ORIGINAL INVESTIGATION

Overuse of Transthoracic Echocardiography in the Diagnosis of Native Valve Endocarditis

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Background: Infective endocarditis (IE) is a diagnostic challenge due to its variable presentation and nonspecific clinical findings. The use of transthoracic echocardiography (TTE) has greatly improved the ability to diagnose IE early, and therefore reduce high mortality and morbidity rates. However, reliance on TTE to exclude IE may lead to overuse of this technology in patients with a low pretest probability of IE.

Methods: Prospective observational study of all patients referred for TTE to diagnose IE. Clinical factors were used to determine likelihood of IE based on the Von Reyn criteria, and the resulting diagnostic probabilities were correlated with abnormal TTE findings as well as duration of antibiotic therapy.

Results: One hundred eleven TTEs performed on 98 patients were included in the analysis. Over 70% of TTEs were obtained in patients in whom the diagnosis of IE was *rejected* by Von Reyn criteria. Therapeutic management (prolonged antibiotic administration) was associated significantly with Von Reyn categorization, and not significantly affected by TTE results.

Conclusions: Most TTEs are obtained in patients with a low pretest probability of IE and do not contribute to therapeutic decision making. We propose a diagnostic algorithm to direct the use of TTE to patients with intermediate or high pretest probability of IE.

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INFECTIVE ENDOCARDITIS (IE) is a disease with high mortality, which requires early diagnosis to give appropriate treatment. Early identification of patients at risk for IE continues to present a challenge because clinical findings can vary widely.[1] To aid diagnosis, formal criteria were published by Pelletier and Petersdorf[2] in 1977. In 1981, Von Reyn et al[3] modified these criteria and proposed strict case definitions, generating 4 categories: *definite* (based on pathological findings), *probable*, *possible*, and *rejected* (see Appendix 1 of Von Reyn et al[3]). During the 1980s, transthoracic echocardiography (TTE) became widely used in the evaluation of valvular abnormalities, and the technology has since gained sensitivity for identifying vegetations and valvular regurgitation. In 1994, Durack et al[4] proposed the addition of TTE findings to the diagnostic criteria of endocarditis (referred to as the Duke criteria) (see Appendixes 2 and 3 of Durack et al[4]). In the ensuing years, several groups have confirmed the increased sensitivity of the Duke criteria as compared with the older Von Reyn criteria. Most of these later studies have been retrospective, and have used pathological specimens or autopsy results to define the positive cases.[5-15]

Two prospective studies have compared the Duke and Von Reyn criteria.[16,17] These studies have examined selected patient populations with a high pretest probability of IE: all patients had both TTE and transesophageal echocardiography (TEE) performed. Shapiro et al[17] noted that a "number of patients" who were clinically classified as not having IE and had normal TTE findings were treated with a prolonged course of antibiotics for "possible IE," indicating that a negative TTE, even in patients with a low pretest probability of IE clinically, may not provide clinicians with the reassurance to shorten the course of empiric antibiotic treatment.

Generally, diagnostic tests are most useful in the evaluation and management of patients with intermediate or high pretest likelihood of a given disease, and are less useful in patients with a low pretest probability. Transthoracic echocardiography, in the diagnosis of IE, is no exception.[18-20] We suspected that many TTEs in our hospital are obtained to "rule out" IE

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METHODS

An "episode" is defined as a TTE performed to evaluate IE. All requests for TTEs indicating a suspicion of IE (stated explicitly, "rule out vegetations," or history of intravenous drug use [IVDU] with fever) were reviewed between December 1, 1998, and March 15, 1999. Patient charts were reviewed by one of the authors (J.C.K.) to abstract clinical findings associated with IE. Historical risk factors included IVDU, presence of an indwelling vascular catheter, predisposing invasive procedure, human immunodeficiency virus status, prior history of endocarditis or valve disease, and immunocompromise (other than acquired immunodeficiency syndrome); clinical findings included fever, cardiac murmur, petechiae, splinter hemorrhage, Roth spots, Janeway lesions, Osler nodes, and suspected site of infection other than IE. Clinical findings were included only if they were documented in the chart before or on the date the TTE was ordered. Patients with prosthetic valves were excluded from this study.

The following laboratory data were collected: white blood cell count, band percentage, hematocrit, microscopic hematuria, number of blood cultures, number of positive blood cultures, number of days for cultures to become positive, organisms identified from positive cultures, positive cultures from sites other than blood, and evidence of embolic phenomena on radiological studies. In the case of blood culture results, we recorded whether the results of the culture were available to the treating clinician at the time the TTE was ordered (since cultures and TTEs were often requested on the same day that IE was first suspected or considered).

Transthoracic echocardiography was performed at the University of Maryland Adult Echo Lab, Baltimore, using a Sonos 5500 with harmonic imaging ultrasound system (Agilent Technologies, Andover, Mass). Transthoracic echocardiograms were read by 1 of 3 cardiologists blinded to the clinical information other than the indication for requesting the TTE. Reported results were reviewed for abnormal findings. All abnormal TTEs (vegetation, valve abnormality, moderate or severe regurgitation, or perivalvular abscess) were reviewed by one of us (M.C.) to confirm whether the TTE was diagnostic of IE.

Each episode was categorized by the Von Reyn criteria into probable, possible, or rejected based on clinical data available (see Appendix 1 of Von Reyn et al[3]). The Von Reyn criteria were used because they are the most recently defined criteria that do not rely on echocardiographic information to define likelihood of IE. Since the Von Reyn criteria rely strongly on the presence and persistence of positive blood cultures, the final results of blood cultures after 5 days of incubation were used to calculate Von Reyn category, whether or not the results were available to the treating clinician at the time the TTE was ordered.

Discharge diagnosis, clinical outcome, and length of antibiotic treatment were obtained from dictated discharge summaries. When discharge summaries were not available, the chart was reviewed again to obtain this information from the progress notes or discharge instructions.

The primary objective was to compare clinical diagnosis of IE with TTE results. We also looked at the association of both Von Reyn category and TTE results with demographic variables, discharge diagnosis of endocarditis, and duration of antibiotic therapy.

Statistical analysis was performed using Statview (Abacus Concepts Inc, Berkeley, Calif). Categorical data were analyzed with the Fisher exact test, and nominal data were analyzed with unpaired *t* tests. All tests were performed at the 5% significance level, and used 2-tailed analysis.

in patients with low pretest probability of IE. We conducted a prospective observational study of all patients referred for TTE to rule out IE in a large, urban, tertiary referral hospital (1) to determine the pretest likelihood of IE and (2) to test the impact of TTE results on clinical management and outcome.

RESULTS

One hundred twenty-eight TTE requests meeting the screening criteria were selected for review, of which 17 were excluded: in 11, TTE was not done; in 4, chart review revealed that the TTE request was erroneous or for an indication other than IE; 1 patient was known to have IE with a preexisting valvular vegetation; and 1 patient had a prosthetic valve. Thus, 111 TTEs were included in the analysis.

DESCRIPTIVE ANALYSIS OF STUDY POPULATION

One hundred eleven TTEs, or episodes, occurred in 98 patients. The mean age was 46 years (range, 15-82 years), and 61% were male. Seventy percent were African American, 46% had a history of IVDU, and 31% were infected with human immunodeficiency virus. In the latter, CD4 counts ranged widely (0-841/μL), with a mean of 132/μL. Immunocompromised states other than human immunodeficiency virus seropositivity, including diabetes mellitus, immunosuppressive therapy, and neutropenia were present in 34 patients (35%). Ten patients had preexisting valvular disease: 2 with rheumatic heart disease, 2 with nonrheumatic valvular abnormalities, and 6 with a prior (remote) history of IE. No patient had a documented history of mitral valve prolapse.

DESCRIPTIVE ANALYSIS OF VON REYN CRITERIA FACTORS

Table 1 and **Table 2** list the association of clinical factors and outcomes with either Von Reyn categorization or TTE findings, respectively.

The factors that contributed to assigning each episode as probable, possible, or rejected IE by Von Reyn criteria were as follows: persistently positive blood cultures (46 episodes, 41%), cardiac murmur (42 episodes, 38%), predisposing heart disease (10 episodes, 9%), fever (70 episodes, 68%), vascular phenomena as evidenced by embolic phenomena on physical examination or by radiography, or immunological phenomena (ie, Osler nodes and Roth spot) (32 episodes, 29%). These factors led to defining 22 episodes as probable (20%), 10

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Table 1. Demographic Factors Associated With Von Reyn Categorization and Echocardiographic Results*

Characteristic	Von Reyn Categorization: Probable/Possible (n = 32)	Von Reyn Categorization: Rejected (n = 79)	*P* Value	Echocardiographic Results: Abnormal (n = 7)	Echocardiographic Results: Normal (n = 104)	*P* Value
Age, mean (SD), y	43 (16)	48 (13)	.06	46 (13)	47 (14)	.89
Male	72	58	.18	71	62	.71
African American	75	70	.57	100	69	.19
HIV positive	28	34	.54	28	33	>.99
Immunocompromised	41	34	.52	14	38	.42
Intravenous drug use	44	46	.86	43	45	>.99
Intravascular catheter	50	34	.12	28	39	.70
History of rheumatic fever	3	1	.50	0	2	>.99
Prior valve disease	3	1	.50	0	2	>.99
History of prior IE	9	5	.41	43	4	.005
Invasive procedure	28	22	.46	28	23	.67

*Data are given as percentages unless otherwise indicated. HIV indicates human immunodeficiency virus; IE, infective endocarditis.

Table 2. Clinical Findings and Outcomes Associated With Von Reyn Categorization and Echocardiographic Results*

	Von Reyn Categorization: Probable/Possible (n = 32)	Von Reyn Categorization: Rejected (n = 79)	*P* Value	Echocardiographic Results: Abnormal (n = 7)	Echocardiographic Results: Normal (n = 104)	*P* Value
Embolic phenomena	34	8	<.01	57	12	.01
Hematuria	38	4	<.001	28	12	.24
Culture results available	87	68	.06	71	73	>.99
Other infection suspected	84	78	.48	71	81	.62
Staphylococcus aureus isolated blood	41	28	.19	43	31	.68
No. of days from admission to echocardiogram, mean (SD)	14 (17)	7 (12)	.02	4 (5)	9 (14)	.33
Length of hospital stay, mean (SD), d	34 (27)	18 (16)	<.001	20 (17)	23 (21)	.69
IE at discharge diagnosis	19	8	.09	71	6	<.001
Valve surgery done	9	0	.02	43	0	<.001
Mortality	9	6	.69	0	8	>.99

*Data are given as percentages unless otherwise indicated. IE indicates infective endocarditis.

as possible (9%), and 79 as rejected (71%). Due to small numbers, the probable and possible categories were combined, and the pooled category probable/possible was compared in all analyses with the episodes that were rejected.

In 3 of 111 episodes, no blood cultures were obtained prior to getting an echocardiogram. Of the 108 episodes with at least 1 blood culture, TTEs were ordered in 29 instances before blood culture results were reported by the clinical laboratory. In these cases, the TTE was ordered on the same day that the blood cultures were drawn. Of these 29 episodes, 25 ultimately yielded negative culture results.

Of the 44 blood cultures that met the Von Reyn definition of "persistently positive," TTE was ordered after the culture results were available in 40 (91%). In contrast, culture results were available at the time of TTE in only 8 (28%) of 29 episodes in which the cultures ultimately showed no growth (91% vs 28%; $P<.001$). In other words, in patients with culture-proven bacteremia, TTEs were more likely to be ordered when positive blood culture results were available, whereas in patients without bacteremia, the TTE was more likely to be ordered before negative culture results were known.

BIVARIATE ANALYSIS OF OTHER CLINICAL FACTORS WITH VON REYN CLASSIFICATION

Comparing the 32 probable/possible episodes with the 79 rejected episodes, there were no differences between mean age, sex, race, human immunodeficiency virus seropositivity, immunocompromised status, history of IVDU, presence of indwelling vascular catheter, history of rheumatic heart disease or other valvular abnormality, or prior invasive procedure. Episodes that fell in the probable/possible category were strongly associated with presence of hematuria (38% vs 4%; $P<.001$).

More than half (52%) of the TTEs were ordered within the first 3 days of hospital stay, 11 at admission, 20 on the first day following admission, 17 on day 2, and 10 on day 3. Transthoracic echocardiograms ordered later in the hospitalization were no more likely than those ordered in the first 3 days to reveal a pathological condition; however, those episodes in which the TTE was performed later than 3 days into hospitalization were more likely to fall into the probable/possible category than rejected ($P=.03$, Mann-Whitney test). Length of hospitalization showed no association with likelihood of IE. Mortality was not significantly associated with Von Reyn

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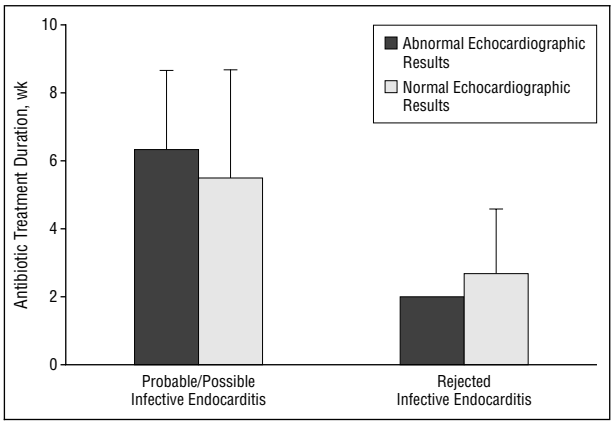

Figure 1. Histogram showing that antibiotic treatment was significantly prolonged in cases that met the criteria of *probable* or *possible* infective endocarditis compared with cases that were *rejected* by the Von Reyn criteria (P=.006, analysis of variance). Abnormal transthoracic echocardiography results did not influence duration of antibiotic treatment (P=.95 for transthoracic echocardiography results alone and P=.55 in combination with Von Reyn category).

classification. Surprisingly, discharge diagnosis of IE was also not associated with Von Reyn classification. Valve surgery was performed in 3 patients, none of whom were rejected by the Von Reyn classification (P=.02).

BIVARIATE ANALYSIS OF OTHER CLINICAL FACTORS WITH TTE RESULTS

Five of 111 TTEs showed valvular vegetations. In 2 additional TTEs, valvular abnormalities other than vegetations were demonstrated, 1 showing severe tricuspid regurgitation that was new compared with a prior TTE available for that patient, and 1 showing an abnormality consistent with abscess adjacent to the aortic valve. This latter case was the only abnormal TTE of the 7 that fell into the rejected Von Reyn category. On review of prior TTEs obtained in this patient, this abnormality had been seen on multiple occasions and was unchanged for more than a year, and therefore did not represent active IE. This patient was diagnosed as having pneumonia and *Clostridium difficile* colitis, and received 2 weeks of intravenous antibiotics. Thus, 6 TTEs were diagnostic of IE.

COMPARISON OF VON REYN CLASSIFICATION WITH TTE RESULTS

Excluding the abnormal TTE result in the patient who had the stable abnormality, 6 of 6 abnormal TTEs met Von Reyn criteria for probable/possible (the Fisher exact test, P<.001). Twenty-six of the 104 normal TTEs (25%) were in the probable/possible category, with the remaining majority falling in the rejected category.

THE EFFECT OF VON REYN CLASSIFICATION AND TTE RESULTS ON DURATION OF ANTIBIOTIC THERAPY

Data on antibiotic therapy duration were available in 99 of the 111 episodes, and these 99 episodes were analyzed for differences in mean number of weeks of therapy based on either Von Reyn category or TTE results. Thirty-one cases in the probable/possible category were treated for a mean ± SD duration of 5.6 ± 3.0 weeks, and of these, 25 had normal findings on TTE with a mean ± SD duration of antibiotics of 5.5 ± 3.2 weeks. The 6 probable/possible cases with abnormal TTE findings were treated for 6.3 ± 2.3 weeks. Sixty-eight cases in the rejected category were treated for 2.7 ± 1.9 weeks. Included in these 68 was the 1 abnormal TTE finding that was not changed from prior studies, and this patient received antibiotics for 2 weeks, stressing the importance of clinical findings over echocardiographic results, and also indicating the need to review prior studies to confirm that valvular abnormalities are changed. **Figure 1** shows the relationship between antibiotic duration in weeks in either the probable/possible or rejected Von Reyn categories, and the influence of TTE results on duration in both groups. Duration of antibiotic therapy (mean ± SD, 5.0 ± 3.0 weeks vs 2.0 ± 1.9 weeks; P<.001) and hospitalization (34 vs 18 days; P=.005) was significantly longer in the probable/possible category compared with the rejected category (echocardiographic abnormalities did not significantly affect duration of therapy [P=.03]). Furthermore, a negative TTE did not correlate with shorter length of hospitalization (20 [TTE abnormal] vs 23 [TTE normal] days; P=.69).

DESCRIPTION OF PATIENTS DIAGNOSED CLINICALLY WITH IE

Twelve episodes resulted in a clinical diagnosis of IE. Nine of these episodes grew *Staphylococcus aureus* in at least 1 blood culture; of the remaining 3 episodes, 1 grew *viridans Streptococcus*, 1 grew *Streptococcus intermedius*, and the last was culture negative (3 sets of blood cultures drawn); and the diagnosis was based on the presence of a splenic infarct on a computed tomographic scan. Nine of 12 met the Von Reyn definition of "persistently positive" blood cultures, but only 6 of 12 fell into the probable/possible category. Five of 12 had abnormalities on TTE. One patient was treated for only 2 weeks with antibiotics, and the remaining 11 were treated for at least 4 weeks.

COMMENT

We conducted a prospective observational study to characterize the use of TTE in the evaluation and management of IE in our hospital. Our main finding is that a large proportion (>70%) of TTEs are ordered in patients with a low pretest probability of IE by Von Reyn criteria. This percentage was much higher than predicted at the outset of the study. Our finding is consistent with that reported by Lindner et al[21]; however, our study differs in that all adult patients referred with suspicion of IE were included, and our hospital is located in an inner-city environment, where the likelihood of IE may be higher than in a nonurban hospital.

We found that TTE results do not significantly affect duration of antibiotic therapy. Rather, duration depended solely on clinical factors. This result is also consistent with the results reported by Lindner et al,[21] who found that clinical parameters were predictive of antibi-

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otic course, and were unaffected by either TTE or TEE. Ali et al[22] also found in a retrospective review of 2750 serial TTEs that demonstration of a vegetation in 15 of 20 cases had little effect on initiation of IE therapy in patients with a low clinical suspicion of IE.

Lindner et al[21] prospectively evaluated 105 patients with suspected endocarditis to assess the utility of either TTE or TEE in the diagnosis of IE. They tested the impact of echocardiographic findings on clinical management, and found that duration of antibiotic therapy was dependent on clinical factors, and was not affected significantly by TTE results, either TTE or TEE. They concluded that echocardiography is not useful in the clinical management of cases with a low pretest probability of IE, and is most useful in evaluating patients with an intermediate risk of IE. Their study population came from a nonurban setting, and only 4 (4%) of their patients had a history of IVDU, thus, their results may not be applicable in an urban hospital. Their subjects also underwent both TTE and TEE, thereby imposing a selection bias, since all subjects must be able and willing to consent to an invasive procedure (TEE).

Heidenreich et al[23] recently performed a cost-effectiveness analysis based on previous clinical studies, and concluded that patients with a pretest probability of IE that is less than 2% are optimally treated empirically for bacteremia (with 10-14 days of intravenous antibiotics), that patients with a pretest probability of greater than 60% should be treated for IE no matter what the echocardiographic results are, and that patients with pretest probability between 4% and 60% are best evaluated with TEE. This wide margin reflects the importance of maintaining a low threshold of suspicion for IE. Our study indicates that many TTEs are ordered in patients with a low pretest probability. The challenge to clinicians is in quantifying the pretest probability; how can one prospectively estimate the difference between a less than 2% likelihood and a less than 4% likelihood? Patient characteristics cited by Heidenreich et al[23] to define a probability of less than 2% were cases in which there was a firm alternate diagnosis or resolution of endocarditis syndrome within 4 days (Duke "rejected IE" category) or gram-negative bacteremia with clear noncardiac source of infection (Weinstein[24]). The Duke "rejected IE" category depends on 4 days of clinical observation, implying that TTE should not be ordered until 4 days have elapsed from the moment that IE was first suspected. Since our results indicate that TTEs ordered after at least 3 days of hospitalization are less likely to be low probability (ie, rejected by Von Reyn criteria) it is likely that the number of TTEs would be substantially reduced by simply allowing enough time for growth of cultures, and collecting additional clinical data to assess the clinical likelihood of IE.

Since our survey demonstrates that a large number of TTEs are ordered in the first 3 days of hospital stay, and blood culture results are not known in many cases prior to obtaining a TTE, we propose the following algorithm in the approach to the diagnosis of IE (**Figure 2**). In all patients suspected of having IE, 3 blood cultures should be drawn from separate sites, with the first and last cultures separated temporally by at least 1 hour. All cultures should be obtained before empiric antibiotic therapy is started. Urinalysis should be obtained to document the presence of microscopic hematuria, which has been shown in our study and by others to increase the sensitivity of clinical assessment of IE.[9,25] Radiographic studies may aid in the documentation of embolic phenomena. If hemodynamic compromise is present, a TTE is warranted at the outset to identify the underlying cardiac status; however, in the hemodynamically stable patient, TTE should be forestalled until the patient has received 4 days of appropriate antibiotic therapy with routine monitoring and documentation of clinical course. After 4 days of clinical observation and antibiotic therapy to cover likely sources of infection and the availability of culture results, if IE is still a diagnostic consideration, TTE should be used to identify valvular abnormalities diagnostic of IE, and to assist in decision making regarding antibiotic duration or surgical intervention. In our study population, using this diagnostic algorithm, 59 (53%) of 111 of the TTEs obtained would have been avoided, without loss of diagnostic accuracy. Interestingly, of 13 patients who were considered to have IE, clinically (as noted in discharge summaries), they were evenly distributed between Von Reyn categories (6 in the probable/possible category and 7 in the rejected category). None of the 7 cases in the rejected category had positive findings on TTE.

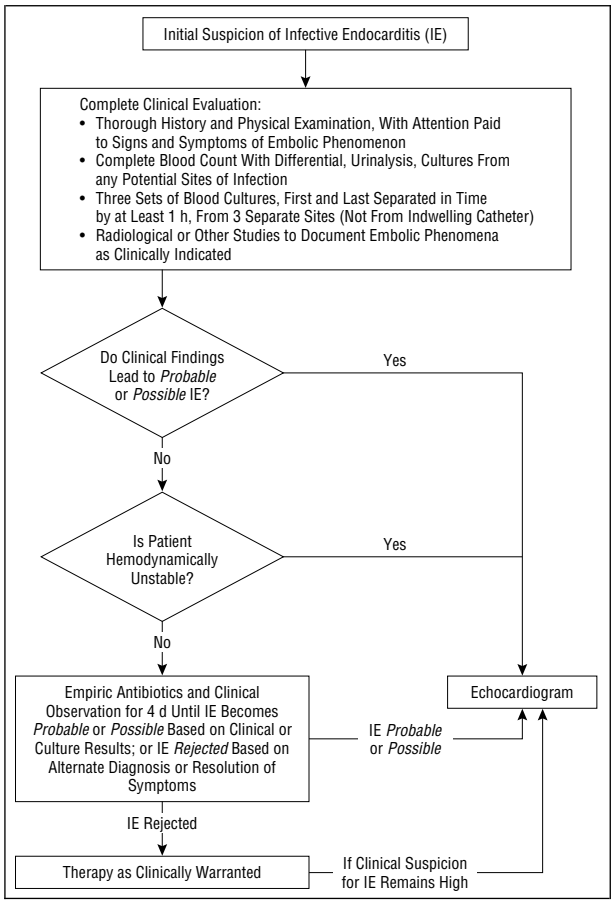

Figure 2. Proposed algorithm for diagnosis of infective endocarditis (IE) based first on consideration of clinical presentation and blood cultures, and proceeding to transthoracic echocardiography when intermediate or high probability cases are suspected and an alternative diagnosis is not made.

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The TTE should contribute to the diagnosis and/or management of IE in at least 1 of the following ways: (1) to distinguish between bacteremia and IE to shorten the course of antibiotic therapy; (2) to predict the risk of complications of IE such as heart failure or emboli; and (3) to assess the need for surgical intervention. Our results, with Lindner et al,[21] demonstrate that antibiotic therapy is not altered by results of TTE. Others have shown that echocardiographic findings do not predict risk of embolic complications from IE[26,27]; however, Goldman et al[28] found TTE results to be predictive of major complications such as development of heart failure, embolic episodes, and need for surgery, particularly with vegetation involving the aortic valve and measuring larger than 1.8 cm. In the latter study, presence of embolic phenomena at admission was predictive of further embolic episodes, and in our study, embolic phenomena were associated with abnormal TTEs; thus, it may be more accurate to say that embolic episodes predict abnormal echocardiographic findings, rather than the reverse. Thus, the main clinical utility of TTE in the management of IE may lie in evaluating patients with a high or intermediate clinical probability of IE to decide on surgical intervention or duration of therapy.[29]

Despite significant advances in technology, diagnosis of IE remains a clinical diagnosis, requiring collection and interpretation of clinical, laboratory, and microbiological data. Transthoracic echocardiography in low-risk patients does not add diagnostic information, and does not alter therapeutic strategies. Based on our findings, TTE is overused in the diagnosis of IE, primarily because it is obtained before all clinical information is available. Echocardiography in the diagnosis and management of IE should be reserved for patients with intermediate or high probability of IE, based on clinical findings and positive blood culture results.

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