

ASSESSMENT OF THE DUKE CRITERIA FOR THE DIAGNOSIS OF INFECTIVE ENDOCARDITIS AFTER TWENTY YEARS. AN ANALYSIS OF 241 CASES

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Abstract

Background and aims. In the absence of classical features (fever, cardiac murmur, and peripheral vascular stigmata) the diagnosis of infective endocarditis (IE) may be difficult. Current clinical guidelines for the diagnosis and management of IE recommend the use of modified Duke criteria. Correct and prompt diagnosis of IE is crucial for the treatment and outcome of the patients.

The aim of this study was to evaluate the presence and the individual value of each criterion of the modified Duke criteria in our patients with infective endocarditis.

Methods. We performed a prospective observational study between January 2008 – June 2014, in which we enrolled consecutive adult patients admitted for suspicion of IE to the Hospital of Infectious Diseases and at the Heart Institute. We used an extensive database in order to collect demographic data, laboratory and echocardiography results, evolution and outcome of the patients. Using the modified Duke criteria we identified 3 categories of IE: definite, possible and rejected. In order to evaluate the importance of each criterion in the diagnosis of IE we tested two hypotheses. First, we excluded each criterion from the final diagnosis and we counted how many cases fell into a lower category. Second, after adding each major and minor criterion, we tested how many cases would have been classifiable as definite IE.

Results. The study included 241 adult patients with a mean age 58.16 years and sex ratio male/female 1.94. According to the modified Duke criteria 137 patients had definite IE, 79 patients had possible IE and 25 cases had rejected IE. We had blood cultures positive IE in 109 cases and blood culture negative IE (BCNE) in 132 (71.21%) cases. Antibiotic treatment prior to blood culture was recorded in 152 (63.07%) patients. In the absence of the echocardiography major criterion, 43% of cases would become possible. After extraction of major microbiological criterion, only one third of definite cases would become possible. Minor criteria such as fever and predisposition contributed to the diagnosis only in 10% of cases. In the presence of vascular or immunological phenomena, or in the presence of minor microbiological criterion, half of the possible IE cases could become definite.

Conclusion. Twenty-years after their launch, the Duke criteria for the diagnosis of IE continue to be important tools. Low index of suspicion of IE and inappropriate use of antibiotics may have a great negative impact on the diagnosis of IE. Nowadays, the scarcity of classical Osler manifestations - bacteremia, fever and peripheral stigmata - makes the diagnosis of IE a challenge.

Keywords: infective endocarditis, diagnosis, blood culture

Background and aims

Infective endocarditis (IE) is the microbial infection of the endothelial lining of the heart which usually involves native or prosthetic valves but can also affect the adjacent structure of the valve, mural thrombus or cardio-vascular devices. In the presence of classical features such as fever, cardiac murmur, bacteremia and peripheral stigmata, the diagnosis of IE may be established easily. Unfortunately, in everyday clinical practice, this presentation is rarely seen and atypical presentation occurs more frequently. The clinical diagnosis of IE relies on integration of clinical, microbiological, echocardiography and laboratory findings.

In order to assist the diagnosis of IE, Pelletier and Petersdorf proposed the first case definitions in 1977 [1]. Four years later, in 1981, von Reyn and his colleagues proposed new strict case definitions for the diagnosis [2]. According to these case definitions, a definite diagnosis of IE was possible only by direct evidence of IE obtained from histology or bacteriology exam of the valvular vegetation removed by surgery or at autopsy. The combination of blood culture results and presence of fever, cardiac murmur, predisposing heart disease or vascular phenomena classified IE cases in probable, possible or rejected. Thus, in the absence of surgery, a clinical definite diagnosis of IE was not possible. Von Reyn's definitions developed in the same time with the introduction of echocardiography, as a new tool for the diagnosis of IE. As a result, in 1994, new diagnostic criteria were proposed by Durack et al and the Duke Endocarditis Service [3]. In these criteria, pathological findings, meaning direct evidence of microorganism and/or pathological lesions, in vegetation or intracardiac abscess, are the gold standard criteria for definite infective endocarditis, as in the previous criteria. Using the model of Jones' criteria for rheumatic fever, the Duke criteria for infective endocarditis combine major and minor clinical criteria. Positive blood culture results for IE and evidence of endocardial involvement from echocardiography, are the two major Duke criteria. Minor criteria are fever, predisposing cardiac condition, vascular phenomena, immunological phenomena and microbiologic and echocardiogram evidence which are not fulfilling the major criterion. Simultaneous presence of the two major criteria allows the clinical diagnosis of definite IE. Furthermore, the clinical diagnosis of definite IE becomes also possible in the presence of only one major

and 3 minor criteria or in the presence of five minor criteria. Besides definite IE, possible and rejected categories are also defined by Duke criteria. While for rejected IE, case definition is very clear, possible IE includes all cases that are not meeting criteria for definite IE and are not rejected IE. Several studies have confirmed the good sensitivity and specificity of the original Duke criteria [4,5,6]. Still, several pitfalls were also identified such as low specificity in the cases of blood culture negative IE, prosthetic valves IE and the overly broad categorization of the possible IE [7]. In 2000, as a consequence of the widespread use of the transesophageal echocardiography, the growing importance of *Staphylococcus aureus* bacteremia in IE, the poor sensitivity of Duke criteria in suspected cases of Q-fever IE and the need to reduce the size of possible IE group, new modifications of the diagnostic criteria have been proposed [8].

These modified Duke criteria include positive serology for *Coxiella burnetii* or one single blood culture with this etiology as major criteria, exclusion of minor echocardiography criterion and clear definition of possible IE (only cases with one major and 1 minor criteria or 3 minor criteria) [8]. Current guidelines for the diagnosis and management of IE recommend the use of modified Duke criteria for the diagnosis of IE [9]. Although is compared with the original Duke criteria, the modified criteria have better sensitivity especially for Q-fever IE, several issues still remain unsolved such as low sensitivity in blood culture negative IE, elderly people and prosthetic valves IE [10].

Correct and prompt diagnosis of IE is crucial for the treatment and outcome of the patients.

Though diagnostic criteria are important additional tools for the clinicians, they cannot and should not replace the clinical judgment.

The aim of this study was to evaluate the presence and the individual value of each criterion of the modified Duke criteria in our patients with infective endocarditis.

Methods

We performed a prospective observational study between January 2008 – June 2014, in which we enrolled consecutive adult patients hospitalized with the suspicion of infective endocarditis. Patients were hospitalized and treated in two settings: Infectious Diseases Hospital and the Heart Institute. We included patients with suspicion of infective endocarditis that came either from home or were referred with suspicion of infective endocarditis from

Manuscript received: 13.05.2015

Accepted: 27.05.2015

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other hospitals. At least two blood cultures were collected on admission concomitantly with routine blood tests. Transthoracic echocardiography and/or transesophageal echocardiography were performed as soon as practicable. An extended database using Microsoft Access was elaborated including: all demographic data, clinical data, laboratory results, echocardiography results, evolution and outcome of the patients. Data about antibiotic treatment prior to admission were recorded.

The study was approved by the ethical committee of our university and the ethical committees of both settings. Informed consent for participating in this study was obtained for each patient.

We applied retrospectively the modified Duke criteria for the final diagnosis of IE [4]. According to these criteria three categories were identified: definite IE, possible IE and rejected IE (Table I and Table II).

Table I. Definition of terms in modified Duke criteria for the diagnosis of infective endocarditis.

Major criteria

1) Blood culture positive for IE

- a) Typical microorganisms consistent with IE from 2 separate blood culture
 - Viridans streptococci, Streptococcus bovis, HACEK group, Staphylococcus aureus; or
 - Community- acquired enterococci, in the absence of a primary focus; or
- b) Microorganism consistent with IE from persistently positive blood cultures, defined as follows:
 - At least 2 positive cultures of blood samples drawn >12 h apart; or
 - All of 3 or a majority of ≥ 4 separate cultures of blood (with first and last sample drawn at least 1h apart)
- c) Single positive blood culture for *Coxiella burnetii* or antiphase I Ig G antibody titer $>1 > 800$

2) Evidence of endocardial involvement

- a) Echocardiogram positive for IE (TEE recommended in patient with prosthetic valves; rated at least „possible” IE by clinical criteria or complicated IE (paravalvular abscess); TTE as first test in other patients), defined as follows :
 - Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or
 - Abscess; or
 - New partial dehiscence of prosthetic valve
- b) New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)

Minor criteria

- Predisposition, predisposing heart condition or injection drug use
- Fever, temperature $>38^{\circ}\text{C}$
- Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages and Janeway's lesions
- Immunologic phenomena: glomerulonephritis, Osler's nodes,

Roth's spots and rheumatoid factor

- Microbiological evidence: positive blood culture but does not meet a major criterion as noted above* or serological evidence of active infection with organism consistent with IE

*Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis

In order to evaluate the diagnostic importance of each major and minor criterion in the final diagnosis of IE, we followed a model used by Rognon et al. [11]. This author and his coworkers evaluated the value of each individual Duke criteria on a study population of 179 patients. Following their model, for each of the major and minor criteria we tested two hypotheses. First, each major and minor criterion was excluded from the final classification and we counted how many cases fell into a lower category (e.g. how many definite cases have become possible or rejected and how many possible cases have become rejected). Second, after adding just one criterion we counted how many possible and rejected cases would have been classifiable as definite. This way we determined the number of situations in which a given criterion is decisive for the final diagnostic classification

Table II. Modified Duke criteria.

Definite infective endocarditis

Pathological criteria

- Microorganism: demonstrated by culture or histology in a vegetation or in a vegetation that has embolized, or in an intracardiac abscess or
- Pathologic lesions : vegetation or intracardiac abscess present confirmed by histology showing active endocarditis

Clinical criteria , using specific definitions for these terms as listed in table 1

- 2 major criteria , or
- 1 major and 3 minor,
- or 5 minor

Possible infective endocarditis, at least

- 1 major and 1 minor, or
- 3 minor

Rejected

- Firm alternate diagnosis explaining evidence of infective endocarditis, or
- Resolution of infective endocarditis syndrome, with antibiotic therapy for 4 days or less, or
- No pathologic evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for 4 days or less

Results

A number of 241 patients (82 women and 159 males, male/female ratio 1.94.) were included in this study; mean age was 58.16 years (range: 18.08-85.38 years).

There were 170 patients who came from home and 71 were patients referred from other hospitals.

Native valves were involved in 184 cases (76.34%) and prosthetic valves in 57 cases (23.65%). 175 cases (95.10%) were native left sided IE and 9 (4.89%) cases, right sided native IE. We had blood cultures positive IE in 109 cases and blood culture negative IE (BCNE) in 132 (71.21%) cases. Antibiotic treatment prior to blood culture was recorded in 152 (63.07%) patients. In BCNE, 94 patients (71.21%) had antibiotic treatment prior to blood sample. According to the modified Duke criteria 137 patients had definite IE, 79 patients had possible IE and 25 cases had rejected IE. Pathological criteria for definite IE were available in 68 cases from which in 60 cases after surgery and in 10 cases, results were obtained at the autopsy (two of this had surgery and autopsy). When we excluded the pathologic criteria, only 43 (63.32%) from the 68 cases remained definite IE by clinical Duke criteria, twenty-three cases became possible IE and 2 cases became undetermined (with less than one major and 1 minor criteria or less than 3 minor criteria). From those 43 definite, 3 cases had 2 major criteria and 3 minor; 9 cases had 2 major and 2 minor criteria; 22 cases had 2 major and one minor; 1 case had one major and four minor criteria, 6 cases had one major and three minor criteria and none of the cases had five minor criteria. Combination of clinical criteria among the 23 possible IE cases was: 10 cases with one major and one minor criteria, 13 cases with one major and 2 minor and 6 cases with 1 major and three minor. The two undetermined (or rejected) cases had only one major criterion.

Tables III and IV present the proportion of each diagnostic criteria and the percent of modification resulted after subtracting and adding each criterion.

The major microbiological criterion

Major microbiological criteria were present in 97 (40.24%) cases, from which 91 were definite cases, five cases were possible IE and 1 case was rejected IE. In 144 patients the blood culture results were negative, 113 patients (78.47%) being previously treated with antibiotic.

In the absence of the major microbiological criteria, from the 137 definite criteria, 43 cases (32.85%) cases would become possible and 2 undetermined. When we tested what would happen if all cases had the major microbiological criteria, we found that the number of definite IE cases increased from 137 cases to 211, 74 cases would become definite from possible IE, meaning a change of 93.67%.

Echocardiographic evidence of endocardial involvement

Two hundred and nineteen patients (90.87%) had the major criterion of endocardial involvement present. This criterion was present in 135 of definite IE cases, 74 of possible IE and 10 of the rejected cases.

When we excluded this criterion, the number of definite IE decreased from 137 cases to 78 cases, meaning a change of 43.07% and the number of possible IE decreased from 79 cases to 5 cases, 74 cases becoming undetermined.

Eighty-nine patients (64.96%) with definite IE had both major criteria present (blood culture positive and echocardiographic evidence of endocardial involvement).

Minor criteria

In our study population, the cardiac predisposition criterion was present in 116 patients (48.13%). Of these, 63 patients had definite IE, 45 patients had possible IE and 8 cases had rejected IE. None of our patients had intravenous drug abuse as a predisposition of IE. In the absence of this minor criterion, 11 definite cases (9.49%), would have become possible IE. When we added cardiac predisposition criterion to all cases, 8 from the possible IE became definite IE, meaning a change of 10.13%.

Fever was present in 181 patients (75.10%) from which 109 patients with definite IE, 62 patients with possible IE and 10 patients with rejected IE. The rest of our patients either had subfebrilities, meaning a body temperature between 37.5-38°C or they had been afebrile. When we excluded this criterion, 13 cases of definite IE became possible IE, meaning 9.49% cases and when we added this minor criterion, 8 possible cases became definite IE, meaning 10.13%.

A minor criterion, vascular phenomena, was present in 44 patients, from which 34 patients with definite IE and 7 patients with possible IE. None of the rejected patients had this minor criterion. Arterial embolism was present in 41 cases, one case had cerebral hemorrhage, one case had Janeway's lesion and one case had mycotic aneurysm.

Table III. Modification of the 137 cases of definite IE after extraction of each individual criterion.

Criterion	Remaine „definite” N (%)	Become „possible” N (%)
Microbiology (major)	92 (67.15)	45 (32.85)
Echocardiography (major)	78 (56.93)	57 (43.07)
Predisposition	126 (91.97)	11 (8.03)
Fever	124 (90.51)	13 (9.49)
Vascular phenomena	130 (94.98)	7 (5.11)
Immunologic phenomena	133 (97.08)	4 (2.92)
Microbiology minor	130 (94.89)	7 (5.11)

Table IV. Possible IE cases that would become definite with the addition of one individual criterion.

Criterion	Remain possible IE N(%)	Become definite IE N (%)
Microbiology (major)	5 (6.32)	74 (93.67)
Echocardiography (major)	74 (93.67)	5 (6.33)
Predisposition	71 (89.87)	8 (10.12)
Fever	71 (89.87)	8 (10.12)
Vascular phenomena	42 (53.16)	37 (46.83)
Immunologic phenomena	40 (50.63)	39 (49.37)
Microbiology minor	39 (49.63)	40 (50.63)

Exclusion of this criterion relegates 7 of the definite IE into possible IE, meaning a change of 5.11%. After adding the vascular phenomena criterion to all cases, 37 of the possible cases became definite IE, meaning a change of 46.84%.

The immunological phenomena criterion was present in 27 cases. Rheumatoid factor was present in 25 cases from 43 tested cases, (19 definite IE cases, 5 possible IE and 1 rejected IE cases), glomerulonephritis was present in one case and Osler's nodes in one case. When we added rheumatoid factor criterion, 39 of the possible IE cases became definite IE, meaning a change of 49.37%.

Minor microbiological criterion was present in 15 patients, 11 with definite IE and 4 with possible IE. When we excluded this criterion, 7 definite IE cases relegated into possible IE and when we added this criterion, 40 possible IE cases became definite, meaning a change of 50.63%. Minor serological criterion was searched in suggestive epidemiological context and in was found positive in only one case.

Discussion

In this study, the modified Duke criteria showed a sensitivity of 63.23%, given that from the 68 IE cases confirmed by pathological examination, only 43 cases remained definite IE in the absence of this test. This value is lower than that reported by other studies, in which Duke criteria had a sensitivity of 80% [4,5]. Our findings could be explained by the high frequency of BCNE, which represents 60% of cases. In cases of BCNE the sensitivity of Duke criteria is diminished [12].

Another study reported a 21% sensitivity of Duke criteria in BCNE [10].

BCNE usually represents 2.5-31% of IE, some studies reported 48% [13]. The most important cause of BCNE is antibiotic treatment prior to blood culture sample [10]. In our study 71.21% of patients with BCNE were pretreated with antibiotics.

Major microbiology criterion had a significant importance in the clinical diagnosis of IE since 32.85% of definite IE would become possible in his absence and after adding this criterion 93.67% of possible IE became definite. Nevertheless, a high percentage of patients with BCNE could explain why in the study of Rognon et al. the major microbiological criterion had an even higher impact on the diagnosis [11].

Echocardiographic evidence of endocardial involvement had the major contribution in diagnosis of IE cases. In the absence of this criterion only 56.93% of IE cases would remain definite and 93.67% of possible IE would become undetermined cases. In our study 135 of 137 (98.54%) definite IE cases had the major echocardiographic criterion. These figures are higher than those reported in other studies and we assume that the widespread use of echocardiography and the improvement of diagnostic skills have lead to the growing importance of this tool in the

diagnosis of IE.

Overall, the importance of each minor criterion in the diagnosis of IE was extremely variable, depending on their prevalence.

Compared to the study of Rognon et al, in which the minor criterion predisposition was present in 70% of patients, we found this criterion in only 48% of our patients. Recent studies reported a growing number of IE patients without known underlying cardiac disease [14]. Instead, there is a growing incidence of cardiac risk factors such as the presence of cardio-vascular devices (e.g. pacemaker, intracardiac defibrillator), chronic hemodialysis, conditions that are not included in the minor Duke criteria.

Another important aspect that we found in this study is the relatively low prevalence of fever, second minor criteria of IE. In our study, only 75.10% patients had fever above 38°C. This frequency is lower than that reported in the Rognon et al. study, but is included in the 46%-96% frequency interval, generally reported by other studies [15,16].

Low incidence of fever in our study could be correlated with the predominance of blood-culture negative IE [15].

Vascular phenomena had a frequency of 17% in our study, similar with recent reported results. Presence of these criteria could be very important, almost one half of our possible IE became definite after adding this minor criterion.

Although the rheumatoid factor is a minor criterion of IE, included in the immunologic criteria, it was investigated in a small proportion of cases (17.84%). Presence of rheumatoid factor in IE, has proof a very good specificity and negative predictive value in confirming IE [17].

In our study, the presence of this criterion could upgrade almost half of the possible IE to definite IE.

Microbiology minor criterion showed the same clinical impact, its presence could have a great impact in the final diagnosis of IE.

Thus, in those cases in which one minor criteria could make the difference between different diagnosis categories of IE, careful search and evaluation of these criteria are extremely important.

One limitation of our study could be the inclusion of referral cases in the analysis. Importance of referral bias has been mentioned in previous studies [18]. Still, more recent reports found no significant differences between referral and community cases in terms of clinical characteristics [16].

We think that the analysis presented in this study reflects the real situation of IE cases that are seen in every day bedside medical practice.

Conclusion

Twenty-years after their launch, the Duke criteria for the diagnosis of IE continues to be important tools. Nevertheless, the final diagnosis should not rely only on these criteria; clinical judgment, integration of whole clinical and laboratory findings should be performed.

In our study the major echocardiographic criterion had the greatest importance in the diagnosis of IE. On the other hand, the major microbiological criterion which is the cornerstone in identifying the presence of bacteremia in IE, was present only in 40%. The reason for this low incidence of blood culture positivity was a high percent of inappropriate antibiotic treatment prior to blood sampling. In the particular situation of BCNE, where the sensitivity of Duke criteria is diminished, searching for all possible minor Duke criteria can make the difference for the final diagnosis. Nowadays, the scarcity of classical Osler manifestation - bacteremia, fever and peripheral stigmata - makes the diagnosis of IE a challenge. The rheumatoid factor should be searched in all cases of IE since in the presence of a positive result almost half of the possible IE cases could become definite IE. Almost half of the possible IE cases in this study could become definite IE in the presence of this minor criterion.

In the actual context of increased number of IE cases with atypical presentation and BCNE, reevaluation of the minor Duke criteria and perhaps searching for new minor criteria in order to improve sensitivity of this diagnostic schema without decreasing the specificity, could be useful. Low index of suspicion of IE and inappropriate use of antibiotics may have a great negative impact on the diagnosis of IE.

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