Infective Endocarditis
(Bacterial Endocarditis)

Infective endocarditis (IE) is a microbial infection of the endothelial surface of the heart or heart valves that most often occurs in proximity to congenital or acquired cardiac defects. A clinically and pathologically similar infection that may occur in the endothelial lining of an artery, usually adjacent to a vascular defect (e.g., coarctation of the aorta) or a prosthetic device (e.g., arteriovenous [AV] shunt), is called *infective endarteritis.*

Bacteria most often cause these diseases, as well as fungi and other microorganisms may also cause infection; thus, the term *infective endocarditis (IE)* is used to reflect this multimicrobial origin. The term *bacterial endocarditis (BE)* commonly is used, reflecting the fact that most cases of IE are due to bacteria; however, *IE* has become the preferred term and thus will be used in this chapter. Previously, IE was classified as acute and subacute, to reflect the rapidity of onset and duration of symptoms prior to diagnosis; however, this classification was found to be somewhat arbitrary. It has now largely been replaced by a classification that is based on the causative microorganism (e.g., streptococcal endocarditis, staphylococcal endocarditis, candidal endocarditis) and the type of valve that is infected (e.g., native valve endocarditis [NVE], prosthetic valve endocarditis [PVE]). IE is also classified according to the source of infection, that is, whether community acquired or hospital acquired, or whether the patient is an intravenous (IV) drug user. IE is a disease of significant morbidity and mortality that is difficult to treat; therefore, emphasis has long been directed toward prevention.

EPIDEMIOLOGY

IE is a serious, life-threatening disease that affects more than 15,000 patients each year in the United States; the overall mortality rate approaches 40%. IE is a relatively rare disease that is most common in middle-aged and elderly persons, and is more common in men than in women. The incidence rate varies with the population under study. In the general population, it has remained relatively stable over the past 4 or 5 decades, ranging between 1.7 and 4.9 cases per 100,000 person-years.

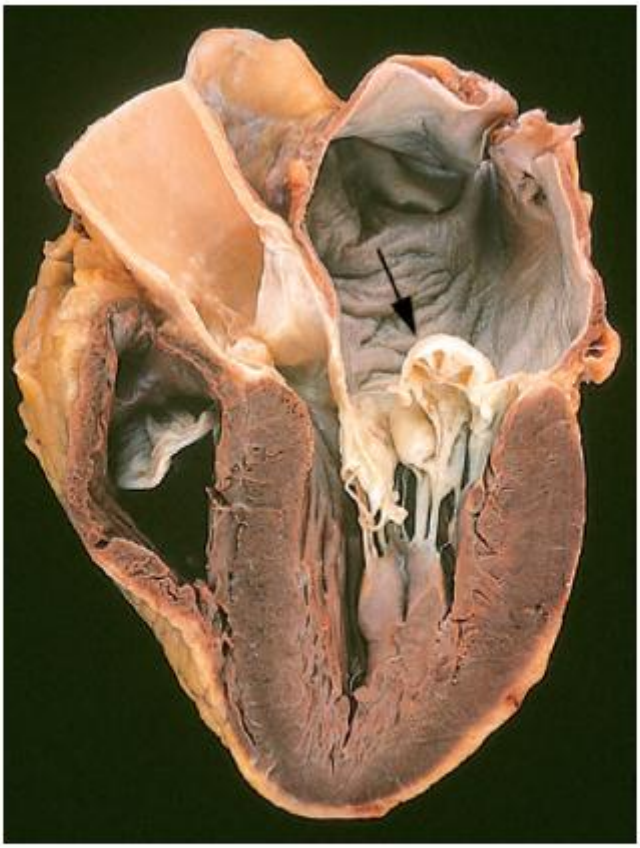

Figure 2-2. Prolapse of the posterior mitral valve leaflet into the left atrium. (Courtesy of William D. Edwards, MD, Mayo Clinic, Rochester, Minn. From Kumar V, Abbas AK, Fausto N. Robbins and Cotran Pathologic Basis of Disease, 7th ed. Philadelphia, Saunders, 2005.)

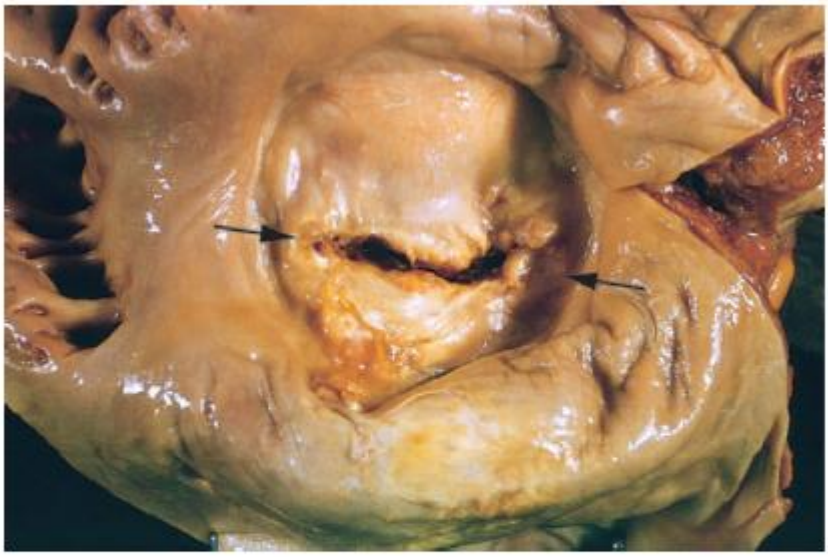

Figure 2-1. Mitral stenosis with diffuse fibrous thickening and distortion of the valve leaflets in chronic rheumatic heart disease. (From Kumar V, Abbas AK, Fausto N. Robbins and Cotran Pathologic Basis of Disease, 7th ed. Philadelphia, Saunders, 2005.)

ETIOLOGY

A total of 80% to 90% of cases of identified IE are due to streptococci and staphylococci. This variation depends on the type of valve infected (i.e., native or prosthetic), whether the infection is community acquired or hospital acquired (nosocomial), and whether or not the patient is an IVDU. Streptococci continue to be the most common cause of IE, but staphylococci have been gaining increasing importance. Viridans streptococci (alpha-hemolytic streptococci), constituents of the normal oral flora and gastrointestinal tract, remain the most common cause of community-acquired NVE, without regard for IV drug abuse, and they cause 30% to 65% of cases of IE.

The species that most commonly cause endocarditis are *Streptococcus sanguis, Streptococcus oralis (mitis), Streptococcus*

salivarius, *Streptococcus mutans,* and *Gemella morbillorum* (formerly called *Streptococcus morbillorum*).Group D streptococci, which include *Streptococcus bovis* and the enterococci *(Enterococcus faecalis),* are normal inhabitants of the gastrointestinal (GI) tract and account for 5% to 18% of cases of IE. *Streptococcus pneumoniae* has decreased in incidence and now accounts for only 1% to 3% of cases of IE. Group A beta-hemolytic streptococci rarely cause IE.

SIGNS AND SYMPTOMS

The classic findings of IE include fever, heart murmur, and positive blood culture, although the clinical presentation may be varied. It is of particular significance that the interval between the presumed initiating bacteremia and the onset of symptoms of IE is estimated to be less than 2 weeks in more than 80% of patients with IE. In many cases of IE that have been purported to be due to dentally induced bacteremia, the interval between the dental appointment and the diagnosis of IE has been much longer than 2 weeks (sometimes months), and thus it is very unlikely that the initiating bacteremia was associated with dental treatment. Fever, the most common sign of IE, occurs in up to 95% of patients. It may be absent, however, in the elderly or in patients with heart failure or renal failure. New or changing heart murmurs, systolic or diastolic, are found in 80% to 85% of patients. Heart murmurs are often not heard initially in patients who are IVDUs but appear later in the course of the disease. This is characteristic of tricuspid valve IE caused by *S aureus.* Peripheral manifestations of IE due to emboli and/or immunologic responses are less frequently seen since the advent of antibiotics. These include petechiae of the palpebral conjunctiva, the buccal and palatal mucosa, and extremities, Osler's nodes (small, tender,

subcutaneous nodules that develop in the pulp of the digits), Janeway lesions (small, erythematous or hemorrhagic, macular nontender lesions on the palms and soles), splinter hemorrhages in the nail beds, and Roth spots (oval retinal hemorrhages with pale centers), Other signs include splenomegaly and clubbing of the digits. Sustained bacteremia is typical of IE, and blood cultures are positive in most cases. Although up to 30% of cases of IE are initially found to be "culture negative," when strict diagnostic criteria are used, only 5% of patients are negative. Many patients with negative blood cultures have taken antibiotics prior to the diagnosis of IE. Three separate sets of blood cultures obtained over a 24-hour period are recommended in the evaluation of a patient for suspected IE.The diagnosis of IE should be considered for a patient with fever with one or more of the following cardinal elements of IE: a predisposing cardiac lesion or behavior pattern, bacteremia, embolic phenomena, and evidence of an active endocardial process. The clinical presentation of IE is variable, and other conditions can cause similar signs and symptoms. The Duke criteria were developed and later modified to facilitate the definative diagnosis of IE. This set of diagnostic criteria assesses the presence or absence of major and minor criteria.

Major criteria include the following:

• Positive blood cultures

• Evidence of endocardial involvement (e.g., positive echocardiography, presence of new valvular regurgitation)

Minor criteria include those listed here:

• Predisposing heart condition or IV drug use

• Fever

• Vascular phenomena

• Immunologic phenomena

• Microbiologic evidence other than positive blood culture

Definitive diagnosis of IE requires the presence of two major criteria, one major and three minor criteria, or five minor criteria.

LABORATORY FINDINGS

Other than blood culturing, laboratory tests used for the diagnosis and treatment of IE are basic and nonspecific and may include a complete blood count with differential, electrolytes, renal function tests, urinalysis, chest x-ray, and electrocardiogram (ECG). Patients with IE frequently have a normocytic, normochromic anemia that ends to worsen as the disease progresses. The white blood cell count may or may not be elevated. Urinalysis often reveals microscopic hematuria and proteinuria. Chest x-ray may be abnormal with evidence of heart failure. ECG may show evidence of conduction block with myocardial involvement or infarction. Other abnormal findings may include an elevated erythrocyte sedimentation rate, increased immune globulins, circulating immune complexes, and positive rheumatoid factor. Echocardiography, transthoracic or transesophageal, is used to confirm the presence of vegetation in patients suspected of having IE; it has become a cornerstone in the diagnostic process. Positive echocardiographic evidence of vegetation is one of the major findings included in the Duke criteria.

MEDICAL MANAGEMENT

Prior to the advent of antibiotics, IE was almost always fatal. This has changed dramatically with early diagnosis and the institution of antibiotic therapy and/or surgery. Although the survival rate has greatly improved, the

overall mortality rate still hovers around 40%. However, the mortality rate varies significantly among different groups. For example, patients with viridans group streptococcal PVE have a mortality of approximately 20%, but the mortality of viridans group streptococcal NVE is 5% or less. For nonaddicted patients with *S aureus* endocarditis, the mortality rate ranges between 25% and 40%, and for fungal endocarditis, the mortality rate exceeds 80%. For patients who are IV drug abusers with IE of the tricuspid valve, the mortality rate is between 2% and 4%. The management of patients with IE requires effective antibiotic therapy and, for cases with significant structural damage, cardiac or surgical intervention. Recently, guidelines for the diagnosis, antimicrobial therapy, and management of infective endocarditis have been revised as an American Heart Association (AHA) Scientifi c Statement. Most strains of viridans streptococci, "other" streptococci (including *Streptococcus pyogenes*), and onenterococcal group D streptococci (primarily *S bovis*) are exquisitely sensitive to penicillins, with a minimal inhibitory concentration (MIC) of less than 0.2 μg/mL. Bacteriologic cure rates ≥98% may be anticipated in patients who complete 4 weeks of therapy with parenteral penicillin or ceftriaxone for NVE caused by highly penicillin-susceptible viridans group streptococci or *S bovis.* The addition of gentamicin sulfate to penicillin exerts a synergistic killing effect in vitro on viridans group streptococci and *S bovis.* A 2-week regimen of penicillin or ceftriaxone combined with single dailydose gentamicin is appropriate for uncomplicated cases of endocarditis caused by highly penicillin-susceptible viridans group streptococci or *S bovis* in patients at low risk for adverse events caused by gentamicin therapy. For patients who are unable to tolerate penicillin or ceftriaxone, vancomycin is the most effective alternative. Patients with endocarditis that is complicating

prosthetic valves or other prosthetic material caused by a highly penicillin-susceptible strain (MIC ≤0.12 μg/mL) should receive 6 weeks of therapy with penicillin or ceftriaxone, with or without gentamicin for the first 2 weeks. Those with endocarditis caused by a strain that is relatively or highly resistant to penicillin (MIC >0.12 μg/mL) should receive 6 weeks of therapy with penicillin or ceftriaxone combined with gentamicin. Vancomycin therapy is recommended only for patients who are unable to tolerate penicillin or ceftriaxone. Regardless of whether IE is community or hospital acquired, most *S aureus* organisms produce betalactamase; therefore, the condition is highly resistant to penicillin G. In this case, the drugs of choice for treatment of IE caused by methicillin-susceptible *S aureus* (MSSA) are the semisynthetic, penicillinase-resistant penicillins such as nafcillin or oxacillin sodium. For patients with native valve *S aureus* endocarditis, a 6-week course of oxacillin or nafcillin with the optional addition of gentamicin for 3 to 5 days is recommended. Staphylococcal PVE is treated similarly to NVE, except that treatment is given for a longer period. For strains resistant to oxacillin, vancomycin is combined with rifampin and gentamicin. Surgical intervention may be necessary to facilitate a cure for IE or to repair damage caused by the infection. Indications for surgery include moderate to severe heart failure caused by valvular dysfunction, unstable or obstructed prosthesis, infection uncontrollable by antibiotics alone, fungal endocarditis, and intracardiac complications with PVE.

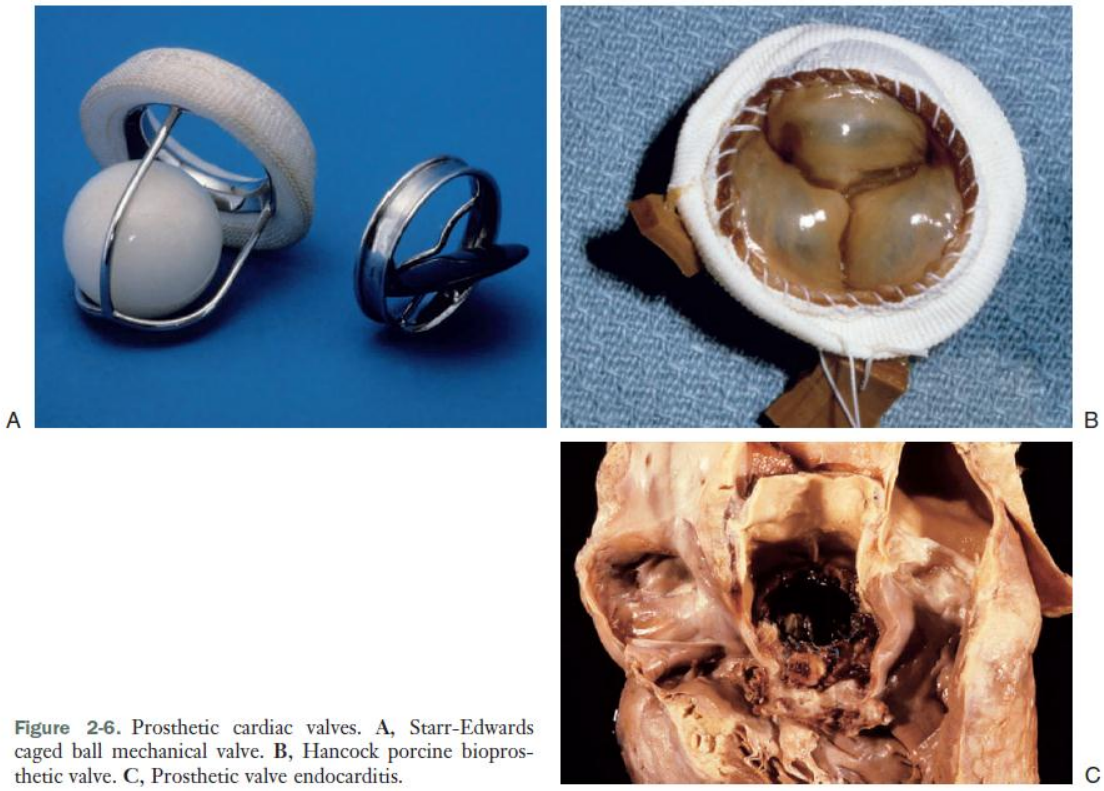

Figure 2-6. Prosthetic cardiac valves. **A,** Starr-Edwards caged ball mechanical valve. **B,** Hancock porcine bioprosthetic valve. **C,** Prosthetic valve endocarditis.

DENTAL MANAGEMENT

Antibiotic Prophylaxis

Dental treatment has long been implicated as a significant cause of IE. Conventional wisdom has taught that in a patient with a predisposing cardiovascular disorder, IE was most often due to a bacteremia that resulted from an invasive dental procedure, and that through the administration of antibiotics prior to those procedures, IE could be prevented. Based on these assumptions, over the past 50 years, the AHA published nine sets of recommendations for antibiotic prophylaxis for dental patients at risk for IE. These recommendations, first put forth in 1955 and revised every few years,

varied in terms of identification of risk conditions, selection of antibiotics, timing of antibiotic administration, and route of administration of antibiotics. It is important to recognize that although these recommendations were a rational and prudent attempt to prevent life-threatening infection, they were largely based on circumstantial evidence, expert opinion, clinical experience, and descriptive studies in which surrogate measures of risk were used. Furthermore, the effectiveness of these recommendations has never been proved in humans. Recently, accumulating evidence suggests that many of the widely held assumptions on which these previous recommendations were made may not be accurate

TABLE 2-3
Summary of Nine Previous Iterations of American Heart Association–Recommended Antibiotic Regimens (from 1955-1997) for Dental/Respiratory Tract Procedures (for adults)

Year	Primary Regimens for Dental Procedures
1955	600,000 U of aqueous penicillin and 600,000 U of procaine penicillin in oil containing 2% aluminum monostearate administered intramuscularly 30 minutes before the operative procedure
1957	For 2 days prior to surgery, 200,000 to 250,000 U of penicillin by mouth 4 times a day. On day of surgery, 200,000 to 250,000 U by mouth 4 times a day and 600,000 U aqueous penicillin with 600,000 units procaine penicillin IM 30 minutes before surgery. For 2 days after, 200,000 to 250,000 U by mouth 4 times a day
1960	Step 1: Prophylaxis 2 days before surgery with 600,000 U of procaine penicillin intramuscularly on each day Step 2: Day of surgery: 600,000 U procaine penicillin intramuscularly, supplemented by 600,000 U of crystalline penicillin intramuscularly 1 hour before surgical procedure Step 3: For 2 days after surgery: 600,000 U procaine penicillin intramuscularly each day
1965	Day of procedure: Procaine penicillin 600,000 U, supplemented by 600,000 U of crystalline penicillin intramuscularly 1 to 2 hours before the procedure For 2 days after procedure: Procaine penicillin 600,000 U intramuscularly each day
1972	600,000 U of procaine penicillin G with 200,000 U of crystalline penicillin G intramuscularly 1 hour prior to procedure and once daily for 2 days after the procedure
1977	Aqueous crystalline penicillin G (1,000,000 U intramuscularly) mixed with procaine penicillin G (600,000 U intramuscularly). Give 30 minutes to 1 hour prior to procedure, and then give penicillin V 500 mg orally every 6 hours for 2 doses
1984	Penicillin V 2 g orally 1 hour before procedure; then, give 1 g 6 hours after initial dose
1990	Amoxicillin 3 g orally 1 hour before procedure; then, 1.5 g 6 hours after initial dose
1997	Amoxicillin 2 g orally 1 hour before procedure

From Prevention of Infective Endocarditis. Guidelines From the American Heart Association. A Guideline From the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group.

BOX 2-1

Cardiac Conditions Associated With the Highest Risk of Adverse Outcome From Endocarditis for Which Prophylaxis With Dental Procedures Is Recommended

- Prosthetic cardiac valve
- Previous infective endocarditis
- Congenital heart disease (CHD)†
  - Unrepaired cyanotic CHD, including those with palliative shunts and conduits
  - Completely repaired CHD with prosthetic material or device by surgery or catheter intervention during the first 6 months after the procedure*
  - Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device, which inhibits endothelialization
- Cardiac transplantation recipients who develop cardiac valvulopathy

BOX 2-2

Dental Procedures for Which Endocarditis Prophylaxis Is Recommended for Patients in Box 2-1

- All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa
- This includes all dental procedures except the following procedures and events:
  - Routine anesthetic injections through noninfected tissue
  - Taking of dental radiographs
  - Placement of removable prosthodontic or orthodontic appliances
  - Adjustment of orthodontic appliances
  - Shedding of deciduous teeth and bleeding from trauma to the lips or oral mucosa

TABLE 2-5
Antibiotic Regimens for a Dental Procedure

Situation	Agent	Regimen: Single Dose 30-60 Minutes before Procedure	
		Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin or Cefazolin or Ceftriaxone	2 g IM or IV 1 g IM or IV	50 mg/kg IM or IV 50 mg/kg IM or IV
Allergic to penicillins or ampicillin (oral)	Cephalexin*† or Clindamycin	2 g 600 mg	50 mg/kg 20 mg/kg
	Azithromycin or Clarithromycin	500 mg	15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medication	Cefazolin or Ceftriaxone†	1 g IM or IV	50 mg/kg
	Clindamycin phosphate	600 mg IM or IV	20 mg/kg IM or IV

From Prevention of Infective Endocarditis. Guidelines From the American Heart Association. A Guideline From the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Copyright © 2007, American Heart Association, Inc.
IM, Intramuscularly; IV, intravenously.
*Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.
†Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria following penicillins or ampicillin.

Suggestive Reading

James W Little, Craig S Miller, Nelson L Rhodus. Dental management of medically compromised patient, 9th edition, Elsevier, 2018