

The Role of Transthoracic Echocardiography in the Diagnosis of Infective Endocarditis in Children

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Background: Infective endocarditis (IE) is frequently suspected but infrequently diagnosed in children. Clinicians often order echocardiograms to “rule out” IE. In an era of cost constraint, clinically efficient strategies must be developed to eliminate unnecessary tests. We hypothesized that transthoracic echocardiography (TTE) is only useful in children in whom there is a high clinical suspicion of IE based on history, physical examination, and persistently positive blood cultures.

Objective: To determine the role of TTE as a screening test for suspected IE in children.

Methods: Echocardiographic reports and medical records were reviewed retrospectively for 173 consecutive patients who underwent TTE to rule out IE from January 1993 to August 1996.

Results: Persistent fever was the predominant symptom leading to a suspicion of IE (120 patients [69.4%]). Fifty-seven (32.9%) of the 173 patients had congenital heart disease and 95 patients (54.9%) had indwelling ve-

nous catheters. Twenty-six patients (15.0%) were diagnosed and treated for IE. Twelve (46.2%) of these 26 patients had vegetations seen on TTE. The conditions of the remaining 14 patients were diagnosed clinically and these patients had persistently positive blood cultures. By univariate analysis, the risk factors associated with the diagnosis of IE were malaise, congestive heart failure, new or changing heart murmur, leukocytosis, hematuria, and the presence of 2 or more positive blood cultures for the same organism. The risk factors associated with positive TTE were malaise, congestive heart failure, new or changing heart murmur, leukocytosis, hematuria, and 2 or more positive blood cultures. The presence of an indwelling catheter or immunocompromised status were not predictive of vegetation or IE.

Conclusions: Transthoracic echocardiography has poor sensitivity as a screening test for IE in patients with low clinical probability of the disease. A diagnostic algorithm for IE is suggested based on these data.

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Editor’s Note: I wonder if TTE is a better “screening” test for IE in adults. Try to understand that without reading at least the abstract.

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INFECTIVE ENDOCARDITIS (IE) continues to be associated with significant morbidity and mortality in children. The definitive diagnosis of IE is challenging because it requires the pathological evidence of vegetations or abscess at surgery or autopsy. Endocarditis is more often a clinical diagnosis that is made when certain criteria are present. Two-dimensional transthoracic echocardiography (TTE) has contributed greatly to the evaluation of patients with IE by noninvasively demonstrating the presence of vegetations. Transthoracic echocardiography has been reported to have a sensitivity of 40% to 80% for the detection of vegetations associated with IE that are more than 5 mm in diameter in adult patients.¹⁻⁴ Clinicians often use TTE as a tool in the diagnosis of suspected

IE in children. Our clinical experience has suggested that TTE is often overused in the evaluation of suspected IE. Screening patients with TTE, while noninvasive, is an expensive approach in an era in which cost containment is emphasized. Therefore, we sought to examine the criteria used to evaluate these patients and develop strategies for effective evaluation.

We hypothesized that TTE is only useful in children who have a high clinical suspicion of IE based on history, physical examination, and persistently positive blood cultures. We sought to determine the utility of TTE as a screening test in children with suspected IE. Using this information, we developed a diagnostic algorithm that aims to minimize the unnecessary use of TTE and increase its sensitivity.

RESULTS

HISTORICAL FINDINGS

Between January 1993 and July 1996, 173 TTEs were performed to screen 145 inpa-

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PATIENTS AND METHODS

PATIENT POPULATION

The files of the echocardiography laboratory of the division of cardiology at the Children's Hospital of Michigan, Detroit, were reviewed to identify patients who underwent TTE as a part of a diagnostic evaluation for suspected IE between January 1993 and August 1996. These were compared with the hospital medical records of patients who had had IE as a primary or secondary discharge diagnosis during the same period. The entry event was TTE and not the patient, since several patients re-entered the study during the period being examined. Studies were excluded from the list if (1) TTE was done after the diagnosis of IE was made, (2) TTE was a follow-up study for the same episode of IE, or (3) TTE was repeated within 6 weeks of an initial normal study.

For each patient, historical, clinical, and laboratory data were obtained. The historical data included age, sex, race, presence or absence of congenital heart disease, prosthetic valves, indwelling central venous catheters, immunocompromised status, and history of rheumatic fever or drug abuse. Records of history and physical examination near the time of request of TTE were reviewed. These data included the presence or absence of fever (temperature 38°C orally or 38.5°C rectally) and its duration, malaise, rash, vascular and embolic phenomena (petechiae, splinter hemorrhages, Janeway lesions, conjunctival hemorrhages, Roth spots, aseptic meningitis, Osler nodes, and pulmonary, central

nervous system, or peripheral emboli), hepatosplenomegaly, congestive heart failure, and the presence of a new heart murmur or a change in the quality of an existing murmur. Malaise was defined as fatigue and a general feeling of being seriously ill described subjectively by the patient or his or her parent and an ill appearance as described by the examining physician. Laboratory data included blood cultures (number of cultures and type of organisms), hematocrit (anemia defined as <0.30), white blood cell count (leukocytosis $>15 \times 10^9/L$ white blood cells), hematuria (>5 red blood cells per high-power field), erythrocyte sedimentation rate, and serum rheumatoid factor.

STATISTICAL METHODS

Two outcome measures were considered: the presence of vegetations on TTE and the clinical diagnosis of IE. Data were summarized using means and SDs or medians and ranges in cases where the data were skewed. Univariate tests, including *t* tests, and the nonparametric Mann-Whitney test for continuous data, χ^2 , or Fisher exact tests for categorical data were used to investigate the relevance of variables for the outcome of interest. All variables that were significant at $P < .10$ using univariate tests, or those that were thought a priori to be important, were included in multivariate analyses. Logistic regression and classification trees were used to determine which variables best predicted a positive outcome. Results of the analyses are summarized in a tree diagram. In addition, we have included a decision tree based on the analyses that allows for the inclusion of all positive cases.

tients for suspected IE. This is compared with 51 259 hospital admissions (1 in 309 admissions) and 4757 inpatient echocardiograms (1 in 29) during the same period. The hospital medical record computer files showed that 33 patients had IE as a primary or secondary discharge diagnosis. Seven patients were excluded from the study based on the exclusion criteria.

There were 72 females and 101 males among the 173 patients undergoing TTE. This racially mixed population included 95 whites, 68 African Americans, 5 Hispanics, and 5 Asians. The median age was 8.5 years, with a range from 0.5 to 29.3 years. Twenty-six patients had more than 1 TTE for different episodes of suspected IE more than 6 weeks apart. Fifty-seven studies were performed for patients who had congenital heart disease (32.9%) of whom 5 (2.9%) had prosthetic valves. Ninety-five studies (54.9%) were done in patients with indwelling central venous catheters. Sixty-one studies (35.3%) were done in patients who had different oncologic diseases, were receiving chemotherapy, and were felt to be immunocompromised. None of the patients had a documented history of rheumatic fever or intravenous drug abuse.

By univariate analysis, the presence of congenital heart disease was a significant risk factor for IE ($P = .006$) but not for a positive TTE. Immunocompromised status was a predictor of a negative TTE ($P = .06$) and no IE ($P \leq .001$). Indwelling venous catheters were associated with no IE ($P = .01$). Historical data are presented in **Table 1**. Historical variables that were not significant

for IE or a positive TTE included age, sex, race, prosthetic valves, and history of rheumatic fever or drug abuse.

CLINICAL FINDINGS

The clinical data are outlined in **Table 2**. One hundred twenty patients (69.4%) presented with fever with a duration of 1 to 14 days prior to TTE. Thirty patients (17.3%) had malaise. Four patients (2.3%) had documented signs and symptoms of congestive heart failure, 5 patients (2.9%) had a new heart murmur or a change in an existing one, and 3 patients (1.7%) had splenomegaly. None of the patients had vascular or embolic phenomena.

By univariate analysis, the presence of fever did not predict positive TTE or IE. Malaise, despite being a very nonspecific clinical finding, was a significant predictor ($P < .001$) of IE and a positive TTE. Congestive heart failure ($P \leq .001$) and a new or a change in a previously existing heart murmur ($P \leq .001$ and $.002$) were also significant predictors of IE and a positive TTE. Splenomegaly, petechiae, and embolic manifestations were not significant for either outcome variable.

LABORATORY FINDINGS

The laboratory data are outlined in **Table 3**. Sixty-one patients (35.3%) had 1 positive blood culture and 45 patients (26%) had 2 or more positive blood cultures for the same organism. Fifty-three patients (30.6%) had leukocy-

Table 1. Association of Historical Data With Clinical Diagnosis of IE and Presence of Vegetations on TTE*

Variable	IE (n = 26)	No IE (n = 147)	P	TTE (n = 12)	No TTE (n = 161)	P
CHD	15 (57.7)	42 (28.6)	.006	3 (25)	54 (33.5)	.75
Indwelling catheters	8 (30.8)	87 (59.2)	.01	7 (58.3)	88 (54.7)	>.99
Immunocompromised	1 (3.8)	60 (40.8)	<.001	1 (8.3)	60 (37.3)	.06
Prosthetic valves	1 (3.8)	4 (2.7)	.56	0 (0.0)	5 (3.1)	>.99
Rheumatic fever	0 (0.0)	0 (0.0)	...	0 (0.0)	0 (0.0)	...
IV drug use	0 (0.0)	0 (0.0)	...	0 (0.0)	0 (0.0)	...

*Data are presented as number (percentage) of patients unless otherwise indicated. IE indicates infective endocarditis; TTE, transthoracic echocardiography; CHD, congenital heart disease; ellipses, not applicable; and IV, intravenous.

Table 2. Association of Clinical Variables With the Diagnosis of IE and Presence of Vegetations on TTE*

Variable	IE (n = 26)	No IE (n = 147)	P	TTE (n = 12)	No TTE (n = 161)	P
Fever	21 (80.8)	99 (67)	.25	8 (6.7)	112 (69.6)	>.99
Malaise	23 (88.5)	7 (4.8)	<.001	10 (83.3)	20 (12.4)	<.001
CHF	4 (15.4)	0 (0.0)	<.001	3 (25)	1 (0.6)	<.001
Heart murmur	5 (19.2)	0 (0.0)	<.001	3 (25)	2 (1.2)	.002
Splenomegaly	1 (3.8)	2 (1.4)	.39	1 (8.3)	2 (1.2)	.20
Petechiae	0 (0.0)	0 (0.0)	...	0 (0.0)	2 (1.2)	.20

*Data are presented as number (percentage) of patients unless otherwise indicated. IE indicates infective endocarditis; TTE, transthoracic echocardiography; CHF, congestive heart failure; and ellipses, not applicable.

Table 3. Association of Laboratory Data With Diagnosis of IE and Presence of Vegetations on TTE*

Variable	IE (n = 26)	No IE (n = 147)	P	TTE (n = 12)	No TTE (n = 161)	P
≥ 2 Positive blood cultures	23 (88.5)	22 (15.4)	<.001	11 (91.7)	34 (21.1)	<.001
Leukocytosis	21 (80.8)	32 (21.8)	<.001	11 (91.7)	42 (26.1)	<.001
Anemia	5 (19.2)	21 (14.3)	.55	4 (33.3)	22 (13.7)	.09
Hematuria	10 (38.5)	9 (6.1)	<.001	6 (50)	13 (8.1)	<.001

*Data are presented as number (percentage) of patients unless otherwise indicated. IE indicates infective endocarditis; TTE, transthoracic echocardiography.

toxic, 26 patients (15.0%) had anemia, and 19 patients (11.5%) had hematuria. The erythrocyte sedimentation rate was elevated (>20 mm/h) in 8 patients (4.6%) and was normal or not done in the rest of the patients. Rheumatoid factor, mentioned as an indicator of IE in other studies, was not determined in any of our patients. By univariate analysis, the presence of 2 or more positive cultures for the same organism was a significant risk factor associated with the diagnosis of IE and positive TTE ($P \leq .001$). Leukocytosis ($P \leq .001$) and hematuria ($P \leq .001$) were significant predictors of both IE and a positive TTE. However, the presence of anemia was not significantly associated with either variable.

ECHOCARDIOGRAPHIC FINDINGS

Of 26 patients who were diagnosed with and treated for IE, 12 (46%) had vegetations detected by TTE. A vegetation was defined as an oscillating echogenic intracardiac mass on a valve or a supporting structure or in the path of a turbulent jet, present in more than 1 imaging plane and seen consistently through the cardiac cycle in the absence of an alternative anatomical explanation.^{3,5,6} The vegetations varied in size between 0.6 mm

and 1.9 mm in the greatest dimension. Five of the vegetations were attached to the wall of the right atrium, 3 each were attached to the tricuspid and the mitral valves, respectively, and 1 was attached to the left atrial wall.

STATISTICAL EVALUATION

Using a multivariate approach, both logistic regression and classification tree approaches found that the existence of 2 or more positive blood cultures, the interaction with the presence of an indwelling catheter, and the presence of malaise consistently were the significant variables in predicting the outcome of treatment for IE. The interaction term was protective with an odds ratio of 0.04 and the other 2 increased risk with odds ratios of 23 and 120, respectively. From these models, we developed a screening strategy. Using this strategy, no cases of IE would be missed and no cases treated as IE would be missed either.

COMMENT

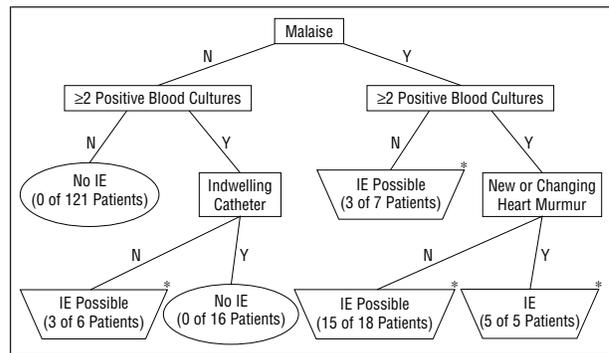
The diagnosis of IE has been challenging to pediatricians because its clinical manifestations in children are highly variable and nonspecific. The management includes par-

enteral antibiotic treatment for a minimum of 2 to 4 weeks. Cardiac surgery may also be required, which carries a significant mortality and morbidity risk.^{7,8} There is a need for criteria that have diagnostic strength in the early phase of the disease, when no pathology results are available. Various diagnostic criteria have been proposed as guidelines for the diagnosis of IE in adults.⁹ Under these criteria, the definite diagnosis of IE is based on histological analysis of samples from surgery or autopsy or the documentation of a specific bacteria in valvular vegetations or peripheral emboli. These latter vascular manifestations of IE are rare and often overlooked in children. Von Reyn et al⁹ in 1981, before the era of modern echocardiography, proposed 4 diagnostic categories for IE in adult patients: definite, probable, possible, and rejected. While they had strict criteria for definite diagnosis that included the presence of direct evidence IE based on histological analysis of samples from surgery or autopsy, or on bacteriological analysis (Gram stain or culture) of valvular vegetation or peripheral embolus, their criteria for rejected cases were weak. The recently published Duke criteria incorporate echocardiographic findings among the clinical criteria for the diagnosis of IE in adults.⁶ Several studies have shown that the Duke criteria classify significantly more episodes of definite IE than the Von Reyn criteria in adults^{10,11} and in children.¹² The Duke criteria propose 3 levels of diagnostic possibilities: definite endocarditis, possible endocarditis, and no endocarditis (diagnosis rejected). The authors of these criteria propose strict criteria for accepting or a rejecting a diagnosis of IE similar to the Jones criteria for the diagnosis of rheumatic fever. For example, the diagnosis of definite IE requires the presence of 2 major, 1 major and 3 minor, or 5 minor criteria. However, a weakness in this proposal is that the vascular and immunologic phenomena are included within the minor criteria. These findings are rarely seen in children.

In our study, 12 patients had vegetations seen on TTE among the 26 who were diagnosed with IE. Applying the Duke criteria to our case group, only 11 patients (42.3%) fulfilled the requirement for definite IE (a positive echocardiogram and 2 positive blood cultures). Using the same criteria, none of the 26 patients would have had the diagnosis of IE rejected and the remaining 15 patients would have fallen in the possible IE group. This suggests that the Duke criteria may not have adequate specificity when applied to a pediatric population such as ours.

The reported incidence of vegetations that can be detected by TTE in children with IE varies from 46.2% (our data) to 67%.¹³ Previous reports have suggested that once the clinical diagnosis of IE is made, TTE plays an important role in evaluation of complications such as valvular regurgitation, obstruction, perforation, and abscess formation.^{14,15} It has been shown that neither TTE nor transesophageal echocardiography significantly influenced antibiotic use in patients with IE. Such a decision is determined primarily by the clinical profile and microbiological results.¹⁶

Our results demonstrate that IE remains a clinical diagnosis based on history, physical examination, and persistently positive blood cultures. The diagnostic value of TTE in cases of suspected IE depends greatly on the clinical probability of the disease. In a recent study, both TTE



A proposed diagnostic algorithm for suspected infective endocarditis (IE). Asterisk indicates that a transthoracic echocardiogram is recommended; N, no; and Y, yes.

and transesophageal echocardiography were performed in 105 consecutive adult patients with suspected IE. Both TTE and transesophageal echocardiography had a low diagnostic yield in patients who had a low clinical probability of IE.¹⁶ A recent retrospective medical record review of 133 children with suspected IE supports the importance of clinical suspicion over testing. Of the 59 patients (44%) who had persistently positive blood cultures and/or physical findings suggestive of IE, 10 (17%) were diagnosed with IE, yet TTE was positive for vegetations in only 7 patients. The authors further demonstrated that embolic phenomena and dependency on mechanical ventilation are risk factors associated with positive TTE, neither of which were shown in our study.¹⁷

The **Figure** shows a proposed algorithm for the diagnosis of IE in children beyond the neonatal period. The goal of this algorithm was elimination of the unnecessary use of TTE in cases with a low clinical probability of IE while retaining the highest sensitivity for detecting cases of IE. In our patient population, the presence of an ill-appearing child (malaise) was the most significant clinical risk factor associated with the diagnosis of IE and a positive TTE by multivariate analyses. This "soft" variable of malaise should be evaluated in the clinical context of a suspicion of infection within the heart. In many ways the strength with which it appeared in the analysis states the obvious. Children with IE are sick and ill-appearing. But this variable appeared in this study only after a clinical suspicion of IE was entertained by the clinician. That is, all ill-appearing children, regardless of clinical circumstance, were not suspected of having IE. Only those with indwelling lines, congenital heart disease, and so on were probably preselected by the clinicians for this consideration.

As expected, laboratory evidence of 2 or more positive blood cultures was found to be much more indicative of the presence of IE than a single blood culture result. The presence of a new or a changing heart murmur, in combination with clinical malaise and at least 2 positive blood cultures, was found in a higher percentage (100%) of patients with IE, but the absence of this finding did not negate the need for TTE. Conversely, the patient who does not appear ill or have 2 positive blood cultures should have the diagnosis of IE rejected according to the algorithm. Endocarditis as a diagnosis is also rejected by the analysis in those patients who do not present with malaise and have indwelling venous catheters even if they have 2 or more

positive blood cultures (16 of 16 patients). Usually, this represents line sepsis and the management usually includes parenteral antibiotics and/or removal of the indwelling catheters. For patients who have at least 2 positive blood cultures and no malaise and do not have indwelling venous catheters, the diagnosis of IE is more likely (3 of 6 patients). The clinical question that remains is whether these represent cases of transient bacteremia without endocardial involvement or actual cases of IE. In these cases, TTE is recommended for evaluation of endocardial involvement. The duration of treatment depends on the clinical situation and the type of microorganism. The diagnosis of IE remains possible in patients who present with malaise even if they do not have at least 2 positive blood cultures (3 of 7 patients). In fact, all of the 3 patients with IE in this group had only 1 positive blood culture. Although the presence of positive blood cultures is critical for the diagnosis of IE, several cases of culture-negative IE have been described.¹⁸⁻²⁰ This may be particularly true in pediatrics, where patients with IE and fever are frequently treated with antibiotics for flulike illness before blood cultures are obtained. In one study of culture-negative IE, 62% of the patients had a history of prior antibiotic treatment before blood cultures were drawn.²¹ Those patients need close observation for other supporting evidence of IE. Transthoracic echocardiography might be helpful in this group in documenting evidence of endocardial involvement.

Applying our algorithm prospectively would have resulted in only 36 TTE studies instead of 173, without missing any cases of IE. The health care cost savings that might have resulted would have been between \$68 500 and \$95 900 (conservatively assuming a total charge of \$500 to \$700 per TTE study). The proposed diagnostic algorithm seems simple and easy to follow but still needs to be validated in a prospective manner. Planning for such a study is under way.

In summary, the diagnosis of IE should be based on strong clinical suspicion in a predisposed patient who has positive blood cultures. We proposed a diagnostic algorithm that aims at the elimination of the unnecessary use of TTE in cases with a low clinical probability of IE. Applying this algorithm retrospectively in our patient population would have decreased the number of TTEs by almost 80%. Once the diagnosis of IE is made, TTE plays an important role in confirming the diagnosis and detecting complications such as valvular regurgitation, perforation, or abscess formation.

Because our institution is a tertiary care referral center, selection bias of patients is always possible. The incidence of IE in our study is consistent with the published figures in children.^{22,23} Many patients in our study had different types of cancers and frequently presented with fever that was not responsive to antibiotics within 24 to 48 hours. Echocardiograms were then ordered to rule out IE. This may overestimate the total number of TTEs as this may reflect institutional, not ubiquitous, practice. The retrospective nature of this study resulted in an occasional lack of accurate documentation of signs and symptoms of IE in the history and physical examination by the admitting physicians, despite careful review of the medical record. Malaise, which was not a clinical finding that we considered strongly in our original hypothesis, became an un-

expectedly strong predictor for the presence of clinical IE or a vegetation seen on TTE. We considered malaise a positive finding only when there was consistency between the history and the physical examination performed by the physician. Despite our attempts to identify more objective variables within the data, this finding remained dominant in the statistical evaluation. This is not surprising from a clinical perspective. Children with IE should be ill-appearing and feel sick. Yet this finding remains, admittedly, a variable that may change from examiner to examiner.

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