

# An assessment of the current diagnostic criteria for infective endocarditis

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A firm diagnosis of infective endocarditis is difficult to establish. Clinicians often face a decision-making dilemma about whether to treat a patient presenting with some features that suggest endocarditis. This article summarizes both the previous and the recently proposed criteria for the diagnosis of infective endocarditis, and reviews the efficacy of the new criteria. The authors also discuss the experience at The Toronto Hospital, Toronto, Ontario, with this disease, paying specific attention to the application of the new criteria in the diagnostic process.

**Key Words:** *Diagnosis, Guidelines, Infective endocarditis*

## Évaluation des critères actuels en vue du diagnostic de l'endocardite infectieuse

**RÉSUMÉ :** Le diagnostic formel de l'endocardite infectieuse est difficile à confirmer. Les cliniciens font souvent face à un dilemme lorsque vient le temps de traiter un patient qui présente certains signes évocateurs de l'endocardite. Cet article résume les anciens critères et les nouveaux critères proposés pour le diagnostic de l'endocardite infectieuse et passe en revue les avantages de ces nouveaux critères. Les auteurs décrivent également l'expérience menée au *Toronto Hospital* de Toronto, en Ontario, à propos de cette maladie en accordant une attention spécifique à l'application de nouveaux critères dans le processus diagnostique.

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**I**nfective endocarditis (IE) is a condition in which microbial infection occurs on the endothelial surface of the heart. It is characterized by the formation of valvular vegetations, fenestration, abscess and dehiscence of prosthetic valves. Patients with IE may develop fever, malaise, weight loss, anorexia, and symptoms of immunological and embolic phenomenon. However, because of the protean manifestations of IE and the inaccessibility of the involved organ, the disease is often diagnosed with uncertainty based on clinical manifestations. For example, a new onset of a prolonged PR interval on an electro-

cardiogram may be indirect evidence of myocardial abscess, but this method is limited by its low sensitivity. The diagnosis of IE is never absolutely certain until explanted valves are assessed pathologically or an autopsy is available. There have been very few published guidelines that assist in the diagnosis of IE. Newly trained physicians often associate the presence of a febrile illness in a patient with a prosthetic heart valve with endocarditis and may subject patients to unnecessary invasive studies and therapy. Should all patients who have prosthetic heart valves and fever undergo an echocardi-

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**TABLE 1**  
**von Reyn criteria for diagnosis of infective endocarditis**

<b>Definitive</b>
Direct evidence of infective endocarditis based on histology from surgery or autopsy, or on bacteriology (Gram stain or culture) of valvular vegetation or peripheral embolus
<b>Probable</b>
A. Persistently positive blood cultures* plus one of the following: new regurgitant murmur predisposing heart disease <sup>†</sup> and vascular phenomena <sup>‡</sup>
B. Negative or intermittently positive blood cultures <sup>¶</sup> plus three of the following: fever new regurgitant murmur vascular phenomena
<b>Possible</b>
A. Persistently positive blood cultures, plus one of the following: predisposing heart disease vascular phenomena
B. Negative or intermittently positive blood cultures with all three of the following: fever predisposing heart disease vascular phenomena
C. For <i>Viridans streptococcus</i> cases only: at least two positive blood cultures without an extracardiac source and fever
<b>Rejected</b>
A. Endocarditis unlikely, alternative diagnosis generally apparent
B. Endocarditis likely, empiric antibiotic therapy warranted
C. Culture negative endocarditis diagnosed clinically but excluded by postmortem

\*At least two blood cultures obtained, with two of two positive, three of three positive, or at least 70% of cultures positive if four or more cultures obtained; <sup>†</sup>Definite valvular or congenital heart disease or a cardiac prosthesis (excluding permanent pacemakers); <sup>‡</sup>Petechiae, splinter hemorrhages, conjunctival hemorrhages, Roth spots, Osler's nodes, Janeway lesions, aseptic meningitis, glomerulonephritis, and pulmonary, central nervous system, coronary or peripheral emboli; <sup>§</sup>Any rate of blood culture positivity that does not meet the definition of persistently positive. Adapted from reference 2 with permission of the publisher Excerpta Medica Inc

graphic study to evaluate the possibility of IE? Who should be treated with a full course of antibiotics for suspected IE? The purpose of this article is to review the diagnostic criteria used to diagnosis IE.

### VON REYN CRITERIA

In 1981, von Reyn et al (1) published clinical pathological criteria for classifying patients suspected of having IE. The criteria classified cases into definite, probable, possible and rejected endocarditis (Table 1). These criteria have been criticized in recent years for a variety of reasons. First, pathological confirmation is necessary to designate a case as definite IE. Because only some patients require surgery, a substantial portion of cases are classified as 'possible IE', and some of them rejected. Second, the criteria do not incorporate information provided by echocardiography, which plays a critical role in the assessment of patients with suspected endocarditis. Third, they do not consider intravenous drug abus-

**TABLE 2**  
**Duke criteria for diagnosis of infective endocarditis**

<b>Definite</b>
Pathological criteria:
1. Microorganisms: demonstrated by culture or histology in a vegetation, or in a vegetation that has embolized, or in an intracardiac abscess, or
2. Pathological lesions: vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis
Clinical criteria, using specific definitions listed in Table 3:
two major criteria, or
one major and three minor criteria, or
five minor criteria
<b>Possible</b>
Findings consistent with infective endocarditis that fall short of 'definite' but not 'rejected'
<b>Rejected</b>
1. Firm alternate diagnosis for manifestations of endocarditis, or
2. Resolution of manifestations of endocarditis, with antibiotic therapy for four days or less, or
3. No pathological evidence of infective endocarditis at surgery or autopsy, after antibiotic therapy for four days or less

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ers as high risk and predisposed to IE due to needle-sharing. Because of these criticisms, there is a need for a more comprehensive set of guidelines for diagnosing IE.

### DUKE CRITERIA

Durack et al (2) from Duke University, Durham, North Carolina introduced a new set of criteria that incorporated findings from the two-dimensional echocardiogram and a history of intravenous drug use into the clinical assessment. The new criteria were modelled after the Jones criteria (3) used for the identification of cases of rheumatic fever.

The proposed Duke criteria defined cases of suspected IE into definite, probable and rejected (Table 2). 'Definite IE' was intended to identify patients with a very high likelihood of having IE. Cases for which pathological confirmation is available are classified into this category. On the other hand, because only one-third of patients with native valve IE undergo surgery or autopsy during the acute illness, cases that fulfil certain clinical parameters that are considered typical of IE are also included in this category (Table 3). The 'rejected IE' group comprises cases in which the syndrome resolves spontaneously with a short course of antibiotic therapy or when an alternate diagnosis that explains the presentation is made. Cases that belong to the 'possible IE' category are those that do not meet all the criteria for 'definite IE' and yet manifest findings that are sufficiently suggestive of IE to make rejection of the diagnosis clinically unjustified.

The clinical features of IE are separated into two major and five minor criteria under the Duke criteria. Cases that have two major, one major plus three minor, or five minor criteria are considered definite cases of IE. Two features that are crucial with respect to blood cultures are persistent bacteremia and typical microorganisms. *Viridans streptococcus*, *Streptococcus bovis* and the members of HACEK group (*Haemophilus* species, *Actinobacillus actinomycetemcomitans*, *Cardiobacte-*

**TABLE 3**  
Definitions of terminology used in the Duke criteria

**Major criteria**

- Positive blood culture for infective endocarditis  
 Typical microorganism for infective endocarditis from two separate blood cultures
- *Viridans streptococci*\*, *Streptococcus bovis*, HACEK group, or community-acquired *Staphylococcus aureus* or enterococci, in the absence of a primary focus, or
- Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from: blood cultures drawn more than 12 h apart, or all of three or a majority of four or more separate blood cultures, with first and last drawn at least 1 h apart

**Evidence of endocardial involvement**

- Positive echocardiogram for infective endocarditis  
 oscillating intracardiac mass, on valve or supporting structures, or in the path of regurgitant jets, or on implanted material, in the absence of an alternative anatomic explanation;  
 abscess; or  
 new partial dehiscence of prosthetic valve
- New valvular regurgitation (increase or change in pre-existing murmur not sufficient)

**Minor criteria**

- Predisposition: predisposing heart condition or intravenous drug use
- Fever: higher than 38.0°C (100.4°F)
- Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions
- Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor
- Microbiological evidence: positive blood culture but not meeting major criterion as noted previously<sup>†</sup> or serological evidence of active infection with organism consistent with infective endocarditis
- Echocardiogram: consistent with infective endocarditis but not meeting major criterion as noted previously

<sup>†</sup>Including nutritional variant strains; <sup>‡</sup>Excluding single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis. HACEK Haemophilus species, Actinobacillus actinomyces-comitans, Cardiobacterium hominis, Eikenella species and Kingella kingae. Adapted from reference 2 with permission of Excerpta Medica Inc

*rium hominis*, *Eikenella* species and *Kingella kingae*) are common causes of IE and are infrequently isolated from blood cultures of patients without IE. On the other hand, *Staphylococcus aureus* and enterococcus may be typical endocarditis pathogens, but they also cause bacteremia in patients with confirmed extracardiac infections without IE, especially those that are acquired nosocomially. The Duke schema weighs persistent enterococcal and staphylococcal bacteremias as major criteria only when they are both community acquired and arise without an apparent primary focus of infection. Coagulase-negative staphylococcus can cause IE but is often isolated from blood culture usually because of contamination. This explains why persistent bacteremia is a key feature of these criteria.

The echocardiographic manifestations of IE include discrete, echogenic oscillating intracardiac masses located at sites of endocardial injury, periannular abscess and new dehiscence of a prosthetic valve. Based on the authors' clinical

**TABLE 4**  
Comparison of clinical diagnosis of infective endocarditis using von Reyn criteria and Duke criteria in the pathologically proven cases from four independent centres (2,4-6)

von Reyn criteria	Duke criteria			Total (%)
	Definite	Possible	Rejected	
Probable	88	5	0	93 (57)
Possible	32	5	0	36 (23)
Rejected	10	21	2	33 (20)
Total (%)	130 (80)	31 (19)	2 (1)	163 (100)

**TABLE 5**  
Comparison of clinical diagnosis in patients evaluated for diagnosis of infective endocarditis from four independent centres (2,4-6) using von Reyn criteria and Duke criteria excluding pathologically proven cases

von Reyn criteria	Duke criteria			Total (%)
	Definite	Possible	Rejected	
Probable	116	13	12	141 (30)
Possible	88	62	15	165 (34)
Rejected	18	93	58	169 (36)
Total (%)	222 (47)	168 (35)	85 (18)	475 (100)

experience, echocardiography does not appear to be sensitive enough to pick up fenestrations of valvular leaflets; however, identification of fenestrations should be as a major criterion. Nonspecific valve thickening is not evidence of echocardiographic definite IE. False positive echocardiographic features in prosthetic valves could be related to stitches to the valvular ring or noninfective paravalvular leak. New valvular regurgitation by auscultation, however, is considered a main criterion under the Duke classification.

Predisposing factors include patients who have had previous mechanical or tissue prosthetic valves, intracardiac instrumentation or intravenous drug use. The presence of an ischemic leg or focal neurological manifestation consistent with stroke belongs to the vascular phenomenon. These conditions must be confirmed radiologically. Splinter hemorrhages, subconjunctival hemorrhages and clubbing are considered too nonspecific, and, therefore, they are not included in this category. Immunological phenomena include immune complex-mediated events such as glomerulonephritis, Osler's nodes and Roth's spots. Echocardiographic features of the Duke minor criteria are those that are suggestive of IE but are not mentioned in the major category; valvular thickening and nodules are examples of this. Microbiological features include bacteremia not due to the typical organisms causing IE or serological evidence of recent infection by a pathogen known to cause valvular lesions (eg, brucella, legionella, chlamydia or *Coxiella burnettii*), where routine blood cultures may not be able to isolate the pathogen. *Bartonella* species have been recently recognized as an important cause of apparent 'blood culture-

**TABLE 6**  
The Toronto Hospital experience with diagnosis of infective endocarditis (IE) from 1989 to 1995

	Number of patients	
Patients with discharge diagnosis of IE	206	
Using Duke criteria:		
Definite IE	183	
Probable IE	23	
Rejected IE	0	
Among 183 patients who fulfilled definite Duke criteria:		
Age (years)	50.7 ± 17.8	
Sex	68 females	
Clinical diagnosis of IE with:		
Two major criteria	152 patients	
One major and three minor criteria	30 patients	
Five minor criteria	2 patients	
	Number of patients	
	Native valve (%)	Prosthetic valve (%)
Number of patients	126 (100)	57 (100)
Major criteria		
Positive blood culture	125 (98)	50 (88)
Typical echocardiographic features	114 (90)	45 (79)
Minor criteria		
Predisposition	62 (49)	57 (100)
Temperature higher than 38°C	110 (87)	52 (91)
Vascular phenomenon	35 (28)	13 (23)
Immunological phenomenon	18 (14)	6 (11)
Minor echocardiogram features	6 (5)	9 (16)
Minor microbiological features	0	1 (2)
Organisms		
<i>Staphylococcus aureus</i>	39 (31)	13 (23)
<i>Staphylococcus epidermis</i>	8 (6)	11 (19)
<i>Viridans streptococcus</i>	45 (36)	11 (19)
Other streptococcal species	23 (11)	6 (11)
HACEK group	3 (2)	4 (7)
Gram-positive bacilli	3 (2)	1 (2)
Gram-negative bacilli	3 (2)	4 (7)
Gram-negative anaerobes	1 (1)	0
Negative blood cultures	1 (1)	7 (12)

HACEK *Haemophilus species*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella species* and *Kingella kingae*

negative' endocarditis in several reports (4-6), especially in patients who are alcoholics or are homeless. At this time, isolation of these organisms fulfils a minor Duke criterion.

#### EVALUATION OF THE DUKE CRITERIA

In addition to the internal evaluation by the Duke Endocarditis Service, the recently proposed criteria were also evaluated independently by several other centres, namely the University of Southern California in Los Angeles (7), the Uni-

**TABLE 7**  
Clinical course of patients with infective endocarditis at The Toronto Hospital

	Native valve	Prosthetic valve
Mean duration from the onset of symptoms to the time of diagnosis (range 1 to 210 days)	33 days	29 days
Mean duration of hospital stay (ranged 1 to 281 days)	30 days	40 days
Number of patients who proceeded with TEE after TTE	74 (59%)	37 (65%)
Number of patients who had TEE without TTE	12 (10%)	11 (19%)
Number of patients suffered from at least one embolic event before undergoing echocardiography	36 (29%)	6 (11%)
Outcome		
Requiring urgent cardiac surgery	63 (50%)	27 (47%)
Cerebral infarct	26 (21%)	3 (5%)
Systemic embolism	24 (19%)	0
Pulmonary embolism	4 (3%)	1 (2%)
Congestive heart failure	28 (22%)	5 (26%)
Death	25 (20%)	11 (19%)

TEE Transesophageal echocardiogram; TTE Transthoracic echocardiogram

versity of Nancy Medical Center in Vandoeuvre cedex, France (8) and the University of Alberta (9). Summarizing the results reported from the four centres, a total of 638 patients with suspected IE were evaluated; 163 had IE proven pathologically and 475 did not (Tables 4,5). Calculation of sensitivity and specificity was difficult because the pathology (the gold standard) is not available on all patients. However, the conclusion drawn from these studies is that, using the new set of criteria, more cases would be classified as definite versus probable, possible or even rejected compared with the old criteria. Dodds et al (10) showed that the negative predictive value of the new criteria was as high as 98% during a three-month follow-up of patients in whom the diagnosis of IE was rejected. In this study, no new cases were found in these patients except one case where the patient's autopsy revealed evidence that might represent missed IE. Thus, the Duke criteria are more sensitive than the old criteria because they include more patients in the positive test category. Moreover, a patient failing to satisfy the criteria for probable IE is very unlikely to have IE.

#### THE TORONTO HOSPITAL EXPERIENCE

**Patient selection:** The Toronto Hospital is a tertiary referral centre. The authors' experience with IE from 1989 to 1995 matched the data reported from other centres. Two hundred and six cases were identified based on a discharge diagnosis of IE reported to the hospital registry. The hospital charts were reviewed retrospectively, and each case was classified as 'def-

inite', 'probable' or 'rejected' based on the Duke criteria (Table 6).

**Results:** The clinical characteristics of the patients, including the causative organisms and the course in the hospital, are presented in Tables 6 and 7. One hundred and eighty-three and 23 cases were labelled as 'definite IE' and 'probable IE', respectively, under the new criteria (ie, no cases were rejected under the new criteria). There were 90 'definite IE' patients and two in the 'probable IE' group who underwent cardiac surgery. The two patients who belonged to the 'probable' group presented with one major (positive blood culture) and two minor criteria; however, during surgery only one patient was identified as having active infective endocarditis.

Of note, 98% of the patients with native valve endocarditis had typical blood cultures, and a large portion of patients also had typical echocardiographic features of IE (Table 6). This implies that in the absence of bacteremia and no preceding antibiotic use, patients who have native valves and present with other features of IE are in fact unlikely to have endocarditis.

In addition, more than half of the patients proceeded to transesophageal echocardiography after transthoracic scanning. Moreover, a higher percentage of patients with prosthetic valves had transesophageal echocardiogram as the initial radiological test compared with native valve group, probably because of a high pretest suspicion (presence of positive blood culture and prosthesis) and poor acoustics of prosthesis using transthoracic method.

Among patients with prosthetic valves, the majority had typical microorganisms cultured from their blood, but typical echocardiographic features were seen less frequently than in those with native valve IE. This is likely due to the difficulty of detecting vegetations in the presence of valvular prosthesis, mainly as a result of acoustic shadowing on echocardiograms. Our anecdotal experience suggested that patients whose blood cultures were positive for typical organisms and had a history of previous prosthetic valve surgery should be treated with full antibiotic therapy, as if endocarditis was present.

## CONCLUSIONS

Infective endocarditis is difficult to diagnose with certainty. Clinicians often face a diagnostic dilemma when a patient presents with some symptoms suggesting IE, especially in cases when patients with prosthetic heart valves present with febrile illness. However, careful examination using the guidelines from the Duke criteria may assist clinicians in making a diagnosis of IE with greater certainty, and thus the decision regarding antibiotics administration may be made more appropriately. In our centre, the Duke criteria identified most patients with definite endocarditis except for one patient who subsequently was proven to have IE during surgery. The Duke criteria, therefore, provide a more satisfactory set of guidelines than the previous guidelines for diagnosing IE and determining which patients should be treated.

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