Value and Limitations of the von Reyn, Duke, and Modified Duke Criteria for the Diagnosis of Infective Endocarditis in Children

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ABSTRACT. *Objective.* **To compare the sensitivity of 3 different criteria—von Reyn, Duke, and modified Duke—in diagnosing infective endocarditis (IE) in children.**

Study Design. **Retrospective case study in a tertiary pediatric hospital.**

Methods and Results. **Between 1985 and 2001, 41 episodes of IE were documented in 40 children (median: 7 years old; range: 1 week to 18 years). The diagnosis was based on echocardiographic and microbiologic or pathologic findings. The initial echocardiogram suggested IE in 95% of the cases. Main findings were vegetations in 36, perivalvular abscess in 4, and/or new valvular leaks in 6 cases. In 31 (76%) of the 41 episodes, the causative organisms were identified directly by specimen bacteriology or blood cultures (BCs) or indirectly by polymerase chain reaction or serology. Sensitivities of the von Reyn, Duke, and modified Duke criteria in diagnosing IE were 63%, 81%, and 88%, respectively. In 10 cases (22%), the diagnosis of IE was "rejected" by the von Reyn criteria but was "definite or possible" by the Duke and modified Duke criteria. In 3 cases, the diagnosis of IE was "possible" by the Duke but "definite" by the modified Duke criteria: 2 of the 3 cases had 1 major and ≥3 minor symptoms, and 1 had Q fever. Five episodes (12%) were classified as "possible" IE by the modified Duke criteria: although major findings were present on echocardiography, no organism was identified on repeat BCs. Positive BC was the only criterion that differentiated "definite" from "possible" IE.**

Conclusions. **The modified Duke classification was more sensitive in diagnosing IE in children than the von Reyn and Duke criteria. Still, 12% failed to be classified as "definite" IE by the modified Duke criteria. This illustrates the importance of positive BCs as a major IE criterion while significant echocardiographic findings are less considered by the presently used criteria.** *Pediatrics* **2003;112:e467–e471. URL: http://www.pediatrics.org/cgi/content/full/112/6/e467; *endocarditis, pediatric, diagnosis, infection.***

ABBREVIATIONS. IE, infective endocarditis; BC, blood culture; PCR, polymerase chain reaction; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography.

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The clinical diagnosis of infective endocarditis (IE) may be challenging, which explains the need for a precise and uniform diagnostic approach. The initial classification elaborated by von Reyn and colleagues[1] was based primarily on clinical and pathologic findings including demonstration of the infection by histopathology or positive blood cultures (BCs). The von Reyn classification, invented before the introduction of two-dimensional and Doppler ultrasonography, does not consider characteristic echocardiographic findings related to endocardial infection, which may explain its limited value in diagnosing IE when BCs remained negative.[2,3] In 1994, Durack et al[4] proposed a new classification, the Duke criteria, which includes echocardiographic anomalies as major findings. The Duke criteria have been shown to be more sensitive in diagnosing IE in adults and children when compared with the von Reyn criteria.[4–6] Nonetheless, Habib et al[7] found that in some pathologically proven cases of IE, the definite diagnosis had been missed either because BCs remained negative or the endocarditis had been caused by Q fever. To increase the diagnostic sensitivity, the Duke criteria were modified recently and tested in a heterogeneous adult population.[8] The modified Duke criteria utility in children is not known. This study aimed to assess the value of the von Reyn, Duke, and modified Duke classification in children who had been diagnosed to have IE since the introduction of high-resolution two-dimensional and Doppler ultrasound techniques at our center.

PATIENTS AND METHODS

Patients

All episodes of IE diagnosed between January 1985 and December 2001 were identified by using the diagnostic database at University Children's Hospital of Geneva, Switzerland. Medical charts were systematically reviewed for demographic and clinical data, which included patient age and clinical status at presentation, signs and symptoms of endocardial infection, earliest echocardiographic documentation, predisposing factors, causative microorganisms, treatment, and outcome. Although considered a gold standard for IE diagnosis, pathologic confirmation of IE was obtainable only on postoperative tissue samples. In this situation, IE diagnosis was considered a combination of obvious echocardiographic, histologic, bacteriologic, and clinical findings. However, identification of the causative microorganism was always required unless the patient had been started on antimicrobial treatment before the diagnosis of IE.

Diagnostic Criteria (Tables 1 and 2)

von Reyn, Duke, and modified Duke classifications were applied according to their original descriptions.[1,4,8] According to the von Reyn criteria, patients were classified as "definite," "probable," "possible," or "rejected" IE. Based on the Duke and modified

TABLE 1. von Reyn, Duke, and Modified Duke Classification*

von Reyn classification	
Definite	Direct evidence of IE based on histology or bacteriology of vegetation or peripheral embolus
Probable	≥2 positive BCs plus one of the following: New regurgitation murmur Acquired or congenital heart disease ≤2 or negative BC, plus fever, new regurgitation murmur, and vascular phenomena
Possible	≥2 positive BCs plus one of the following: Acquired or congenital heart disease Vascular phenomena ≤2 or negative BC plus fever, acquired or congenital heart disease, and vascular phenomena For *Viridans streptococci* IE only: ≥2 positive BCs without an extracardiac origin and fever
Rejected	IE unlikely, alternate diagnosis IE likely, empiric antibiotic therapy warranted Culture-negative IE diagnosed clinically
Duke and modified Duke classifications	
Definite	Pathologic criteria: Microorganism demonstrated by culture or histologic examination of vegetation, emboli, intracardiac abcess; or Active endocardial lesions on pathology examination Clinical criteria: 2 major criteria; or 1 major criterion and 3 minor criteria; or 5 minor criteria
Possible	1 major criterion and 1 minor criterion; or 3 minor criterion
Rejected	Alternate diagnosis; or Resolution of IE syndrome after ≤4 days of antibiotherapy; or No pathologic evidence of IE after ≥4 days of antibiotherapy; or Does not meet criteria for possible IE.

* Adapted from von Reyn et al,[1] Durack et al,[4] and Li et al.[8]

Duke criteria the diagnosis of IE was "definite," "possible," or "rejected."

Microbiology

Daily, 1 to 2 blood samples were systematically drawn in all patients with suspected IE. Blood samples were cultured for 21 days under aerobic and anaerobic conditions. All microorganisms were identified by using standardized procedures at University Children's Hospital's Central Laboratory of Bacteriology. In 1 case, broad-range polymerase chain reaction (PCR) amplification was performed on excised mitral valvular tissue, sequenced, and compared with sequences of bacterial 16S ribosomal RNA genes obtainable from GenBank and the European Molecular Biology Laboratory databases.[9,10]

Echocardiography

All children underwent complete transthoracic two-dimensional and Doppler transthoracic echocardiography (TTE) studies at diagnosis and follow-up by using Vingmed Diasonics CFM 700 or System Five ultrasound systems mainly with 5- to 7-MHz phased-array transducers. Six patients underwent additional transesophageal echocardiography (TEE) with 5-MHz multiplane probes. Unlike in adults, TTE and TEE are considered equally accurate for the diagnosis of IE in children, in particular for the detection of vegetations.[11,12] Potential sources for false-negative studies may include vegetations that are smaller than the lower limit of ultrasound resolution (<2 mm), previous embolization of vegetations, and inaccurate imaging to detect small abscesses.[4] Echocardiographic examinations were read by 2 observers. All ultrasound studies were videotaped and available for off-line analyses. Detected anomalies were classified either as major or minor findings according to the Duke and the modified Duke classification.[4,8]

Statistical Analysis

To determine the sensitivities of the 3 analyzed criteria, only patients with probable IE by von Reyn and definite IE by von Reyn, Duke, or modified Duke were considered to have true IE. Patients with only possible or rejected diagnosis of IE were considered to be "uncertain" or "false-negative" results. A 2-tailed Fisher's exact test was performed to analyze differences in major and minor modified Duke criteria between cases with definite and possible IE diagnosis. A P value of <0.05 was considered to be significant.

RESULTS

Patients

Forty-one episodes of IE were diagnosed in 40 consecutive children at a median age of 7 years (range: 1 week to 18 years). The majority of these patients had been referred for cardiothoracic surgery from northern ($n = 20$) or sub-Saharan ($n = 13$) Africa, and 7 children were European. All children were in a reasonably good health condition, although few were severely ill and required urgent surgery. Most of the 33 children from the African continent were severely or mildly malnourished with significant height (mean ± standard deviation: −1.47 ± 1.41) and weight (mean ± standard deviation: −2.00 ± 1.14) retardation. Since 1987, HIV serology was systematically performed in all patients. None had positive HIV serology. Not surprisingly, most had cyanotic ($n = 21$) or acyanotic ($n = 9$) congenital heart disease or rheumatic heart disease ($n = 7$). Nineteen episodes occurred after cardiac surgery. Four episodes were diagnosed in structurally normal hearts: this included 2 children with liver or kidney transplantation and 2 prematurely delivered newborns who required indwelling central catheters. One patient, with tetralogy of Fallot, sustained 2 IE

TABLE 2. Definition of Clinical Criteria of the Duke Classification With Addition of the Modified Duke Criteria (in Boldface)

Major criteria	Positive blood culture (BC)
	2 separate positive BCs consistent with IE (*V. streptococci*, *Streptococcus bovis*, HACEK group, *S. aureus*, and enterococci) in the absence of a primary focus
	≥2 positive BCs drawn >12 hours apart or ≥4 positive BCs irrespective of the timing
	1 positive BC for *C. brunetii* or antiphase-I immunoglobulin G antibody titer >1:800
	Evidence of endocardial involvement
	Positive echocardiogram (**TEE recommended in prosthetic valves, rated at least possible IE by clinical criteria, or complicated IE; TTE as the first test in other patients**):
	Vegetation on valve or supporting structure
	Abscess
	New partial dehiscence of prosthetic valve
	New valvular regurgitation
Minor criteria	Predisposition
	Fever
	Vascular phenomena (major arterial emboli; intracranial or conjunctival hemorrhage, or Janeway's lesions)
	Immunologic phenomena (glomerulonephritis, Osler's node, Roth's spots, or rheumatoid factor)
	Microbiological evidence: positive BC that does not meet major criteria or serological evidence of infection
	Echocardiographic minor criteria eliminated

episodes, 3 months apart, before and after surgery with a different bacteriologic pattern.

Echocardiography

Findings compatible with endocardial infection were found in 39 (95%) of the 41 episodes on initial TTE examination. TEE to confirm the IE diagnosis was done in 6 patients. IE lesions failed to be detected in 2 cases by ultrasound imaging, although the diagnosis was established in both cases by histologic examination of tricuspid valve that was obtained during surgery. This included the only patient in our series with concomitant glomerulonephritis, which was confirmed by renal biopsy. Of the detected anomalies, 36 vegetations, 4 perivalvular abscesses, and 6 new valvular regurgitations were found in 39 cases. Vegetations were right-sided in 17 (tricuspid valve: $n = 9$; pulmonary valve: $n = 4$; patch: $n = 3$; atrium: $n = 1$) and left-sided in 19 (mitral valve: $n = 8$; aortic valve: $n = 8$; left atrium: $n = 1$; patch: $n = 2$) cases. Valvular regurgitation related to infectious lesions was initially an infrequent finding, present in only 15% of the cases. On follow-up, it emerged in another 14 cases, affecting a total of 49% of the cases.

Microbiology

BCs (16 cases with ≥2 positive BC and 5 cases with 1 positive BC) or tissue specimen and serologic testing were found positive in 31 of the 41 (75.6%) IE episodes. Gram-positive microorganisms ($n = 17$ [41%]: *Staphylococcus aureus* and *Staphylococcus epidermidis*, *Staphylococcus mitis*, *Staphylococcus mileri*, and *Staphylococcus sanguis*, *Corynebacterium diphtheriae*, *Enterococcus faecalis*, *Propionibacterium acnes*, and *Actinomyces odontolyticus*) and fungi ($n = 9$ [22%]: *Candida albicans*, *Candida guillermondi*, and *Hansenula anomala*) predominated. Less common causes of IE were from the HACEK group ($n = 3$ [7%]: *Haemophilus paraprophilus*, *Haemophilus influenzae*, and *Haemophilus aphrophilus*), Gram-negative bacteria ($n = 3$ [7%]: *Pseudomonas aeruginosa*, *Bartonella quintana*, and *Salmonella typhi*), and Q fever ($n = 1$ [2%]: *Coxiella burnetti*). One episode had multiple isolates. Ten episodes (24%) remained culture-negative (Table 3).

Value of Compared Criteria

The sensitivities of the von Reyn, Duke, and modified Duke criteria in diagnosing IE were 63%, 81%, and 88%, respectively. Only 16 of the 41 cases (39%) were classified as definite IE by all 3 studied criteria (Fig 1). In 9 (22%), the diagnosis of IE was rejected by using the von Reyn criteria, whereas the diagnosis was never rejected by using the Duke or modified Duke criteria. All but 1 case of probable or possible IE using the von Reyn criteria became definite with the Duke and modified Duke criteria. Among 8 episodes of possible IE by the Duke criteria, 3 were classified as definite IE by using the modified Duke;

TABLE 3. Characteristics of the 10 Negative BC Cases

Duke Modified Classification	Pathologic Criteria	Cinical Criteria	
		Major	Minor
D	+	Regur	Pred, f, immuno*
D	+	Veget	Pred, f
D	+	Veget	Pred
D	+	Veget, regur	Pred, f
D	+	Veget, regur	Pred, f
D	+	Veget, regur	Pred, f
P	−	Veget	Pred
P	−	Veget	—
P	−	Veget	Pred, f
P	−	Regur	Pred, f

D indicates definite IE; P, probable IE; veget, vegetation; regur, new valvular regurgitation; pred, predisposition; f, fever; and immuno, immunologic phenomena.
* Glomerulonephritis.

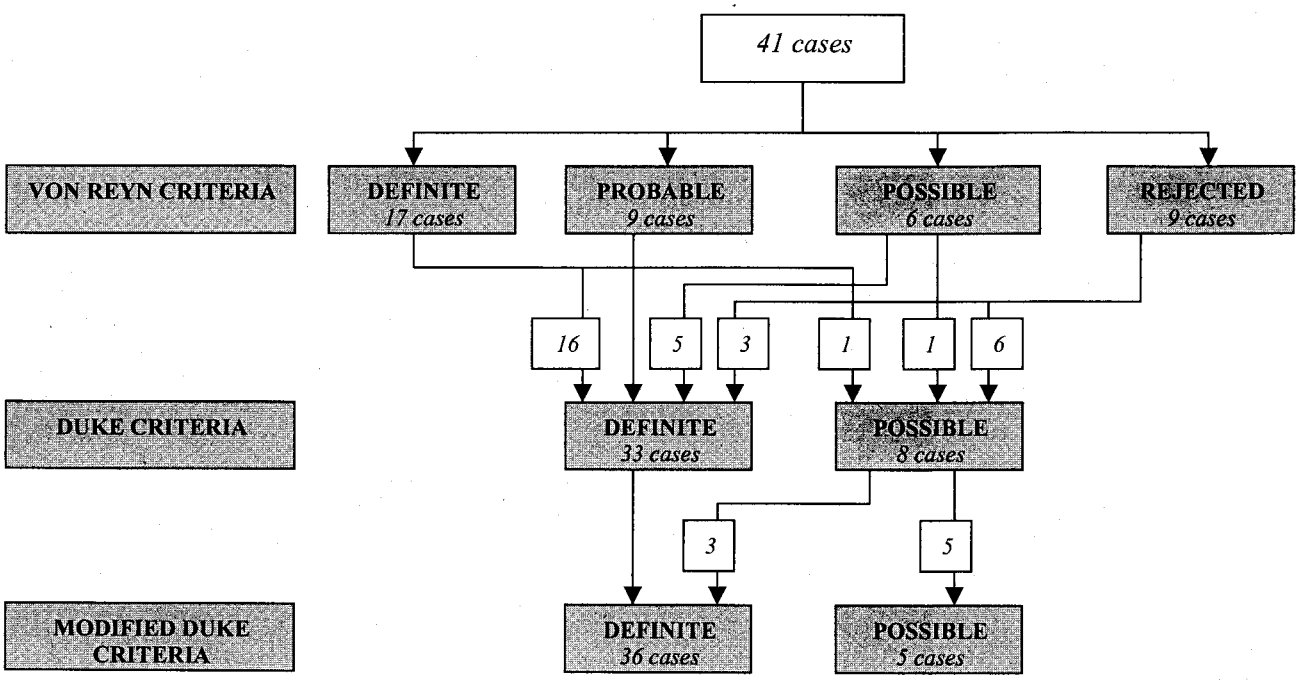

Fig 1. Repartition of 41 cases of IE in children according to von Reyn, Duke, and modified Duke criteria.

1 had positive Q-fever serology; and the remaining 2 cases met 1 major and at least 3 minor criteria.

Major and Minor Criteria and Reason for Misclassification

Applying the modified Duke criteria to our patient series, 36 episodes were considered to be definite and 5 possible IE (Fig 1). Nineteen definite cases were associated with 2 major criteria, 10 met 1 major and 3 minor criteria, and 7 cases met pathologic criteria. All but 1 of the definite IE cases had major echocardiographic findings. These findings became particularly helpful in the 10 cases without bacteriologic evidence. However, with the exception of positive BC as a major criteria ($P = .027$), all criteria were similarly often observed in definite and possible IE based on the modified Duke criteria (Table 4). Of the minor Duke and modified Duke criteria, fever was almost always present at the time of diagnosis, whereas immunologic and vascular phenomena were rare. Applying the modified Duke major criteria, positive BC showed a specificity of 100%, sensitivity of 73%, and positive predictive value of 100% in distinguishing between definite and IE. The initial TTE had a comparable high sensitivity (97%) in diagnosing definite IE. Of the 5 possible IE cases, 1 major and 2 minor criteria were found in all but 1 cases (80%). Endocardial involvement was found in all patients. However, all but 1 child had negative BCs. This included 3 children who had already been started on broad-spectrum antibiotic therapy and 1 other that fulfilled minor microbiologic criteria. Of the 6 other children with negative BCs, IE diagnosis was established on pathologic examination of endocardial samples obtained at surgery.

DISCUSSION

IE plays an important role in the differential diagnosis of unusual and prolonged fever, particularly in the child with congenital or acquired cardiac malfor-

TABLE 4. Difference Between Definite and Possible Diagnosis of IE Using the Modified Duke Criteria

	Definite IE ($n = 36$) (%)	Possible IE ($n = 5$) (%)	P Value
Major criteria			
Positive BC/serology	52.8	0	.027*
Positive echocardiographic examination	97.2	80	NS†
New valvular regurgitation	52.8	20	NS
Minor criteria			
Predisposition	100	100	NS
Fever	78	60	NS
Vascular phenomena	22.2	0	NS
Immunologic phenomena	2.7	0	NS
Microbiologic evidence other than major criteria	13.9	20	NS

NS indicates not significant.
* Specificity: 100%; sensitivity: 79.2%; positive predictive value: 100%.
† Specificity: 20%; sensitivity: 97.2%; positive predictive value: 89.7%.

mation. Rapid diagnosis followed by appropriate treatment may be of critical importance for the physical integrity and the survival of an affected patient, which explains the need for sensitive diagnostic aids.

In the 1980s, high-resolution two-dimensional and Doppler echocardiography emerged as the primary cardiovascular imaging modality. Typical lesions, resulting from bacterial or fungal infection of the native endocardium and implanted patches and mechanical devices, had suddenly become detectable noninvasively. The inclusion of vegetations, perivalvar abscesses, and valvar leaks as major diagnostic findings in the Duke and modified Duke criteria has improved the accuracy in diagnosing IE significantly.[13] Similar to previously published data,[7] there was a high detection rate of vegetations (85%) with TTE in our series. The demonstration of vegetations is most helpful if BCs are inaccurately withdrawn and are slowly or not growing. The American Heart Association recommends that the search for the causing microorganism ideally should include "3 BCs, obtained by separate venipunctures on the first day, followed by 2 more if there is no growth by the 2nd day of incubation."[14] In our experience, this is not always practical, particularly in the small neonate with restricted vascular access, whereas it is of limited value in the patient who is already receiving antimicrobial therapy. By using conventional BC procedures, no causing microorganism was demonstrated in a quarter of our patients. PCR on tissue samples and serologic techniques may help in this situation: 2 BC-negative cases in our series were diagnosed as having Bartonella endocarditis and Q fever, respectively.[10] Although PCR-based testing may prove beneficial for the identification of certain organisms,[8] the use of this new technology to find major criteria should be deferred until it can be validated.

Our analysis of the diagnostic value of 3 different criteria in children demonstrates that the modified Duke criteria is most helpful in diagnosing IE. The inclusion of echocardiographic findings has contributed significantly to the improved diagnostic accuracy, whereas positive BCs remain the mainstay in IE diagnosis. Still, 12% of our cases were classified only as having possible IE. All 5 cases had endocardial involvement, and most had 2 minor criteria. Most children with IE do have predisposing cardiac anomalies and present with unspecific clinical symptoms such as fever and anorexia. Nevertheless, striking vascular or immunologic abnormalities are unusual in the pediatric age group.[13,14] Data issued from some series demonstrated elevated inflammatory markers (elevated erythrocyte sedimentation rate or C-reactive protein) and new clinical findings (new clubbing, splenomegaly, and microscopic hematuria) in patients with IE.[15,16] Increased sensitivity of the elevated erythrocyte sedimentation rate in cases of IE seems to be even more relevant in patients who did not undergo surgery.[17] In our series, of the 5 possible IE, 4 had an elevated erythrocyte sedimentation rate. Therefore, further modifications with a refinement of the present minor IE criteria may help to improve the diagnostic accuracy, in particular in children with negative BC and echocardiographic criteria for IE.

Limitations

Most of our patients originated from Africa and had been referred for cardiovascular surgery of sometimes long-standing acquired or congenital heart disease in combination with malnutrition. This may have influenced the spectrum of encountered microorganisms and the clinical and echocardiographic findings of IE in some of our patients. Our study did demonstrate a higher sensitivity in diagnosing IE with the modified Duke criteria, but, because of the retrospective study design, we were not able to assess the specificity and positive predictive values of the various criteria. This is of clinical importance, because a false-positive or false-negative diagnosis may have an impact on the management and outcome of children with IE. Although there was no "gold standard" for IE diagnosis, misclassification may have occurred to the few patients with possible IE. Considering the rarity of endocardial infection, a prospective multicenter study is needed, probably with the inclusion of new minor diagnostic findings.

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