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European Society of Cardiology-Proposed Diagnostic Echocardiographic Algorithm in Elective Patients with Clinical Suspicion of Infective Endocarditis: Diagnostic Yield and Prognostic Implications in Clinical Practice

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Abstract

Background: Echocardiography plays a central role in diagnosing infective endocarditis (IE). Accordingly, the European Society of Cardiology (ESC) has proposed a diagnostic echocardiographic algorithm. However, new studies are still needed to evaluate the degree of implementation of these guidelines in clinical practice and their consequences on incidence and prognosis of IE. **Aim:** This study aims to investigate the diagnostic yield of the ESC proposed echocardiographic algorithm in patients with suspected IE. We also examined the association among IE diagnosis and clinical outcomes. **Methods:** Retrospective analysis of a series of patients undergoing the ESC algorithm for clinical suspicion of IE at our institution. **Results:** Between 2009 and 2013, 323 cases were managed by a multidisciplinary team for clinical suspicion of IE. Following ESC algorithm, 26 (8%) patients were diagnosed with IE and 297 (92%) had IE excluded. In 92% of patients with a good-quality negative transthoracic echocardiography (TTE) and low level of clinical suspicion, the first TTE was considered sufficient to rule out IE. During a mean follow-up of 2.3 ± 1.4 years, patients who had a final diagnosis of IE showed similar mortality (P = 0.2) and rates of combined endpoint (all-cause death, stroke/transient ischemic attack, advanced atrioventricular block, and heart failure) compared to patients without echocardiographic diagnosis of IE (P = 0.5). Only 1% of the patients who had IE excluded experienced IE in the following 3 months, none of them in the subgroup of patients, in which a first negative TTE was considered sufficient to rule out IE. **Conclusions:** In spite of the current ESC recommendation TTE is used as part of a routine fever screen. Consequently, only a minority of patients had a final echocardiographic diagnosis of IE. Although in patients with low clinical suspicion a first negative TTE is sufficient to rule out IE, the incidence of clinical events is similar regardless the final diagnosis of IE.

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Full Text

Introduction

Infective endocarditis (IE) still carries poor prognosis and high mortality despite major advances in both diagnostic and therapeutic procedures.[1] Transthoracic echocardiography (TTE) is the initial technique of choice for investigation but has a sensitivity of 60%–65%.[2] Nonetheless, a normal scan in low-risk patients provides rapid noninvasive confirmation that IE diagnosis is unlikely.[3] On the other hand, transesophageal echocardiography (TEE) has a sensitivity of 85%–98% and after years of heated debate about TEE indications, a consensus was achieved on including this technique in the diagnostic strategy in most of left side IE cases and when clinical course is complicated by uncontrolled infection or heart failure (HF).[2]

Accordingly, a Task Force of the European Society of Cardiology (ESC) has proposed a diagnostic echocardiographic strategy in 2009[4] endorsed also in 2015 guidelines.[5] This algorithm has the advantage of having rationalized the echocardiographic diagnostic approach of suspected IE. Therefore, our institution implemented such a policy, but new studies are still needed to evaluate the degree of implementation of these guidelines in clinical practice and evaluate their consequences on the incidence and prognosis of IE. Therefore, we analyzed our practices as measured by (1) how the guidelines are applied in our institution and (2) how the recommended diagnostic algorithm performs.

Methods

Patient selection

We conducted a retrospective study of patients admitted to our echocardiography laboratory for clinical suspicion of IE from January 2009 to June 2013. A policy of routine consultation with an infectious diseases specialist for patients with suspected IE was mandated. The attending infectious diseases physician prescribed TTE, sometimes after consulting with the echocardiography laboratory cardiologists regarding its indication and timing.[6]

Exclusion criteria

Age younger than 18 years old, emergent indication to TTE (i.e. patient with severe features of IE, directly admitted into intensive care units) and residents outside Modena province, Italy. Patients in chronic hemodialysis were also excluded because of greater morbidity and mortality that IE causes in this group compared to the general population.[7]

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Institution's Human Research Committee.

Echocardiographic data

All examinations were performed using Acuson Sequoia ultrasound system, Siemens Medical Solutions, Mountain View, California and were performed and/or supervised by cardiologists fully trained in echocardiography with long-standing experience with the technique and intense hands-on training period with interpretation of >750 studies.

Indication for echocardiography was at discretion of the treating physician. According to the diagnostic algorithm proposed by the ESC guidelines, all patients with clinical suspicion of IE underwent a first complete TTE. Following an initially negative examination, TTE was repeated after 7–10 days in case of persistent clinical suspicion, whereas TEE was done in cases of positive TTE and negative TTE if associated with high clinical suspicion, poor quality TTE, or in the presence of prosthetic valves or intracardiac device.[4] Confirmatory evidence of IE was defined according to the major echocardiographic criteria stated in the Duke classification.[8] Briefly, these are an oscillating mass on a valve or supporting structures, in the path of regurgitant jets, or on implanted material, in the absence of an alternative anatomical explanation; an abscess related to a prosthetic valve; new partial dehiscence of a prosthetic valve; and new valvular regurgitation. We used findings on TEE as the reference standard for diagnosing IE. In patients who did not undergo TEE, the definition of “conclusively negative TTE” was performed using strict echocardiographic criteria of a negative test result and applied only to patients with optimal acoustic window, without prosthetic valve, and without indeterminate TTE result (i.e., absence of vegetation in the setting of any functional or structural valvular abnormality on TTE).

All cases were checked for accuracy and in accordance with the guidelines. Cases were validated by 2 independent physicians, an infectious diseases specialist and a cardiologist.

All echocardiographic data were entered into an electronic database at the time of the echocardiogram, no modification from the original database was applied, and no measurement was made offline. Hence, the study consisted in a retrospective analysis of data prospectively entered in the electronic echocardiographic database.

Clinical data

Age, gender, weight, and height were recorded at the time of first TTE. Data such as diabetes, presence of chronic kidney disease (assessed by creatinine value), intravenous drug abuse, and HIV status were collected from review of patients' personal and hospital clinical charts.

The infective endocarditis team organization

ESC guidelines on the prevention, diagnosis, and treatment of IE were implemented after their release in 2009 in our laboratory to promote standardized high-quality diagnosis and management.[4] As a large nonsurgical center, we designated a team consisting of a specialist in infectious diseases and cardiologists with recognized competencies in valve disease (A. B., F. B.).[9] If immediate surgery was not required, patients underwent a complete antibiotic therapy and monitoring in the Infectious Diseases Department.

Patients with IE were reviewed and examined daily under the direct supervision of the specialist team. Triggers were in place for urgent discussion with the cardiac surgery center, i.e. new signs of HF. There was a low threshold for transferring a patient to surgical center, particularly for IE on prosthetic valves. In nonemergent or urgent cases surgery was indicated according to the ESC guidelines, usually after 4–6 weeks of appropriate antibiotic therapy. Patients' cases were discussed at admission and afterward to agree on triggers and timing for surgery with an expert cardiac surgeon (G.S.).

After surgery, patients underwent formal follow-up at 1, 3, 6, and 12 months after discharge and thereafter at appropriate frequency for the residual valve disease. Infective markers and blood cultures were taken routinely during the initial visit and otherwise if clinical suspicion occurred.

Follow-up

For the purpose of this study, we selected all-cause mortality as the primary end point. The secondary end point was the cumulative incidence of hospitalizations for HF, stroke or transient ischemic attack (TIA), and advanced atrioventricular block. Endocarditis during follow-up was recorded as a separate end point (this included recurrent IE for patients with IE and new IE diagnosis for those patients in whom IE was excluded by the application of ESC algorithm). Diagnoses were derived from hospital discharge codes. Whether more than one code was reported, only the first one was considered to define the cause of hospitalization.

Vital clinical status was obtained from the National Death Index, where all citizens' status is constantly updated and is 100% complete. Cardiovascular morbidity requiring hospitalization (after the index echocardiogram) was assessed using the electronic archives of the health service of Modena province. All public hospitalization records of citizens resident in Modena province are stored in a digital format and may be accessed online after obtaining permission and access password. This archive allows a nearly complete knowledge of all clinical events requiring hospitalization in Modena province since 1999. The diagnoses were classified according to International Classification of Disease, 9th revision, Clinical Modification.

All events were ascertained by an investigator (R.L.) blinded to the patient's past medical history and echocardiographic results.

Statistical analysis

Data are presented as percentages for categorical variables and as mean ± standard deviation for continuous variables. For direct comparison between patients with or without echocardiographic diagnosis of IE, we performed the t-test for continuous variables and Chi-square or Fischer exact test for categorical variables as appropriate. Hospitalization for HF, stroke or TIA, total atrioventricular block, and survival rates, estimated using Kaplan–Meier method, were compared using log-rank test.

All tests were two-tailed. $P < 0.05$ was considered statistically significant. Analyses were performed using JMP version 9.0.1 (SAS Institute Inc., Cary, NC, USA) and SPSS, Version 15.0 for Windows, Chicago, IL, USA.

Results

Clinical characteristics

Demographic and clinical characteristics are shown in [Table 1]. Mean age was 58 ± 20 years. The study cohort consisted mainly of men; 7% of patients had HIV-infection and 3% were intravenous drug abuser. Comparison between patients with and without IE revealed higher prevalence of men in patients with IE compared to patients without IE (92% vs. 54%, P = 0.0001). Patients with IE showed a worse renal function as demonstrated by serum creatinine levels (1.3 ± 1.1 vs. 0.9 ± 0.5 mg/dl, P = 0.002).{Table 1}

Blood cultures had been performed before the index echocardiogram only in 70% of cases. Of these, 81% were positive. The prevalent microorganisms isolated were Staphylococcus aureus in 29%, coagulase-negative Staphylococci in 11%, Streptococci in 35%, and Enterococci in 15%.

During the study period, 323 cases with clinical suspicion of IE were managed according to the ESC algorithm at our echocardiographic laboratory and met the inclusion criteria [Figure 1].{Figure 1}

In 280 (87%) patients, the first TTE resulted negative for IE. In 23 of these patients with a first negative TTE, there was persistent clinical suspicion of IE, thus in 10 patients, the TTE examination was repeated after 7–10 days, while 15 of these were evaluated with TEE (3 had both TTE and TEE). In 257 patients with a first negative TTE and low level (80% of the entire population, 92% of those with negative TTE) of clinical suspicion; this examination was considered sufficient to exclude IE, and no further examination was performed.

For 18 patients (6%), the first TTE was positive for IE; it was considered sufficient for diagnosis and for establishing the management, only in 6 patients, while 12 patients underwent subsequent TEE. Fifteen patients underwent TEE for inadequate acoustic window or the presence of prosthetic valves or intracardiac devices. Totally 42 (13%) patients underwent TEE.

At the end of echocardiographic diagnostic workup, 26 (8%) patients were diagnosed with IE and for 297 (92%) patients IE was excluded [Figure 1]. In 16 (61%) patients, IE was diagnosed at the first TTE. In 6 patients, this result was considered sufficient to establish a clinical diagnosis and a proper management of IE, whereas 12 patients underwent TEE. Three patients had a first negative TTE, but due to persisting high clinical suspicion of IE in the following 7–10 days, they were referred for another TTE, which resulted positive in one case and negative in the other two cases. These three patients subsequently underwent TEE with a positive result for IE.

Native aortic valve was the most frequently involved (12 patients, 46%, of whom 6 had bicuspid aortic valve), followed by prosthetic aortic valve (8 patients, 30%). In most cases, TTE showed the presence of vegetations (77%). TTE demonstrated abscess in 23% of cases, paravalvular complications in 35%, new at least moderate regurgitation in 46%, new prosthetic paravalvular regurgitation in 15%, and perforations in 27% of cases.

Nineteen (73%) patients underwent cardiac surgery: 16 (84%) had aortic valve replacement and 3 (16%) had mitral valve surgical repair.

Follow-up

During mean follow-up of 2.3 ± 1.4 years, 62 (19%) patients died; three patients (11%) of those with final IE diagnosis and 59 (20%) of those in whom IE was excluded. Among patients with final IE diagnosis, one died from septic shock (3 days after IE diagnosis), one patient died in the immediate postoperative period (11 days after IE diagnosis), and one patient died from pancreatic cancer 2 months after IE diagnosis. The combined end point was observed in 75 patients: 5 (19%) with final diagnosis of IE and 70 (24%) patients without IE. Among patients with final IE diagnosis, one patient was hospitalized for HF and one patient was hospitalized for advanced atrioventricular block while none had stroke or TIA. Among patients in whom IE was excluded, 12 were hospitalized for HF, 9 for stroke/TIA, and none had advanced atrioventricular block.

In our cohort, patients diagnosed for IE showed similar mortality [Figure 2], P = 0.297 and similar rates of combined end point (death, stroke or TIA, advanced atrioventricular block, and HF) compared to patients without echocardiographic diagnosis of IE [Figure 3] P = 0.526.{Figure 2}{Figure 3}

Among patients diagnosed for IE at the initial workup, 2 (8%) were hospitalized for recurrent IE during follow-up, specifically at 2 and 4 months after the diagnosis. Among patients not diagnosed with IE after applying ESC algorithm, three patients (1%) were hospitalized for IE during follow-up, specifically at 2, 7, and 11 months later. In the subgroup of patients without final IE diagnosis, having a first negative TTE examination, the incidence of combined end point events was 22% (61 patients) and none had IE diagnosis throughout the follow-up.

Discussion

Our analysis provides current information about how the echocardiographic diagnostic algorithm proposed by ESC may work in elective patients with clinical suspicion of IE. The principal finding was that TTE is performed in all patients with high or even low probability of IE ("exclusion" of IE) in spite of the current recommendations emphasizing that TTE should not be used as part of a routine fever screen but only if at least a moderate clinical suspicion of IE exists. Consequently, in many cases, a first negative TTE is sufficient to exclude IE in patients with low clinical suspicion and the final diagnosis of IE by echocardiography is relatively infrequent. Of note, in the context of appropriate IE management and timed treatment (i.e. 73% underwent cardiac surgery), the incidence of clinical events was similar regardless the final diagnosis of IE.

In our series, TTE was performed in patients with "low clinical probability" of the disease as attested by the fact that only 70% of patients had blood cultures and 87% had initial negative TTE. Indeed, the 70% rate of blood cultures does not correspond to the standard workup for suspected IE. Although there is no given definition of "low clinical probability," we believe that interpretation is guided by an example: "fever and previously known heart murmur."

Owing to their excellent sensitivity and specificity, the Duke criteria have achieved widespread use, but they do not indicate whether echocardiography is necessary in all patients with "low clinical probability".[10] Of note, the validity of the Duke classification in a population with only 70% of blood cultures is debatable. In our cohort, only 8% had definite diagnosis at the end of the echocardiographic workup, a finding important to underline in the current cost-conscious era. This finding, which parallels previous observations,[3] may be due to the wide interpretation of the term "low level of clinical suspicion" in the absence of a stringent set of defining criteria. Although the absence of certain clinical criteria indicated a near-zero probability of TTE showing evidence of IE,[3] it is difficult to define a threshold to use TTE diagnostic workup. Nowadays clinicians increasingly rely on echocardiography since a variety of cardiac diseases such as silent valvular disease and mass lesions (vegetations) are elusive to the physical examination even when performed by experienced clinicians.[11] These data, in aggregate, likely criticize clinical practice whereby a significant number of the TTE requested are of little practical value (poor sensitivity as a screening test). Instead, the probabilistic approach based on clinical suspicion and echocardiography significantly reduce time to diagnosis than that based on the Duke and the modified Duke criteria.[12] This approach may have a strong clinical impact while awaiting case definition by means of the Duke criteria in guiding clinicians to the appropriate therapy (early empiric antibiotic therapy, surgical option, and need for further diagnostic tests in doubtful or negative cases), or toward other diseases.

In the present study, TTE was considered sufficient in almost 80% of cases if a good-quality negative TTE was associated with low level of clinical suspicion.[13]

The reasons for low TEE utilization are not well understood and likely include factors specific to providers, patients, and institutions. Certainly, improvements in TTE image quality have narrowed the diagnostic gap between TTE and TEE modalities, especially for the evaluation of native valves.[14] It is noteworthy that rapid clearance of blood cultures is among the criteria that previous authors have used to determine the risk of IE. Infectious disease physicians may also have omitted TEE because they identified a secondary focus that required prolonged antibiotics, presumably a duration sufficient to treat IE.[15] Consistently with these studies, our infectious disease providers did not routinely use TEE to exclude IE for patients with a low perceived risk of IE. Additional studies are needed to determine if omission of TEE in some patients affects treatment failure and clinical outcomes. However, the evidence that among patients who did not have final IE diagnosis after only 3 (1%) were hospitalized for IE during follow-up is reassuring. Moreover, Khatib et al.[16] reported that IE present on TTE, and not TEE alone, is associated with increased mortality and major embolic events.

Finally, the observation that in our cohort patients with definite IE has outcomes similar to patients in whom the diagnosis of IE was excluded was not surprising since reductions in all-cause mortality are very uncommon or nonexistent with systematic application of screening tests, especially in frail patient with significant comorbidities. Indeed, although the sepsis-associated mortality seems to be decreasing, approximately 20% of patients with organ dysfunction die in hospital.[17] Therefore, we can assume a considerable role of noncardiovascular mortality in our cohort of patients during follow-up.

Limitations

The relatively limited sample size and number of events represent the most important limitations of the present study. However, our report fulfilled good methodological quality criteria based on completeness of data on baseline characteristics and follow-up for the entire cohort.

The generalizability of our results to other practice settings may be debated. In this regard, it is critically important to understand that we observed a selected sample of patients who had been treated by a multidisciplinary medical team according to ESC guidelines. Importantly, the study took place in an echocardiography laboratory, so we failed to include patients with IE who never reached our department because either their condition was deemed too severe to consider aggressive treatment such as valve replacement (e.g., patients with massive stroke, patients included in palliative care for severe comorbidities) or they presented with the most fulminant features of IE, including multiple organ failure, and thus were directly admitted into intensive care units, where a notable proportion of IE-related deaths occurs.

The retrospective nature of our study, the potential selection bias and nonblinded echocardiographic interpretation, all contributed to the overall quality of the study. However, only prospective studies could confirm our results by evaluating a large sample of consecutive patients with suspected IE with blinded reading of TTE and TEE.

The role of new imaging techniques such as cardiac computed tomography (CT) scan, cerebral magnetic resonance imaging, 18F-fluorodeoxyglucose position emission tomography/CT and leukocyte-labeled single-photon emission CT/CT have been delineated only in the most recently released version of ESC guidelines which was published after the completion of the present study, thus it could not be investigated.

Conclusions

In a contemporary series of patients with clinical suspicion of IE managed according to ESC echocardiographic diagnostic algorithm, only a minority of patients had a final diagnosis of IE. Therefore, echocardiography seems to be used as a screening test with low diagnostic yield. Although in patients with low clinical suspicion, a first negative TTE is sufficient to rule out IE, in this series, the incidence of clinical events is similar regardless the final diagnosis of IE.

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Conflicts of interest

There are no conflicts of interest.

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