Infective endocarditis (IE) and its complications

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Infective endocarditis (IE) is an infection of the endocardial surface of the heart that may include the heart valves, the endocardium, or a septal defect. The complications from IE include severe valvular insufficiency, which may lead to intractable congestive heart failure and myocardial abscesses; or, a wide variety of systemic signs and symptoms secondary to both sterile and infected emboli and various immunological mechanisms. It is currently estimated that approximately 20,000 new cases of IE occur in the United States annually. IE affects greater numbers of males than females, with a reported 2:1 male to female ratio. Approximately 50% of IE cases involve patients greater than 50 years of age. Sadly, the outcome has remained unchanged for the past three decades in the United States despite advances in diagnostic techniques and medical therapies. Prognosis is can be poor in severe cases, with 1-year mortality approaching 30% in many series. In addition, the numerous complications that occur with IE add considerable morbidity to this life-threatening disease.

Pathophysiology: IE typically occurs due to nonbacterial thrombotic endocarditis, which results from turbulence in blood flow or trauma to the endothelial surface of the heart. A transient bacteremia then seeds the sterile platelet-fibrin thrombus, with IE developing as the final end-point. Pathologic effects secondary to infection include local tissue destruction and embolic phenomena. In addition, secondary autoimmune effects, such as immune complex glomerulonephritis and vasculitis may also be present.

Types of infective endocarditis

1. Native valve endocarditis (NVE): Acute NVE frequently involves normal valves and usually has an aggressive course. Organisms such as Staph aureus and group B streptococci, are the typically causative agents of this type of IE. Underlying structural valve disease may not be present in this type of IE. Subacute NVE, in contrast, typically affects only abnormal valves. Its clinical course, even in untreated patients, is usually more indolent. Alpha-hemolytic streptococci or enterococci, typically are the causative agents of this type of IE. Rheumatic heart disease, which was common etiology in the past, currently accounts for less than 20% of cases IE. Approximately 50% of elderly patients have calcific aortic stenosis as the underlying pathology. Congenital heart disease accounts for 15% of cases, with the bicuspid aortic valve being the most common lesion. In the young patients, Mitral valve prolapse is the most common predisposing condition (present in 30% of cases of NVE in this age group). IE also has been demonstrated to complicate 5% of
cases of asymmetrical septal hypertrophy, usually involving the mitral valve.

2. Prosthetic valve endocarditis (PVE): PVE accounts for 10-20% of cases of IE. Over their life span, 5% of mechanical and bioprosthetic valves develop IE. Mechanical valves are more likely to be infected within the first 3 months of surgery; bioprosthetic valves are more likely to be infected after 1 year. The valves in the mitral valve position are more susceptible than those in the aortic areas. Early PVE occurs within 60 days of valve implantation with coagulase-negative staphylococci, gram-negative bacilli, and candida being the common infecting organisms. Late PVE occurs 60 days or more after valve implantation and staphylococci, alpha-hemolytic streptococci, and enterococci are the common causative organisms. Recent data, however suggests that staph aureus may now be the most common infecting organism in both early and late PVE.

3. Intravenous drug abuse (IVDA) endocarditis: No underlying valvular abnormalities are noted in vast majority of cases of IVDA IE (upto 75%), and 50% of these infections seem to involve the tricuspid valve. Staph aureus is the most common causative organism involved with this type of IE.

4. Pacemaker IE: Infections of implantable pacemakers and cardioverter-defibrillators are similar to PVE. Usually, these devices are infected within a few months of implantation. Infection of pacemakers most commonly involves the generator pocket, but is also seen as IE of the proximal leads, and of the portions of leads in direct contact with the endocardium. This last category represents true pacemaker IE, is fortunately the least common infectious complication of pacemakers as it is very difficult to treat. Majority of pacemaker infections are caused by staphylococci.

5. Nosocomial IE (NIE): NIE is defined as an infection that manifests 48 hours after the patient is hospitalized, or an infection that is associated with a procedure performed within 4 weeks of clinical disease onset. The term healthcare-associated infective endocarditis (HCIE) is now preferred, since it is inclusive of all sites that deliver patient care, such as hemodialysis centers.

**Diagnostic Criteria for IE**

Duke diagnostic criteria: Combination of clinical, microbiological, pathological, and echocardiographic characteristics.

Definitive pathological diagnosis is established by identifying microorganisms, on culture or histology, in vegetations removed during surgery, embolectomy, or drainage of an intracardiac abscess.

Alternatively, a definitive clinical diagnosis is made based on:
a) presence of 2 major criteria; b) presence of 1 major criterion and 3 minor criteria; or c) presence of 5 minor criteria.
Major blood culture criteria:
- Two blood cultures positive for organisms typically found in patients with IE (i.e., S. viridans, Streptococcus bovis, a HACEK group organism, community-acquired S. aureus, or enterococci in the absence of a primary focus)
- Blood cultures persistently positive for one of the above organisms from cultures drawn more than 12 hours apart
- Three or more separate blood cultures drawn at least 1 hour apart

Major echocardiographic criteria:
- Echocardiogram positive for IE, documented by an oscillating/mobile intracardiac mass on a valve or on supporting structures, in the path of regurgitant jets, or on implanted foreign material
- Myocardial abscess
- Development of partial dehiscence of a prosthetic valve
- New-onset valvular regurgitation

Minor criteria include:
- Predisposing cardiovascular conditions or intravenous drug use
- Fever of 38°C (100.4°F) or higher
- Vascular phenomenon, including major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, or Janeway lesions
- Immunological phenomenon such as glomerulonephritis, Osler nodes, Roth spots, and rheumatoid factor
- Positive blood culture results not meeting major criteria or serologic evidence of active infection with an organism consistent with IE (e.g., Brucella, C. burnetii [i.e., Q fever], Legionella)
- Echocardiogram results consistent with IE but not meeting major echocardiographic criteria

Rejection criteria for the diagnosis of IE are:
- The presence of a sound alternative diagnosis of the manifestations of endocarditis
- Resolution of manifestations of endocarditis after 4 or fewer days of antimicrobial therapy
- No pathologic evidence of IE at surgery or autopsy after 4 or fewer days of antimicrobial therapy

A diagnosis of possible IE is made when findings consistent with IE fall short of the criteria for definite IE but do not meet the criteria for rejection.

Differential Diagnoses to be considered when evaluating for IE:
- Cardiac Neoplasms,
- Atrial Myxoma
- Antiphospholipid Syndrome
- Systemic Lupus Erythematosus
- Lyme Disease
Polymyalgia Rheumatica
Reactive Arthritis

**Role of Echocardiography in IE**

**Class I indications for TTE or TEE:**
- TTE to be able to characterize the hemodynamic severity of the valve lesions in known IE. Among symptomatic patients, TEE is recommended if TTE is nondiagnostic.
- TTE to be able to detect valvular vegetations with or without positive blood cultures for the diagnosis of IE. Among patients with positive blood cultures, TEE is recommended if TTE is nondiagnostic.
- TTE for reassessment of high-risk patients, as defined by virulent organism, clinical deterioration, persistent or recurrent fever, a new murmur, or persistent bacteremia.
- TTE or TEE to assess complications of IE (such as abscesses, perforations, and shunts). TEE is recommended for preoperative evaluation of patients going to surgery unless the indication for surgery is apparent on TTE or imaging will delay urgent surgery.
- TEE as a first-line diagnostic test for prosthetic valve IE and to detect complications.
- Intraoperative TEE for patients undergoing valve surgery for IE.

**Class IIa indications for TTE or TEE:**
- Among patients with a prosthetic valve, TTE to be able to diagnose IE in patients with persistent fever without bacteremia or a new murmur.
- TEE to diagnose possible IE in patients with persistent staphylococcal bacteremia who do not have a known source.

**Class IIb indications for TTE or TEE:**
- Among patients with prosthetic valve IE, TTE for reevaluation during antibiotic therapy in the absence of signs of clinical deterioration.
- TEE to be able to diagnose possible IE in patients with NIE staphylococcal bacteremia.

**Echocardiography techniques in IE**

When evaluating a suspected lesion with 2D imaging, specific echocardiographic findings consistent IE should be determined. These characteristics include: a) location of the lesion in the path of a high velocity regurgitant jet (vegetations are present on the inflow side of the valves), b) oscillation/motion independent of the valve motion, c) or gray scale texture similar in reflectance to the myocardium and different from the echogenecity of valvular structures.
Vegetations may not be identified in nearly 10% of cases; therefore, associated lesions, such as new regurgitation, damage to valve apparatus, or pericardial effusion should increase suspicion for IE. Additionally, knowledge of lesions whose etiology is
noninfectious is also necessary. Lambli's excrescence, the presence of Chiari network, or valve degeneration with fibrous stranding in older patients may be mistaken as pathologic. Other masses such as fibroelastomas, thrombus, previously healed endocarditis, or Libman-Sack's endocarditis may be present. Although primarily noninfectious, these lesions also may become secondarily infected, and a previous echocardiogram would be informative for management.

**Transthoracic vs Transesophageal Echocardiography**

The overall detection rate for vegetations by TTE in patients with a clinical suspicion of endocarditis ranges from 40% to 60%, and specificity is approximately 98%. Majority of patients with suspected IE could be initially examined using TTE, with the exception of patients with prosthetic heart valves and staphylococcus bacteremia. For the left-sided valves and prosthetic valves, the sensitivity of TTE for detection of vegetations is low while the risk of delay in adequate treatment for Staphylococcus infection favors the use of TEE. The detection of vegetations using TTE is influenced by several factors, including size of vegetation and location, presence of previous valvular disease, and technical quality of the image. Obesity, pulmonary disease, and chest wall deformity interfere with image quality. The reduced sensitivity with TTE may be particularly important in elderly patients, whose acoustic windows may be poorer or whose valves may have degenerative changes. IE involving right-sided cardiac structures are more readily diagnosed using TTE because of the easier visualization. Interestingly, studies have also shown that for right-sided lesions, TEE may not have higher sensitivity than TTE.

Although TTE is useful for the identification of the hemodynamic and pathologic consequences of infection, such as valvular regurgitation, associated complications should be further characterized with TEE. Even if transthoracic views identify diagnostic vegetations, TTE may be inadequate in comprehensively excluding complications such as abscess, leaflet perforation, or fistulae.

The sensitivity of TEE approaches 100% for native valves and under ideal conditions, it may diagnose lesions as small as 1 mm. However, a single negative TEE study alone may not have sufficient diagnostic accuracy to rule out IE. Although the negative predictive value is 95%, it is important to note a false-negative echocardiographic study may result by previous embolization of infected material or early infection that may have vegetations that are so small as to fall below the detectable limits of resolution. Therefore, if the clinical suspicion is of IE, a repeat TEE study after 7 to 10 days to re-evaluate for vegetation or abscess should be considered.

**Echocardiographic predictors of systemic embolization in IE:**

Large valvular vegetations (>1 cm in diameter)
Multiple vegetations
Mobile or pedunculated vegetations
Noncalcified vegetations
Vegetations that are increasing in size
Prolapsing vegetations
**Anatomic and echocardiographic definitions of IE and its complications:**

<table>
<thead>
<tr>
<th>Vegetation</th>
<th>Surgery/necropsy</th>
<th>Echocardiography</th>
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<tbody>
<tr>
<td>Infected mass attached to an</td>
<td>Oscillating or non-oscillating</td>
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<tr>
<td>endocardial structure, or on</td>
<td>intracardiac mass on valve or other endocardial</td>
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<td>implanted intracardiac</td>
<td>structures, or on implanted intracardiac material</td>
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<tr>
<td>material</td>
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<tr>
<td>Abscess</td>
<td>Perivalvular cavity with necrosis and purulent material not communicating</td>
<td>Thickened, non-homogeneous perivalvular area with echodense or echolucent</td>
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<td></td>
<td>with the cardiovascular lumen</td>
<td>appearance</td>
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<tr>
<td>Pseudoaneurysm</td>
<td>Perivalvular cavity communicating with the cardiovascular lumen</td>
<td>Pulsatile perivalvular echo-free space, with color-Doppler flow detected</td>
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<tr>
<td>Perforation</td>
<td>Interruption of endocardial tissue continuity</td>
<td>Interruption of endocardial tissue continuity traversed by color-Doppler flow</td>
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<tr>
<td>Fistula</td>
<td>Communication between two neighbouring cavities through a perforation</td>
<td>Color-Doppler communication between two neighboring cavities through a perforation</td>
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<tr>
<td>Valve aneurysm</td>
<td>Saccular outpouching of valvular tissue</td>
<td>Saccular bulging of valvular tissue</td>
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<tr>
<td>Dehiscence of a prosthetic valve</td>
<td>Dehiscence of the prosthesis</td>
<td>Paravalvular regurgitation identified by TTE/TEE, with or without rocking motion</td>
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<td>of the prosthesis</td>
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**Limitations of echocardiography in the diagnosis of IE**

Although echocardiography occupies a pivotal position as an important test for IE and provides definite diagnosis in a majority of patients, indeterminate results are possible, particularly early in the disease, and in patients with prosthetic materials in the heart. It is critical to recognize that both the sensitivity and specificity of TTE and TEE are not 100%. A negative echocardiographic examination does not rule out IE and a repeat TTE/TEE may be necessary in some situations. Additionally, results of the echocardiographic study must take into account the clinical presentation and the probability of IE in a particular patient.
ACC/AHA guideline summary: Surgery for valve IE and role of echocardiography

The recommendation for optimal timing of surgery in valvular IE are included in the 2006 ACC/AHA guidelines on the management of valvular heart disease. Echocardiography is indeed very helpful in the evaluation of candidates for surgery for prosthetic valve and native valve IE. In general, heart failure, perivalvular infection, and high embolic risk are the three main indications for early surgery.

ACC/AHA guideline summary: Surgery for native valve IE (NVE)

Class I indications:
- Heart failure secondary to valve stenosis or regurgitation.
- Aortic or mitral regurgitation with hemodynamic evidence of elevated left ventricular end-diastolic or atrial pressures such as premature closure of the mitral valve with aortic regurgitation, rapid decelerating mitral regurgitation signal by CW Doppler, or moderate to severe pulmonary hypertension.
- IE that is secondary to fungal or other highly resistant organisms.
- Complications such as heart block, annular or aortic abscess, or destructive penetrating lesions such as fistula from the sinus of valsalva to the right or left atrium or right ventricle, mitral leaflet perforation with IE of the aortic valve, or infection in annulus fibrosa.

Class IIa indications:
- Recurrent emboli and persistent vegetations despite appropriate antibiotic therapy.

Class IIb indications:
- Mobile vegetations larger than 1 cm with or without emboli.

ACC/AHA guideline summary: Surgery for prosthetic valve endocarditis (PVE)

Class I indications:
- Heart failure secondary to valve stenosis or regurgitation.
- Dehiscence diagnosed by cine fluoroscopy or echocardiography.
- Evidence of increasing valve obstruction or worsening regurgitation.
- Serious complications such as abscess formation.

Class IIa indications:
- Persistent bacteremia or recurrent emboli despite appropriate antibiotics.
- Recurring infections

Class III indications (surgery is not indicated):
- Uncomplicated IE caused by a first infection with a sensitive organism.

In summary, echocardiography plays a key role in diagnosis of IE and its complications, as well as in its prognostic assessment. TEE remains the imaging modality of choice although TTE can be employed for initial assessment in majority of cases. Echocardiography determination of IE is critical in planning for surgical interventions in valvular IE.
REFERENCES:


