Frank Lowy

Infective Endocarditis

1. <u>Introduction</u>

Infective endocarditis (IE) is an infection of the heart valves. A large number of different microorganisms are capable of causing this disease. Depending on the particular pathogen, endocarditis can be indolent, progressing slowly over weeks to months, or fulminant, presenting with a very toxic picture over several days. In the preantibiotic era, this disease was almost uniformly fatal. While endocarditis can now be treated medically, it is a classic example of an infectious disease where "bactericidal" antibiotics are absolutely necessary because the local and systemic host defense mechanisms are of limited benefit.

Definition: Infective endocarditis is an infection of a cardiac valve or the endocardium caused by bacteria, fungi, or chlamydia. Pathological findings include the presence of often friable, valvular vegetations containing bacteria, fibrin, platelets and inflammatory cells. There is often valvular destruction with local intracardiac complications. A chunk of the friable vegetation may break off and embolize. Bacteria may also seed other tissues causing metastatic infections.

2. <u>Epidemiology</u>

The incidence of IE has not changed appreciably in the past 30 years and is estimated to be 1.7-6.2 cases per 100,000. There has been a change in the epidemiology of the disease since the introduction of antibiotics. This change includes the type of underlying valvular disease, bacterial pathogens, increasing age of subjects presenting with endocarditis as well as the factors that predispose individuals to the development of this disease.

a) Incidence of underlying valvular disease. There has been considerable change in the type of underlying valvular disease encountered in patients with IE since the advent of antibiotics. Rheumatic valvular disease is far less common and atherosclerotic cardiovascular diseases as well as mitral valve prolapse with insufficiency have become more common. Patients presenting with no antecedent history of valvular disease are also more common (25-30%).

b) Etiologic agents in IE. IE is predominantly a Gram positive bacterial infection although Gram negatives and fungi are infrequently isolated. A breakdown of pathogens is presented below.

Microbiology of Infective Endocarditis - Prospective International Cohort Study*

Organisms	Percent Cases
Staphylococcus aureus	31.6
Coagulase negative staphylococci	10.5
Viridans group streptococci	18.0
Streptococcus bovis	6.5
Other streptococci	5.1
Enterococcus spp.	10.6
Gram negative bacilli	3.8
Fungi	1.8
Polymicrobial	1.3
Culture negatives	8.1

*Fowler *et al., JAMA 2006*

Several points to note concerning these pathogens:
i) Viridans streptococci remain the major pathogens in subacute endocarditis
ii) *Streptococcus bovis* has a unique association with colonic carcinoma.
iii) *S. aureus* accounts for about 80% of cases of acute endocarditis and is also the predominant pathogen in intravenous drug use-related and nosocomial endocarditis.
iv) Coagulase negative staphylococci are the major pathogens in prosthetic valve endocarditis.
v) Culture negative cases account for about 4-10% of cases.
vi) Nosocomial endocarditis is increasingly common in part due to the increased number of invasive procedure performed in the hospital.

        c) Predisposing factors. The traditional risk factors for this disease include antecedent dental, genitourinary or gastrointestinal procedures (often quite minor) producing a transient bacteremia. More recently other factors have also been recognized as potentially important. These include intravenous drug abuse, invasive medical procedures such as intravenous lines, hemodialysis, or surgical replacement of cardiac valves.

3.   Pathogenesis and Pathology of IE
        Lewis and Grant (Heart 10:21, 1923) were the first to clearly describe the pathogenesis of IE. They recognized that the disease often followed a transient bacteremia in individuals with an anatomically deformed cardiac valve. We now understand that infection results from a sequence of events: transient bacteremia, seeding of a valvular surface and formation of a mature vegetation. The factors associated with these events are summarized below.
         a) Transient bacteremia. Individuals with preexistent valvular disease are at risk of subacute IE resulting from transient bacteremias. Numerous studies have demonstrated that minor trauma (tooth brushing, use of oral irrigation devices, urethral catheterization) may be associated with a low grade bacteremia. In acute IE the bacteremia may also be from an inapparent focus (i.e. uninfected), from another site of infection, or from direct intravenous injection.
        b) Site of bacterial seeding on the cardiac valve
         i) Nonbacterial thrombus (NBT). In subacute infective endocarditis bacteria seed sites of previous micro or macroscopic damage. These sites are characterized by the

deposition of a platelet-fibrin thrombus. This was first recognized by Angrist and called a nonbacterial thrombus. These lesions form as a result of mechanical stress or antecedent valvular disease. In acute IE, the NBT may not be necessary, the more virulent organisms appear capable of colonizing normal cardiac valvular surfaces.

ii) Hemodynamic factors. Infective endocarditis develops on one or more cardiac valves; more often on the left side than on the right. The proportion of cases involving the tricuspid valve is greater with ABE (acute bacterial endocarditis) and with drug addicts. Rodbard demonstrated that the following hemodynamic features predicted the anatomic site of vegetation formation:

a. the presence of a high-pressure source (*e.g.* left ventricle).
b. high velocity flow through a narrow orifice (such as an
insufficient mitral or aortic valve).
c. a low-pressure chamber or "sink" beyond the orifice (such as left atrium, or left ventricle during diastole).

He subsequently showed that infected vegetations from cases of endocarditis generally exist on the low-pressure side of the high pressure narrow orifice system: *i.e.* atrial surface of mitral valve leaflets in mitral insufficiency. Satellite vegetations may also develop due to the jet stream from the primary vegetation.

c) Bacterial factors. Endocarditis is predominantly a Gram positive bacterial infection. Gram positive bacteria adhere to cardiac valvular surfaces more avidly than Gram negatives. This is due to the presence of surface components (adhesins) such as the extracellular polysaccharide, dextran, for streptococci that mediates bacterial binding to and colonization of valvular surfaces. Other factors include the serum resistance of Gram positives and their capacity to interact with platelets.

d) Vegetation formation. Once bacteria have colonized the valvular surface a vegetation forms. This consists of bacteria encased in a meshwork of platelets and fibrin. The vegetation serves as a barrier to host defenses. It is not vascularized, has few mononuclear or PMNs and is therefore not easily sterilized by host factors or antimicrobials.

e) Pathology. The gross appearance of vegetations is variable. There may be single or multiple lesions. Destruction of the underlying valve is often present. There is often greater necrosis and friability of the lesions associated with acute IE. Adjoining structures e.g. chordae, myocardial abscesses may also be involved.

4.   Clinical manifestations
The diagnosis of IE often rests initially on the signs and symptoms of the disease. Most of the clinical manifestations of IE can be explained on the basis of four pathogenetic processes which occur during the course of the illness: 1) valvular destruction and local intracardiac complications; 2) bland or septic embolization of vegetations to other organs;

3) sustained bacteremia which contributes to metastatic seeding; 4) immunopathologic phenomena. Onset of the disease is typically insidious in subacute or abrupt in acute IE. The findings in this disease are protean, involving virtually any organ of the body. Among the systemic findings are fever (85-95%), fatigue, anorexia, general malaise and weight loss (about 25%).

   a) Cardiac. Heart murmurs are present in 85-99% of cases in SBE. However, in acute IE, as is seen in intravenous drug use-related cases, a murmur is present in 1/3 involving the aorta or mitral valve and less frequently when the tricuspid valve is involved. The development of a new regurgitant murmur leads to congestive heart failure in > 90% of cases.

   b) Bland or septic embolization. Major arterial embolization with subsequent tissue infarction may occur to virtually any organ. However, the most common sites include coronary vessels (resulting in myocardial infarction), kidneys, central nervous system, or the spleen. These are usually bland in SBE but may be septic in ABE. With tricuspid valvular ABE, the lung is frequently seeded.

   c) Sustained bacteremia. A relatively continuous bacteremia results from the steady detachment of organisms from the infected vegetation into the bloodstream. Equilibrium is established between the source of the organisms and their removal from the bloodstream by the reticuloendothelial system. The net result is a low concentration of organisms present in the peripheral blood at all times in most cases (at least 80% of patients with SBE). Arterial and venous blood obtained from all extremities are equally positive.

   d) Immunologic features of IE. Rheumatoid factor (IgM antibody which is anti-IgG) is seen in about 50% of patients with the disease for >6 weeks in duration. The titer declines with treatment. Because of the constant antigenic load in prolonged infections, circulating immune complexes and hypocomplementemia are also seen. One sequela of this is the development of an immune complex glomerulonephritis.

   e) Other sites of involvement. The skin is frequently involved with petechiae (20-40%), Osler nodes (a necrotizing vasculitis of the glomus body) and Janeway lesions. Central nervous system findings include emboli seen in $\geq$ 1/3 of all cases. Rupture of infected cerebral aneurysms (mycotic) can also occur.

5.   Laboratory Findings

   The single most important laboratory test is the blood culture. In 2/3 of the cases, 100% of cultures will be positive. Three sets of blood cultures results in a $\geq$95% yield. Antecedent use of antibiotics will obviously reduce the ability to recover organisms. Other laboratory findings of note include anemia (present in 50-80%) hematuria (30-50%), RBC casts (12%) and hypocomplementemia (5-15%). Although nonspecific, the erythrocyte sedimentation rate is almost uniformly elevated and circulating immune complexes are usually detectable.

6.   Special types of IE
   a) Prosthetic valve endocarditis. Infections following insertion of prosthetic cardiac

valves are generally divided into early (< 60 days after surgery) and late (> 60 days after surgery). Early onset IE occurs in less than 2% of patients. The most common species is coagulase negative staphylococcus. Mortality is high (40-80%). Therapy often requires replacement of the prosthetic valve as well as use of antibiotics. Late onset occurs in 2-4% of patients. Organisms involved are related to dental, genitourinary or skin sources. Low virulence streptococci are the most common. The clinical manifestations are similar to SBE. The mortality is lower than in early cases and cure is often achieved without replacement of the prosthetic valve.

      b) Culture-negative endocarditis. Occurs in ~4% of cases. If no antibiotic has been previously administered, the frequency is lower. There are both infectious and noninfectious explanations for these cases.

         i) Infectious etiology. These include primarily fastidious organisms which are often difficult to culture by traditional techniques. The organisms include fastidious Gram negatives (HACEK group), fungi, nutritionally variant streptococci, anaerobes or rickettsiae. Because the diagnosis is difficult to establish, mortality in this group is higher.

         ii) Noninfectious etiology. This may occur after prolonged illness as a result of immunologic clearing of bacteria from the bloodstream with bacterial persistence in the valvular tissue. Mural endocarditis can result from infected pacer wires or thrombi. Finally marantic (uninfected NBTE) or other diagnoses that can clinically mimic endocarditis such as myxomas must be considered.

7.   <u>Diagnosis</u>

    Diagnosis is established using a constellation of physical, laboratory and historical findings. A set of criteria known as the Duke Criteria have been used to help establish a diagnosis of IE as definite or probable. It relies on pathological, clinical and laboratory data and is modeled after the Jones criteria (used in the diagnosis of Rheumatic Fever).

8.   <u>Treatment</u>

    Local host defenses at the infected vegetation are unable to control the infection. Therefore antimicrobial therapy is necessary to eliminate all organisms. This requires the following:

      a) Use of bactericidal antimicrobial agents. Agents that are primarily bacteriostatic will often lead to disappearance of many symptoms and signs of the disease but will be associated with relapse almost all of the time because the vegetation is not sterilized. This infection requires the use of bactericidal antibiotics administered over a relatively prolonged time period.

      b) Timing of initiation of antimicrobial therapy. Treatment should be started early, but great urgency for the initiation of therapy is primarily limited to cases of acute endocarditis where rapid valve destruction is likely.

9.   <u>Outcome</u>

    IE was uniformly fatal in the preantibiotic era. Depending on the particular pathogen as well as the individual, the mortality is now about 5-30%. Deaths are now more commonly due to congestive heart failure or emboli rather than uncontrolled infection. The

following factors adversely effect prognosis: increased age, culture negative endocarditis, aortic valve involvement, congestive heart failure, relatively-resistant or virulent pathogens or early prosthetic valve endocarditis.

10.   Prevention

Transient bacteremias often follow dental, genitourinary and gastrointestinal instrumentation or surgery. This bacteremia may be suppressed by the administration of antibiotics prior to and during the procedure. Antibiotics are directed against those normal flora of the involved area that may potentially cause endocarditis. It is generally recommended for patients with known valvular disease. Prophylaxis is generally administered to patients undergoing dental, genitourinary, or gastrointestinal procedures known to be associated with transient bacteremia. Prophylaxis is directed against viridans streptococci for upper respiratory tract or dental procedures and against enterococci for gi and gu procedures.

Reading (optional): Weiss, S. Self-observations and psychologic reactions of medical student A.S.R. to the onset and symptoms of subacute bacterial endocarditis. J. Mt. Sinai Hosp. 8:1079, 1942.

A graphic description of the disease by a medical student with endocarditis in the pre-antibiotic era.

Weinstein, L. and Schlesinger, J.J. Pathoanatomic, pathophysiologic and clinical correlations in endocarditis. New Eng. J. Med. 291:832,1122, 1974.

This remains the classic article on the pathogenesis of endocarditis.

Mylonakis, E. and Calderwood S.B. Infective endocarditis in adults. NEJM 345:1318, 2001.

A more recent thorough review of the disease.