Complication and Treatment of Infectious Endocarditis

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Review Article

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ABSTRACT

IE can be a lethal disease. Over the last decades, the incidence of disease has not decreased due to the change of risk conditions. Complications of IE may involve cardiac structures when the infection spreads within the heart or extra cardiac ones when the cause is usually from embolic origin. In most of the patients, there are a variety of problems. The literature reports one complication of IE in 57%, two in 26% and three or more in about 14% of patients examined. The infecting pathogen, duration of disease before therapy, and type of treatment are some of the variables that affect the occurrence of specific complications. It is difficult to assess the true incidence of complications because the published reviews are based on retrospective chart reviews and different diagnostic criteria are used. The decision over either indication or timing of surgery should be individualized and based on at least cardiologists and cardiac surgeons. The most important cause of IE is Congestive heart failure. Periannular abscesses are a relatively common complication of IE (42% to 85% of cases during surgery or at autopsy respectively), associated with a higher morbidity and mortality. Embolization can affect the central nervous system, but also other organs. Due to direct seeding of the spleen by an embolus or a bland infarction, there is a rare complication of IE. Neurological complications develop in 20% to 40% of patients with IE and represent a dangerous subset of complications.

Keywords: Lethal disease; Neurological; Dangerous subset; Patients; Periannular abscesses

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INTRODUCTION

Infective Endocarditis (IE) carries a high risk of morbidity and mortality. Rapid diagnosis, effective treatment, and prompt recognition of complications are essential to good patient outcome. Therapy of IE caused by the more commonly encountered organisms, including streptococci, enterococci, staphylococci, and the HACEK organisms (*Hemophilus parainfluenzae*, *Hemophilus aphrophilus*, *Actinobacillus* (*Hemophilus*) *actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* species, and *Kingella* species), has been addressed previously by this committee. Likewise, the antimicrobial prevention of endocarditis has also been previously addressed. In this article, we review and update the current literature with respect to diagnostic challenges and strategies, difficult therapeutic situations, and management choices in patients with IE. This article focuses predominantly on adults with IE. A separate article, currently in preparation, will address the issues of IE in childhood [1].

LITERATURE REVIEW

Diagnosis

Clinical criteria: The diagnosis of IE is straightforward in those patients with classic oslerian manifestations: Bacteremia or fungemia, evidence of active valvulitis, peripheral emboli, and immunologic vascular phenomena. In other patients, however, the classic peripheral stigmata may be few or absent. This may occur during acute courses of IE, particularly among Intravenous Drug Abuse (IVDA) patients in whom IE is often due to Staphylococcus aureus infection of right sided heart valves, or in patients with IE caused by microorganisms such as HACEK. Acute IE evolves too quickly for the developments of immunologic vascular phenomena, which are more characteristic of sub acute IE. In addition, acute right sided IE valve lesions do not create the peripheral emboli and immunologic vascular phenomena that can result from left sided valvular involvement.

The variability in the clinical presentation of IE requires a diagnostic strategy that will be both sensitive for disease detection and specific for its exclusion across all the forms of the disease. In 1981, von Reyn, et al., proposed a scheme for strict case definitions of IE (the Beth Israel criteria). These criteria were designed to be very stringent: cases were identified as "definite IE" only if pathological confirmation from surgical or autopsy specimen was available. "Probable IE" included patients with persistent bacteremia and evidence of either new valvular regurgitation or vascular phenomena in the face of underlying valvular heart disease. Several problems became apparent as these criteria were broadly applied to patients suspected of having IE. First, fewer than one third of IE patients require valvular surgery in the acute phase of their infection, and therefore only a minority of patients with bona fide IE could be classified as definite cases. Second, IVDA was not recognized as an important predisposing condition for the development of IE. Finally, echocardiographic findings were not included in the stratification strategy. As a result of these limitations, many IVDA patients with overt right sided *S. aureus* IE were rejected as definite cases, as were patients with blood culture negative IE [2].

A more recent diagnostic strategy was proposed by Durack and colleagues from Duke University in 1994. These Duke criteria combine the important diagnostic parameters contained in the Beth Israel criteria (persistent bacteremia, new

regurgitant murmurs, and vascular complications) with echocardiographic findings. Moreover, IVDA is now recognized as an increasingly important underlying comorbid condition for development of IE. The Duke criteria stratify patients suspected of having IE into 3 categories: Definite cases identified clinically or pathologically (IE proven at surgery or autopsy), possible cases (not meeting the criteria for definite IE), and rejected cases (no pathological evidence of IE at autopsy or surgery, rapid resolution of the clinical syndrome with either no treatment or short term antibiotic therapy, or a firm alternative diagnosis).

Major criteria in the Duke strategy include IE documented by data obtained at the time of open heart surgery or autopsy (pathologically definite) or *via* well-defined microbiological (blood culture) and echocardiographic data (clinically definite). To maintain the high specificity of blood culture results for IE, the Duke criteria require that some patients with bacteremia with common IE pathogens also fulfill secondary criteria. For example, bacteremia due to viridans streptococci and members of the HACEK group of fastidious Gram-negative rods, which are classic IE pathogens but rarely seen in patients without IE, are given primary diagnostic weight. In contrast, *S. aureus* and *Enterococcus faecalis* commonly cause both IE and non-IE bacteremias. The Duke criteria, therefore, give diagnostic weight to bacteremia with staphylococci or enterococci only when they are community acquired and without an apparent primary focus; these types of bacteremias have the highest risk of being associated with IE.

The Duke criteria incorporate echocardiographic findings in the diagnostic strategy. Major diagnostic weight is given to only 3 typical echocardiographic findings: Mobile, echo dense masses attached to valvular leaflets or mural endocardium; periannular abscesses; or new dehiscence of a valvular prosthesis [3].

Six common but less specific findings of IE are also included as minor criteria: Intermittent bacteremia or fungemia, fever, major embolic events, nonembolic vascular phenomena, underlying valvular disease or IVDA, and echocardiographic abnormalities that fall short of typical valvular vegetations, abscesses, or dehiscence. Clinically definite IE by the Duke criteria requires the presence of 2 major criteria, 1 major criterion and 3 minor criteria, or 5 minor criteria. Direct comparison of the Duke and Beth Israel criteria has been made in 11 major studies including nearly 1700 patients comprising geographically and clinically diverse groups (adult, pediatric, elderly (aged >60 years), patients from the community, those with and without IVDA, and patients with both native and prosthetic valves). These studies have confirmed the improved sensitivity of the Duke criteria and the diagnostic utility of echocardiography in identifying clinically definite cases.

The calculated negative predictive value (number of true negatives divided by number of true negatives plus false-negatives) of the Duke criteria was >98% in a study in which 52 consecutive "IE rejected" patients were followed up for ≥ 3 months for a missed diagnosis of IE or late development of the infection. In another study, the specificity of rejecting a case as IE by these criteria was evaluated in 100 patients with fever of unknown origin who had multiple blood cultures, as well as echocardiography, performed. Only 1 patient in whom a firm, alternative non-IE diagnosis had been established was reclassified as having clinically definite, blood culture negative IE. This resulted in a specificity of 99% for the clinical diagnosis of IE by the Duke criteria. A retrospective study of 410 patients showed that the Duke criteria had good agreement (72% to 90%) with expert clinical assessment by infectious disease experts blinded to underlying IE risk factors [4].

Several refinements in the Duke criteria are pending. Specific serological data may be included to more precisely establish the diagnoses of "culture-negative" endocarditis. Such serological criteria would be applied in circumstances in which the etiologic organism is either slow growing or requires special culture media (eg, *Brucella*) or in which the organism is not readily cultivated in most clinical microbiology laboratories (eg, *Coxiella burnetii*, *Bartonella quin-tana*). Expansion of "minor criteria" to include elevated erythrocyte sedimentation rate or C-reactive protein, the presence of newly diagnosed clubbing, splenomegaly, and microscopic hematuria has been proposed. In a study of 100 consecutive cases of pathologically proven native valve IE, inclusion of these additional parameters with the existing Duke minor criteria resulted in a 10% increase in the frequency of cases being deemed clinically definite, with no loss of specificity. Finally, adjustment of the Duke criteria to require a minimum of 1 major criterion or 3 minor criteria to designate a case as "possible IE" would reduce the proportion of patients assigned to that category. Thus, on the basis of the weight of clinical evidence involving nearly 1700 patients in the current literature, it would appear that patients suspected of having IE should be clinically evaluated, with the Duke criteria used as the primary diagnostic schema. It is hoped that the proposed modifications to the Duke criteria outlined above will provide even more sensitivity and specificity to this schema [5].

Echocardiography

Echocardiography plays an important role in the diagnosis and management of IE. Characteristic vegetations, abscesses, new prosthetic valve dehiscence, or new regurgitation are 4 powerful identifiers of IE in combination with other clinical parameters. Echocardiography is not an appropriate screening test in the evaluation of patients with fever or a positive blood culture that is unlikely to reflect IE. Nevertheless, some form of echocardiography should be performed in all patients suspected of having IE. Transthoracic Echocardiography (TTE) is rapid, noninvasive, and has excellent specificity for vegetations (98%). The overall sensitivity for vegetations, however, is <60%. Vegetations >2 mm in diameter, particularly those on the right sided valves (which lie closer to the chest wall), are readily detected by TTE. TTE views may be inadequate in up to 20% of adult patients because of obesity, chronic obstructive pulmonary disease, or chest wall deformities. In patients suspected of having IE, TTE alone cannot exclude several important aspects of IE, including infection on prosthetic valves, periannular abscess, leaflet perforation, and fistulae.

In patients in whom IE or its complications are strongly suspected (for example, patients with prosthetic valves, community acquired staphylococcal bacteremia, or new atrioventricular block), a negative TTE of even the highest quality will not definitely rule out IE. Moreover, a positive TTE in such patients may demonstrate vegetations but will not suffice to rule out the important complications. In patients with a relatively low risk for IE (for example, bacteremia due to enterococci in patients with an obvious primary focus and without other stigmata of IE), a good-quality negative TTE is generally adequate to rule out IE. Subsequent Transesophageal Echocardiography (TEE) can be performed if the clinical picture changes, if there is no improvement with therapy, or if complications are suspected.

TEE is safe in experienced hands and has sensitivity for detection of vegetations in IE that is very high. TEE images benefit from higher ultrasonic frequencies, which improve spatial resolution and the elimination of interference from interposed tissues. TEE has a substantially higher sensitivity (76% to 100%) and specificity (94%) than TTE for perivalvular extension of infection because the TEE transducer in the esophagus is in physical proximity to the aortic root and basal septum, where most such complications occur. TEE also enhances visualization of prosthetic valves, with 86% to 94% sensitivity and 88% to 100% specificity for IE vegetations. Also, prosthetic valvular insufficiency is

much better defined on TEE, in which valve structures do not interfere with the Doppler signal. The sensitivity of TEE can be further improved by imaging in ≥ 2 planes, because incremental planes decrease the number of false negative studies and improve the definition of vegetation extent and mobility. The excellent performance of TEE makes it the method of choice in the diagnosis of IE in patients who are difficult to image, in possible prosthetic valve IE, in patients with intermediate or high clinical suspicion of IE, and in those patients with a high risk for IE related complications. One recently published study comparing TTE and TEE in patients with *S. aureus* Bacteremia (SAB) found TEE was essential to establish a diagnosis of IE and to detect associated complications. The authors concluded that TEE "should be considered part of the early evaluation of patients with SAB." TEE, like other forms of gastrointestinal endoscopy, does not require antibiotic prophylaxis, although the physician may choose to administer prophylaxis to patients with high risk underlying cardiac conditions (eg, prosthetic heart valves) and poor dental health [6].

Clinical suspicion of IE may persist after an initially negative TEE. A negative TEE does not have enough diagnostic accuracy to rule out vegetative IE. Potential sources of false negative TEE studies include vegetations that are smaller than the limits of resolution, previous embolization of vegetation, or inadequate views to detect small abscesses. Accurate differentiation between true vegetations and other IE related changes, such as ruptured chordae, is frequently difficult. It is also important to emphasize that there are blind spots with TEE. For example, the same prosthetic shadows that interfere with TTE views may obstruct structural visualization by TEE. Multiple TEE planes combined with TTE views must be exploited to minimize the risk of missing a significant finding when images are technically difficult to obtain. When both TEE and TTE studies are negative, there is a 95% negative predictive value. When clinical suspicion of IE is high and the TEE results are negative, a repeat TEE study is warranted within 7 to 10 days, which may demonstrate previously undetected vegetations or abscesses. Follow-up echocardiographic studies at the completion of therapy demonstrate persistent vegetations in 59% of cases; in the absence of severe valvular regurgitation or ongoing clinical symptoms, such persistence does not correlate with late complications. In contrast, increase in vegetation size by echocardiography over the course of therapy may identify a subset of patients with a higher rate of complications, independently of the presence of persistent bacteremia or overt clinical stigmata of IE [7].

Approach to the patient with apparent blood culture negative IE

Positive blood cultures are a major diagnostic criterion for IE and are key in identifying the etiologic agent and its antimicrobial susceptibility. Continuous bacteremia and a high frequency of positive blood cultures are typical of this infection. In a study of 206 patients with blood culture positive IE, 95% of 789 blood cultures yielded the causative microorganism, and all the cultures were positive in 91% of cases. However, the intensity of the bacteremia may not be great; fewer than 50 colony forming units per milliliter of blood were detected in the majority of patients.

Blood cultures are negative in ≤ 5% of patients with IE diagnosed by strict diagnostic criteria. Failure to culture the organism in IE may result from inadequate microbiological techniques, infection with highly fastidious bacteria or nonbacterial microorganisms, or most importantly, from the administration of antimicrobial agents before blood cultures are obtained. Blood from patients suspected of having IE should be cultured in 3 sets (each set equals 1 aerobic plus 1 anaerobic bottle). The blood should be diluted at least 1:5 into the broth media, and the laboratory should be advised that the clinical diagnosis is IE. When all blood cultures remain negative after 48 to 72 hours, the microbiology laboratory should incubate these cultures for a more prolonged period (at least 2 to 3 weeks),

microscopically examine an acridine orange stained aliquot from all bottles (even in the absence of detectable growth), and on day 7, day 14, and at the end of the incubation period, blindly subculture an aliquot on chocolate agar for further incubation (3 to 4 weeks) in an atmosphere of increased carbon dioxide (candle jar). These steps may facilitate recovery of fastidious bacteria.

The administration of antimicrobial agents to patients with IE before blood cultures are obtained reduces the recovery rate of bacteria by 35% to 40%. The antimicrobial susceptibility of the organism and the duration and nature of prior antimicrobial therapy together determine the length of time that blood cultures will remain negative. IE patients with initially negative blood cultures after only a few days of antibiotic therapy may have positive blood cultures after several days without antibiotics. The blood cultures of patients who received longer courses of high dose bactericidal antimicrobials may remain negative for weeks. Among patients with a clinical syndrome consistent with IE who have recently received antibiotics, empiric antimicrobial therapy should be delayed if they do not have a toxic appearance and have no clinical or echocardiographic evidence of severe or progressive valve regurgitation or of Congestive Heart Failure (CHF). If the initial blood cultures are negative, a delay of 2 to 4 days will allow additional blood cultures to be obtained without the confounding effect of further antibiotic therapy and without increased morbidity from IE. Special efforts to neutralize or inactivate antimicrobial agents present in blood, such as the addition of penicillinase, have not been shown to substantially enhance the yield of blood cultures in IE and are not routinely recommended. However, in most large hospitals, automated blood culture detection systems are used that are highly sensitive, and these systems frequently use blood collection vials with antibiotic binding resins.

Some IE pathogens are difficult to isolate from blood cultures. To recover the HACEK organisms, prolonged incubation and subcultures as noted above may be required. *Bartonella* species, recently recognized as an important cause of apparent culture negative IE, can also be isolated by prolonged incubation and subculture of the aerobic broth media. The nutritionally variant streptococci (now classified as *Abiotrophia* species) account for ≈ 5% to 7% of streptococcal IE cases. These strains frequently fail to grow when the blood cultures are subcultured onto standard blood agar media. These organisms can be grown on blood agar as satellite colonies around an *S. aureus* streak or when the agar media is supplemented with l-cysteine or pyridoxal hydrochloride. Isolation of *Brucella* species is facilitated by the prolonged incubation of cultured blood in castaneda bottles containing biphasic soybean casein digest medium, with a carbon dioxide enriched atmosphere, but they may also grow in media used for the automated blood culture detection systems. Legionella species, a rare cause of prosthetic valve IE, can be isolated from blood by subculture of aerobic blood culture bottles or lysis concentration pellets on buffered charcoal yeast extract agar. Some fungi that cause IE are almost never recovered from blood (eg, *Aspergillus* species), whereas others are isolated in sporadic blood cultures. The frequency of isolation for these latter fungi (eg, *Candida* species, *Cryptococcus neoformans*, and other yeasts) is increased with the use of the lysis centrifugation technique or castaneda bottles. These yeasts will also grow in media used in the automated instruments.

In addition to blood cultures and serological assays, culture of valve tissue or vegetations that have embolized to peripheral arteries and have been removed surgically may reveal the causative organism. Specific light microscopy fluorescent labeled antibody stains, electron microscopy, or molecular techniques to recover specific DNA or 16'S rRNA from blood or tissue samples may also assist in diagnosis. Polymerase chain reaction performed on blood may be useful for diagnosis of endocarditis caused by *Tropherema whipelli* or *Bartonella* species. As experience with this

technique in patients with IE grows, polymerase chain reaction may prove useful for the diagnosis of infection caused by other microorganisms.

Management

Therapy of unusually encountered organisms

Coagulase negative staphylococci: Although Coagulase Negative Staphylococci (CNS) are the most common cause of prosthetic valve IE, until recently they had been infrequently associated with native valve IE. However, over the past decade, there have been a number of reports documenting the occurrence of native valve CNS IE. Most of the reported patients had documented underlying valvular abnormalities, particularly mitral valve prolapse. The clinical course of these patients is typically indolent, with good responses to medical or surgical therapy. An important subset of patients with CNS IE has been identified recently: those with infection caused by *Staphylococcus lugdunensis*. This CNS organism tends to cause a substantially more virulent form of IE than other CNS, with high rates of perivalvular extension of infection and metastatic seeding to distant organs, despite uniform susceptibility *in vitro* to most antibiotics. Most experts recommend that IE caused by this organism be treated with standard regimens based on the *in vitro* susceptibility profiles of the strain and that the patient be monitored carefully for development of periannular extension or extra cardiac spread of infection. The differentiation of *S. lugdunensis* from other CNS may be difficult in the microbiology laboratory with routine commercial identification schema and may require referral to a reference laboratory.

Coxiella burnetii

Coxiella burnetii possesses a gram negative like cell wall and is a strict intracellular pathogen that grows in the acidic phagolysosome of the host cell. Q fever is a relatively common cause of IE in geographic areas of the world in which cattle, sheep, and goat farming are common. The organism is resistant to desiccation; inhalation of aerosols of contaminated soil is the major mode of transmission, although ingestion of infected unpasteurized milk may also transmit the disease. Q-fever IE usually affects prosthetic or previously damaged aortic or mitral valves. The small vegetations from this predominantly sub endothelial infection are often missed by echocardiography some authorities have suggested a minimum of 3 years' therapy once phase I IgG antibody titers drop below 1:400 and IgA phase I antibodies are undetectable.

Candida and *Aspergillus*

Candida and *Aspergillus* species cause the majority of fungal IE. Intravenous drug abusers, prosthetic valve recipients, and patients with long-term central venous catheters are at highest risk for IE, which should be suspected in the presence of negative blood cultures, bulky vegetations, metastatic infection, perivalvular invasion, or embolization to large blood vessels. Amphotericin B, the only fungicidal agent available, has poor penetration into vegetations; cure usually requires valve surgery in addition to amphotericin B. Although the imidazoles (eg, fluconazole or itraconazole) have no proven efficacy in human fungal IE, a number of case reports (particularly in adults who are not valve replacement candidates) suggest that long-term suppressive therapy with these agents may be effective.

Legionella

All cases of *Legionella* IE have had a febrile course that extended over months, with cardiac signs of newly developed murmurs and extremely high anti-legionella antibody titers. Most patients have had prosthetic cardiac valves blood cultures, which are usually sterile on routine media, will grow the organism when special media are used annular abscess and small vegetations have been visible at surgery, although echocardiograms have been negative. Embolic events are unusual, in contrast to their frequency with other culture negative endocarditis, such as Q fever and fungal endocarditis.

Cure has been obtained in patients by prolonged parenteral antimicrobial therapy with either doxycycline or erythromycin, followed by prolonged oral therapy with these agents. Response to therapy has been associated with a falling antibody titer. The total duration of therapy has usually been 6 to 17 months. Most patients have additionally required valve replacement because of valvular incompetence but not necessarily for persistent infection or embolic events.

Pseudomonas

Most cases of *Pseudomonas* IE are caused by *P. aeruginosa* and occur in the setting of IVDA isolated right sided pseudomonal IE can generally be managed with antibiotic therapy, with or without valve surgery. Large doses of an antipseudomonal penicillin (eg, piperacillin 18 g/d) combined with an aminoglycoside (eg, tobramycin 5 to 8 mg• kg^{-1}• d^{-1}) are the usual treatment. However, medical therapy alone has rarely been effective in left-sided disease; valve replacement is considered mandatory for cure of left sided pseudomonal IE.

Congestive heart failure

Among the complications of IE, CHF has the greatest impact on prognosis. In native valve IE, acute CHF occurs more frequently in aortic valve infections (29%) than with mitral (20%) or tricuspid disease (8%). CHF may develop acutely from perforation of a native- or bioprosthetic valve leaflet, rupture of infected mitral chordae, valve obstruction from bulky vegetations, or sudden intracardiac shunts from fistulous tracts or prosthetic dehiscence.

CHF may also develop more insidiously, despite appropriate antibiotics, as a result of a progressive worsening of valvular insufficiency and ventricular dysfunction. Patients who have normal ventricular function or only mild CHF at initial diagnosis of IE may progress to severe CHF during treatment, and two thirds of those patients will do so within the first month of therapy CHF in IE, irrespective of the course or mechanism, portends a grave prognosis with medical therapy alone and is also the most powerful predictor of poor outcome with surgical therapy. Delaying surgery to the point of frank ventricular decompensation dramatically increases operative mortality, from 6% to 11% for patients without CHF and 17% to 33% for patients with CHF.

Echocardiographic evaluation of IE patients delineates the causes and severity of CHF. Ventricular size, wall motion, and dynamic function can be readily defined and valve insufficiency quantified. Progressive chamber enlargement, elevation of pulmonary arterial pressures, and increasing wall stress on serial evaluation all indicate a trend toward decompensation. Medical and surgical management decisions can be guided by echocardiographic detection of abscesses, fistulae, prosthetic dehiscence, obstructive vegetations, or flail leaflets, none of which will resolve with medical therapy alone. Table 5 lists the echocardiographic features that suggest potential need for surgical

intervention.

The decision to operate on the patient with IE is driven primarily by the severity of CHF. Poor surgical outcome is predicted by preoperative New York Heart Association class III or IV CHF, renal insufficiency, and advanced age. In any patient, a decision to delay surgery to extend preoperative antibiotic treatment carries with it the risk of permanent ventricular dysfunction. The incidence of reinfection of newly implanted valves in patients with active IE has been estimated to be 2% to 3%, far less than the mortality rate for uncontrolled CHF.

Surgical approaches to IE patients with CHF must be tailored to the distortion of the valve and its surrounding structures. Severe valvular disruption will require prosthetic replacement, although in some cases successful valve repair procedures, as an alternative to valve replacement, have been reported. Ruptured mitral chordae may sometimes be repaired with a combination of leaflet resection, chordal reattachment or transposition, and annular support. Leaflet perforations may be repairable with small pericardial patches if the surrounding leaflet tissue is well-preserved and valve motion can be maintained. Similarly, in selected cases, discrete vegetations on aortic or mitral leaflets have been excised along with underlying leaflet tissue and repaired with a patch. Experience with vegetation excision has been limited to date.

Risk of embolization

Systemic embolization occurs in 22% to 50% of cases of IE Emboli often involve major arterial beds, including lungs, coronary arteries, spleen, bowel, and extremities. Up to 65% of embolic events involve the central nervous system, and >90% of central nervous system emboli lodge in the distribution of the middle cerebral artery. These latter emboli are associated with a high mortality rate. The highest incidence of embolic complications is seen with aortic- and mitral valve infections and in IE due to *S. aureus* and Candida species and HACEK and abiotrophia organisms. Emboli can occur before diagnosis, during therapy, or after therapy is completed, although most emboli occur within the first 2 to 4 weeks of antimicrobial therapy. Of note, the rate of embolic events drops dramatically during the first 2 weeks of successful antibiotic therapy, from 13 to <1.2 embolic events per 1000 patient days. Prediction of individual patient risk for embolization has proven extremely difficult. Many studies have attempted to use echocardiography to identify a high risk subset of IE patients who might benefit from early surgery to avoid embolization. Several studies using TTE have demonstrated a trend toward higher embolic rates with left sided vegetations that are >1 cm in diameter. In a study based on TEE, mitral vegetations >1 cm in diameter were associated with the greatest incidence of embolism. The association was strengthened when analysis was limited to those patients who had not yet experienced a clinical embolic event. Among such patients, the predictive accuracy for embolism with large mitral vegetations was nearly 100%. Another prospective TEE study, however, found no clear correlation of vegetation size with embolization. Overall, these data are compatible with previous observations that in general, mitral vegetations, regardless of size, are associated with higher rates of embolization (25%) than aortic vegetations (10%) of interest, the highest embolic rate (37%) has been seen in the subset of patients with mitral vegetations attached to the anterior rather than the posterior mitral leaflet. This implies that the mechanical effects of broad and abrupt leaflet excursion, occurring twice per heartbeat, may contribute to the propensity of a vegetation to fragment and embolize.

DISCUSSION

In another study, the effect of vegetation size on embolic potential was specific to the infecting organism, with large vegetations independently predicting embolic events only in the setting of streptococcal IE. In contrast, staphylococcal or fungal IE appears to carry a high risk of embolization that is independent of vegetation size. The number of vegetations, the number of valves involved, and vegetation characteristics (eg, lack of calcification) predicted embolic complications in one study vegetation mobility has not been shown to be an independent risk factor for embolic events, probably because it is strongly correlated with vegetation size.

Embolic events do appear to be predicted by an increase in vegetation size by TEE over 4 to 8 weeks of therapy. The embolic event rate among patients with IE and increasing vegetation size was twice that of patients with static or decreasing vegetation size. In addition, a second peak of late embolic events occurred at 15 to 30 weeks after diagnosis of IE and was associated with nonhealing vegetations (failure of a vegetation to stabilize or diminish in size) as defined by echocardiography.

The traditional indications for valvular surgery in IE to avoid embolization have been $\geq$ 2 major embolic events these criteria are arbitrary and exclude cutaneous embolization, which is common, or embolism occurring before the institution of therapy. Because of the known decrease in embolic risk over the first 2 weeks of antibiotic therapy, the benefit of surgery in avoiding catastrophic embolic events is greatest early in the course of the IE. Early surgical intervention may preclude a primary or recurrent major embolic event but exposes the patient to both the immediate and the life-long risks of valve replacement. At this time, the strategy for surgical intervention to avoid systemic embolization in IE remains specific to the individual patient, with benefit being greatest in the early phase of IE when embolic rates are highest and when other predictors of a complicated course (*i.e.,* recurrent embolization; CHF; aggressive, antibiotic resistant organisms; or prosthetic valve IE) are present. Surgical options must be considered when large vegetations are detected on the mitral valve, particularly the anterior leaflet. Failure of a vegetation to stabilize or diminish in size on TEE during clinically adequate therapy may also predict later embolic events.

Periannular extension of infection

Extension of IE beyond the valve annulus predicts higher mortality, more frequent development of CHF, and the need for cardiac surgery. Perivalvular cavities form when annular infections break through and spread into contiguous tissue. In native aortic valve IE, this generally occurs through the weakest portion of the annulus, which is near the membranous septum and atrioventricular node. The anatomic vulnerability of this area explains both why abscesses occur in this location and why heart block is a frequent sequela. Periannular extension is common, occurring in 10% to 40% of all native valve IE, and complicates aortic IE more commonly than mitral or tricuspid IE. Periannular infection is of even greater concern with prosthetic valve IE, occurring in 56% to 100% of patients perivalvular abscesses are particularly common with prosthetic valves because the annulus, rather than the leaflet, is the usual primary site of infection. Most periannular infections involving the mitral area are associated with prosthetic mitral valves.

Under the influence of systemic intravascular pressures, abscesses may progress to fistulous tracts that create

intracardiac or pericardial shunts. In some cases, progressive periannular infection totally disrupts the ventricular aortic continuity or the mitral aortic trigone. Such structural lesions and intracardiac fistulas may be catastrophic; even if their hemodynamic impact is tolerated, such lesions will not heal with medical management alone, and they require urgent operative intervention.

Clinical parameters for the diagnosis of perivalvular extension of IE are inadequate. Persistent bacteremia or fever, recurrent emboli, heart block, CHF, or a new pathological murmur in a patient with IE who is taking adequate antibiotics may suggest extension. Only aortic valve involvement and recent IVDA have been prospectively identified as independent risk factors for perivalvular abscess On ECG, new atrioventricular block has an 88% positive predictive value (number of true positives divided by number of true positives plus false positives) for abscess formation but has a low sensitivity (45%). Patients at risk for perivalvular extension of IE require prompt evaluation. The size of vegetations is not helpful in predicting perivalvular extension. The sensitivity of TTE to detect perivalvular abscess is low (18% to 63% in prospective and retrospective studies, respectively TEE dramatically improves the sensitivity for defining periannular extension of IE (76% to 100%) while retaining excellent specificity (95%) and positive and negative predictive values (87% and 89%, respectively. When it is combined with spectral and color Doppler techniques, TEE can demonstrate the distinctive flow patterns of fistulae and pseudoaneurysms and can rule out communications from unruptured abscess cavities. Because of these combined capabilities, TEE is the modality of choice for initial assessment of any patient at risk for perivalvular extension of IE

A small number of patients with periannular extension of infection or myocardial abscess may be treated successfully without surgical intervention. These patients include those who do not have heart block, echocardiographic evidence of progression of abscess during therapy, valvular dehiscence, or insufficiency. Such patients should be monitored closely with serial TEE, and TEE should be repeated at intervals of 2, 4, and 8 weeks after completion of antimicrobial therapy.

Surgery for patients with perivalvular extension of IE is directed toward eradication of the infection as well as correction of hemodynamic abnormalities. Drainage of abscess cavities, excision of necrotic tissue, and closure of fistulous tracts often accompanies valve replacement surgery. Although valve replacement is usually required, this may be complicated in the face of extensive destruction of the periannular supporting tissues. In these conditions, human aortic homografts, when available, can be used to replace the damaged aortic valve as well as to reconstruct the damaged aorta. Homografts have a constant but low risk for the development of sewing ring infections and IE, possibly related to improved penetration of antibiotics.

Splenic abscess

Splenic abscess is a well-described but rare complication of IE. This infection develops *via* 1 of 2 mechanisms: bacteremic seeding of a bland infarction, created *via* splenic artery occlusion by embolized vegetations, or direct seeding of the spleen by an infected embolus also originating from an infected valvular vegetation. Although splenic infarction is a common complication of left-sided IE (≈ 40% of cases), it is estimated that only ≈ 5% of patients with splenic infarction will develop splenic abscess. Viridans streptococci and *S. aureus* each account for ≈ 40% of cases in which splenic abscess cultures are positive, whereas the enterococci account for ≈ 15% of cases. Aerobic Gram-

negative bacilli and fungi are isolated in <5% of cases. Clinical splenomegaly, present in up to 30% of cases of IE, is not a reliable sign of splenic infarction or abscess. Splenic infarction delineated by imaging techniques is often asymptomatic; back, left flank, or left upper quadrant pain or abdominal tenderness, when present, may be associated with either splenic infarction or abscess. Splenic rupture with hemorrhage is a rare complication of infarction. Persistent or recurrent bacteremia, persistent fever, or other signs of sepsis are suggestive of splenic abscess, and patients with these findings should be evaluated with ≥ 1 of the imaging studies discussed below.

Abdominal CT or MRI appears to be the best tests for diagnosis of splenic abscess, with sensitivities and specificities of ≈ 90% to 95%. By CT, splenic abscess is frequently seen as single or multiple contrast enhancing cystic lesions, whereas infarcts typically are peripheral low density, wedge shaped areas. On ultrasonography, a sonolucent lesion suggests abscess. 99 mTc liver spleen scans, labeled white blood cell scans, and gallium scans have become obsolete for the diagnosis of splenic abscess.

Differentiation of splenic abscess from bland infarction may be difficult. Infarcts are generally associated with clinical and radiographic improvement during appropriate antibiotic therapy. Ongoing sepsis, recurrent positive blood cultures, and persistence or enlargement of splenic defects on CT or MRI suggest splenic abscess, which responds poorly to antibiotic therapy alone. Definitive treatment is splenectomy with appropriate antibiotics, and this should be performed immediately, unless urgent valve surgery is planned. Percutaneous drainage or aspiration of splenic abscess has been performed successfully, this procedure may be an alternative to splenectomy for the patient who is a poor surgical candidate. Splenectomy should be performed before valve replacement surgery because of the risk of infection of the valve prosthesis as a result of the bacteremia from the abscess.

Mycotic aneurysms

Mycotic Aneurysms (MAs) are uncommon complications of IE. They result from septic embolization of vegetations to the arterial vasa vasorum or the intraluminal space, with subsequent spread of infection through the intima and outward through the vessel wall. Arterial branching points favor the impaction of emboli and are the most common sites of MA development. MAs due to IE occur most frequently in the intracranial arteries, followed by visceral arteries and arteries of the lower and upper extremities.

Intracranial MAs

Twenty to forty percent of patients with IE develop neurological complications. Intracranial MAs (ICMAs) represent a relatively small but extremely dangerous subset of these. The overall mortality rate among IE patients with ICMAs is 60%. Among those without rupture, the mortality rate is 30%; this approaches 80% if rupture occurs. The reported occurrence of ICMAs in 1.2% to 5% of cases is probably an underestimate because some ICMAs remain asymptomatic and resolve with antimicrobial therapy. Streptococci and S. *aureus* account for ≈ 50% and ≈ 10% of cases, respectively, and are seen with increased frequency among IVDA patients with IE. The distal middle cerebral artery branches are most often involved, especially the bifurcations. ICMAs are multiple in 20% of cases; mortality rates are similar for multiple or single distal ICMAs. The mortality rate for patients with proximal ICMAs exceeds 50%

The clinical presentation of patients with ICMAs is highly variable. Patients may develop severe localized headache,

altered sensorium, or focal neurological deficits such as hemianopsia or cranial neuropathies; the neurological signs and symptoms may suggest a mass lesion or an embolic event. Some ICMAs leak slowly before rupture and produce mild meningeal irritation. Typically, the spinal fluid in these patients is sterile and contains erythrocytes, leukocytes, and elevated protein. In other patients, there are no clinically recognized premonitory findings before sudden subarachnoid or intraventricular hemorrhage.

ICMAs may heal with medical therapy: Bingha reported that ICMAs resolved between an initial and follow-up angiogram in 52% of patients treated with effective antibiotic therapy. A decrease in ICMA size was seen in an additional 29%. In 19% of patients, however, the ICMA increased in size by the time of the second angiogram, and a new ICMA was discovered in 10%. Whereas it is clear that ICMAs treated with antibiotics alone will heal in many patients, in others, rupture may lead to significant morbidity or death. The risk of neurosurgical intervention is affected by patient age, underlying comorbid conditions, and the location of the ICMA. Currently, there are no data that precisely identify patients at risk for imminent rupture, and decisions concerning medical versus surgical therapy must be individualized. It is generally felt that a single ICMA distal to the first bifurcation of a major artery (eg, middle cerebral artery) should be monitored with frequent serial angiograms and excised promptly if the aneurysm enlarges or bleeds. Multiple ICMAs present a complex surgical problem and should be monitored closely with frequent serial angiograms and CT scans. If ≥ 1 aneurysm enlarges, prompt surgical excision should be considered. ICMAs that occur proximal to the first bifurcation are less amenable to surgical excision. Such ICMAs frequently arise from major vessels, and ligation may result in severe neurological deficits. Proximal aneurysms should be monitored with serial angiograms and CTs; in these lesions, if signs of enlargement or leakage develop, surgical intervention should be attempted. Occasionally, proximal ICMAs stabilize and form a thrombus with antimicrobial therapy.

Some patients with IE require both cardiac valve replacement and ICMA ligation. Although data are limited in this situation, an approach that uses staged procedures, with the more severe problem dictating the procedure to be performed first, has been suggested. A bioprosthetic valve, which does not require anticoagulant therapy, may be preferable to a mechanical valve in this circumstance.

Extracranial MAs

Intrathoracic or intra-abdominal MAs are often asymptomatic until leakage or rupture occurs. Presumably most Extracranial MAs (ECMAs) will rupture if not excised. The appearance of a tender, pulsatile mass in a patient with IE should suggest an ECMA. Hematemesis, hematobilia, and jaundice suggest rupture of a hepatic artery MA; arterial hypertension and hematuria suggest rupture of a renal MA; and massive bloody diarrhea suggests the rupture of an ECMA into the small or large bowel.

Proximal and distal ligation with excision of all infected material is ideal but generally not feasible. Moreover, the risk of reinfection and rupture of interposed vascular grafts is high. Revascularization is usually established *via* extra anatomic routes through uninfected tissue planes. Autologous venous grafts have a lower risk of recurrent infection than synthetic materials. Long term, suppressive, oral antimicrobial therapy may be desirable in patients at high risk of recurrence of infection, such as those with interposed vascular grafts in infected areas.

Despite improved diagnostic techniques and more aggressive surgical therapy, mortality among patients with IE and

ECMA is high, which is attributable to suture line infection with vessel or graft rupture. For most patients, however, surgical intervention represents the only hope for radical cure of the ECMA and survival.

Anticoagulation issues

Questions arise as to whether anticoagulant therapy can be safely used during the treatment of IE. Anticoagulation per se is not a therapeutic regimen that should be used to treat IE. Most authorities feel that anticoagulation is contraindicated in native valve endocarditis because of the risk of intracerebral hemorrhage. Patients with prosthetic valve endocarditis who normally take maintenance anticoagulation, however, are usually maintained on anticoagulant therapy during treatment of IE, provided there is no evidence of cerebral events.

CONCLUSION

The incidence of IE continues to rise, with a yearly incidence of $\approx$ 15000 to 20000 new cases. Thus, IE now represents the fourth leading cause of life threatening infectious disease syndromes (after urosepsis, pneumonia, and intra-abdominal sepsis). Although advances in antimicrobial therapy and the development of better diagnostic and surgical techniques have reduced the morbidity and mortality of IE, it remains a potentially life threatening disease. The use of new clinical criteria, emphasizing echocardiography, will certainly guide the practitioner in correct diagnosis of this disease. Prompt recognition and management of the major complications of IE, such as heart failure, periannular extension of the infection, splenic abscess, and MAs, are also essential to successful patient outcome. Because of the rising incidence of IE, its significant morbidity and mortality rates, and its substantial prognostic and financial implications for the patient, it is vital to continue to fund research on endocarditis. This will in turn provide more information on the pathophysiology of the disease, as well as novel and better treatment and prophylactic strategies.

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