Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 33, No. 7, 1999
ISSN 0735-1097/99/$20.00
PII S0735-1097(99)00116-3

Value and Limitations of the Duke Criteria for the Diagnosis of Infective Endocarditis

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OBJECTIVES The purpose of this study was to assess the value and limitations of Duke criteria for the diagnosis of infective endocarditis (IE).

BACKGROUND Duke criteria have been shown to be more sensitive in diagnosing IE than the von Reyn criteria, but the diagnosis of IE remains difficult in some patients.

METHODS Both classifications were applied in 93 consecutive patients with pathologically proven IE. Blood cultures, and transthoracic and transesophageal echocardiography were performed in all patients.

RESULTS Sensitivities for the diagnosis of IE were 56% and 76% for von Reyn and Duke criteria, respectively. Fifty-two patients were correctly classified as "probable IE" by von Reyn and "definite IE" by Duke criteria (group 1). However, discrepancies were observed in 41 patients. Eleven patients (group 2) were misclassified as "rejected" by von Reyn, but were "definite IE" by Duke criteria; this difference could be explained by negative blood cultures and positive echocardiogram in all patients. In eight patients (group 3), the diagnosis of IE was "possible" by von Reyn but "definite" by Duke criteria. This difference was essentially explained by the failure of the von Reyn classification to consider echocardiographic abnormalities as major criteria. Twenty-two patients (group 4) were misclassified as possible IE using Duke criteria, being false negative of this classification. Echocardiographic major criteria were present in 19 patients, but blood cultures were negative in 21 patients. The cause of negative blood cultures was prior antibiotic therapy in 11 patients and Q-fever endocarditis diagnosed by positive serology in three cases.

CONCLUSIONS Twenty-four percent of patients with proved IE remain misclassified as "possible IE" despite the use of Duke criteria, especially in cases of culture-negative and Q-fever IE. Increasing the diagnostic value of echographic criteria in patients with prior antibiotic therapy and typical echocardiographic findings and considering the serologic diagnosis of Q fever as a major criterion would further improve the clinical diagnosis of IE. (J Am Coll Cardiol 1999;33: 2023–9) © 1999 by the American College of Cardiology

The clinical diagnosis of infective endocarditis (IE) has always been difficult and a need for a precise and uniform classification exists; usually, IE presents with repeatedly positive blood cultures (BC) in patients with predisposing cardiac disease; the older classification of von Reyn (1) was based on clinicopathologic criteria including positive BC and direct evidence of IE based on histology or bacteriology. Unfortunately, this classification did not include echocardiographic criteria and was of limited value when BC were negative (2–4). More recently, a new classification including echocardiographic criteria was proposed by Durack et al. (Duke criteria [DC]) and was shown to be more sensitive than the von Reyn criteria (VRC) for the diagnosis of IE (4). Unfortunately, transesophageal echocardiography (TEE) was not performed in all patients in the initial series of Durack, and some patients remain misclassified even with the use of Duke criteria.

Thus, the aim of our study was as follows:

1. To compare VRC and DC in a large population of patients with proven endocarditis studied with TEE; and
2. To assess the value and limitations of both VRC and DC for the diagnosis of IE, with special attention to the false negative results of Duke criteria.

METHODS

Patients. Among 131 consecutive patients in whom the diagnosis of IE was obtained at discharge from our center,

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Manuscript received March 17, 1998; revised manuscript received January 19, 1999, accepted February 10, 1999.

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June 1999:2023–9

Abbreviations and Acronyms

BC = blood cultures
DC = Duke criteria
IE = infective endocarditis
TEE = transesophageal echocardiography
TTE = transthoracic echocardiography
VRC = von Reyn criteria

93 had a pathologic confirmation by surgical intervention. The 38 other patients had no pathologic confirmation, but they were presumed to have endocarditis because of clinical, bacteriologic, and echocardiographic evidence of IE, associated with absence of alternative diagnosis during follow-up, and resolution of manifestations of IE with antibiotic therapy; however, they were excluded from the analysis, and only the study group of 93 patients with pathologic confirmation was considered as the reference for the diagnosis of IE and was used to assess the value of diagnostic criteria. Infective endocarditis involved a native valve in 63 patients, and a prosthetic valve in 30. Transthoracic echocardiography (TTE), BC and TEE were performed in all.

Echocardiography. Transthoracic echocardiography and TEE were performed in all cases on a Vingmed Diasonics, CFM 700, CFM 800, or System Five; TEE was performed with 5-MHz monoplane (n = 10) or multiplane (n = 83) probes. No patient had to be excluded because of inadequate echocardiographic examination. Echocardiographic findings were considered as major or minor criteria, according to the Duke classification (4), based on both TTE and TEE findings. Findings consistent with IE included vegetations, abscesses and new paravalvular prosthetic leakage; usual definitions of vegetations and abscesses were used (4–6); new valvular regurgitation, valvular destruction or perforation as assessed by two-dimensional and color Doppler imaging were also considered major echocardiographic criteria for IE.

Blood cultures. In an attempt to standardize the bacteriologic procedures, all patients had a "endocarditis diagnostic kit," using an automate (Bactec Becton Dickinson, Sparus, Maryland) including standard BC and special samples for isolation of intracellular pathogens, and for various specific antibodies (7). Additional BC were systematically performed if the temperature was >38.5°C and cultures of the leads and of the pacemaker device were systematically obtained in patients with IE on pacemaker leads. Major bacteriologic criteria were BC positive for typical endocardial pathogens or persistently positive for microorganisms consistent with IE. Because Q-fever endocarditis has a particularly high incidence in our country, special attention was paid to the diagnosis of this form of IE, either by direct isolation or by serologic procedure (7).

Blood cultures were positive in 60 (64%) patients, *Streptococci* (n = 32) and *Staphylococci* (n = 21) being the most frequently observed organisms; Q-fever endocarditis was identified in four patients. Thirty-three (36%) patients had culture-negative IE.

Table 1. Definition of Patient Groups According to von Reyn and Duke Criteria

	Duke Criteria	von Reyn Criteria
Group 1 (n = 52)	Definite	Probable
Group 2 (n = 11)	Definite	Rejected
Group 3 (n = 8)	Definite	Possible
Group 4 (n = 22)	Possible	Rejected (21) or possible (1)
Total (n = 93)		

Diagnostic criteria. von Reyn criteria and DC were applied in all patients.

Using DC, IE was considered "definite" in the presence of either two major criteria, or one major and three minor criteria, or five minor criteria. Major and minor criteria were defined according to the Duke classification (4). As recommended by Durack et al. (4), prosthetic dehiscence and regurgitant murmur had to be documented to be new to constitute a major criterion for IE. Infective endocarditis was "rejected" in the presence of a firm alternate diagnosis, when the manifestations of IE resolved within four days of antibiotic therapy or when no evidence of IE was present at surgery. Infective endocarditis was "possible" when findings were consistent with IE, but were neither "definite" nor "rejected" (4).

Using VRC, IE was considered "probable," "possible" or "rejected" on the basis of the initial definitions of von Reyn (1).

According to these classifications, patients were separated into four groups (Table 1):

- Group 1 includes 52 patients correctly classified as "probable" IE by VRC and "definite" IE by DC;
- Group 2 includes 11 patients in whom the diagnosis of IE was "rejected" by VRC but was "definite" by DC;
- Group 3 includes eight patients in whom IE was "possible" by VRC but "definite" by DC, and
- Group 4 includes 22 patients misclassified as "possible" IE by DC, all being "rejected" (n = 21) or "possible" (n = 1) by VRC.

Statistical analysis. The Fisher exact test was performed to compare the incidence of diagnostic criteria between groups (minimum expected frequency less than 20 in a 2 × 2 table).

For the purpose of determining the sensitivity of VRC and DC in our series, only patients with "probable" IE by VRC and "definite" IE by DC were considered true IE. Patients with only "possible" or "rejected" IE by VRC and DC were considered false negative results for the diagnosis of IE. Thus, to establish the sensitivity of VRC, only patients from group 1 were considered "true positive" for the

diagnosis of IE; patients from groups 2, 3 and 4 were considered "false negative." Similarly, to establish the sensitivity of DC, patients from groups 1, 2 and 3 were considered "true positive" for the diagnosis of IE; patients from group 4 were "false negative."

To compare the diagnostic sensitivities of DC and VRC, the McNemar chi-square test was performed. For all analyses, two-sided tests of significance were performed with an alpha of 0.05. Statistical analyses were performed using BMDP statistical software (University of California, Berkeley, California).

RESULTS

Echocardiographic data. Echocardiography was positive for IE in 87 among the 93 patients (93%), showing vegetations in 75 (81%) patients, abscesses in 16 (17%) patients, new periprosthetic regurgitation in 3 patients and aneurysm or perforation of the mitral valve in 8 patients. In six patients, echocardiography was not positive for IE, but in four patients, it was consistent with the diagnosis of IE, without meeting a major criterion. Among the 18 patients without detectable vegetation, 12 had another major criterion (nine abscesses, three new periprosthetic regurgitations), 4 had only a minor echocardiographic criterion (valvular thickening or nonoscillating mass), 1 had a very small vegetation only detectable by surgical inspection and 1 had a negative initial TEE but developed vegetations on a repeat study.

Sensitivities of diagnostic criteria. The sensitivity for the diagnosis of IE was better using DC than VRC (76% vs. 56%, respectively [$p < 0.0001$]). In 32 cases the diagnosis of IE was rejected using VRC; in no case was this diagnosis rejected using DC (Table 2). When the four patients with Q-fever endocarditis were excluded from the analysis, sensitivities of VRC and DC were 58% and 80%, respectively ($p < 0.0001$).

Repartition of major and minor criteria. Table 3 lists the various combinations of major and minor clinical criteria that classified episodes as definite or possible IE using the Duke classification. Among patients with "definite IE" by DC (groups 1, 2 and 3), most were associated with two major criteria, and the diagnosis of IE was never made by the presence of five minor criteria; most "possible IE" by DC (group 4) were associated with one major and two minor criteria.

Table 2. Comparison Between von Reyn and Duke Criteria

	von Reyn			
	Probable	**Possible**	**Rejected**	**Total**
Duke				
Definite	52	8	11	71
Possible	0	1	21	22
Rejected	0	0	0	0
Total	52	9	32	93

Table 3. Repartition of Diagnostic Criteria Between Groups

	Group 1 (n = 52)	**Group 2 (n = 11)**	**Group 3 (n = 8)**	**Group 4 (n = 22)**
2 major criteria	51	7	6	
1 major, 3 minor	1	4	2	
5 minor criteria	0	0	0	
1 major, 2 minor				19
1 major, 1 minor				3
3 minor criteria				0

Table 4 shows the repartition of diagnostic criteria among the four patient groups. Among major criteria, positive BC were less frequently observed among patients with "possible" IE by DC (group 4) than in the other groups ($p < 0.0001$); the incidence of endocardiac involvement was not significantly different between groups (p = NS). Among minor criteria, fever ($p = 0.001$) and vascular phenomena ($p < 0.01$) were less frequent among group 4 patients than in other groups.

Results by patient groups and reasons for misclassification. Among the 93 patients of the study, 52 were correctly classified using both criteria (group 1) (Table 4). Most were associated with two major criteria, including positive BC and typical echocardiographic findings. However, discrepancies between VRC and DC were observed in 41 patients.

In 11 patients (group 2), the diagnosis of IE was "rejected" by VRC, but "definite" by DC. The difference could be explained by negative BC and positive echocardiograms in all patients. The cause of negative BC was prior antibiotic therapy in 7/11 patients.

In eight patients (group 3), the diagnosis of IE was "possible" by VRC but "definite" by DC. Blood cultures were positive in all patients, and echographic major criteria were present in six (75%) patients. Six patients met two major criteria in the Duke classification; two had one major and three minor criteria. The misclassification by VRC in these patients was essentially explained by the failure to consider echocardiographic abnormality as a major criteria.

Twenty-two patients (group 4) were misclassified as possible IE using DC, being false negative in this classification; IE was "rejected" in all but one patient of this group using VRC; the diagnosis of IE was subsequently confirmed by pathology in all 22 patients. Predisposing cardiac disease was a prosthetic valve in 11 patients; three patients presented with IE on a pacemaker lead. Table 5 shows the repartition between major and minor criteria in group 4. One major and two minor criteria were present in 19/22 patients, not allowing the "definite" diagnosis of IE. Echocardiographic major criteria were present in 19 patients, but BC were negative in 21 patients. The cause for negative BC was prior antibiotic therapy in 11 patients and Q-fever endocarditis diagnosed by positive serology in three cases.

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Table 4. Repartition of Duke Major and Minor Criteria Between the Four Groups

	Group 1 (n = 52)	Group 2 (n = 11)	Group 3 (n = 8)	Group 4 (n = 22)
Major criteria				
1. Positive blood culture	51 (98%)	0	8 (100%)	1 (5%)
2. Evidence of endocardiac involvement	52 (100%)	11 (100%)	6 (75%)	21 (95%)
Positive echocardiogram	51 (98%)	11 (100%)	6 (75%)	19 (86%)
Vegetation	49 (94%)	7 (63%)	5	14 (63%)
Abscess	7 (13%)	4 (36%)	1	4 (18%)
New dehiscence	1	0	0	2 (9%)
New valvular regurgitation	35 (67%)	7 (63%)	0	2
Minor criteria				
1. Predisposition	37 (71%)	8 (73%)	8 (100%)	19 (86%)
Heart disease	34	6	7	19
Intravenous drug use	3	2	1	0
2. Fever ≥38°C	50 (96%)	10 (91%)	8 (100%)	15 (68%)
3. Vascular phenomena	21 (40%)	3 (27%)	0	1 (5%)
Arterial emboli	16	3	0	1
Mycotic aneurysm	2	0	0	0
Cerebral hemorrhage	3	0	0	0
4. Immunologic phenomena	10 (19%)	1 (9%)	0	0
Glomerulonephritis	2	0	0	0
Osler's node	6	1	0	0
Roth spot	0	0	0	0
Rheumatoid factor	2	0	0	0
5. Microbiologic evidence	0	1 (9%)	0	4 (18%)
6. Suggestive echocardiography	1	0	2 (25%)	1 (5%)

In three patients, the reason for misclassification was a negative echocardiogram; one patient (No. 16, Table 5) had prior antibiotic therapy and presented with a new murmur and fever; echocardiography showed a nonoscillating mass adherent to the aortic valve, considered only a minor criteria, and BC were negative. However, surgical inspection showed a small vegetation, and *Staphylococcus aureus* was subsequently identified by the culture of the excised valve. In another patient with an aortic bioprosthetic valve and a positive BC for *Streptococcus faecalis,* an initial TEE was negative for IE, but a repeat TEE showed the apparition of vegetations and periprosthetic abscess, subsequently confirmed by surgery.

Echocardiographic and surgical findings in patients with negative BC (n = 33). Culture-negative IE was essentially observed among group 2 and group 4 patients. All 11 patients from group 2 and 21 of 22 group 4 patients had negative BC; the cause for negative BC was prior antibiotic therapy in 18 of these 33 patients; echocardiography was positive in 31 of them, showing vegetations in 21 cases, perivalvular abscesses in 8 cases and 2 aortic vegetations with associated mitral perforation. Echocardiographic pathologic lesions (vegetation or abscess) were confirmed by surgery and by histology showing active IE in all patients. Moreover, in 10 patients, a microorganism was subsequently identified by culture or histology in a vegetation or an abscess, whereas preoperative BC were negative.

DISCUSSION

Adequate classification of IE is desirable, for both epidemiologic and clinical reasons (3). Although the DC, including echocardiography, have shown a higher sensitivity than the older VRC, the diagnosis of IE may be difficult in some patients even with the use of the more recent criteria. Our study was designed to compare the limitations of both criteria in a large population of patients with proved IE, systematically studied with TEE and complete BC and serologic studies, with special focus on patients misclassified by DC.

Sensitivity of von Reyn and Duke criteria for the diagnosis of IE. The sensitivities of both criteria have been well studied. In their initial study, Durack and colleagues (4) obtained a sensitivity of 80% in 69 pathologically confirmed cases of IE. This better sensitivity as compared with VRC was explained by the incorporation of both echocardiographic findings and knowledge of intravenous drug abuse into the clinical assessment (4). Similar results were independently obtained by Bayer et al. (3), and in the present study with a sensitivity of 76% for DC and 56% for VRC.

Diagnosis of IE: major role of echocardiography. The better sensitivity of DC is partly explained by the major incremental value of echocardiographic criteria, as already outlined by Dodds and Durack (8). Transthoracic echocardiography and TEE have both been shown to be of great

Table 5. Repartition of Diagnostic Criteria in Group 4 and Causes for Misclassification

Case No.	Blood Cultures	Echographic Findings	New Murmur	Duke Criteria	Cause for Misclassification
1	Negative	Vegetation	No	1 major, 1 minor	ATB therapy
2	Negative	Abscess	No	1 major, 2 minor	Q fever
3	Negative	Abscess	No	1 major, 2 minor	?
4	Negative	Vegetation	No	1 major, 2 minor	Q fever
5	Negative	Prosthetic dehiscence	No	1 major, 2 minor	Q fever
6	Negative	Vegetation	No	1 major, 2 minor	?
7	Negative	None	Yes	1 major, 2 minor	Negative TEE
8	Negative	Abscess	No	1 major, 2 minor	ATB therapy
9	Negative	Vegetation	No	1 major, 2 minor	?
10	Negative	Vegetation	No	1 major, 2 minor	ATB therapy
11	Negative	Vegetation	No	1 major, 2 minor	?
12	Negative	Vegetation	No	1 major, 2 minor	ATB therapy
13	Negative	Prosthetic dehiscence	No	1 major, 2 minor	?
14	Positive	None	No	1 major, 2 minor	Negative TEE
15	Negative	Vegetation	No	1 major, 1 minor	?
16	Negative	None	Yes	1 major, 2 minor	ATB therapy, negative TEE
17	Negative	Vegetation	No	1 major, 2 minor	ATB therapy
18	Negative	Vegetation	No	1 major, 2 minor	ATB therapy
19	Negative	Vegetation and abscess	No	1 major, 1 minor	ATB therapy
20	Negative	Vegetation	No	1 major, 2 minor	ATB therapy
21	Negative	Vegetation	No	1 major, 2 minor	ATB therapy
22	Negative	Vegetation	No	1 major, 2 minor	ATB therapy

ATB = antibiotic; TEE = transesophageal echocardiography.

value in diagnosing IE, TEE being particularly helpful for the detection of vegetations (9–14), especially in patients with prosthetic valves (15,16), abscesses (5) and perivalvular lesions (17). In our series, the sensitivity of echocardiography combining TTE and TEE was 93%, similar to other series of IE with pathologic confirmation (11,13). The excellent sensitivity of DC is probably due to the systematic use of TEE in our population. The high detection rate of vegetations in our series (81%) also reflects the high sensitivity of multiplane TEE and was particularly helpful in patients with negatived BC by prior antibiotic therapy in group 2, but also in patients with positive BC as in group 3.

Limitations of Duke criteria. The high sensitivity (18), but also high specificity (19,20) of DC have lead some authors to replace the VRC by the DC in clinical practice. However, DC also present with some limitations; although Bayer et al. obtained a 100% sensitivity in 10 patients with pathologically confirmed IE (3), only 80% of the 69 pathologically confirmed cases were correctly classified as "definite" IE in the initial series of Durack et al. (4). The causes for misclassification of 14 out of 69 patients were not specified in the series of Durack. In the series of Cecchi et al. (21), 28 patients had the diagnosis of IE confirmed by surgery or autopsy, of whom six were only classified as "possible" IE by DC. In our series, 22 such patients were observed; the causes of misclassification in these 22 patients are important to assess to further improve the clinical diagnosis of IE.

CULTURE-NEGATIVE AND Q-FEVER ENDOCARDITIS. Twenty-one of these 22 patients presented with negative BC. The main reason for negative BC in clinical practice is prior antibiotic therapy, a point emphasized by Cecchi et al. (21) that was observed in 11 of 22 group 4 patients in our series. As shown in Tables 3 and 4, 19 out of 22 patients presented with one major and two minor criteria; thus, they would have been well categorized if positive BC were present, even with only one additional minor criterion; thus, it might be proposed that the presence of one major and two minor criteria could be sufficient for the "definite" diagnosis of IE in patients with prior antibiotic therapy and typical echocardiographic findings, but this new classification has to be validated by prospective studies to certify that it does not result in a decrease in specificity.

The second cause of culture-negative endocarditis in our series was Q-fever endocarditis. Q fever is a worldwide zoonosis caused by *Coxiella burnetii* and is particularly frequent in France; we have previously shown (7) that the application of DC in 20 cases of pathologically proven Q-fever IE resulted in misclassification in 20% of patients as "possible" cases. We thus proposed that the Q-fever serologic result be converted from minor to major criteria (7); applying this modification to the present series would increase the sensitivity of DC from 76% to 80%, all three patients in group 4 with this diagnosis being well classified as "definite" with this new classification. Although Q-fever endocarditis is a rather rare disease, we believe that consid-

ering the serologic diagnosis of Q fever as a major criterion allows a modest but significant improvement in the diagnostic value of Duke criteria.

INFECTIVE ENDOCARDITIS WITH NEGATIVE ECHOCARDIOGRAPHIC STUDIES. Another explanation for misclassification is a negative echocardiographic study. Echocardiography has been shown to be of major value in diagnosing IE, especially with the advent of TEE (6,9–17); identification of vegetations with TTE depends on image quality and may be compromised by imperfect image resolution and artifacts produced by prosthetic material (9), whereas TEE has no such limitations; however, sensitivity of echocardiography in IE is not 100%, even with the use of TEE. In addition, a vegetation may be absent at the time of the first TEE study and be detected only on repeat TEE examination (22), as in one patient in our study. However, this condition is infrequent, and, despite these limitations, TEE allows identification of vegetations in the majority of patients with IE (81% in our series) and is essential for the diagnosis of IE.

OTHER LIMITATIONS OF DUKE CRITERIA. Finally, the application of DC for the diagnosis of IE has been shown to be of lower value in some patient groups, such as patients with prosthetic valves (23) and patients with IE affecting pacemaker leads (24). In the recent series of Klug et al. (24), application of clinical DC allowed the diagnosis of "definite" IE before leads cultures in only 25% and 59.3% of the patients in the acute and chronic groups, respectively. Thus, the authors proposed that other clinical criteria, such as local symptoms and pulmonary infections, could be added to conventional criteria in such patients. Fourteen patients in group 4 had either a prosthetic valve or a pacemaker lead IE.

Study limitations. Several limitations of the study may be pointed out. First, TEE was not performed in all patients with multiplane transducers. The rate of detection of vegetations, abscesses and other cardiac lesions may be lower when monoplane transducers are used (22); however, only 10 patients had monoplane TEE studies, whereas multiplane TEE was performed in the other 83 patients. Second, Q fever is particularly frequent in our country and its serologic diagnosis may be difficult in some centers (7); thus, the inclusion of this new criterion will possibly be difficult to accept by clinicians all over the world. The validity of this new criterion must be confirmed by other prospective studies including analysis of specificity and accuracy.

Conclusions. Our results confirm the known better sensitivity of DC over VRC, and the major value of including echocardiographic criteria as major criteria for the diagnosis of IE. In addition, our study demonstrated that the diagnostic value of echocardiography was particularly important in patients with negatived BC by prior antibiotic therapy. However, despite the systematic use of TEE, 24% patients with proven IE were misclassified as "possible" IE by the DC, especially in cases of culture-negative or Q-fever endocarditis. Increasing the diagnostic value of echographic criteria in patients presenting with prior antibiotic therapy and typical echocardiographic findings and considering the serologic diagnosis of Q fever as a major criterion would further improve the value of DC. Further studies are needed to reduce the number of patients misclassified as "possible" IE and to increase the sensitivity of diagnostic criteria, but without having deleterious effect on their specificity.

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