

Negative Predictive Value of the Duke Criteria for Infective Endocarditis

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With use of new Duke criteria, 405 episodes of suspected endocarditis were previously classified as "definite," "possible," or "rejected" endocarditis. To determine the negative predictive value of the Duke clinical criteria for the classification of suspected endocarditis, chart review and follow-up were performed for the 52 episodes in which the diagnosis of endocarditis was rejected. Three of 52 episodes were reclassified as possible endocarditis; 49 episodes in 48 patients met the criteria for rejected endocarditis. Of these 49 episodes, 31 (63%) had a firm alternate diagnosis other than endocarditis, 17 (35%) had resolution of the clinical syndrome leading to the suspicion of endocarditis with ≤ 4 days of antibiotics, and 1 patient had no evidence of endocarditis at surgery. Echocardiograms recorded in

3 patients with rejected endocarditis had evidence of oscillating valvular masses, and blood cultures were positive in 13 episodes; none of these patients had evidence of endocarditis at follow-up. Follow-up or outcome information was available in all 49 episodes. Excluding the 5 in-hospital deaths, mean duration (\pm SD) of follow-up was 39.9 ± 28.8 months (range 0.5 to 108.0); in living patients, mean time to final follow-up was 56.2 ± 25.2 months (range 25.0 to 108.0). One patient had possible infective endocarditis at autopsy. No patient in our series whose diagnosis of endocarditis had been rejected had proven endocarditis. Therefore, the negative predictive value of the Duke clinical criteria for endocarditis is at least 92%.

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New criteria for the classification of suspected infective endocarditis (IE)¹ have recently been shown to be more sensitive in diagnosing the presence of IE than the criteria popularized by von Reyn et al.² The criteria by von Reyn et al have long defined the degree of certainty in diagnosing endocarditis. However, the validity of the von Reyn criteria remains controversial,³⁻⁶ and the ability of either set of criteria to exclude the diagnosis of endocarditis has not been examined. Indeed, most studies involving IE have focused on criteria to confirm the presence of endocarditis.^{2,7-9} Studies that examine the specificity of diagnostic criteria are few.⁴ Yet it is important that the diagnosis of IE not be incorrectly rejected in patients with suspected endocarditis, as an erroneous exclusion could result in clinical disaster. For these reasons, the present study was designed to evaluate the negative predictive value of the new Duke criteria (Table 1) for excluding IE.

METHODS

Study design and patient selection: Four hundred five cases of suspected IE were previously classified as "definite" (n = 204), "possible" (n = 149), or "rejected" (n = 52).¹ Three criteria were used for rejecting a diagnosis of IE: (1) a firm alternate diagnosis for manifestations of IE existed; (2) clinical manifestations compatible with IE resolved after ≤ 4 days of antibiotic therapy; or (3) no pathologic evidence of IE was found at surgery or autopsy (such patients must also not have had > 4 days of antibiotic therapy). For the present study, the entire medical chart for each of the

52 rejected episodes was again reviewed by 1 of the investigators (GAD) to ascertain that each case actually met the above criteria.

Chart review: Each chart was reviewed for the clinical manifestations that led to the suspicion of IE. These included findings mentioned in the medical history, physical examination, and progress notes, as well as criteria that were met in the classification scheme. If there was a discrepancy between physicians' notations and the Duke criteria, the clinician's notation that a finding was present was accepted as a reason for suspecting IE. The terms "index admission" and "index discharge" refer to the initial admission and discharge for the suspected episode of endocarditis.

Positive blood cultures were considered to be community-acquired if they were obtained within 72 hours of index admission. Reports of all echocardiograms performed during the episode of suspected IE were reviewed. Because an oscillating valvular mass is a major criterion in the Duke schema, the original tape in all cases in which an oscillating mass was reported was reviewed again by a senior echocardiographer (only the 3 of 49 cases in which an oscillating mass was present were reviewed).

The outcome of each episode was defined as follows: (1) in-hospital death; (2) out-of-hospital death (i.e., patient died any time after index discharge); or (3) living (documented by phone follow-up).

Follow-up: To ascertain whether any patient with a diagnosis of rejected IE subsequently developed true IE, we sought a minimal follow-up period of 3 months after index discharge and the completion of antimicrobial therapy (initial follow-up). Follow-up notes documenting a physician's examination were obtained whenever available. For patients who died before 3 months after index discharge, physicians' notes and/or recollection of the patient's clinical status from surviving relatives were

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TABLE I Duke Criteria for Diagnosis of Infective Endocarditis

Definite infective endocarditis
Pathologic criteria
Microorganisms demonstrated in vegetation or abscess, or pathologic lesions with confirmatory histology
Clinical criteria
2 major, 1 major and 3 minor, or 5 minor criteria
Possible infective endocarditis
Findings consistent with but short of "definite," but not rejected
Rejected
Firm alternate diagnosis for manifestations, or resolution of manifestations with ≤ 4 days antimicrobial therapy, or no pathologic evidence at surgery or autopsy after ≤ 4 days of antimicrobials
Major criteria
Positive blood culture
Microorganism typical for endocarditis
Persistently positive blood culture
Evidence of endocardial involvement
Echocardiogram positive for endocarditis
New valvular regurgitation
Minor criteria
Predisposition: heart disease or intravenous drug use
Fever $\geq 38.0^{\circ}\text{C}$ (100.4°F)
Vascular phenomena
Immunologic phenomena
Microbiologic evidence consistent with endocarditis (not meeting major criterion)
Echocardiogram consistent with endocarditis (not meeting major criterion)

Adapted with permission from Durack et al.¹

sought. In addition to this minimum (initial) follow-up, information concerning the present status of each patient was sought (final follow-up). A copy of the autopsy report was obtained for all patients who had postmortem examination; in all other deceased patients a copy of the death certificate was obtained.

Time intervals were determined to the nearest half month. Unless otherwise specified, values are given as mean \pm SD.

RESULTS

Forty-nine episodes in 48 patients met the criteria for rejected IE (Figure 1 and Table II). Three cases classified as rejected IE in the original case series were reclassified as possible IE by using the criteria previously described.

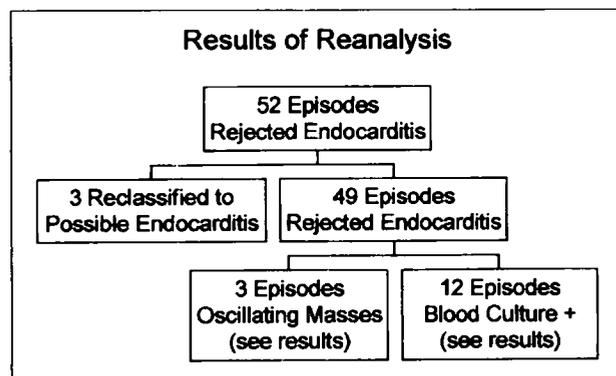


FIGURE 1. Flow chart of selected features of current reanalysis of cases from the Duke endocarditis database¹ in which the diagnosis of endocarditis had been rejected.

Of these 49 episodes, 31 (63%) had a firm alternate diagnosis. In 17 episodes (35%), there was either complete resolution of the clinical syndrome that precipitated the clinical suspicion of IE or patients remained well after ≤ 4 days of antimicrobial therapy. One patient (2%) had no pathologic evidence of IE at surgery despite receiving no antimicrobial therapy.

Echocardiograms recorded in 3 patients deemed to have rejected IE had evidence of oscillating valvular masses. After unblinded review of these data by a senior echocardiographer, the finding of an oscillating mass was judged to be a misreading by the original clinical reader in 1 case, and an equivocal finding in another case. The oscillating mass noted on the echocardiogram in the remaining patient was considered compatible with endocarditis. The latter 2 cases are described below:

A 58-year-old man (case 5) with obstructive lung disease was admitted with progressive shortness of breath, fever, leukocytosis, and patchy infiltrates on the chest roentgenogram. Transesophageal echocardiography (TEE) disclosed a small oscillating mass (equivocal on review) on a thickened, calcified aortic valve. The diagnosis was pulmonary aspergillosis; he received 3 weeks of antifungal therapy and he died of invasive aspergillosis on the 34th hospital day. Antibactericidal therapy was not given. No aortic valve vegetations or other evidence of IE was seen on postmortem examination.

A 77-year-old woman (case 7) with hypertrophic cardiomyopathy and congestive heart failure was transferred after cardiopulmonary arrest at another hospital. She had fever, a systolic murmur, hematuria, thrombocytopenia, and first-degree atrioventricular block. A single blood culture drawn on hospital day 21 was positive for enterococcus. A TEE revealed an oscillating mass on the left coronary cusp of the aortic valve. Her congestive heart failure was treated and antimicrobial therapy was not used. At the time of follow-up 1, 7, 11, and 20 weeks after discharge she remained well. A transthoracic echocardiogram recorded 13 months later revealed no oscillating masses on the aortic valve.

Blood cultures were positive in 12 episodes in which the diagnosis of IE was rejected. Positive blood cultures in 3 episodes were considered to be contaminants (cases 25, 26, and 32). One patient with a positive blood culture was not treated with antimicrobial therapy and was described above. The remaining 8 patients with positive blood cultures had firm alternate diagnoses to explain the positive cultures.

A few demographic features of our patient population are worth noting (Table II). Six episodes occurred in pediatric patients. In 12 episodes, the patients had prosthetic heart valves. Of the 7 of 49 rejected episodes in which patients received most of their care in the intensive care setting, 6 of 7 (86%) had the diagnosis of IE rejected because of an alternate diagnosis. Two of 3 patients evaluated in the outpatient setting had resolution of the suspected manifestations of IE with < 4 days of antimicrobial therapy.

Follow-up or outcome information was available in all 49 episodes. There were 5 in-hospital deaths (10%); excluding these cases, duration of follow-up was 40 ± 29 months (range 0.5 to 108). In 18 episodes (37%), the

patients died after discharge (mean follow-up 16 ± 13 months; range 0.5 to 48). Twenty-six patients (53%) were alive at the time of final follow-up (56 ± 25 months after discharge, range 25 to 108). Follow-up by telephone was established with all living patients, either directly ($n = 20$) or with a close relative ($n = 6$).

Deceased patients: No death was attributable to a missed diagnosis of IE. Postmortem examination was performed in 7 patients. Of the 5 patients who died during their initial hospitalization, 4 had an autopsy; none had postmortem evidence of IE. All 4 had a firm alternate diagnosis to IE. Three patients died during subsequent admissions and underwent autopsy. One patient had evidence that might represent missed IE, and 1 patient subsequently developed IE. These last 2 cases are described below.

A 73-year-old woman (case 8) was admitted with anemia and leukocytosis after recent aortic and mitral valve replacements. She was afebrile, and 4 blood cultures were negative. Her illness was attributed to prosthetic valve dysfunction with intravascular hemolysis. She was treated with antibiotics. She died 1 month later. Autopsy showed nodular vegetations on the mitral valve sewing ring; however, no microscopic or bacteriologic examination of the vegetations was performed.

A 42-year-old woman (case 9) with mechanical prosthetic aortic and mitral valves had an index discharge diagnosis of infected thigh hematoma. During her index admission, 6 blood cultures and an echocardiogram were negative. There was no clinical evidence of IE at follow-up 6 and 9 months after discharge. She returned to the hospital 91/2 months later complaining of lethargy and was admitted after she had a hypoglycemic seizure and cardiorespiratory arrest. She died 1 day later of presumed sepsis and ventricular tachycardia. Postmortem mitral vegetation cultures revealed gram-negative rods, and there was a paravalvular abscess involving the mitral valve.

In the remaining 16 episodes in which the patients died during follow-up, postmortem examinations were not performed. Only 1 of these patients died during the index admission (case 3). In this patient, 16 blood cultures during a 5-week admission were negative and adult respiratory distress syndrome was deemed the cause of death. Another patient (case 21) underwent aortic and mitral valve replacement surgery 9 days after index discharge. No antimicrobial therapy was given before surgery, and culture and pathologic examination of the removed valves revealed no evidence of IE. Of the remaining 14 patients, 2 died <3 months after index discharge.

A 68-year-old man (case 11) with chronic lung disease, right heart failure, and respiratory failure was admitted with leukocytoclastic vasculitis. Four blood cultures were negative and he received intravenous corticosteroids and only 1 day of antimicrobial therapy. He was discharged with no antibiotic therapy and was recovering well when seen 1 week after discharge. He died at home the next day of chronic lung disease and right heart failure.

A 65-year-old woman (case 14) admitted to the hospital for evaluation of aortic and mitral valve disease

TABLE II Characteristics of 49 Episodes of "Rejected" Infective Endocarditis

Age (yr) (mean \pm SD)	47 \pm 23 (range 0.5-91)
Female	18 (37)
Race	
White	31 (63)
Black	17 (35)
Other	1 (2)
Patient source	
Referred	29 (59)
Emergency department	13 (27)
Duke patient	7 (14)
Care setting	
Intensive care unit	7 (14)
General inpatient	39 (80)
Outpatient	3 (6)
Reasons for suspecting infective endocarditis*	
Predisposing heart disease	39 (80)
Fever	33 (67)
Positive blood cultures	12 (24)
Leukocytosis	12 (24)
Intravenous drug use	6 (12)
Murmur	6 (12)
Oscillating mass on echocardiogram	3 (6)
*These data may differ from numbers fulfilling criteria in Duke schema (see Methods). Values are expressed as number (%).	

developed a fever during the admission. A diagnosis of endocarditis was rejected and an alternate diagnosis of urinary tract infection was made. After 2 days of intravenous antimicrobial therapy, a 2-week course of oral trimethoprim/sulfamethoxazole was prescribed. Two sets of blood cultures were negative. She died 9 weeks after discharge after developing a sacral decubitus ulcer complicated by sepsis.

In the remaining 12 episodes (11 patients), the patients had a minimum follow-up of 3 months before their deaths. None had evidence of IE during the follow-up period. During their index admissions, resolution of the clinical syndromes leading to the suspicion of IE occurred with <4 days of antibiotics in 8 of 12 episodes. In the remaining 4 episodes a firm alternate diagnosis was made.

Follow-up of living patients: In 26 episodes, the patients were alive at the time of final follow-up. In 22 of 26 episodes (85%), initial follow-up included examination by a physician (during readmission [$n = 5$] or at an outpatient visit [$n = 17$]). The median interval from discharge to initial follow-up in these 22 episodes was 5 months (interquartile range 3.5, 7.5, range 3 to 33). In the remaining 4 episodes, the absence of any evidence suggesting endocarditis during the interval from index discharge to initial follow-up was documented only by patient recall. For these 4 patients, time from discharge to initial follow-up was 54 ± 28 months (median 55, range 27 to 79).

Reclassified patients: In the original series of 405 episodes of suspected IE, a total of 52 episodes were considered to be rejected IE. After careful review of all clinical data from these 52 episodes, we reclassified 3 episodes from rejected IE to possible IE.

A 43-year-old man was admitted for respiratory and renal insufficiency and developed a new aortic regurgi-

tant murmur. A total of 12 blood cultures (all drawn after initiation of antibiotic therapy) were negative. An echocardiogram revealed severe aortic regurgitation and he underwent aortic valve replacement. At surgery, friable vegetations were noted on the valve; however, special stains revealed no microorganisms or inflammatory cells. A pathologic diagnosis of marantic endocarditis was made; thus, this case was considered rejected IE in the original series.

A 56-year-old man with hypertension, diabetes mellitus, and end-stage renal disease was admitted with a 2-week history of fever. Six of 6 blood cultures were positive for nonhemolytic streptococci. His dialysis graft site showed no clinical signs of infection and results of an echocardiogram were normal. He was treated with vancomycin intravenously for a total of 4 weeks. His index discharge diagnosis was graft-associated streptococcal bacteremia. This alternate diagnosis led to a classification of rejected IE in the original series.

A 72-year-old man with hypertension, peripheral vascular disease, and coronary artery disease was admitted for endophthalmitis. Three of 3 blood cultures drawn at another hospital were positive for group A streptococcus and 1 of 3 was also positive for *Clostridium perfringens*. An echocardiogram was negative for endocarditis. He was treated with intravenous cefazolin and gentamicin and the involved eye was eviscerated. His alternate diagnosis in the original series was endophthalmitis.

These 3 cases did not meet the criteria for rejecting the diagnosis of IE. In the first of these cases, the patient received 3 weeks of intravenous antibiotic therapy prior to valve replacement and had no evidence of malignancy; thus, we reclassified this case as possible IE. We reclassified the last 2 cases as possible IE because of the lack of a confirmed source of bacteremia and use of antibiotics. In summary, of the 49 cases in which the diagnosis of IE was rejected after a rigorous review, 1 patient had evidence of possible endocarditis during follow-up. Thus, the negative predictive value of the Duke criteria in this series was as high as 98%; however, if the 3 reclassified cases are treated as diagnostic failures, the negative predictive value is 92%.

DISCUSSION

This is the first case series of which we are aware that provides complete, detailed follow-up on a group of patients in whom the diagnosis of IE was considered but subsequently rejected. No patient in our series of rejected IE had proven IE, in contrast to published reports of the failure of previous criteria in this regard.^{2,4} No death was attributable to a missed diagnosis of IE, and the patients whose episodes we reclassified as possible IE had no deleterious outcomes based on the original assessment. All patients who were alive 3 months after their episode of rejected IE remained free of clinical evidence of missed IE. Furthermore, no patient with rejected IE who died within 3 months of index discharge had a subsequent diagnosis of IE. The 3 cases of rejected IE that were reclassified to possible IE, and the single case with nodular vegetations found on a prosthetic valve at autopsy 1 month after index discharge could be considered diagnostic failures of our endocarditis criteria sys-

tem. However, even if all 4 of these cases are considered to be incorrect diagnoses, the negative predictive value of our IE criteria is 92%. Reclassification of 3 of the original 52 episodes from rejected to possible endocarditis represents the variation that is likely to occur when different investigators (even investigators at the same institution) apply the same criteria to a retrospective review of complex clinical illnesses. To our knowledge, no previous study has critically evaluated criteria to exclude the diagnosis of IE. Other studies that examined criteria for the diagnosis of IE either did not address the negative predictive value of criteria for IE,⁸⁻¹⁰ or provided inadequate or incomplete follow-up information. For instance, von Reyn et al² applied their system of diagnostic criteria to 123 episodes of suspected IE and rejected the diagnosis in 19 episodes (15%). However, data were not provided concerning the follow-up in these 19 patients with rejected IE, 4 of whom received empiric antimicrobial therapy for IE.

Follow-up in our study was complete. Contact was made with all patients alive at the time of follow-up. The autopsy results were reviewed in all cases in which the patient underwent postmortem examination, and in all other deaths the death certificate was obtained. We believe complete follow-up is important in all studies of diagnostic criteria for IE, because IE can rarely remain unrecognized for months.^{3,8,10} Our choice of 3 months of minimum follow-up is empiric.

Study limitations: Our study is limited by its reliance on a selected patient population. Although criteria for the diagnosis and/or exclusion of IE serve as important guidelines in evaluating patients with suspected IE, the pretest probability of disease in any patient population affects the utility of diagnostic criteria.³ Because our intention was to validate the negative predictive value of the Duke criteria, we evaluated all patients who were listed as rejected IE in the original series. Although we recognize that this is a diverse group with varying probabilities of disease, other case series evaluating criteria for IE were based on similar patient populations.^{2,9}

Another limitation of our study is that a retrospective evaluation of episodes of suspected IE (as was performed in the original series) may introduce bias. Patients in whom the diagnosis of IE was initially rejected may have subsequently returned to medical care to be correctly diagnosed, treated, and classified as possible or definite IE. When classified prospectively, the initial period of medical contact may be a separate episode of rejected IE in which IE later developed; however, a retrospective review might consider this initial illness as the beginning of an episode of possible or definite IE, falsely improving the negative predictive value of the criteria.

Because endocardial involvement is a sine qua non of endocarditis, echocardiographic findings have been given major significance in the Duke criteria for diagnosing the presence of IE. However, even patients with no evidence of IE by TEE may be erroneously classified as not having IE. For instance, Sochowski and Chan¹¹ reported a series of hospitalized patients with suspected IE (no diagnostic criteria given) and an initial TEE free of evidence of endocarditis. Some of their

patients developed IE during follow-up, highlighting the need for accurate and specific criteria for the diagnosis and/or exclusion of IE.

Despite the clinical utility of criteria designed to exclude the presence of IE, it is important to emphasize that absence of proof is not proof of absence. When direct evidence of the absence of IE is not available, patients must be followed up carefully for the emergence of manifestations of IE.

Future studies must address the problem of determining if cases of possible IE discovered during follow-up are actually cases of IE. Such a determination is often difficult; for example, case 8 in our series illustrates this problem. Vegetations were seen at autopsy, yet no microscopic or bacteriologic investigations were performed to assess if the vegetations were infective.

Recommendations for future research: We propose that future studies investigating the negative predictive value of clinical criteria for excluding the diagnosis of IE must accomplish the following: (1) A minimum of 3 months of follow-up should occur after discharge and completion of antimicrobial therapy; (2) procurement of death certificates in all patients who are dead at the time of final follow-up; (3) review of all autopsy reports; and (4) adjudication of the clinical significance of possible or definite IE found during follow-up. We look forward to validation of the negative predictive value of the Duke criteria in prospective studies.

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