Are the Duke criteria really useful for the early bedside diagnosis of infective endocarditis? Results of a prospective multicenter trial

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Diagnosis; Echocardiography; Infective endocarditis.

Background. **To date, no studies have evaluated the usefulness of the Duke vs the modified Duke criteria for the early diagnosis of infective endocarditis (IE), nor is it known whether a probabilistic approach may be useful in establishing an early clinical diagnosis of IE. The aim of this study was 1) to assess and compare the clinical usefulness of the Duke vs the modified Duke criteria for the early diagnosis of IE, and 2) to evaluate the diagnostic utility of a probabilistic approach based on the echocardiographic criterion.**

Methods. **From January 2000 to December 2001, 267 consecutive patients with suspected IE were enrolled in a prospective multicenter trial.**

Results. **IE was diagnosed in 147 cases (55%) and rejected in 120 cases (45%). The Duke and the modified Duke criteria had a high similar sensitivity, specificity and accuracy. The time to diagnosis was 8.15 ± 7.4 days for the Duke criteria and 8.18 ± 7.1 days for the modified Duke criteria. The time to diagnosis based on a probabilistic approach was shorter than that based on the Duke and the modified Duke criteria (4.96 ± 7.1 days, for all $p < 0.001$).**

Conclusions. **Although the Duke and the modified Duke criteria have a very similar sensitivity, specificity and accuracy, the delay in the time to diagnosis may be significant. A probabilistic approach based on clinical suspicion and echocardiographic evidence may be useful for decision-making, whilst awaiting case definition by means of the Duke criteria.**

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Introduction

The clinical presentation of infective endocarditis (IE), involving various organs and systems, may include cardiac and extracardiac manifestations. This often renders the diagnosis difficult necessitating comprehensive assessment of the clinical, laboratory, and echocardiographic findings.

The primary purpose of case definition for IE should be to standardize the epidemiologic and etiologic data and to compare different treatments and outcomes so as to assist clinicians in the diagnosis of the disorder[1].

A simple case definition will also avoid underdiagnosis, with the attendant risk of clinical catastrophe and death, or overdiagnosis possibly resulting in protracted and unnecessary antimicrobial management, excessive costs, and the risk of drug-related side effects.

The first case definition for IE proposed by Pelletier and Petersdorf[2] in 1977 was later modified by Von Reyn et al.[3] in 1981 to improve its sensitivity (SN) and specificity (SP). This resulted in a frequent classification of probable or possible IE, wherein definite IE could only be classified by direct histopathologic evidence.

New criteria that combined predisposing factors, blood cultures, echocardiographic findings and clinical and laboratory data were proposed by a study group at the Duke University in 1994[4]. Subsequent validation of these "Duke criteria" and the demonstration of their superiority led to their replacing the Von Reyn criteria for the diagnosis of IE[5-15].

Although the Duke criteria have good diagnostic SN and SP, optimum case definition remains controversial, particularly in more complicated cases. Proposed modifications to these criteria have not been fully evaluated, nor has the usefulness of the

Duke vs the modified Duke criteria for the early diagnosis of IE been investigated.

Studies evaluating the diagnostic value of echocardiography based on a probabilistic approach[16,17] have shown that much depends on the disease pre-test probability; however, its real usefulness in the early diagnosis of IE is still unknown.

The aim of this study was 1) to assess the clinical utility of the Duke criteria for early diagnosis and to compare the Duke criteria vs the modified Duke criteria, and 2) to compare the diagnostic utility of the Duke criteria with a probabilistic approach based on the Duke echocardiographic criterion.

Methods

Study population and data collection. This prospective multicenter study was conducted from January 2000 to December 2001 in Piedmont (north western Italy), a region with 4.2 million inhabitants. The study design complied with the Helsinki Declaration and was approved by the local ethics committee. Informed consent was obtained from all subjects.

Of the region's 90 facilities for medicine, cardiology, heart surgery and infectious diseases invited to participate, 37 (41%) agreed to collaborate in the study. One monitor from each center collected the data on a specific case report form. Instructions on the procedures to standardize patient inclusion (Table I), data collection, blood culture sampling, management protocol, echocardiography and the interpretation of the Duke criteria were provided at two meetings. Blood culture studies and transthoracic echocardiography (TTE) were to be performed in all patients; transesophageal echocardiography (TEE) was to be performed in patients with valve prostheses or when previous TTE studies were of poor quality or in case of an intermediate or high probability of disease. Each case of suspected IE was classified according to the Duke and modified Duke criteria[18] (Tables II-IV) and compared with the final diagnosis. All data were collected, reviewed and analyzed by two cardiologists at the study center (Cardiology Department, Maria Vittoria Hospital, Turin). Two echocardiographists blindly evaluated the echocardiographic tapes and agreed on a final diagnosis. The final diagnosis was the discharge diagnosis confirmed at histopathology following surgery or at autopsy or bacteriologic analysis of peripheral emboli or on the basis of the clinical picture after a 3-month follow-up.

Table I. Patient inclusion.

At least two of the following:
- fever (of unknown origin) lasting ≥ 5 days
- abnormal ESR, CRP
- splenomegaly, petechiae, microscopic hematuria
- intravenous line (central or peripheral)
- single minor Duke criterion
- single major Duke criterion
- hemodialysis

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

The study population was subdivided into two main groups. Patients with a final diagnosis of IE formed group A, in which those with a diagnosis confirmed at surgery or autopsy were assigned to group A1, while those with a "clinical diagnosis" of IE only were assigned to group A2. Patients whose final diagnosis was other than IE formed group B, wherein IE was ruled out by 1) a firm alternative diagnosis; 2) resolution of an IE syndrome following ≤ 4 days of antibiotic therapy; 3) no evidence of IE at surgery or autopsy; 4) no clinical evidence of IE during a 3-month follow-up. Patients for whom IE was ruled out by conditions 1, 2 or 3 formed group B1.

Statistical analysis was performed for the 135 cases in group A1 plus group B1.

For all group A1 patients, satisfaction of the Duke and the Li-modified Duke criteria was determined as soon as possible, after which the delay between admission and diagnosis was then calculated. In this group we also calculated the delay between admission and echocardiography.

Statistical analysis. Data are expressed as means ± SD. Between-group differences were compared using the unpaired Student's t-test for continuous variables and a χ^2 analysis for categorical variables, with $p < 0.05$ as the significance cut-off.

The SN, SP, positive (PPV) and negative predictive values (NPV) and accuracy were calculated according to the usual methods[19]. In the calculation, "possible IE" cases were classified as "definite IE" (definition 1), and "rejected IE" (definition 2). Statistical significance was calculated using the comparing ratio test.

Knowing the SN and SP of the echocardiographic Duke major criterion, Bayes' simplified theorem was applied in our population pre-test probability (P1) of IE to obtain the post-test probability (P2)[19,20]. P2 indicates the probable presence of IE and represents the PPV when the test is positive and the reciprocal of the NPV when it is negative.

Results

Epidemiologic and clinical characteristics. Two hundred and sixty-seven patients with suspected IE were enrolled. Their clinical and epidemiologic characteristics are listed in table V. The details have already been reported[21]. IE was diagnosed in 147 group A patients (55%) and rejected in 120 group B patients (45%). In 54 group A patients (37%, group A1), the diagnosis was confirmed at surgery or autopsy. In 81 group B patients (67%, group B1), IE was rejected by a firm alternative

Table II. Duke criteria.

	Comments
Major criteria	
Positive blood cultures	
Typical microorganism isolated from two separate blood cultures or	*Streptococci viridans, Streptococcus bovis, HACEK group, Staphylococcus aureus,* or community-acquired enterococcal bacteremia without a primary focus. In patients with possible infective endocarditis, at least two sets of blood cultures collected by separate venipunctures should be obtained within the first 1 to 2 hours of presentation. Patients with cardiovascular collapse should have 3 blood cultures obtained at 5-10 min intervals and thereafter should receive empirical antibiotic therapy.
Persistently positive blood culture	Defined as the growth of a microorganism consistent with infective endocarditis on: a) blood cultures drawn > 12 hours apart or b) all of three or a majority of ≥ 4 separate blood cultures, with the first and last drawn at least 1 hour apart.
Evidence of endocardial involvement	
New valvular regurgitation or	An increase or a modification in a preexisting murmur is not sufficient.
Positive echocardiogram	Three echocardiographic findings qualify as major criteria: a discrete, echogenic oscillating intracardiac mass located at a site of endocardial injury; a periannular abscess and a new dehiscence of a prosthetic valve.
Minor criteria	
Predisposition to infective endocarditis Certain cardiac conditions or Injection drug use	Predisposing heart diseases: *High-risk conditions:* previous infective endocarditis, aortic valve disease, prosthetic heart valve, aortic coarctation and complex cyanotic congenital heart disease. *Moderate-risk conditions:* mitral valve prolapse with valvular regurgitation or leaflet thickening, isolated mitral stenosis, tricuspid valve disease, pulmonary stenosis, and hypertrophic cardiomyopathy. *Low- or no-risk conditions:* secundum atrial septal defect, ischemic heart disease, previous coronary artery bypass graft surgery, and mitral valve prolapse with thin leaflets in the absence of regurgitation.
Fever	Temperature > 38°C (100.4°F).
Vascular phenomena	Petechiae and splinter hemorrhages are excluded. None of the peripheral lesions are pathognomonic for infective endocarditis.
Immunologic phenomena	Presence of rheumatoid factor, glomerulonephritis, Osler's nodes or Roth spots.
Echocardiogram consistent with infective endocarditis but not meeting a major criterion	
Microbiologic findings	Positive blood cultures that do not meet the major criteria. Serologic evidence of active infection; single isolates of coagulase negative staphylococci and organisms that very rarely cause infective endocarditis are excluded from this category.

diagnosis, resolution of an IE syndrome following ≤ 4 days of antibiotic therapy, or lack of evidence of IE at surgery or autopsy.

As reported in table V, patients with a final diagnosis of IE were older than those without IE (56 ± 16.75 vs 48 ± 18.62 years, $p < 0.001$) and had a higher frequency of predisposing heart disease (69.0 vs 45.0%, $p < 0.001$), positive echocardiographic findings (90.0 vs 3.3%, $p < 0.001$), positive blood cultures (67.0 vs 20.0%, $p < 0.001$), typical microorganisms (48.0 vs 6.6%, $p < 0.001$), and vascular and immunologic phenomena (47.0 vs 9.1%, $p < 0.001$).

The in-hospital and 3-month mortalities were higher in group A than in group B (14.0 vs 5.0%, $p = 0.025$; and 18.0 vs 5.0%, $p = 0.002$, respectively). The frequency of males and injection drug users was similar in both groups, whereas HIV positivity was more frequent in group B (20.0 vs 3.4%, $p < 0.001$). In group A, valve involvement was found in 118 cases (80%); the mitral valve in 53 (45%), the aortic valve in 40 (34%), multiple valves in 13 (8.8%), the tricuspid valve in 11 (7.5%), and the pulmonary valve in 1 (0.6%). Prosthetic valve involvement was recorded in 27 cases (18%).

Table III. Li-modified Duke criteria.

	Li-suggested modifications
*Major criteria**	
Positive blood cultures	
Typical microorganism isolated from two separate blood cultures or	To be added: positive serology of *Coxiella burnetii* as a major criterion (single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titer to *Coxiella burnetii* > 1:800). *Coxiella burnetii* is not readily cultivated in most clinical microbiology laboratories. To be added: bacteremia due to *Staphylococcus aureus* as a major criterion regardless of whether the infection is nosocomially acquired or a removable source of infection is present.
Persistently positive blood culture	
Evidence of endocardial involvement	
New valvular regurgitation or	
Positive echocardiogram	Transesophageal echocardiogram recommended in patients with: a) a prosthetic valve, b) at least possible infective endocarditis by clinical criteria, c) complicated infective endocarditis.
*Minor criteria**	
Predisposition to infective endocarditis	
Certain cardiac conditions or	
Injection drug use	
Fever	
Vascular phenomena	
Immunologic phenomena	
Echocardiogram consistent with infective endocarditis but not meeting a major criterion	To be omitted: echocardiographic minor criteria because of the widespread use of transesophageal echocardiography.
Microbiologic findings	

* see table II for comments.

Table IV. Duke and modified Duke criteria.

Definite infective endocarditis
Pathologic 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, confirmed by histology showing active endocarditis

Clinical criteria
- 2 major criteria *or*
- 1 major criterion and 3 minor criteria *or*
- 5 minor criteria

Possible infective endocarditis
1 major criterion and 1 minor criterion
3 minor criteria

Rejected infective endocarditis
Firm alternative diagnosis for manifestations of endocarditis *or*
Resolution of manifestations of endocarditis, with antibiotic therapy for ≤ 4 days *or*
No pathologic evidence of infective endocarditis at surgery or autopsy after antibiotic therapy for ≤ 4 days

Does not meet criteria for possible infective endocarditis, as above

In group A positive blood cultures were a major Duke criterion in 98 patients (67%) and a minor Duke criterion in 12 (8%). Blood cultures were negative in 37 patients (25%), of whom 22 (59%) had been treated with antibiotics prior to admission. Staphylococci and streptococci were the most common etiological agents (Table VI).

Table VII lists the final diagnoses in group B.

The Duke criteria. A definite diagnosis of IE was established in 46 patients (85%) in group A1 and rejected in 64 (79%) in group B1 (Table VIII). In these two groups, the 25 other cases (18.5%) were classified as possible IE, with 8 (17%) in group A1 and 17 (21%) in group B1. The SN, SP, PPV, NPV and accuracy were 100, 79, 76, 100 and 87% respectively by definition 1, and 85, 100, 100, 91 and 94% respectively by definition 2. These figures were similar for the entire population.

The Li-modified Duke criteria. A definite diagnosis of IE was established in 45 patients (83%) in group A1 and rejected in 65 (80%) in group B1 (Table VIII). In these two groups, the 25 other cases (18.5%) were classified as possible IE, with 9 (17%) in group A1 and 16 (20%) in group B1. By definition 1, the SN, SP, PPV, NPV and accuracy were 100, 80, 77, 100 and 88% respectively, and 83, 100, 100, 90 and 93% respectively by definition 2. These figures were similar to those for the Duke criteria and were applicable for the entire population.

Duke criteria and diagnostic delay. In group A1, the diagnostic delay (time from admission to diagnosis) for definite IE was 8.67 ± 8.64 days (SEM 1.29 days) both for the Duke and the Li-modified Duke criteria. The mi-

Table V. Clinical findings of the study population.

	Group A (n=147)	Group B (n=120)	p
Age (years)	56 ± 16.75	48 ± 18.62	0.001
Range	18-85	15-85	
Sex			NS
Male	98 (67%)	69 (58%)	
Female	49 (33%)	51 (42%)	
Predisposing heart disease	102 (69%)	54 (45%)	0.001
Injection drug use	15 (10%)	22 (18%)	NS
HIV+	5 (3.4%)	24 (20%)	0.001
In-hospital mortality	21 (14%)	6 (5%)	0.025
Total mortality*	27 (18%)	6 (5%)	0.002
Pathological confirmation	54 (37%)	5 (4.1%)	0.000
Echo-positive**	132 (90%)	4 (3.3%)	0.001
Echo-compatible but not diagnostic**	11 (7.4%)	34 (28%)	0.000
Positive blood culture**	98 (67%)	24 (20%)	0.001
Negative blood culture	37 (25%)	91 (76%)	0.000
Intermittently positive blood culture**	12 (8%)	5 (4%)	NS
Typical microorganism**	70 (48%)	8 (6.6%)	0.001
Vascular phenomena**	44 (30%)	6 (5%)	0.001
Immunologic phenomena**	25 (17%)	5 (4.1%)	0.002

* follow-up at 3 months; ** as defined by the Duke criteria.

Table VI. Microbiology.

	Group A (n=147)	Group B (n=120)
Streptococci	55 (37.4%)	5 (4.2%)
S. oralis	26 (17.7%)	0
Group D	24 (16.3%)	0
S. pyogenes	5 (3.4%)	5 (4.2%)
Staphylococci	50 (34%)	19 (15.8%)
S. aureus	28 (19%)	9 (7.5%)
S. epidermidis	12 (8.2%)	4 (3.3%)
Others	10 (6.8%)	6 (5%)
HACEK organisms	3 (2%)	1 (0.8%)
Candida albicans	2 (1.4%)	–
Escherichia coli	2 (1.4%)	1 (0.8%)
Klebsiella oxytoca	1 (0.7%)	–
Pseudomonas aeruginosa	1 (0.7%)	–
Coxiella burnetii*	1 (0.7%)	–
Neisseria spp	1 (0.7%)	–
Brucella spp	–	1 (0.8%)
Cryptococcus neoformans	–	1 (0.8%)

* based on serological positivity.

Table VII. Final diagnosis in group B (n=120).

HIV-related conditions	18 (15%)
Acute respiratory disease	14 (12%)
Fever (of unknown origin)	9 (7%)
Osteomyelitis, arthritis, soft tissue infection	8 (6.6%)
Sepsis*	8 (6.6%)
Nephropathy, urinary tract infections	7 (5.8%)
Meningitis, encephalitis	5 (4.1%)
Autoimmune disease	4 (3.3%)
Pericarditis	4 (3.3%)
Abscess	3 (2.5%)
Liver disease	2 (1.6%)
Heart failure	2 (1.6%)
Hematological disease	2 (1.6%)
Acute appendicitis	2 (1.6%)
Pulmonary embolism	2 (1.6%)
Brucellosis	2 (1.6%)
Pharyngitis	2 (1.6%)
Other	26 (21.6%)

* with an extracardiac focus.

nor echocardiographic criterion and the *Coxiella burnetii* criterion were not found in this group. In the entire population, the results were similar for the Duke criteria (8.15 ± 7.4 days) and the Li-modified criteria (8.18 ± 7.1 days) in group A (Table IX).

Of the 46 patients in group A1 with definite IE according to the Duke criteria, in 24 cases (52%) the first diagnosis was based on two major criteria (e.g. blood culture and echocardiography), in 12 (26%) on an echocardiographic major criterion and three minor criteria, in 6 (13%) on blood culture and three minor criteria, in 3 on blood culture and new regurgitation (6.5%), and in 1 on new regurgitation and three minor criteria (2.1%). No cases were determined by the presence of five minor criteria. Echocardiography as a minor criterion was useful for early diagnosis in only 3 cases (2.6%) in the entire population, but not in group A1. The most frequent major criterion was echocardiography (93/115 cases, 80.9%).

Probabilistic approach. Table X compares the post-test probability (P2) of IE for each variable of the Duke criteria, together with an appropriate SN and SP and with the disease prevalence in the study population (P1 = 0.55). A positive echocardiography strongly related with a diagnosis of IE with a post-test probability of 0.97, while a negative echocardiographic test almost

Table VIII. Cross tabulation of the clinical diagnosis by the Duke and Li-modified Duke criteria in groups A1 and B1.

	Group A1 (n=54)	Group B1 (n=81)
Duke criteria*		
Definite	46	0
Possible	8	17
Rejected	0	64
Li-modified Duke criteria**		
Definite	45	0
Possible	9	16
Rejected	0	65

* definition 1: sensitivity (SN) 100%, specificity (SP) 79%, positive predictive value (PPV) 76%, negative predictive value (NPV) 100%, accuracy 87%; definition 2: SN 85%, SP 100%, PPV 100%, NPV 91%, accuracy 94%; ** definition 1: SN 100%, SP 80%, PPV 77%, NPV 100%, accuracy 88%; definition 2: SN 83%, SP 100%, PPV 100%, NPV 90%, accuracy 93%.

Table IX. Diagnostic delay (days).

Duke criteria	Modified Duke criteria	Probabilistic approach
8.15 ± 7.4	8.18 ± 7.1	4.96 ± 7.1*

* $p < 0.001$ vs Duke and modified Duke criteria.

excluded it (post-test probability of 0.11). TTE without TEE had a post-test probability of 0.96 and 0.26, respectively.

The time to diagnosis was shorter using a probabilistic approach based on the Duke echocardiographic criterion instead of the Duke classical or modified criteria (4.96 ± 7.1 days, $p = 0.001$) (Table IX).

Discussion

Numerous studies have validated the Duke criteria for IE and compared their usefulness with that of the Von Reyn criteria[5-15]. Proposed modifications to the Duke criteria[14,18,22] have not been fully evaluated[23], nor has the usefulness of the Duke and the modified Duke criteria in the formulation of an early diagnosis been investigated.

Our prospective multicenter study confirmed IE in 147 out of 267 patients with suspected IE (55%) admitted to 37 centers in Piedmont (north western Italy) in the years 2000 and 2001. The demographic, clinical and epidemiologic characteristics of this population[21] were similar to those described in another recent study[24].

Statistical analysis was performed solely for the 135 patients with firm final evidence (group A1) or exclusion (group B1) of IE; however, the results were similar to those of the entire population. As reported elsewhere[5-15], the SN, SP, PPV, NPV and the accuracy of the Duke criteria in the clinical diagnosis of IE were satisfactory.

The Duke criteria accurately identified all IE diagnoses when "possible IE" was regarded as "definite IE" according to definition 1. This carries a significant advantage in that underdiagnosis is avoided.

Even so, the "possible IE" category comprises a substantial portion of patients with and without IE[10,25]. In our study, the 25 patients (18.5%) of groups A1 and B1 belonged to this category, of which the 17 patients in group B1 were erroneously treated for IE. In such cases, clinical data from the medical history, physical examination and diagnostic tests (blood culture, laboratory tests, ECG, chest radiograph and repeated echocardiograms) need to be re-evaluated and integrated.

The Li-modified Duke criteria displayed a similar SN, SP, PPV, NPV and diagnostic accuracy due to the low frequency of *Coxiella burnetii* infections. Exclusion of the minor echocardiographic criterion converted some cases of definite IE in group A to possible IE, and some cases of possible IE to rejected IE cases in group B. However, the overall number of possible IE cases was the same in both groups, and the diagnostic accuracy did not change. One main feature of the Li-modified criteria is the recommended wide use of TEE.

Table X. Post-test probabilities (P2) of infective endocarditis with various signs and symptoms in the Duke criteria.

Clinical feature	P1*	Sensitivity	Specificity	Positive test P2	Negative test P2
Positive blood culture	0.55	0.67	0.8	0.8	0.33
Typical microorganism	0.55	0.48	0.93	0.89	0.41
Echo-positive	0.55	0.90	0.97	0.97	0.10
Echo minor criterion	0.55	0.07	0.72	0.23	0.61
Intermittently positive blood culture	0.55	0.08	0.96	0.71	0.54
Vascular phenomena	0.55	0.30	0.95	0.88	0.47
Immunologic phenomena	0.55	0.17	0.96	0.84	0.51
Predisposing heart disease	0.55	0.69	0.55	0.65	0.41
Injection drug use	0.55	0.1	0.82	0.4	0.57
Fever	0.55	0.95	0.1	0.56	0.38

* pre-test probability of infective endocarditis in our population.

This was complied with in our study, particularly in patients with a prosthetic valve, and the expected differences were attenuated.

An early diagnosis of IE shortens the delay in treatment and reduces morbidity, mortality and costs. In our study, the time from admission to diagnosis was similar to that reported elsewhere for patients aged > 65 years[26]. No significant differences in the delay to diagnosis emerged for any of the variables taken into consideration in our study (patient age and sex, the presence or absence of injection drug use or central or peripheral intravenous lines or intravascular devices). In 52% of cases, the diagnosis was determined by two major criteria, whereas the minor criteria were found to be less important. Delays were mainly due to the time required to receive blood culture results, particularly for identifying troublesome microorganisms, or to the progression of IE itself manifesting in the form of vascular and immunologic signs. An early diagnosis may also be influenced by the suspicion index of the physician who first examines the patient. Accordingly, the delay may be related to the time when echocardiographic examination and other procedures are requested. In our series, this may not have been the main reason for the delay due to the high suspicion index for preliminary preparation for the prospective study. Moreover, these results reflect the practical application of the Duke criteria in a multicenter prospective trial in Italy and could be better in a single, excellent center.

In our patients with an intermediate pre-test probability of IE, the application of the simplified Bayes theorem showed that positivity of the Duke major echocardiographic criterion was almost able to confirm IE and could almost exclude it if the echocardiogram was negative. Because an echocardiogram is highly specific, a positive echocardiogram could profoundly change the probability of IE even in other clinical settings with lower disease prevalence. Since the delay in the time to diagnosis was significantly shorter than that based on the Duke criteria, we think that a probabilistic approach should be adopted for the initial evaluation of suspected IE.

Clinical practice, however, needs cornerstones because IE is a complex disease with a host of variables that renders global assessment mandatory for the formulation of a definite diagnosis. In our experience, an initial echocardiographic finding, as validated by a probabilistic approach, should be further confirmed by the Duke criteria. As a result, a good quality TTE should always be promptly performed (in our view, within the first 24 hours) in patients with suspected IE and a TEE carried out within the first 24-48 hours if necessary[27]. We think that a positive result in patients with fever and altered inflammatory indices, particularly in the presence of hemodynamic overload, could motivate the decision to treat while waiting for the results of blood culture and other analyses. In other instances, caution is advisable since echocardiography cannot definitively distinguish infectious from sterile vegetations; false positive results may also be due to strands, myxomatous degenerations with a "cotton wool bud" appearance, exuberant rheumatic vegetations, degenerative valvular disease with nodules, fibrosclerosis and calcifications, Chiari's network, stitches, fibrous membranes prosthetic valves, ruptured or false chords, cardiac tumors (papilloma and fibroelastoma) and primary antiphospholipid syndrome. While, on the one hand, a negative echocardiography does not rule out IE, on the other it may substantially reduce the probability of the disease, suggesting the importance of a differential diagnosis. In addition, the examination should be repeated several days later if there is at least an intermediated probability of disease[27].

In conclusion, the Duke and the modified Duke criteria have a very similar high SN, SP and diagnostic accuracy in the clinical setting; in our study, however, they gave a similarly high number of possible IE. Using only these criteria may significantly delay the time to diagnosis. A probabilistic approach based on clinical suspicion and echocardiography could be useful for decision-making and may sometimes reduce the time to treatment, whilst awaiting case definition on the basis of the Duke criteria.

Appendix

Author Contributions

- *Study Concept and Design:* E. Cecchi, A. Brusca, R. Trinchero
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- *Analysis and Interpretations*: E. Cecchi, R. Gnavi, M. Bobbio, R. Trinchero
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