case but was not “rejected.” A case could only be rejected when a firm alternate diagnosis for the manifestations of IE was found, the manifestations of infection resolved within 4 days of the start of antibiotic therapy, or no pathologic evidence of IE was discovered at surgery or autopsy after antibiotic therapy of no more than 4 days’ duration. Thus it was possible for patients with 1 minor criterion (e.g., fever or the presence of a cardiac valvular lesion) to be considered as having “possible IE.” In order to raise the diagnostic floor, we proposed in an earlier article that patients with “possible IE” have at least 3 minor or 1 major criterion and 1 minor criterion [21].

To test this proposal, we identified 100 consecutive pathologically confirmed cases of IE in our database and analyzed these cases on the basis of their clinical characteristics by using the above definition of “possible IE.” The addition of our proposed floor for the category “possible IE” did not change the classification of any case (table 1). However, the application of our new definition to all previously classified “possible IE” cases in our database (n = 301) resulted in the identification of 50 patients (17%) who did not meet the minimum criteria proposed for our new classification schema (table 2). Follow-up information of at least 6 months was available in 45 of these 50 patients. Of the 45 patients, 25 patients received either no antibiotic treatment or <2 weeks of treatment, and 20 patients received a course of antibiotic therapy for 2–4 weeks (considered appropriate based on the identity of the isolated or suspected pathogen). Three of these 45 patients were subsequently rehospitalized with definite IE during the next 6 months. The difficulty in classifying these cases is illustrated below.

Case 1. A 66-year-old man with a prosthetic mitral valve was transferred to our hospital for management of a recent myocardial infarction and acute pulmonary edema. During this hospitalization, he developed enterococcal bacteremia and was classified as “possible IE” because of nosocomial bacteremia and paravalvular regurgitation seen by TEE. These findings were unchanged from previous echocardiographic studies.

<p>| Table 1. Comparison of clinical diagnosis of 100 pathologically confirmed cases of infective endocarditis according to the Duke criteria and by our modified Duke criteria. |
|-------------------------------------------------|---------------------|-------------------|------------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Modified Duke criteria</th>
<th>Duke criteria, no. of cases</th>
<th>Possible</th>
<th>Rejected</th>
<th>Total no. (%) of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite, no. of cases</td>
<td>76</td>
<td>0</td>
<td>0</td>
<td>76 (76)</td>
</tr>
<tr>
<td>Possible, no. of cases</td>
<td>0</td>
<td>24</td>
<td>0</td>
<td>24 (24)</td>
</tr>
<tr>
<td>Rejected, no. of cases</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>76</td>
<td>24</td>
<td>0</td>
<td>100 (100)</td>
</tr>
</tbody>
</table>

Thereafter, he received antimicrobial therapy for 6 weeks. Two weeks after discontinuation of this therapy, he was re-admitted because of fever. Blood cultures yielded Bacteroides ovatus, and echocardiography showed a new oscillating mass on his prosthetic valve.

Case 2. A 28-year-old woman with a history of injection drug abuse and 3 previous episodes of IE came to our emergency room complaining of shortness of breath. An echocardiogram revealed mitral valve thickening but no vegetations. Several sets of blood cultures were negative. Despite having 2 minor criteria (fever and a predisposing condition), she was discharged after receiving iv antibiotic therapy for only 48 h. After hospitalization, she continued to use injection drugs. Three months later, she was again admitted because of unexplained fever. Several blood cultures were positive for S. aureus and an Osler’s node was noted on 1 of her fingers. An echocardiogram revealed only valve thickening. Thereafter, she received iv antibiotic therapy for 5 weeks and recovered.

Case 3. A 56-year-old man was admitted 2 weeks after insertion of a St. Jude’s mitral valve because of unexplained fever. Numerous sets of blood cultures were negative, and trans-thoracic echocardiography (TTE) revealed no changes from his previous studies. A diagnosis of “possible IE” was made on the basis of fever and a predisposing valvular condition. However, the clinicians caring for him did not believe he had IE, and he was discharged after receiving only 2 doses of ceftriaxone. Three weeks later, he was again admitted because of unexplained fever, and TEE revealed an oscillating mass on his prosthetic valve. Blood cultures were negative. Thereafter, he received vancomycin and ciprofloxacin therapy for 6 weeks and subsequently felt well.

By use of our proposed new definition of “possible IE,” the 3 cases summarized above would have been “rejected” as having IE, yet all 3 patients were subsequently rehospitalized with “definite IE” by Duke criteria. It is of interest that the first patient developed IE because of an organism not present in his initial blood culture and that the second patient was a habitual injection drug user who probably developed her fourth episode of S. aureus IE 3 months after evaluation. Both patients were likely to have acquired IE after their first hospitalization and thus may not represent failures of the proposed modified criteria to diagnose IE. The third patient probably had culture negative IE during his first hospitalization that was not detected by the
modified Duke criteria. It is notable that follow-up of the remaining 25 patients who received ≤2 weeks of antibiotic treatment revealed no other cases in which the diagnosis of IE was subsequently verified. As a result of these data, we believe that the large gain in specificity resulting from the elevation of the diagnostic floor of “possible IE” will lead to only a small decrease in sensitivity.

**Proposed Clarifications and Modifications of Minor Criteria for the Diagnosis of IE**

Our group and others have recently re-evaluated the validity of the minor criteria in the original Duke schema for the diagnosis of IE. A British study of 118 pathologically proven cases of IE showed improved diagnostic sensitivity in this highly selected group, with the addition of the following minor criteria: splenomegaly, splinter hemorrhages, petechiae, newly diagnosed clubbing, elevated erythrocyte sedimentation rate, elevated C-reactive protein level, as well as the presence of central nonfeeding lines, peripheral lines, and microscopic hematuria [14]. Because data concerning the frequency of newly diagnosed clubbing, elevated erythrocyte sedimentation rate or C-reactive protein level, and the presence of central lines and peripheral intravascular devices are not available for patients in our database, we have been unable to validate the utility of such criteria for the diagnosis of IE. However, it has been our clinical experience that newly diagnosed clubbing and splenomegaly are not commonly present in modern American practice, whereas elevated erythrocyte sedimentation rates and intravascular line usage are frequent among many patients with noncardiac diseases. We believe that further prospective studies are needed before these additional modifications can be reliably assessed, since these additional criteria may well decrease specificity, particularly in cases classified as “possible IE.”

We have re-evaluated the original list of minor criteria and believe that 2 of the criteria, vascular phenomena and the echocardiographic minor criteria, require clarification and modification. Von Reyn and Arbier have previously stated that vascular phenomena should be a major criterion for the diagnosis of IE [13]. In order to further evaluate this question, we examined the potential effect of changing vascular phenomena to a major criterion by using all the “definite” and “possible” cases of IE in our current database. Only 23 of 301 “possible” cases (8%) would be reclassified from “possible” to “definite” if the presence of vascular phenomena were considered to be a major criterion. Furthermore, if vascular phenomena were used as a major criterion, numerous febrile patients with stroke, vasculitis, or rickettsial disease could be erroneously classified as having “possible IE.” Although it is usually relatively easy to separate patients with IE from patients with vasculitis and rickettsial disease, it may be exceedingly difficult to distinguish between IE complicated by stroke and stroke complicated by drug fever, fever due to aspiration pneumonia, or a urinary tract infection, particularly if a significant cardiac valvular abnormality is simultaneously present. We believe that vascular criterion should, therefore, remain a minor criterion until further prospective data can be acquired on the impact of these changes to the specificity of the criteria.

A second minor criterion from the original Duke schema, “echocardiogram consistent with IE but not meeting major criterion,” needs re-evaluation. This criterion was originally used in cases where nonspecific valvular thickening was detected by TTE. In a reanalysis of patients in our database, we found that this criterion was used in only 5% of cases and was never used in the final analysis of any patient who underwent TEE. We therefore believe that this minor criterion should be eliminated.

**Redefining the Major Criteria for the Diagnosis of IE**

Reanalysis of the major criteria have led us to believe that redefinition is required in cases of IE due to *S. aureus* and *Coxiella burnetii*. Previous studies by Nolan and Beaty [22], Bayer et al. [23], and Mylotte et al. [24] showed *S. aureus* IE to be unlikely when bacteremia was nosocomially acquired and a primary focus, such as an intravascular device, was present at the time of bacteremia. As a result, the original Duke criteria considered blood cultures that were positive for *S. aureus* to be a major criterion only when the bacteremia was community-acquired in the absence of a primary focus [1]. We have analyzed clinical data that were collected prospectively from 103 consecutive patients with *S. aureus* bacteremia who underwent transesophageal echocardiography. Twenty-five percent of these 103 patients had valvular vegetations [15]. In a separate analysis of 59 consecutive patients with *S. aureus* IE, 45.8% had nosocomially acquired infections and 50.8% had a removable focus of infection [16]. In the most recent analysis, of 262 patients at DUMC with hospital-acquired *S. aureus* bacteremia over the last 4 years, 135 patients (51.5%) had intravascular catheter–associated bacteremia and 127 patients (48.5%) had non-catheter-associated bacteremia. Seventeen patients in each group were subsequently diagnosed with definite IE. Thus 13% of
patients with nosocomially acquired bacteremia developed IE. On the basis of these findings, we believe that the presence of *S. aureus* bacteremia should be considered a major criterion in the Duke schema, regardless of whether the infection is nosocomially acquired or whether a removable source of infection is present.

Another major criterion requiring redefinition regards Q-fever serology. In the original Duke criteria, a positive serology for Q fever was considered a minor microbiological criterion. Subsequently, Fournier et al. [17] studied 20 pathologically confirmed cases of Q-fever IE. By use of the original Duke criteria, 4 of these 20 patients were misclassified as “possible IE.” However, when Q-fever serologic results and a single blood culture positive for *C. burnetii* were considered to be a major criterion, each of these 4 cases was correctly reclassified from “possible” to “definite” IE [17]. On the basis of these data, we agree with Fournier et al. that an antiphase I IgG antibody titer $>1:800$ or a single blood culture positive for *C. burnetii* should be a major criterion in the Duke schema.

In addition, other serologic tests such as serum antibody titers or PCR-based testing for difficult-to-culture organisms, such as *Bartonella quintana* or *Tropheryma whippelii*, may also be suitable as major criteria in the future. At present, there are significant methodologic problems and uncertainties for proposing antibody titers that are positive for *Bartonella* and *Chlamydia* species or for PCR-based testing for *T. whippelii* as major criteria in the Duke schema. For example, in endocarditis, infections caused by *Bartonella* and *Chlamydia* species are often indistinguishable by use of serologic tests because of cross-reactions [25]. Also, PCR-based tests have low sensitivity unless they are performed directly on cardiac valvular tissue [26]. Therefore, until sufficient numbers of cases of these rare types of IE can be validated and the preceding technical problems resolved, the inclusion of such serologic tests as major criteria should be deferred.

Use of TEE in Patients with Suspected IE and Negative Transthoracic Examinations

In addition to the preceding proposed diagnostic modifications to the Duke criteria, we have modified our approach for diagnostic echocardiography. The original Duke criteria relied heavily on the results of TTE; the impact of the results from TEE had not been systemically evaluated. The superior sensitivity of TEE for detecting vegetations has now been well established [27–30], particularly in patients with prosthetic valves [18]. Lindner et al. have evaluated the diagnostic value of TEE in suspected IE on the basis of the pretest probability of disease by using clinical criteria that were not Duke criteria [20]. They concluded that TEE should be reserved for patients who have prosthetic valves and in whom TTE is either technically inadequate or indicates an intermediate probability of IE.

In light of these findings, we recently evaluated the role of TEE versus TTE on the Duke criteria [31]. A total of 113 patients with 115 episodes of IE were studied. All patients were initially classified on the basis of their TTE findings. Subsequently, patients were reclassified by use of their TEE findings. Five patients went from “rejected” to “possible” IE, and 21 patients went from “possible” to “definite” IE. TEE improved the utility of the Duke criteria, primarily in patients with “possible IE” and a negative TTE and intermediate pretest probability of IE. The results of TEE provided minimal incremental benefit over data obtained from TTE in patients with only 1 or 2 minor criteria (fever or predisposing condition alone) or in those with “definite” IE by Duke clinical criteria.

We also evaluated the role of TTE versus TEE in 103 patients with *S. aureus* bacteremia. TTE revealed vegetations in only 7% of patients and was indeterminate as a result of poor image resolution in 18%. TEE identified vegetations in 25% of the same patients and was not indeterminate in any patient. It is

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**Table 3.** Definition of infective endocarditis according to the proposed modified Duke criteria, with modifications shown in boldface.

<table>
<thead>
<tr>
<th>Definite infective endocarditis</th>
<th>Pathologic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or (2) Pathologic lesions; vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis</td>
<td></td>
</tr>
<tr>
<td>Clinical criteria*</td>
<td></td>
</tr>
<tr>
<td>(1) 2 major criteria; or (2) 1 major criterion and 3 minor criteria; or (3) 5 minor criteria</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Possible infective endocarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) 1 major criterion and 1 minor criterion, or (2) 2 minor criteria</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rejected</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Firm alternate diagnosis explaining evidence of infective endocarditis; or (2) Resolution of infective endocarditis syndrome with antibiotic therapy for $\leq 4$ days; or (3) No pathologic evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for $\leq 4$ days; or (4) Does not meet criteria for possible infective endocarditis, as above</td>
</tr>
</tbody>
</table>

* See table 4 for definitions of major and minor criteria.
important to note that TEE detected evidence of IE in 19% of patients with a negative TTE and 21% of patients with an indeterminate TTE [15].

These data illustrate the importance of using TEE results when applying the Duke criteria to patients with suspected IE. We advocate TEE as the initial diagnostic test of choice in patients with at least “possible IE,” according to clinical criteria (using the new diagnostic floor), in patients with suspected complicated IE (i.e., paravalvular abscess) and in patients with suspected prosthetic valve IE. In other patients, we would advise performing a TTE as the initial diagnostic test.

Conclusion

Selecting adequate criteria for diagnostic schema for use in clinical practice is often problematic. For example, a recent study of the 1990 American College of Rheumatology (ACR) classification criteria for diagnosing vasculitis illustrates the difficulty of applying research diagnostic criteria to diagnose uncommon conditions in usual clinical practice [32]. In this study, 75% of patients with vasculitis and 21% of patients without vasculitis met ACR criteria for \( \geq 1 \) types of vasculitis. The positive predictive values for 4 different vasculitides according to ACR criteria were 17%–29% for the entire cohort and only 29%–75% for the patients with a final diagnosis of vasculitis. Further limitations of diagnostic criteria in uncommon conditions include the confounding effect of referral bias in large tertiary medical centers and the inadequacies of data collected retrospectively. For example, the patients included in many earlier studies of IE had the classic peripheral stigmata of IE, primarily because their duration of illness before treatment was lengthy. In modern practice, patients with IE may be diagnosed within a few days of the onset of their infection. As a result, the classic clinical features, such as embolic or vasculitic skin lesions, renal disease due to immune complex deposition, and the immunologic abnormalities of IE, are often absent.

The Duke criteria and the criteria for diagnosing IE that preceded Duke criteria were primarily developed to facilitate epidemiologic and clinical research efforts so that investigators could compare and contrast the clinical features and outcome of various case series of patients. Extending these criteria to the clinical practice setting is more difficult. Because IE is a heterogeneous disease with highly variable clinical presentations, the use of criteria alone will never suffice. Changes that add sensitivity often do so at the expense of specificity and vice versa. As a result, clinical judgement remains a crucial ingredient in the evaluation of patients with suspected IE. Clinicians may appropriately and wisely decide to treat or not treat an individual patient, regardless of whether they meet or fail to meet criteria of “definite” or “possible” IE by the Duke schema. The Duke criteria are meant to be only a clinical guide for diagnosing IE and, certainly, must not replace clinical judgement. However, we believe that the modifications of the Duke criteria that are proposed (tables 3 and 4) will help investigators who wish to examine the clinical and epidemiologic features of IE and serve as a guide for clinicians struggling with difficult
diagnostic problems. These proposed modifications should be further validated by others by use of data from patients who are hospitalized at both community-based and tertiary-care hospitals.

In the future, as advances in cardiac imaging and microbiologic methods evolve, it is likely that further modifications of the Duke criteria will become necessary. The addition of new criteria will require rigorous prospective evaluation to enhance diagnostic sensitivity without compromising specificity. We encourage others to assist us in evaluating future modifications to these important diagnostic criteria.

References