The Duke Criteria for Diagnosing Infective Endocarditis Are Specific: Analysis of 100 Patients with Acute Fever or Fever of Unknown Origin

Bruno Hoen, Isabelle Béguinot, Christian Rabaud, Roland Jaussaud, Christine Selton-Suty, Thierry May, and Philippe Canton

The recently proposed Duke criteria were confirmed to be more sensitive than the former Beth Israel criteria for the diagnosis of infective endocarditis (IE). To assess the specificity of the Duke criteria, we reviewed the records of 100 patients admitted to two internal medicine wards because of acute fever or fever of unknown origin (FUO). IE was considered a possible diagnosis for all patients who had had at least two blood cultures performed and one transthoracic echocardiogram obtained. The diagnosis of IE was rejected in all cases in accordance with the Duke criteria (i.e., a firm alternate diagnosis [n = 23], resolution of symptoms with no antibiotics [n = 39], or both reasons [n = 38]). To calculate the specificity of the Duke criteria, all 100 cases were then reclassified according to these criteria as if the diagnosis of IE had not been rejected. Only one patient, who probably did not have IE, was reclassified as having clinically definite IE. The specificity of the Duke criteria could therefore be calculated to 0.99 (95% confidence interval, 0.97–1). Although the design of the study may have resulted in a slight overestimation of the specificity rate, we conclude that the Duke criteria are highly specific for ruling out IE in patients with acute fever or FUO who are at low risk for IE.

In 1994, Durack et al. [1] proposed new criteria for the diagnosis of infective endocarditis (IE); these criteria are now referred to as the Duke criteria [1], which are displayed in tables 1 and 2. They were designed to update the former Beth Israel criteria that were published in 1981 and were "based on strict case definition" [2]. The sensitivity of the Duke criteria for accurately classifying definite cases of IE is substantially higher than that of the Beth Israel criteria. This improvement in sensitivity was demonstrated not only in Durack's original study but also in two other studies performed with independent series of patients [1, 3, 4]. In these studies, the sensitivity of the Duke criteria was found to be about twice as high as that of the Beth Israel criteria.

Patients and Methods

Hospitals. This study was conducted in two teaching hospitals that serve as tertiary referral centers as well as primary care centers for the 300,000 persons living in the greater Nancy area and the 250,000 persons living in the greater Reims area.

Selection of cases. Our objective was to review the charts of the patients for whom the diagnosis of IE had been considered possible but was eventually rejected. In each hospital, cases were selected from two computerized data bases. We retrieved the cases of patients admitted to the hospital for either acute or prolonged fever from the hospitalization summary files of the respective Departments of Infectious Diseases. We retrieved the cases of patients who underwent echocardiography for suspected endocarditis from the echocardiography report files of the respective Departments of Cardiology. The charts of all the patients who were included in both data bases were subsequently reviewed to determine eligibility for the study. The study period ranged from 1 July 1991 to 31 January 1995.

Eligibility criteria. The following criteria had to be met for inclusion in the study: age, > 18 years; admission to the...
Table 1. Definition of infective endocarditis according to the Duke criteria.

- **Definite infective endocarditis**
  A. Pathologic criteria
  (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.
  B. Clinical criteria*
  (1) two major criteria, or
  (2) one major and three minor criteria, or
  (3) five minor criteria.
- **Possible infective endocarditis**
  Findings consistent with infective endocarditis that fall short of "definite" but are not "rejected."
- **Rejected**
  (1) firm alternate diagnosis explaining evidence of infective endocarditis, or
  (2) resolution of infective endocarditis syndrome with antibiotic therapy for ≤4 days, or
  (3) no pathologic evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for ≤4 days.

*See table 2 for definitions of major and minor criteria.

Analysis of patients’ charts. During a review of each patient’s chart, we extracted all the necessary information pertaining to demographics and medical history and to correct assessment of the Duke criteria. The information included age, gender, history of intravenous drug use, history of heart disease, history of known abnormal cardiac murmur, history of prosthetic valve placement and of infective endocarditis, new regurgitant murmur, presence of any of the vascular or immunologic phenomena defining the corresponding Duke minor criteria [1], total number of blood cultures that were performed (as well as the total number that were positive), detailed analysis of echocardiographic findings, antibiotics administered, final diagnosis, and outcome of the case.

On the basis of these data, we assigned the corresponding Duke major and minor criteria to each case. To calculate the specificity of the Duke criteria, we then reclassified each case in an unblinded fashion, disregarding the fact that in each of them the diagnosis of IE had been formerly rejected. This process allowed us to calculate the proportion of patients reclassified as having clinically definite IE even though they definitely did not have IE. This proportion was equal to 1 – specificity.

Calculation of specificity. Specificity was calculated as the number of cases not reclassified as clinically definite divided by the total number of cases studied. The 95% confidence interval of this percentage was calculated as follows: specificity ± $\epsilon \times [(specificity)(1 – specificity)/n]^{1/2}$, with $\epsilon = 1.96$ for $\alpha = 0.05$ and $n$ representing the sample size ($n = 100$).

Table 2. Definitions of terms used in the Duke criteria for the diagnosis of infective endocarditis.

- **Major criteria:**
  (1) Positive blood culture for IE:
  A. Typical microorganism consistent with IE from two separate blood cultures as noted below:
  (i) viridans streptococci,* Streptococcus bovis, HACEK group, or
  (ii) community-acquired Staphylococcus aureus or enterococci, in the absence of a primary focus, or
  B. Microorganisms consistent with IE from persistently positive blood cultures defined as:
  (i) at least two positive cultures of blood samples drawn >12 hours apart or
  (ii) all of three or a majority of four or more separate cultures of blood (with first and last sample drawn at least 1 hour apart).
  (2) Evidence of endocardial involvement
  A. Positive echocardiogram for IE defined as:
  (i) oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, or
  (ii) abscess, or
  (iii) new partial dehiscence of prosthetic valve
  B. New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)
- **Minor criteria**
  (1) Predisposition: predisposing heart condition or intravenous drug use
  (2) Fever: temperature, ≥38.0°C
  (3) Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway’s lesions
  (4) Immunologic phenomena: glomerulonephritis, Osler’s nodes, Roth’s spots, and rheumatoid factor
  (5) Microbiologic evidence: positive blood culture but does not meet a major criterion as noted in table 2 or serological evidence of active infection with organism consistent with IE
  (6) Echocardiographic findings: consistent with IE but do not meet a major criterion as noted in table 2

*See table 2 for definitions of major and minor criteria.

NOTE. Table was originally published in [4]. HACEK = *Haemophilus* species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* species, and *Kingella kingae*; IE = infective endocarditis.

†Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis.
Table 3. Factors predisposing to infectious endocarditis among 26 of 100 patients with at least one predisposing factor.

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predisposing heart condition</td>
<td></td>
</tr>
<tr>
<td>Native valve disease</td>
<td></td>
</tr>
<tr>
<td>Aortic regurgitation and/or stenosis</td>
<td>7</td>
</tr>
<tr>
<td>Mitral regurgitation and aortic regurgitation or stenosis</td>
<td>4</td>
</tr>
<tr>
<td>Congenital and miscellaneous conditions</td>
<td>4</td>
</tr>
<tr>
<td>Prosthetic valve</td>
<td>7</td>
</tr>
<tr>
<td>Endocavitary pacemaker</td>
<td>2</td>
</tr>
<tr>
<td>Intravenous drug use</td>
<td>2</td>
</tr>
</tbody>
</table>

Results

Patient characteristics. One hundred consecutive cases were analyzed in this study. There were 52 males and 48 females; the mean (±SD) age was 62 ± 17 years (range, 19–91 years). All patients had fever (temperature, >38°C), which was documented at least twice. Twenty-six patients had at least one predisposing factor for IE; 24 of these patients had a predisposing heart condition, and two were intravenous drug users. Predisposing factors are detailed in table 3. Two patients had a history of IE; both had native-valve disease. Twenty-nine patients had an abnormal cardiac murmur that was considered to be new (not preexisting or previously documented), and three of these patients also had a predisposing cardiac abnormality. The remaining 48 patients had FUO.

No vascular phenomena were found in any of the patients, whereas immunologic phenomena were recorded for 14 patients, including one patient with immune complex glomerulonephritis and 13 patients whose sera were positive for rheumatoid factor. It should be noted that the sera of 44 patients were not assayed for rheumatoid factor. Likewise, only nine patients were examined for the presence of Roth’s spots, and all of these patients were negative. In addition, two patients presented with petechial purpura, a condition not listed in the Duke minor criteria defining vascular phenomena.

Blood cultures. A mean of five blood cultures (range, 2–20 blood cultures) per patient were performed for our patient population. None of the blood cultures were either persistently positive or positive for a pathogen that typically causes IE, as defined in the Duke major criteria. However, blood cultures were positive in six cases, two of which fulfilled the Duke minor criteria for microbiological evidence of IE. In one case a single blood culture for a patient with acute pyelonephritis was positive for Escherichia coli. In the other case two blood cultures, performed > 24 hours apart, were positive for Streptococcus pneumoniae; the patient was finally found to have pulmonary tuberculosis and chronic lymphocytic leukemia. In the remaining four cases, only a single blood culture was positive for coagulase-negative staphylococci, a condition that is excluded from the definition of the Duke microbiological minor criteria.

Echocardiographic findings. All patients underwent transthoracic echocardiography (TTE), which failed to disclose any abnormality in 40 cases. Of the 60 cases in which abnormalities were found, 10 fulfilled the Duke definition of either major or minor echocardiographic criteria. In one case, a new dehiscence of an aortic prosthetic valve was evidently fulfilling a Duke major criterion. The patient underwent surgery, and the diagnosis of IE was ruled out; however, inflammatory aortitis was observed and was histologically confirmed to be Takayasu’s disease. No abscess was evident in any of the cases. In one case, an oscillating intracardiac mass was thought to be a vegetation implanted on the mitral valve. However, this finding was not confirmed by transesophageal echocardiography (TEE), which only disclosed a thickened mitral valve. This abnormality was finally regarded as fulfilling a Duke minor criterion rather than a major criterion. In the remaining eight cases (all involving native valves), echocardiographic abnormalities were described as consistent with IE and were therefore regarded as fulfilling a Duke minor criterion. These abnormalities are described in table 4.

In 18 cases, TEE was deemed worth performing to further appraise the abnormalities documented by TTE. Except for the previously described case, in which TEE did not reveal the existence of a vegetation, no TEE examination yielded stronger evidence of IE than TTE had.

Reclassification of cases. According to the Duke criteria, the diagnosis of IE was rejected in all 100 cases for the following reasons: a firm alternate diagnosis for the manifestations of IE was made in 23 cases; the manifestations of endocarditis resolved in 39 cases when antibiotic therapy was administered for ≤ 4 days; and both events occurred in 38 cases. In the 23 cases excluded because of a firm alternate diagnosis, the diagnoses were as follows: malignancy (n = 7), systemic vasculitis and/or rheumatologic disease (n = 6), thromboembolic disease (n = 2), genitourinary tract infection (n = 3), viral infection (n = 2), tuberculosis (n = 1), leptospirosis (n = 1), and amebic liver abscess (n = 1).

Table 4. Nine minor echocardiographic findings consistent with infective endocarditis.

<table>
<thead>
<tr>
<th>Finding, affected valve</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonoscillating target</td>
<td></td>
</tr>
<tr>
<td>Aortic valve</td>
<td>1</td>
</tr>
<tr>
<td>Mitral valve</td>
<td>2</td>
</tr>
<tr>
<td>Nodular valve thickening</td>
<td>3</td>
</tr>
<tr>
<td>Valve thickening and regurgitation</td>
<td>1</td>
</tr>
<tr>
<td>Mitral valve</td>
<td></td>
</tr>
<tr>
<td>Aortic and mitral valves</td>
<td>2</td>
</tr>
</tbody>
</table>
The distribution of the Duke major and minor criteria among our 100 patients who had fever and a suspected— but finally rejected— diagnosis of IE is shown in Table 5. Each case was then reclassified according to the Duke criteria, regardless of the fact that it had been previously classified as rejected. The results of this reclassification are displayed in Table 6. The following is a description of the only case that was reclassified as clinically definite on the basis of one major and three minor criteria.

A 75-year-old female with a history of rheumatic fever underwent implantation of a porcine mitral prosthesis in 1984 (Duke minor criterion). She was admitted to the hospital because of fever (temperature, > 38°C) of 4 days’ duration (minor criterion). Physical examination disclosed a new aortic regurgitant murmur (major criterion). TTE was performed, and no aortic valve abnormality or major evidence of IE was found, but an abnormal thickening of one of the cusps of the prosthetic valve was observed, which was not regarded as consistent with IE. One of three blood cultures (minor criterion) and a urine culture were positive for E. coli. The patient was clinically treated as having acute pyelonephritis with no endocarditis. Cure was achieved after she received a 3-week course of therapy with a third-generation cephalosporin.

Specificity. Because only one of 100 cases was incorrectly reclassified in this series, the specificity of the Duke criteria can be calculated to 0.99 (95% CI = 0.97–1).

Discussion

To our knowledge, this is the first study aimed at evaluating the specificity of the recently proposed Duke criteria for the diagnosis of IE. It is of interest that the specificity of the Beth Israel criteria for excluding the diagnosis of IE has not even been established. The improved sensitivity of the Duke criteria raised concern about their specificity, which we found to be quite high. With use of the Duke criteria, the diagnosis of IE was accurately ruled out in all but one of 100 cases of suspected IE. Whether this case actually represented endocarditis is questionable; it was a case of bactereemic pyelonephritis due to E. coli in a woman with a prosthetic valve who was found to have new aortic regurgitation when she was admitted to the hospital for evaluation of acute fever.

The physicians who cared for this patient rejected the diagnosis of IE for two main reasons: first, echocardiography failed to show any evidence consistent with this diagnosis, and second, E. coli is only exceptionally a causative agent of IE. For instance, in a recent French series of patients with IE, only five (1.2%) of 415 cases were due to E. coli [6]. Even in a series of patients with nosocomial IE, E. coli is infrequently responsible for the infection, as illustrated by the fact that only one case among 23 was found to be due to E. coli [7]. In addition, bactereemia due to E. coli is seldom complicated by endocarditis. In a series of 171 patients with nosocomial bactereemia and prosthetic valves, only one of 10 bactereemic episodes due to E. coli was complicated by IE, whereas 30 of 43 episodes of Staphylococcus epidermidis bactereemia and 15 of 34 episodes of Staphylococcus aureus bactereemia were complicated by IE [8]. To be certain that the rejection of the diagnosis of IE was accurate in our case of E. coli bactereemic pyelonephritis, we interviewed the patient’s general practitioner, who confirmed that she had had no relapse of infection during the year after discharge from the hospital. We also interviewed the general practitioners who cared for the other two patients whose firm alternate diagnoses were genitourinary infections, and we obtained the same confirmation.

It can be argued that the design of our study favored an overestimated specificity rate. However, we tried to avoid selection bias by studying all the cases of patients who had a
suspected diagnosis of IE that was rejected and who were hospitalized during a given period. Furthermore, the diagnosis of IE should have been clinically suspected for these patients since they all had high-grade fevers, they all had five (mean number) blood cultures performed, and they all had undergone TTE at least once. Likewise, >25% of the patients had a well-defined predisposition to IE.

On the other hand, the retrospective design of the study might have biased our results towards a higher specificity rate. For instance, we admit that fundoscopic examination for the presence of Roth’s spots was performed in only 9% of the cases and that assay for rheumatoid factor was not done in 44% of the cases. However, the contribution of these two items to the diagnosis of IE is usually marginal. Furthermore, the results of serological tests for various microorganisms that can cause apparent culture-negative endocarditis (e.g., Coxiella burnetii, Bartonella species, Chlamydia species, and Legionella species [9]) were missing in a majority of the cases. A serological test that was positive for one of these microorganisms might well have established a Duke minor criterion for microbiological evidence of IE. On the other hand, it is unlikely that any of these tests would have been positive, given the subsequent clinical courses of the patients. Although we cannot accurately estimate to what extent the absence of any missing data may have lowered the specificity rate we observed, we believe that this reduction would ultimately have been only minimal. This limitation in our study suggests the need for a prospective evaluation of the Duke criteria.

Another key point of our study is the role of echocardiographic findings in the diagnosis of IE when it is based on the Duke criteria. von Reyn et al. [10, 11] expressed their fear that minor echocardiographic findings might weaken a strict case definition because of their lack of specificity [10, 11]. In our study, such nonspecific echocardiographic findings, though consistent with IE, were recorded in only 9% of cases, which can be considered a low figure in view of the fact that >25% of our patients had known underlying valvular heart disease. In addition, these minor echocardiographic findings did not contribute to the establishment of a definite diagnosis of IE in the nine patients with abnormal echocardiographic findings.

Even in the only case reclassified as clinically definite IE, echocardiographic findings were not part of the three minor criteria that contributed to the incorrect reclassification. It is of interest that TEE did not appear to decrease the specificity of the echocardiographic findings. In none of the 18 cases in which TEE was performed did it provide stronger evidence of IE than TTE had. On the contrary, in one case the application of TEE led to correction of an erroneous diagnosis of vegetation that had previously been considered likely on the basis of the results of TTE.

We conclude that despite a potential bias toward a slight overestimation of the specificity of the Duke criteria, this study establishes that they are highly specific for ruling out IE in patients with acute fever or FUO.

Acknowledgments

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References