AHA Scientific Statement

Diagnosis and Management of Infective Endocarditis and Its Complications

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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 (Helicobacter parainfluenzae, Helicobacter aphrophilus, Actinobacillus [Helicobacter] 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.

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 development of immunologic vascular phenomena, which are more characteristic of subacute 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.

A more recent diagnostic strategy was proposed by Durack and colleagues from Duke University in 1994 (the Duke criteria). These Duke criteria (see Tables 1 and 2) 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 (defined in Table 2) or pathologically (IE proven at surgery or autopsy), possible cases (not meeting the criteria for definite
(Table 1). 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 (Table 3).

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
TABLE 3. Comparison of Duke Criteria With Beth Israel Criteria for the Clinical Diagnosis of IE: Summary of 11 Series5,7–16

<table>
<thead>
<tr>
<th>Patients/Scheme</th>
<th>Clinically Definite</th>
<th>Probable</th>
<th>Possible</th>
<th>Rejected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operated patients with surgically confirmed cases of endocarditis (n=286)*</td>
<td>Beth Israel</td>
<td>N/A</td>
<td>47%</td>
<td>29%</td>
</tr>
<tr>
<td>Duke</td>
<td>74%</td>
<td>N/A</td>
<td>26%</td>
<td>0</td>
</tr>
<tr>
<td>Nonoperated patients with clinically diagnosed cases of endocarditis (n=1395)</td>
<td>Beth Israel</td>
<td>N/A</td>
<td>32%</td>
<td>30%</td>
</tr>
<tr>
<td>Duke</td>
<td>55%</td>
<td>N/A</td>
<td>35%</td>
<td>10%</td>
</tr>
</tbody>
</table>

*Classified as if surgery had not been performed.

An approach to the diagnostic use of echocardiography (echo). *High-risk echocardiographic features include large and/or mobile vegetations, valvular insufficiency, suggestion of perivalvular extension, or secondary ventricular dysfunction (see text). †For example, a patient with fever and a previously known heart murmur and no other stigmata of IE. +High initial patient risks include prosthetic heart valves, many congenital heart diseases, previous endocarditis, new murmur, heart failure, or other stigmata of endocarditis. Rx indicates antibiotic treatment for endocarditis.
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 (Figure). 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, perianular abscess, leaflet perforation, and fistula.

In patients in whom IE or its complications are strongly suspected (Table 4) (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 a 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 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 valvar 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 (Table 4). 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.

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 TEE 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.

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–
be required in some instances. 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 Castañeda 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 Castañeda bottles. These yeasts will also grow in media used in the automated instruments.

Coxiella burnetii (the agent of Q fever) has not been recoverable from blood cultures until recently. Although this organism has now been recovered from the blood of patients with IE by tissue-culture–based techniques, infection with this agent is far more likely to be identified by serological tests. High titers of antibody directed against the phase I antigen (IgG titers >1:400 by complement fixation or ≥1:800 by microimmunofluorescence, or IgA titer ≥1:100) in blood culture–negative patients with echocardiographic evidence of IE is diagnostic in Q-fever IE. The presumptive diagnosis of Brucella, Bartonella, or chlamydial endocarditis can also be made serologically.

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 16S 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 Tropheraema 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 (see Reference 1 for discussion of antimicrobial 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 perianular extension or extracardiac 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. Small vegetations from this predominantly subendocardial infection are often missed by echocardiography. The optimal regimen or duration of antimicrobial therapy for Q-fever IE is unknown. Doxycycline with trimethoprim/sulfamethoxazole, rifampin, or fluoroquinolones is the mainstay of therapy. However, eradication of the organisms from vegetations with medical therapy is unlikely, and reinfection of prosthetic material after surgical replacement of infected valves commonly occurs. The acidic conditions of the phagolysosome, where the organism resides, may inhibit antibiotic activity. Clinical response tends to persist as long as the drug regimen continues, but viable *C. burnetii* can be recovered from valve tissue even after years of antimicrobial therapy. Cures of IE after treatment with a combination of doxycycline and hydroxychloroquine (to alkalize the phagolysosome) for 1 year were reported in 20 patients. However, no long-term follow-up was published regarding these patients. After completion of antimicrobial therapy for Q fever, relapse may occur early or after a prolonged period of time. Accordingly, more data are necessary to clarify the efficacy of doxycycline-hydroxychloroquine therapy for Q-fever endocarditis. Valve replacement is indicated only for CHF, prosthetic-valve involvement, or uncontrolled infection. To prevent reinfection of the newly implanted prosthetic valve from dormant sites of infection, many experts recommend that antimicrobial therapy be continued long-term and possibly indefinitely. Some authorities have suggested a minimum of 3 years’ therapy once phase 1 IgG antibody titers drop below 1:400 and IgA phase 1 antibodies are undetectable.

**Brucella**

*Brucella* are facultative intracellular Gram-negative bacilli that infect humans after ingestion of infected undercooked meat or unpasteurized milk, inhalation of infectious aerosols, or direct contact with infected tissues. Brucellosis is an occupational disease of veterinarians, abattoir workers, livestock handlers, and shepherds; it causes ≈4% of all IE cases in Spain. Previously damaged aortic or mitral valves develop bulky vegetations, followed commonly by valve destruction, perivalvular abscesses, and CHF. Few patients with *Brucella* IE have been cured with antimicrobial agents alone. Most require valve replacement in combination with antimicrobial agents. The optimal regimen or duration of antimicrobial therapy for *Brucella* endocarditis is unknown: doxycycline plus either streptomycin or gentamicin or doxycycline plus trimethoprim/sulfamethoxazole or rifampin have been recommended by some authorities for ≥8 weeks and up to 10 months after valve replacement.

**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 bioprosthesis-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.

### Table 5. Echocardiographic Features Suggesting Potential Need for Surgical Intervention

<table>
<thead>
<tr>
<th>Feature</th>
<th>Indications for Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent vegetation after systemic embolization:</td>
<td><em>See text for more complete discussion of indications for surgery based on vegetation characterizations.</em></td>
</tr>
<tr>
<td>Anterior mitral leaflet vegetation, particularly with size &gt;10 mm†</td>
<td>†Surgery may be required because of risk of embolization.</td>
</tr>
<tr>
<td>One or more embolic events during first 2 weeks of antimicrobial therapy†</td>
<td>†Surgery may be required because of risk of embolization.</td>
</tr>
<tr>
<td>Two or more embolic events during or after antimicrobial therapy†</td>
<td>†Surgery may be required because of heart failure or failure of medical therapy.</td>
</tr>
<tr>
<td>Increase in vegetation size after 4 weeks of antimicrobial therapy†‡</td>
<td>†Surgery may be required because of heart failure or failure of medical therapy.</td>
</tr>
<tr>
<td>Valvular dysfunction</td>
<td></td>
</tr>
<tr>
<td>Acute aortic or mitral insufficiency with signs of ventricular failure‡</td>
<td>‡Surgery may be required because of heart failure or failure of medical therapy.</td>
</tr>
<tr>
<td>Valve perforation or rupture‡</td>
<td></td>
</tr>
<tr>
<td>Perivalvular extension</td>
<td></td>
</tr>
<tr>
<td>Valvular dehiscence, rupture, or fistula‡</td>
<td></td>
</tr>
<tr>
<td>New heart block‡</td>
<td></td>
</tr>
<tr>
<td>Large abscess, or extension of abscess despite appropriate antimicrobial therapy$</td>
<td></td>
</tr>
</tbody>
</table>

*†Surgery may be required because of risk of embolization.
‡Surgery may be required because of heart failure or failure of medical therapy.
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.\(^96,99^{,}100\) 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.\(^101\) The anatomic vulnerability of this area explains both why abscesses occur in this location and why heart block is a frequent sequela.\(^28,102\) 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.\(^82,103,104\) Periannular infection is of even greater concern with prosthetic-valve IE, occurring in 56% to 100% of patients.\(^102\) Perivalvular abscesses are particularly common with prosthetic valves because the annulus, rather than the leaflet, is the usual primary site of infection.\(^57,105\) 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.\(^28,106\) Only aortic-valve involvement and recent IVDA have been prospectively identified as independent risk factors for perivalvular abscess.\(^100\) On ECG, new atriointerventricular 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%).\(^102\)

Patients at risk for perivalvular extension of IE require prompt evaluation. The size of vegetations is not helpful in predicting perivalvular extension.\(^100\) The sensitivity of TTE to detect perivalvular abscess is low (18% to 63% in prospective and retrospective studies, respectively).\(^95,107,108\) 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).\(^28,30,95\) 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.²⁹,₃⁶

A small number of patients with periannular extension of infection or myocardial abscess may be treated successfully without surgical intervention.¹⁰⁹,¹¹⁰ 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.¹¹¹ 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.¹¹²,¹¹³ Homografts have a constant but low risk for the development of sewing-ring infections and IE, possibly related to improved penetration of antibiotics.¹¹⁴

**Splenic Abscess**

Splenic abscess is a well-described but rare complication of IE. This infection develops via 1 of 2 mechanisms: bactereemic 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 abscesses.¹⁵⁻¹⁷ 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 asymptomatic¹¹⁷; back, left-flank, or left-upper-quadrant pain or abdominal tenderness, when present, may be associated with either splenic infarction or abscess.¹¹₅,¹¹₇⁻¹₂₀ Splenic rupture with hemorrhage is a rare complication of infection. 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 appear 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.⁹⁹Tc 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,¹²¹,¹²² and 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.¹²³,¹²⁴

**Intracranial MAs**

Twenty to forty percent of patients with IE develop neurological complications.¹²³ 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.¹²⁶ 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,¹₂₄,¹₂₆,¹₃₁ and are seen with increased frequency among IVDA patients with IE.¹³¹ 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%.¹²₆

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.¹₂₃,¹₂₄,¹₃₀ 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.¹₂₆,¹₃₂

In the absence of clinical signs or symptoms of ICMAs, routine screening with imaging studies is not warranted. Symptomatic cerebral emboli frequently but not invariably
precede the finding of an ICMA. Accordingly, imaging procedures to detect ICMAs are indicated in IE patients with localized or severe headaches, “sterile” meningitis, or focal neurological signs. In patients suspected of having an ICMA, contrast-enhanced CT may provide useful initial information. This technique has a 90% to 95% sensitivity for intracerebral bleed and may thus indirectly identify the location of the MA. Magnetic resonance angiography is a promising new technique for the detection of ICMAs, although its sensitivity for aneurysms smaller than 5 mm is inferior to conventional 4-vessel cerebral angiography. Until more experience is gained with other imaging modalities, conventional angiography remains the diagnostic imaging test of choice.

ICMAs may heal with medical therapy: Bingham reported that ICMAs resolved between an initial and follow-up angiogram in 52% of patients with treated 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 (e.g., 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, hematochezia, 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.

Conclusions

The incidence of IE continues to rise, with a yearly incidence of approximately 15 000 to 20 000 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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