ΛΟΙΜΩΔΗΣ ΕΝΔΟΚΑΡΔΙΤΙΔΑ

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Definition

- Infective endocarditis is defined as an infection, usually bacterial, of the endocardial surface of the heart.
- Infective endocarditis primarily affects the cardiac valves, although the septa between the chambers or the mural endocardium may be involved in some cases.
- Traditionally, infective endocarditis has been categorized as **acute or subacute**, depending on the length of symptoms before presentation; however, this distinction is somewhat arbitrary.
- A classification that considers the causative organism and the valve involved is more clinically relevant.

Epidemiology

- The incidence of infective endocarditis is difficult to determine because of the criteria for diagnosis and the methods of reporting.
- An analysis based on strict case definitions often reveals that only a relatively small proportion (~20%) of clinically diagnosed cases are categorized as definite.
- Nevertheless, in 10 large surveys, infective endocarditis accounted for approximately 1 case per 1000 U.S. hospital admissions, with a range of 0.16 to 5.4 cases per 1000 admissions.
- This incidence has not changed appreciably during the past 30 years.
- Estimates from the American Heart Association place the annual incidence of infective endocarditis in the United States at 10,000 to 20,000 new cases.

Epidemiology

- Men are affected more commonly than women are (mean male-to-female ratio of 1.7:1 in 18 large series).
- However, in patients younger than 35 years, more cases occur in women.
- More than 50% of patients with infective endocarditis in the United States are now older than 50 years.
- This is due to the low incidence of acute rheumatic fever and low subsequent prevalence of rheumatic heart disease compared with prior eras and with developing countries, as well as a simultaneous rise in the prevalence of degenerative heart disease as the population lives longer.
- Cardiac conditions that cause turbulent flow at the endocardial surface or across a valve have been found to predispose patients to infective endocarditis

PREDISPOSING CONDITIONS ASSOCIATED WITH INCREASED RISK OF ENDOCARDITIS

More Common	Less Common
Mitral valve prolapse with murmur	Rheumatic heart disease
Degenerative valvular disease	Hypertrophic obstructive cardiomyopathy
Intravenous drug use[*]	
Prosthetic valve[*]	Pulmonary-systemic shunts[*]
Congenital abnormalities (valvular or septal defect)	Coarctation of the aorta
	Previous endocarditis[*]
	Complex cyanotic congenital heart disease[*]

* Indicates lesions with highest risk for endocarditis.

- Mitral valve prolapse is currently the most common underlying cardiac condition in infective endocarditis, a statistic that reflects its prevalence in the general population (4%).
- Notably, mitral valve prolapse is a risk only in patients with thickened mitral leaflets or regurgitation, in which case the risk of endocarditis increases by about 10-fold above that of the general population.
- In addition, patients with hypertrophic cardiomyopathy are at increased risk of infective endocarditis, particularly in the presence of outflow obstruction.
- Finally, previous endocarditis is among the highest risk factors for infective endocarditis.

• Prosthetic cardiac valves represent an important risk factor for infective endocarditis.

• More than 150,000 heart valves are implanted annually worldwide, and prosthetic valve infective endocarditis develops in 1 to 4% of prosthetic valve recipients in the first year after valve replacement and in approximately 0.8% of recipients annually thereafter.

• Mechanical prosthetic valves may initially be more susceptible to infective endocarditis, but bioprosthetic valves are more likely to develop infective endocarditis after 1 year; overall, the rate is similar with either type of valve.

- The incidence of infective endocarditis in injection drug users may be 30 times higher than in the general population and 4 times higher than the risk in adults with rheumatic heart disease.
- In some areas of the United States, injection drug use is the most common predisposing cause of infective endocarditis in patients younger than 40 years.
- *Staphylococcus aureus* is the predominant organism, and tricuspid valve involvement is noted in 78% of cases, mitral involvement in 24%, and aortic involvement in 8%.
- More than one valve is infected in approximately 20% of cases, and some of these infections are polymicrobial.

- Health care–associated infective endocarditis arises primarily as a consequence of invasive therapies, including intravenous catheters, hyperalimentation lines, pacemakers, and dialysis shunts.
- For example, in a prospective multinational cohort study of 1779 prospectively enrolled patients with definite infective endocarditis from 39 referral and nonreferral centers in 16 countries, 24% had health care–associated infective endocarditis.
- Patients with health care–associated infective endocarditis are typically older and have other comorbid conditions. Health care–associated infective endocarditis in industrialized nations is commonly caused by *S. aureus*, which frequently causes bacteremia and increasingly is antibiotic resistant.

• Systemic medical conditions predispose patients to the development of infective endocarditis.
• For example, human immunodeficiency virus infection is an independent risk factor for the development of infective endocarditis in injection drug users, with the risk increasing as the CD4+ count decreases.
• Catheter-related bacteremia is an important risk factor for nosocomial infective endocarditis.
• Patients with end-stage renal disease, particularly those receiving long-term hemodialysis, and patients with diabetes mellitus are also at increased risk, presumably because of the recurrent vascular access associated with hemodialysis and the low-level immunosuppression associated with both conditions.

- The mitral valve has classically been the most commonly affected valve, followed by the aortic valve.
- Although mitral valve relapse remains the most common underlying condition, the decreasing frequency of rheumatic mitral disease and increasing senescence of the population may account for the increase in aortic valve endocarditis reported in many studies.
- The next most commonly affected valves in descending order of prevalence are the mitral and aortic valves together, the tricuspid valve, mixed right- and left-sided infection, and the pulmonic valve.

Microbiology

- About 90% of community-acquired, native valve infective endocarditis is due to staphylococci, streptococci, or enterococci, each of which is a normal inhabitant of the skin, oropharynx, and urogenital tract with frequent access to the blood stream.
- These organisms express specific receptors for attachment and adherence to damaged valve surfaces.
- Streptococcal species are the most common cause in community-dwelling patients with no history of injection drug use or health care contact.
- In patients with either of these epidemiologic risk factors, *S. aureus* is the predominant cause of infective endocarditis.
- Because of the emergence of health care contact as the predominant risk factor for blood stream infections, *S. aureus* is now the most common cause of infective endocarditis in many regions of the world.

• Viridans streptococci are the most common streptococci implicated in native valve infective endocarditis. This group of organisms, which normally inhabit the oropharynx, includes species such as *Streptococcus sanguis, Streptococcus mutans,* and *Streptococcus mitis.*

• Group B streptococci, β-hemolytic organisms that are also normal oropharyngeal and urogenital flora, most frequently cause infective endocarditis in patients with cirrhosis or diabetes mellitus and in injection drug users.

• By contrast, group A streptococci, although also β-hemolytic, rarely cause infective endocarditis.

• *Streptococcus bovis,* a group D streptococcus, is now a leading cause of infective endocarditis in some parts of the world. Its presence should prompt endoscopic evaluation for adenocarcinoma of the colon or other malignant lesions of the gastrointestinal tract.

• Pneumococcal endocarditis is decreasing in incidence but is fulminant when present; it may occur as part of Austrian's (or Osler's) triad of endocarditis, meningitis, and pneumonia and is associated with high morbidity and mortality.

• The clinical course of *S. aureus* endocarditis is typically acute, with a rapid progression during the course of several days.

• Because approximately 12% of nonselected patients with *S. aureus* bacteremia will have infective endocarditis, the possibility of cardiac involvement should always be considered in any patient with *S. aureus* bacteremia.

• Patients with *S. aureus* bacteremia who manifest clinical risk factors, including persistent bacteremia or fever, community acquisition, and cutaneous findings, are at particular risk for infective endocarditis and other complications.

• Coagulase-negative staphylococci are an unusual cause of native valve disease but important pathogens in prosthetic valve endocarditis; presentation is usually subacute.

• Enterococcal bacteremia is far more common, particularly in hospitalized patients, than enterococcal endocarditis; however, enterococci are still responsible for a significant number of cases of both community-acquired and nosocomial endocarditis.

• In most cases, the source of the bacteria is thought to be the genitourinary tract, and the presentation is usually subacute.

• Enterococcal endocarditis, as opposed to enterococcal bacteremia, is suggested by community acquisition of infection, absence of a clear source of infection, preexistent valvular heart disease, and absence of polymicrobial bacteremia.

• As in most enterococcal infections, the overwhelming majority of cases (>90%) are due to *Enterococcus faecalis.*

• The HACEK group of gram-negative organisms (*Haemophilus* species, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species) accounts for about 5% of cases of endocarditis.

• Because these fastidious organisms will usually grow in blood cultures within 7 days by current methods, prolonged incubation is generally no longer required to isolate HACEK strains.

• Many other gram-negative bacilli have been reported to cause infective endocarditis but are even more unusual.

• Fungal endocarditis is difficult to diagnose and to treat.

• It is most commonly found in patients with a history of injection drug use, recent cardiac surgery, or prolonged use of indwelling vascular catheters, especially those used for total parenteral nutrition.

• The most common fungi found in infective endocarditis are *Aspergillus* and *Candida* species.

•*Aspergillus* rarely grows in blood cultures and must usually be cultured from a pathologic specimen (either an embolic site or vegetation).

• By contrast, *Candida* frequently grows out of blood cultures.

• Mortality is very high, and valve replacement surgery is usually necessary.

Prosthetic valve endocarditis can be classified into one of three groups on the basis of time at onset after valve surgery:

1. early (less than 2 months after surgery)
2. intermediate (2 to 12 months)
3. late (more than 12 months)

Staphylococci, particularly *S. aureus,* predominate during the early period, when most episodes of infective endocarditis are thought to be related to perioperative infection.

The intermediate period has a fairly similar microbiologic spectrum, with unusual gram-negatives and diphtheroids decreasing and streptococci increasing.

In the late period, 1 year and more after surgery, the spectrum of organisms becomes more akin to that of community-acquired native valve disease, in which *S. aureus* and streptococci predominate.

Of note, approximately 50% of prosthetic valve recipients with *S. aureus* bacteremia will develop infective endocarditis.

ETIOLOGY OF PROSTHETIC VALVE ENDOCARDITIS[*]

Early (<2 Months)	Intermediate (2–12 Months)	Late (>12 Months)
Coagulase-negative staphylococci	Coagulase-negative staphylococci	Streptococci
		S. aureus
S. aureus	Enterococci	Coagulase-negative staphylococci
Gram-negative bacilli	*S. aureus*	
Enterococci	Fungi	Enterococci
Fungi	Streptococci	
Diphtheroids		

* Listed in order of relative frequency on the basis of time at onset after surgery.

Pathobiology

• Most cases of infective endocarditis begin with a damaged endocardial surface.
• Damage to the endocardium may be caused by a number of factors, ranging from rheumatic disease to senile degeneration and calcification.
• Indeed, any excessive turbulence or high-pressure gradient may cause injury to the nearby endocardium.
• Next, fibrin-platelet aggregates develop at the site of damage to form sterile vegetations, also termed nonbacterial thrombotic endocarditis.
• Nonbacterial thrombotic endocarditis may occur spontaneously in patients with systemic illnesses (for instance, the marantic endocarditis of malignant disease or other wasting diseases and Libman-Sacks endocarditis in systemic lupus erythematosus).

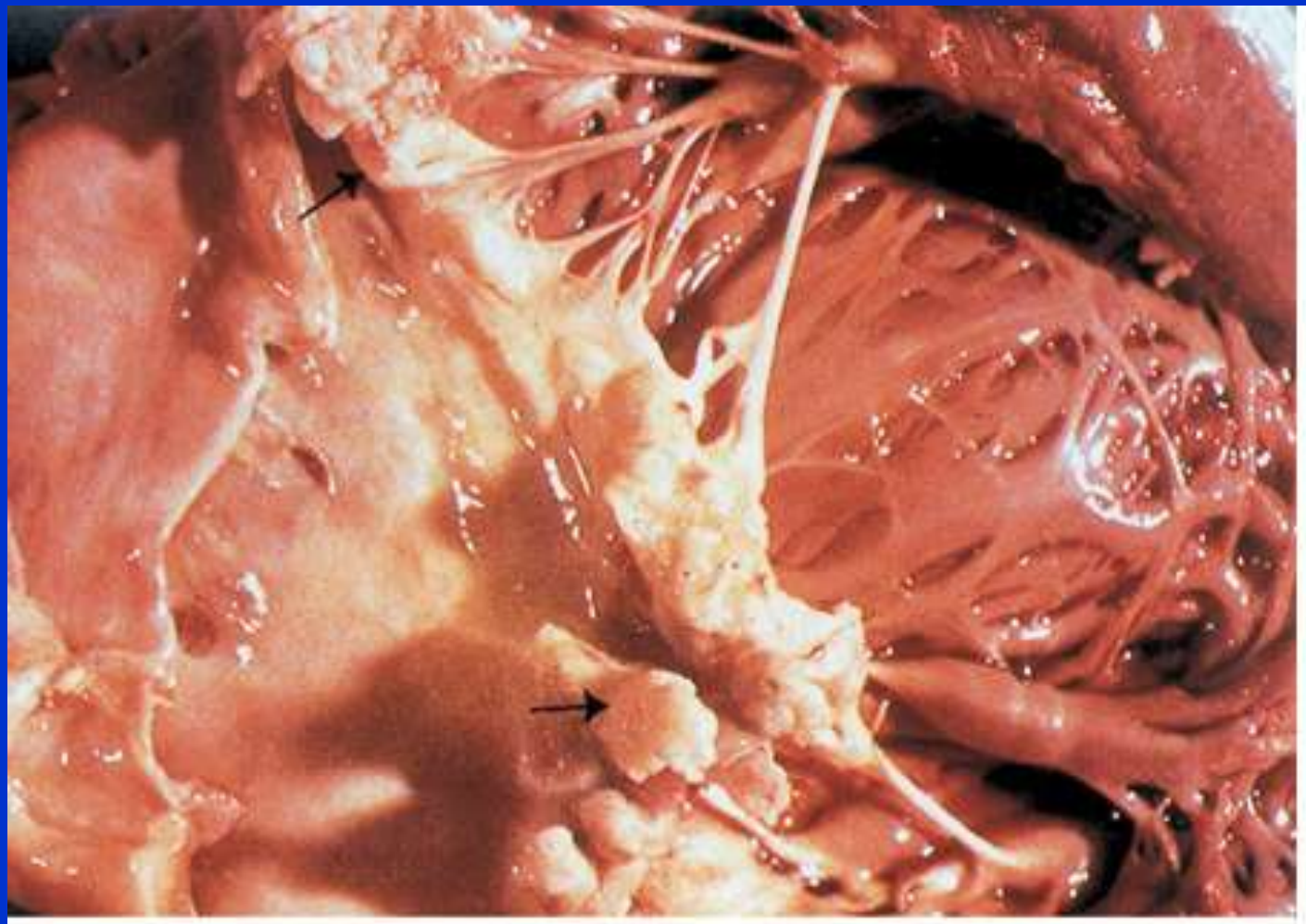
Pathobiology

- When transient bacteremia occurs, for example, as a result of distant infection or gingival disease, the previously sterile vegetation may be seeded.

- Some bacterial species, such as staphylococci and streptococci, are more avidly adherent than others to vegetations and therefore more frequently cause endocarditis.

- The bacteria then proliferate within the vegetation and ultimately may achieve an organism load of 109 to 1011 colony-forming units per gram of tissue.

- The surfaces of cardiac valves and vegetations are avascular, thereby making antibiotic therapy and healing difficult.



Vegetations (*arrows*) due to viridans streptococcal endocarditis involving the mitral valve.

Clinical Manifestations

History

- The initial presentation of infective endocarditis varies enormously from patient to patient, so sometimes it is difficult to make the diagnosis.
- Most patients complain of fever and nonspecific constitutional symptoms, such as fatigue, malaise, and weight loss.
- Nearly 50% of patients complain of musculoskeletal symptoms ranging from frank arthritis to diffuse myalgias.
- 5 to 10% of patients have low back pain as their chief complaint, even in the absence of osteomyelitis or epidural abscess.
- Many intravenous drug users with endocarditis complain of pleuritic chest pain because tricuspid valve endocarditis mimics pneumonia.
- Health care–associated infective endocarditis is more likely to be clinically occult and requires a high index of suspicion.

PHYSICAL EXAMINATION IN INFECTIVE ENDOCARDITIS

Finding	% of Cases
Fever	80–95
Audible murmur	85
New or changed murmur	15–47
Neurologic abnormalities	20–40
Splenomegaly	0–60
Petechiae	20–40
Splinter hemorrhages	15
Osler's nodes	10–25
Janeway lesions	<10
Roth's spots	<5

PHYSICAL EXAMINATION IN INFECTIVE ENDOCARDITIS

- The skin and nails should be carefully examined for embolic phenomena, such as petechiae, Osler's nodes, Janeway lesions, and splinter hemorrhages.

- These findings are uncommon in infective endocarditis in the current era but are extremely helpful diagnostic clues when they are present.

- Petechiae are most often found on the conjunctiva, palate, and extremities; like the other peripheral stigmata of infective endocarditis, they are a nonspecific but suggestive finding.

PHYSICAL EXAMINATION IN INFECTIVE ENDOCARDITIS

Osler's nodes are small, **painful** nodules found most often on the palmar surfaces of the fingers and toes; they frequently wax and wane.

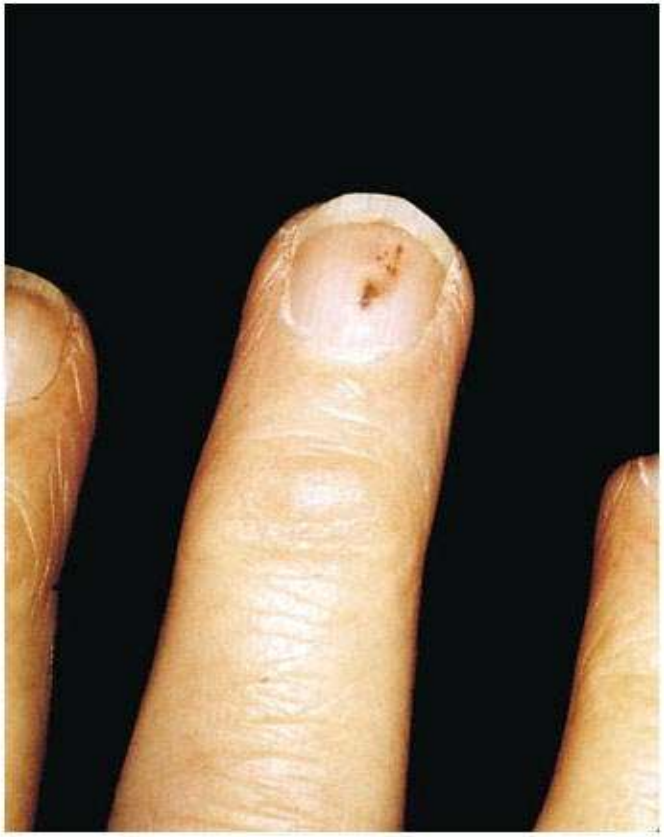
Classically considered to be an immunologic phenomenon, Osler's nodes may have an immune complex–mediated component but are most likely initiated by microemboli.

PHYSICAL EXAMINATION IN INFECTIVE ENDOCARDITIS

Janeway lesions are hemorrhagic, **nonpainful** macules also found primarily on the palms and soles; they are embolic in origin and are less frequently noted than the other cutaneous stigmata.

Splinter hemorrhages are nonblanching, linear, brownish red lesions in the nail beds perpendicular to the direction of growth of the nail; they are nonspecific and may also be found in a significant percentage of hospitalized patients without infective endocarditis.

Splinter hemorrhages



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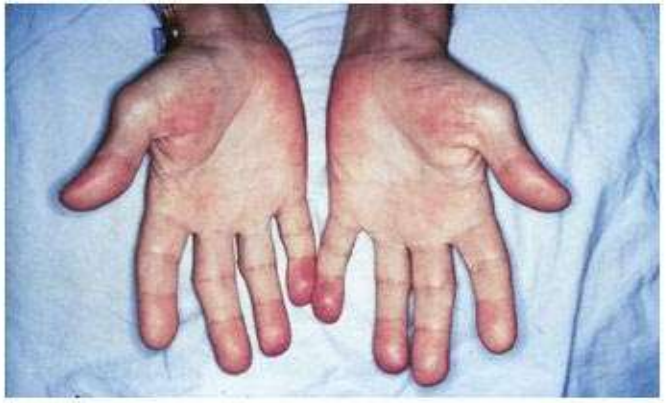
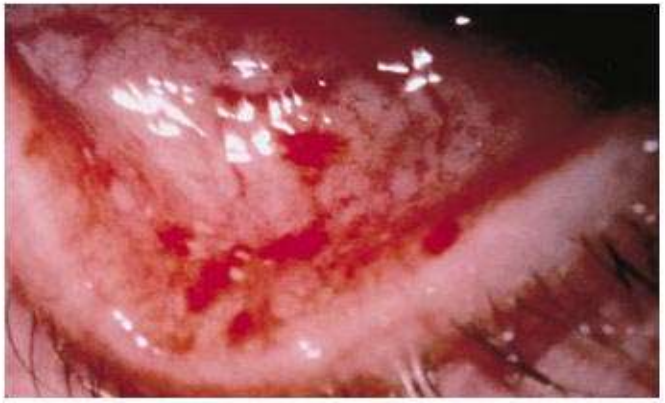


C

Osler's nodes

Conjunctival petechiae



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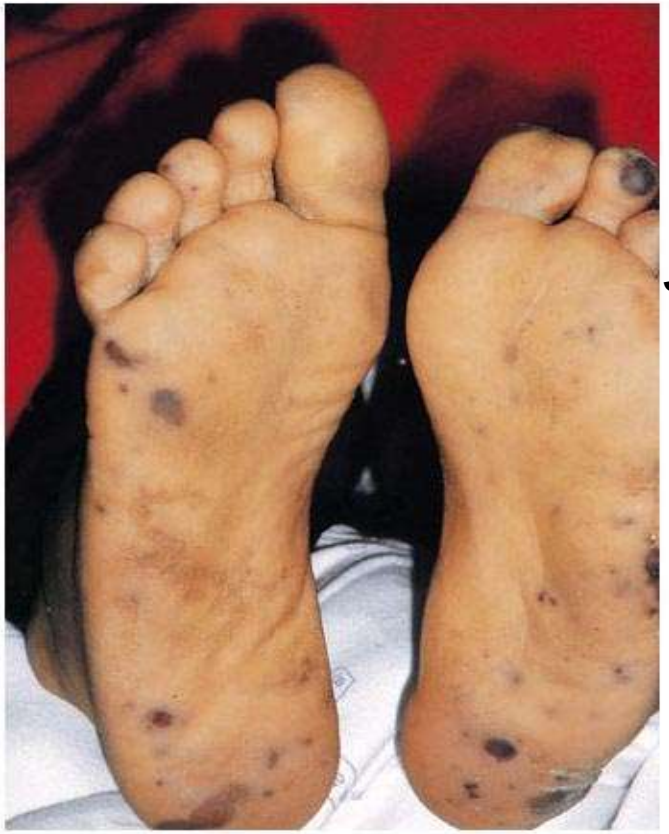
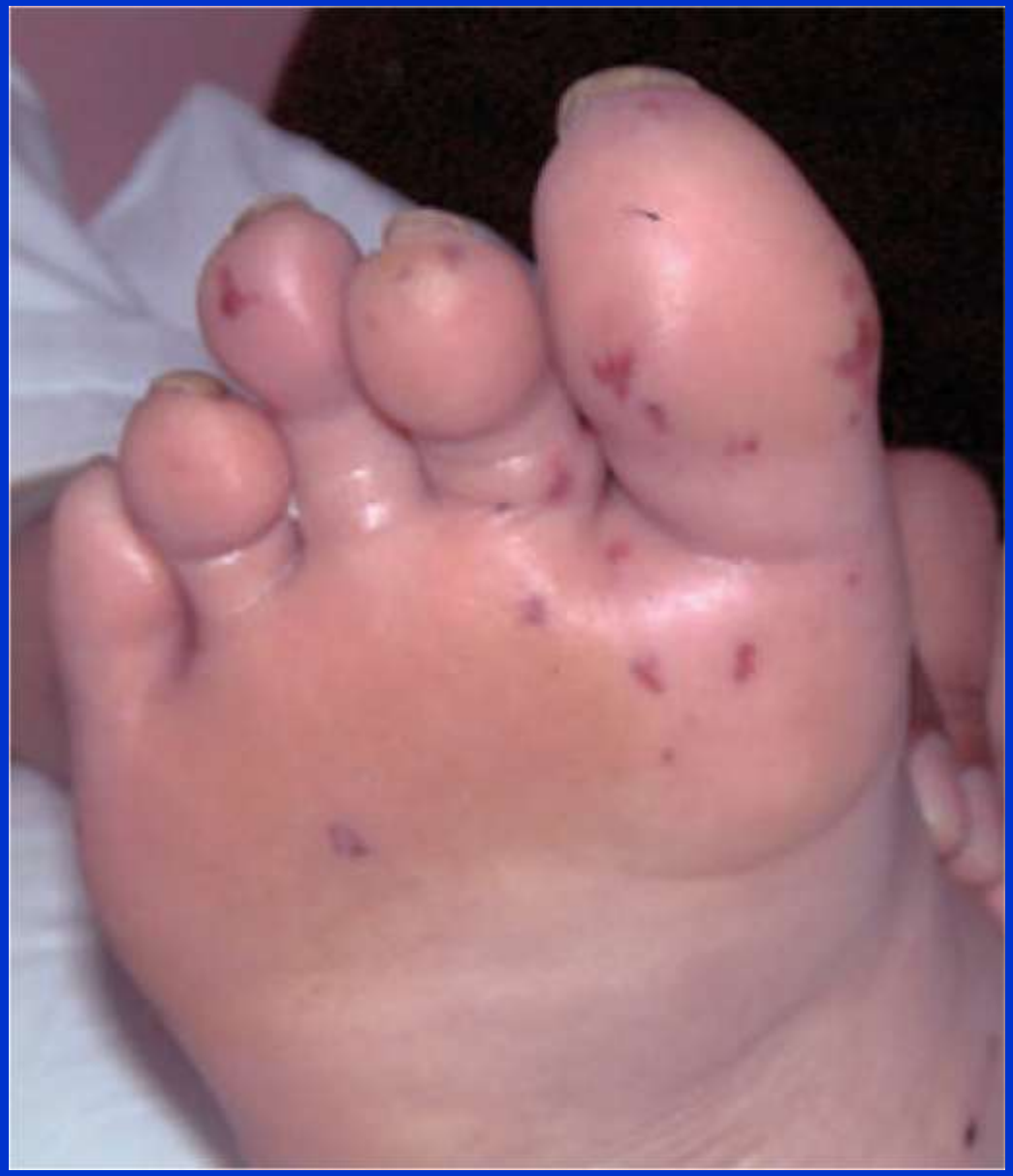
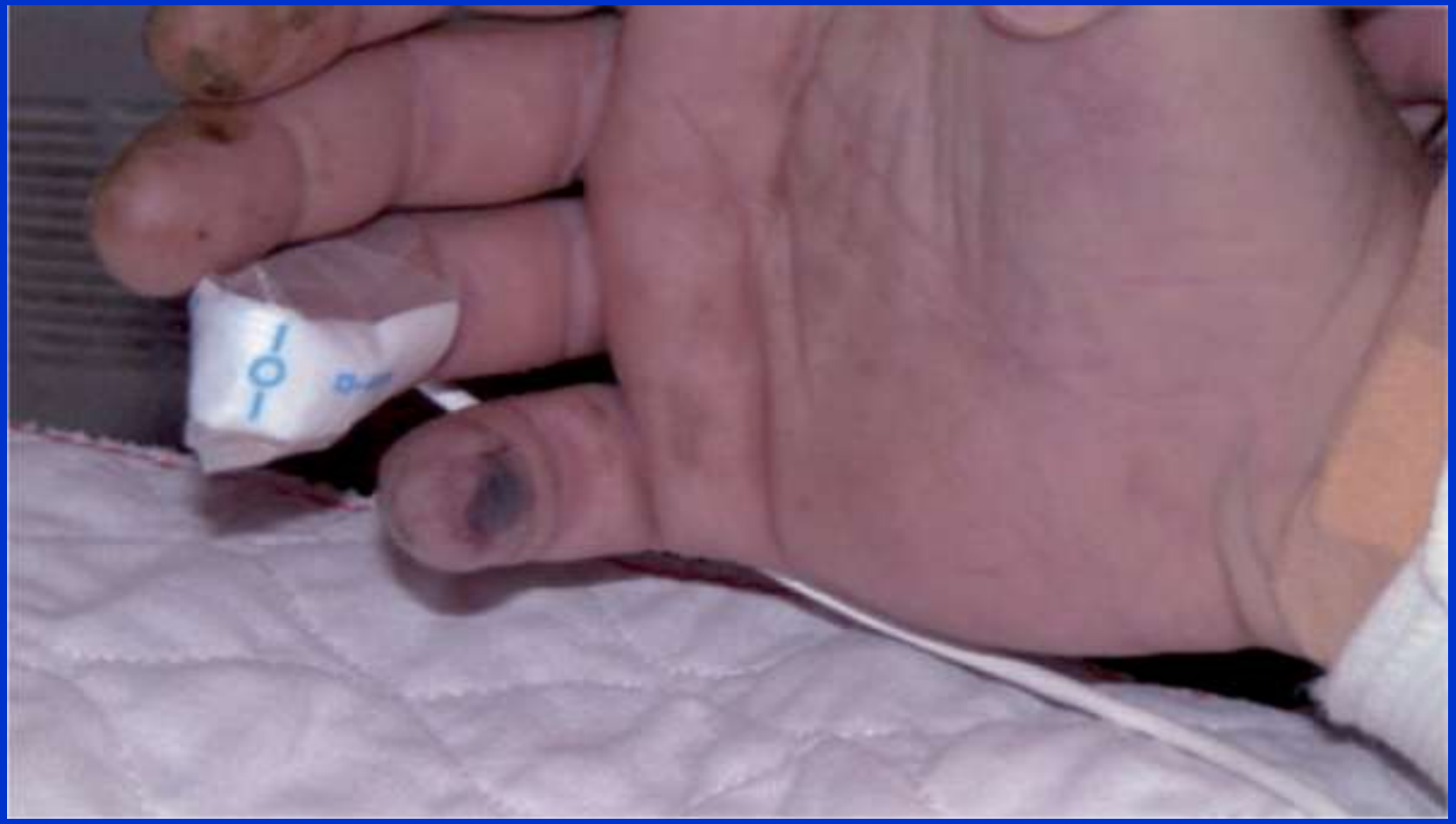


D

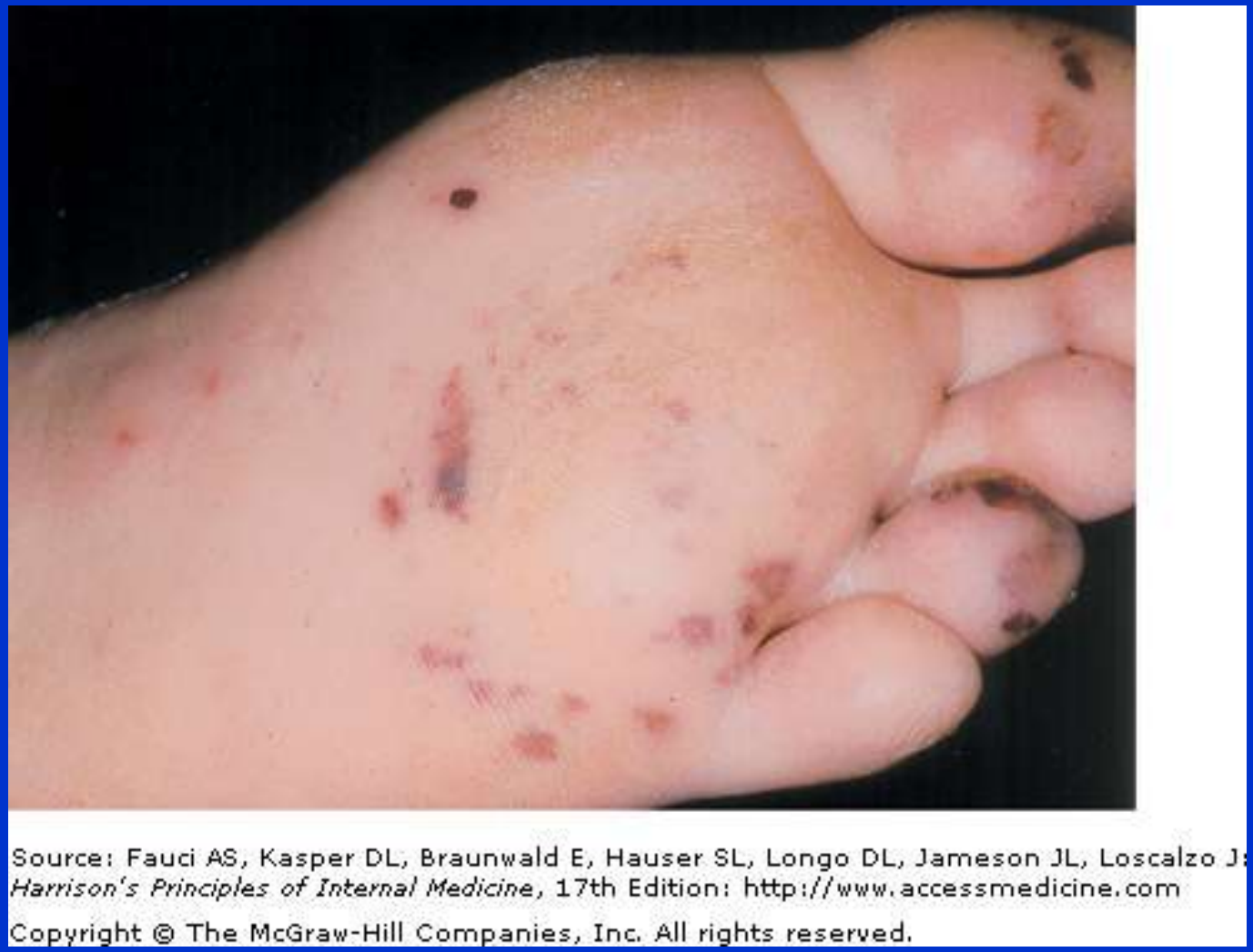
Janeway's lesions



Petechiae in infective endocarditis



Osler's node in infective endocarditis



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J:
Harrison's Principles of Internal Medicine, 17th Edition: http://www.accessmedicine.com

Septic emboli with hemorrhage and infarction due to acute *Staphylococcus aureus* endocarditis

PHYSICAL EXAMINATION IN INFECTIVE ENDOCARDITIS

•Funduscopic examination should be performed to look for Roth's spots, chorioretinitis, and endophthalmitis, the last two of which are present in a substantial proportion of cases of fungal endocarditis.

•A careful cardiac examination should be performed to detect any systolic or diastolic murmurs or evidence of heart failure, which is an ominous sign.

•The abdomen should be examined for evidence of splenomegaly, a finding that is more common in patients with a subacute form of infective endocarditis.

•Finally, a thorough neurologic examination should be performed, both to assess the patient for any focal neurologic deficit and to serve as a baseline during the hospital stay.

LABORATORY FINDINGS IN INFECTIVE ENDOCARDITIS

Finding	% of Cases
Anemia of chronic disease	50–90
Leukocytosis	20–66
Elevated erythrocyte sedimentation rate	90–100
Microscopic hematuria	50–70
Presence of rheumatoid factor	40–50
Abnormal chest x-ray (effusion, infiltrate, septic emboli)	67–85 (right-sided infective endocarditis)

LABORATORY FINDINGS IN INFECTIVE ENDOCARDITIS

- **All patients should receive at least three to six sets of blood cultures and many require echocardiography during their admission.**
- Most patients with subacute infective endocarditis have anemia of chronic disease.
- The white blood cell count may or may not be elevated; it is more frequently elevated in cases of acute infective endocarditis, particularly if *S. aureus* or a fungus is the causative organism.
- Microscopic hematuria is noted in many cases, as is proteinuria.
- The chest radiograph is abnormal, demonstrating consolidation, atelectasis, pleural effusion, or clear septic emboli in the overwhelming majority of patients with right-sided endocarditis; in others, it may provide evidence of congestive heart failure.

LABORATORY FINDINGS IN INFECTIVE ENDOCARDITIS

- The electrocardiogram should be carefully examined for evidence of atrioventricular conduction blocks, which might suggest an aortic ring abscess or other myocardial involvement, or frank myocardial infarction.

- Other ancillary tests might include an erythrocyte sedimentation rate, which is elevated in nearly all cases of infective endocarditis with a mean value of 57 mm/hr.

- **Rheumatoid factor is present in about half of cases, particularly in subacute endocarditis.**

Diagnosis

- The “gold standard” for the diagnosis of infective endocarditis is culture of a pathologic organism from a valve or other endocardial surface.

- However, unless the patient undergoes valve replacement or postmortem examination, the diagnosis is made clinically.

- As a result, various clinical criteria have been proposed; the most widely accepted are the modified Duke criteria, which have an estimated 76 to 100% sensitivity and 88 to 100% specificity, with a negative predictive value of at least 92%.

TABLE 58–4 Diagnosis of Infective Endocarditis (Modified Duke Criteria)

Definitive Infective Endocarditis

Pathological criteria
- Microorganisms: demonstrated by culture or histology in a vegetation, *or* in a vegetation that has embolized, *or* in an intracardiac abscess, *or*
- Pathological lesions: vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis

Clinical criteria, using specific definitions listed below
- Two major criteria, *or*
- One major and three minor criteria, *or*
- Five minor criteria

Possible Infective Endocarditis

One major criterion and one minor criterion or three minor criteria

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Rejected

Firm alternative diagnosis for manifestations of endocarditis, *or*

Sustained resolution of manifestations of endocarditis, with antibiotic therapy for 4 days or less, *or*

No pathological evidence of infective endocarditis at surgery or autopsy, after antibiotic therapy for 4 days or less

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Criteria for Diagnosis of Infective Endocarditis

Major criteria

Positive blood culture
- Typical microorganism for infective endocarditis from two separate blood cultures
  - Viridans streptococci, *Streptococcus bovis*, HACEK group *or* *Staphylococcus aureus* or community-acquired enterococci in the absence of a primary focus, *or*
- Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from:
  - Blood cultures (≥2) drawn more than 12 hr apart, *or*
  - All of three or a majority of four or more separate blood cultures, with first and last drawn at least 1 hr apart
- Single positive blood culture for *coxiella burnetii* or antiphase I IgG antibody titer >1:800

Evidence of endocardial involvement
- Positive echocardiogram
  - (TEE advised for PVE or complicated IE)
  - Oscillating intracardiac mass, on valve or supporting structures, *or* in the path of regurgitant jets, *or* on implanted material, in the absence of an alternative anatomical explanation, *or*
  - Abscess, *or*
  - New partial dehiscence of prosthetic valve, *or*
- New valvular regurgitation (increase or change in preexisting murmur not sufficient)

Minor criteria

Predisposition: predisposing heart condition *or* intravenous drug use

Fever ≥38.0°C (100.4°F)

Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions

Immunological phenomena: glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor

Microbiological evidence: positive blood culture but not meeting major criterion as noted previously* *or* serologic evidence of active infection with organism consistent with infective endocarditis

BLOOD CULTURES IN INFECTIVE ENDOCARDITIS

- At least three to six sets of blood cultures should be obtained from separate sites; each set consists of one aerobic and one anaerobic bottle, with careful attention paid to aseptic technique.

- Ideally, these sets are collected at least 1 hour apart to document continuous bacteremia; however, in cases in which patients are critically ill, this may not be feasible.

- In most cases of endocarditis, in the absence of prior antibiotic therapy, every blood culture is positive because the bacteremia of endocarditis is continuous.

- Blood cultures are truly negative in less than 5% of cases of endocarditis; however, prior antibiotic administration may decrease the yield of blood cultures by up to 35%.

BLOOD CULTURES IN INFECTIVE ENDOCARDITIS

- When blood cultures are negative and endocarditis is suspected, especially when a history of recent antimicrobials is lacking, consideration should be given to fastidious organisms, fungi, and noncultivatable organisms.
- This possibility should receive particular attention when the patient's history reveals a suggestive exposure: farm animals or unpasteurized milk *(Coxiella burnetii, Brucella),* cats *(Bartonella henselae),* body lice *(Bartonella quintana),* or contact with birds or frequent lawn mowing *(Chlamydia psittaci).*
- The traditional practice of “holding” blood cultures for 2 to 4 weeks to investigate culture-negative endocarditis does not appear to be required routinely.
- If the search for a causative organism remains fruitless, consider noninfectious etiologies such as marantic or Libman-Sacks endocarditis and atrial myxoma.

TABLE 2. LABORATORY DIAGNOSIS OF COMMON CAUSES OF CULTURE-NEGATIVE ENDOCARDITIS.*

ORGANISM	APPROACH
Abiotrophia species (previously classified as nutritionally variant streptococci)	Grow in thioglycolate medium of blood culture and as satellite colonies around *Staphylococcus aureus* on blood agar or on medium supplemented with pyridoxal hydrochloride or L-cysteine
Bartonella species (usually *Bartonella henselae* or *B. quintana*)	Serologic tests Lysis-centrifugation system for blood cultures PCR of valve or embolized vegetations[25,28,29]; special culture techniques available, but organisms are slow-growing and may require a month or more for isolation
Coxiella burnetii (Q fever)	Serologic tests PCR, Giemsa stain, or immunohistologic techniques on operative specimens
HACEK organisms	Blood cultures positive by day 7; occasionally require prolonged incubation and subculturing
Chlamydia species (usually *Chlamydia psittaci*)	Culture from blood has been described Serologic tests Direct staining of tissue with use of fluorescent monoclonal antibody
Tropheryma whipplei	Histologic examination (silver and PAS stains) of excised heart valve; PCR[26] or culture of vegetation[30]
Legionella species	Subculture from blood cultures, lysis-centrifugation pellet from blood cultures, or operative specimens on BCYE agar; direct detection on heart valves with fluorescent antibody Serologic tests
Brucella species (usually *Brucella melitensis* or *B. abortus*)	Serologic tests Prolonged incubation of standard or lysis-centrifugation blood cultures
Fungi	Regular blood cultures often positive for candida species; lysis-centrifugation system with specific fungal medium can increase yield; testing urine for *Histoplasma capsulatum* antigen or serum for *Cryptococcus neoformans* polysaccharide capsular antigen can be helpful Accessible lesions (such as emboli) should be cultured and examined histologically for fungi

*PCR denotes polymerase chain reaction; HACEK organisms haemophilus species (*Haemophilus paraninfluenzae, H. aphrophilus,* and *H. paraphrophilus*), *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae;* PAS periodic acid–Schiff; and BCYE buffered charcoal yeast extract.

ECHOCARDIOGRAPHY IN INFECTIVE ENDOCARDITIS

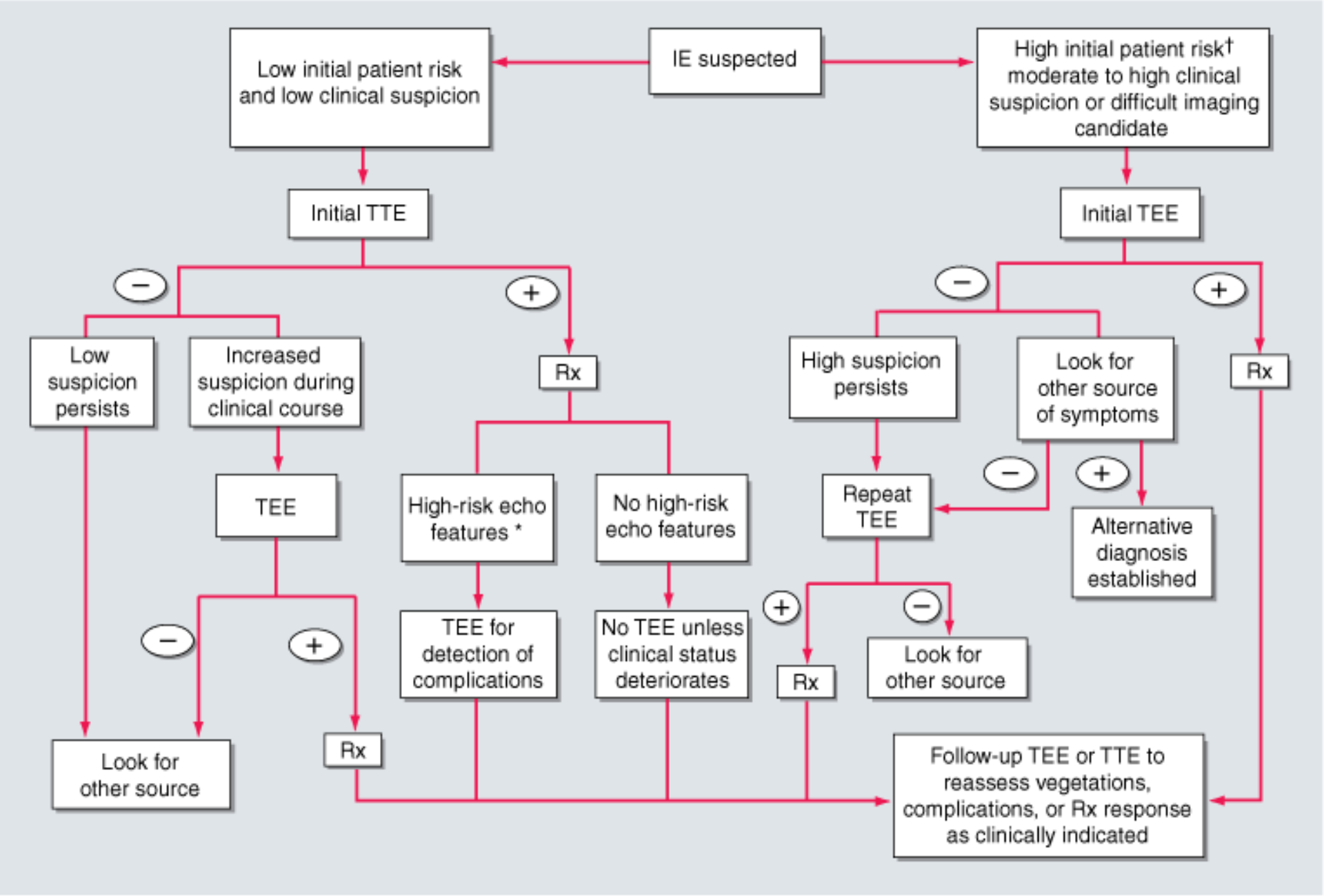
- Both transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) are highly specific tests (98%) as part of the diagnostic evaluation of suspected endocarditis.
- By contrast, TEE has a sensitivity of 90 to 95% in this setting, significantly better than the sensitivity of 48 to 63% usually found with TTE.
- Significant controversy still exists about whether the diagnostic approach to suspected infective endocarditis should begin with TTE or TEE. In most cases in which endocarditis is a serious diagnostic consideration, evaluation should begin with TEE because normal TTE is not sensitive enough to exclude endocarditis.
- In some cases, however, TEE is unavailable, technically impossible, or considered too invasive by the patient, in which case it is reasonable to begin with TTE.

ECHOCARDIOGRAPHY IN INFECTIVE ENDOCARDITIS

TEE should be initially used in the following situations:

- In detecting perivalvular extension of infection.
- In any patient with a new conduction system abnormality or persistent fever—clinical predictors of perivalvular extension.
- In suspected prosthetic valve endocarditis, in which TEE provides superior definition of prosthetic valve vegetations and valve ring abscesses.
- In combination with clinical parameters (e.g., prompt resolution of bacteremia and defervescence) to support the clinical decision to abbreviate therapy in patients with vascular catheter–associated *S. aureus* bacteremia.

- The combination of normal TTE and normal TEE has a negative predictive value of 95%. Nevertheless, when clinical suspicion of endocarditis is high and the initial TEE is normal, repeating the TEE in 7 to 10 days may reveal the diagnosis.



The diagnostic use of transesophageal and transthoracic echocardiography (TEE and TTE, respectively).

COMPLICATIONS OF INFECTIVE ENDOCARDITIS

The complications of infective endocarditis may be divided into four groups:

1. Direct valvular damage and consequences of local invasion
2. Embolic complications (35% of patients have at least one clinically evident embolic event. In fungal endocarditis, the *majority* of patients have at least one embolic event, frequently with a large embolus)
3. Metastatic infections from bacteremia (Renal and splenic abscesses - Vascular aneurysms clinically silent until they rupture, which may be months to years after apparently successful antibiotic treatment)
4. Immunologic phenomena (Directly related to the circulating immune complexes characteristic of the disease. Hypocomplementemic glomerulonephritis. Monarticular and oligoarticular arthritides)

TREATMENT OF INFECTIVE ENDOCARDITIS

- Definitive antibiotic treatment of infective endocarditis is guided by antimicrobial susceptibility testing of the responsible pathogen isolated from clinical culture specimens.

- Frequently, however, it is advisable to begin empirical treatment before definitive culture results are available.

- Not all patients admitted to rule out endocarditis need to be empirically treated.

- Acutely ill patients, patients with evidence of sequelae of endocarditis, and patients who are at high risk for endocarditis should be empirically treated with antibiotics pending culture results.

EMPIRICAL TREATMENT OF ENDOCARDITIS

Characteristics of Patients	Treatment Regimen
Native valve, community acquisition of infection, MRSA unlikely	Nafcillin 2 g IV q4h *plus*
	Penicillin 4 million units IV q4h *plus*
	Gentamicin 1 mg/kg IV q8h
Any of the following: health care–associated infection or other reason to suspect MRSA; severe penicillin allergy	Vancomycin 1 g IV q12h *plus*
	Gentamicin 1 mg/kg IV q8h
Prosthetic valve	Vancomycin 1 g IV q12h *plus*
	Gentamicin 1 mg/kg IV q8h *plus*
	Rifampin 300 mg PO or IV q8h

MRSA = methicillin-resistant *Staphylococcus aureus.*

TABLE 58–6 Treatment for Native Valve Endocarditis Caused by Penicillin-Susceptible Viridans Streptococci and *Streptococcus bovis* (Minimum Inhibitory Concentration ≤0.1 μg/ml)*

Antibiotic	Dosage and Route†	Duration (wk)
Aqueous penicillin G	12-18 million units/24 hr IV either continuously or every 4 hr in six equally divided doses	4
Ceftriaxone	2 gm once daily IV or IM	4
Aqueous penicillin G	12-18 million units/24 hr IV either continuously or every 4 hr in six equally divided doses	2
plus Gentamicin	1 mg/kg IM or IV every 8 hr	2
Vancomycin	30 mg/kg/24 hr IV in two equally divided doses, not to exceed 2 gm/24 hr unless serum levels are monitored	4

TABLE 58–7 Treatment for Native Valve Endocarditis Caused by Strains of Viridans Streptococci and *Streptococcus bovis* Relatively Resistant to Penicillin G (Minimum Inhibitory Concentration >0.1 μg/ml and <0.5 μg/ml)

Antibiotic	Dosage and Route*	Duration (wk)
Aqueous penicillin G	18 million units/24 hr IV either continuously or every 4 hr in six equally divided doses	4
plus		
Gentamicin	1 mg/kg IM or IV every 8 hr	2
Vancomycin	30 mg/kg/24 hr IV in two equally divided doses, not to exceed 2 gm/24 hr unless serum levels are monitored	4

TABLE 58–8 Standard Therapy for Endocarditis Caused by Enterococci*

Antibiotic	Dosage and Route†	Duration (wk)
Aqueous penicillin G	18-30 million units/24 hr IV given continuously or every 4 hr in six equally divided doses	4-6
plus Gentamicin	1 mg/kg IM or IV every 8 hr	4-6
Ampicillin	12 gm/24 hr IV given continuously or every 4 hr in six equally divided doses	4-6
plus Gentamicin	1 mg/kg IM or IV every 8 hr	4-6
Vancomycin‡	30 mg/kg/24 hr IV in two equally divided doses not to exceed 2 gm/24 hr unless serum levels are monitored	4-6
plus Gentamicin	1 mg/kg IM or IV every 8 hr	4-6

TABLE 58–10 Treatment for Staphylococcal Endocarditis in the Absence of Prosthetic Material

Antibiotic	Dosage and Route*	Duration
Methicillin-susceptible staphylococci†		
Nafcillin or oxacillin	2 gm IV every 4 hr	4-6 wk
With optional addition of gentamicin	1 mg/kg IM or IV every 8 hr	3-5 d
Cefazolin (or other first-generation cephalosporins in equivalent dosages)‡	2 gm IV every 8 hr	4-6 wk
With optional addition of gentamicin	1 mg/kg IM or IV every 8 hr	3-5 d
Vancomycin‡	30 mg/kg/24 hr IV in two equally divided doses, not to exceed 2 gm/24 hr unless serum levels are monitored	4-6 wk
Methicillin-resistant staphylococci		
Vancomycin	30 mg/kg/24 hr IV in two equally divided doses, not to exceed 2 gm/24 hr unless serum levels are monitored	4-6 wk

Modified from Wilson WR, Karchmer AW, Dajani AS, et al: Antibiotic treatment of adults with infective endocarditis due to streptococci, enterococci, staphylococci, and HACEK microorganisms. JAMA 274:1706, 1995. Copyright 1995 American Medical Association.

*Dosages are for patients with normal renal function. See Table 58–6, footnote.

†For treatment of endocarditis caused by penicillin-susceptible staphylococci (minimum inhibitory concentration ≤ 0.1 μg/ml), aqueous penicillin G (18-24 million units/24 hr) can be used for 4-6 wk instead of nafcillin or oxacillin.

‡Cefazolin, other first-generation cephalosporins, or vancomycin may be used in selected penicillin-allergic patients.

TABLE 58–11 Treatment of Staphylococcal Endocarditis in the Presence of a Prosthetic Valve or Other Prosthetic Material

Antibiotic	Dosage and Route*	Duration (wk)
Regimen for Methicillin-Resistant Staphylococci		
Vancomycin	30 mg/kg/24 hr IV in two equally divided doses, not to exceed 2 gm/24 hr unless serum levels are monitored	≥6
plus		
Rifampin *and*	300 mg PO every 8 hr	≥6
gentamicin†	1.0 mg/kg IM or IV every 8 hr	2
Regimen for Methicillin-Susceptible Staphylococci		
Nafcillin or oxacillin	2 gm IV every 4 hr	≥6
plus		
Rifampin *and*	300 mg PO every 8 hr	≥6
gentamicin†	1.0 mg/kg IM or IV every 8 hr	2

Modified from Wilson WR, Karchmer AW, Dajani AS, et al: Antibiotic treatment of adults with infective endocarditis due to streptococci, enterococci, staphylococci, and HACEK microorganisms. JAMA 274:1706, 1995. Copyright 1995 American Medical Association.

*Dosages are for patients with normal renal function. See Table 58–6, footnote.

†Use during initial 2 wk of treatment. If strain is gentamicin resistant, see text for alternatives.

TABLE 58–12 Treatment for Endocarditis Caused by HACEK Microorganisms*

Antibiotic	Dosage and Route†	Duration (wk)
Ceftriaxone‡	2 gm once daily IV or IM	4
Ampicillin	12 gm/24 hr IV given continuously or every 4 hr in six equally divided doses	4
plus		
Gentamicin	1 mg/kg IM or IV every 8 hr	4

Modified from Wilson WR, Karchmer AW, Dajani AS, et al: Antibiotic treatment of adults with infective endocarditis due to streptococci, enterococci, staphylococci, and HACEK microorganisms. JAMA 274:1706, 1995. Copyright 1995 American Medical Association.

*HACEK microorganisms are *Hemophilus parainfluenzae, Hemophilus aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species.

†Dosages are for those with normal renal function. See Table 58–6, footnote.

‡Cefotaxime or ceftizoxime in comparable doses may be substituted for ceftriaxone.

• Patients with infective endocarditis may continue to be febrile for some time after the institution of appropriate antibiotic treatment.

• About half of patients defervesce within 3 days of starting antibiotics, and 75% have defervesced at 1 week.

• By 2 weeks, 90% of patients have defervesced. Patients with endocarditis caused by *S. aureus,* gram-negative organisms, or fungi tend to defervesce more slowly than do patients with infective endocarditis related to other organisms.

• Prolonged fever (more than 1 week after institution of appropriate antibiotics) should prompt consideration of several possibilities other than treatment failure: myocardial abscess, extracardiac infection (e.g., mycotic aneurysm, psoas or splenic abscess, vertebral osteomyelitis or septic arthritis), immune complex–mediated tissue damage, or a complication of hospitalization and therapy (e.g., drug fever, nosocomial superinfection, or pulmonary embolism).

- Anticoagulation in individuals with infective endocarditis is controversial. Although anticoagulation in the setting of native valve endocarditis does not appear to provide benefit, some authorities recommend continuing anticoagulation in patients with mechanical prosthetic valve endocarditis.
- However, it is generally advised to discontinue all anticoagulation in patients with *S. aureus* prosthetic valve endocarditis who have experienced a recent CNS embolic event for at least the first 2 weeks of antibiotic therapy to allow the thrombus to organize and potentially prevent the acute hemorrhagic transformation of embolic lesions. Reintroduction of anticoagulation in these patients must be cautious, and the international normalized ratio must be monitored carefully.
- The best option for patients with other indications for anticoagulation, such as deep venous thrombosis, major vessel embolization, or atrial fibrillation, is less clear and should be decided in a multidisciplinary fashion that balances the risks and benefits for each individual patient.

TABLE 58–13 Cardiac Surgery in Patients with Infective Endocarditis

Indications

Moderate to severe congestive heart failure caused by valve dysfunction
Unstable prosthesis, prosthesis orifice obstructed
Uncontrolled infection despite optimal antimicrobial therapy
Unavailable effective antimicrobial therapy: endocarditis caused by fungi, *Brucellae*, *Pseudomonas aeruginosa* (aortic or mitral valves)
Staphylococcus aureus PVE with an intracardiac complication
Relapse of PVE after optimal therapy
Fistula to pericardial sac

Relative Indications*

Perivalvular extension of infection, intracardiac fistula, myocardial abscess with persistent fever
Poorly responsive *S. aureus* NVE (aortic or mitral valves)
Relapse of NVE after optimal antimicrobial therapy
Culture-negative NVE or PVE with persistent fever (≥10 d)
Large (>10 mm diameter) hypermobile vegetation (with or without prior arterial embolus)
Endocarditis caused by highly antibiotic-resistant enterococci

NVE = native valve endocarditis; PVE = prosthetic valve endocarditis.
*Surgery commonly required for optimal outcome.

CARDIAC LESIONS ASSOCIATED WITH ENDOCARDITIS

ENDOCARDITIS PROPHYLAXIS RECOMMENDED	
High risk	Prosthetic valves
	Previous endocarditis
	Complex cyanotic congenital heart disease, e.g., single-ventricle states, transposition of the great vessels, tetralogy of Fallot
	Surgically constructed systemic-pulmonary shunts
Moderate risk	Other congenital heart defects except as below
	Acquired valve dysfunction as follows: valvar stenosis, at least mild aortic insufficiency, at least moderate mitral regurgitation or tricuspid regurgitation, and thickened mitral valve with at least mild mitral regurgitation
	Hypertrophic cardiomyopathy
	Mitral valve prolapse with regurgitation and/or thickened leaflets

CARDIAC LESIONS ASSOCIATED WITH ENDOCARDITIS

PROPHYLAXIS NOT RECOMMENDED	
Negligible risk	Isolated secundum atrial septal defect
	Surgical repair of atrial septal defect, ventricular septal defect, or patent ductus arteriosus without residua beyond 6 months
	Previous coronary artery bypass grafting
	Mitral valve prolapse without mitral regurgitation or thickened leaflets
	Physiologic, functional, or innocent heart murmurs
	Previous rheumatic fever without valvar dysfunction
	Pacemakers and implanted defibrillators

PROCEDURES AND THE NEED FOR ENDOCARDITIS PROPHYLAXIS

ENDOCARDITIS PROPHYLAXIS RECOMMENDED

Dental

- Dental and oral procedures likely to cause significant bleeding, periodontal surgery, scaling, and professional teeth cleaning
- Intraligamentary oral local anesthetic injections
- Intraligamentary oral local anesthetic injections

Respiratory tract

- Surgical operations that involve respiratory mucosa
- Bronchoscopy with a rigid bronchoscope
- Tonsillectomy or adenoidectomy

Gastrointestinal tract

- Sclerotherapy for esophageal varices
- Esophageal stricture dilation
- Endoscopic retrograde cholangiography with biliary obstruction
- Biliary tract surgery
- Surgical operations that involve intestinal mucosa

Genitourinary tract

- Prostatic surgery
- Cystoscopy

Other

- Incision and drainage of infected tissue

TABLE 58–15 Regimens for Prophylaxis Against Endocarditis: Use with Dental, Oral, and Upper Respiratory Tract Procedures

Setting	Regimen*
Standard regimen†	Amoxicillin 3.0 gm PO 1 hr before procedure, then 1.5 gm 6 hr after initial dose
Amoxicillin/penicillin-allergic patients	Erythromycin ethylsuccinate 800 mg, or erythromycin stearate 1.0 gm, PO 2 hr before procedure, then half the dose 6 hr after initial dose *OR* Clindamycin 300 mg PO 1 hr before procedure and 150 mg 6 hr after initial dose
Patients unable to take oral medications	Ampicillin 2.0 gm IM or IV 30 min before procedure, then either ampicillin 1.0 g IM or IV, or amoxicillin 1.5 gm PO, 6 hr after initial dose
Ampicillin/amoxicillin/penicillin-allergic patients unable to take oral medications	Clindamycin 300 mg IV 30 min before procedure, then 150 mg 6 hr after initial dose
Patients considered at highest risk and not candidates for standard regimen	Use standard regimen for genitourinary and gastrointestinal procedures
Ampicillin/amoxicillin/penicillin-allergic patients considered at highest risk	Use regimen for allergic patients undergoing genitourinary and gastrointestinal procedures

*Dosages for adults. Initial pediatric dosages are as follows: Ampicillin or amoxicillin, 50 mg/kg; clindamycin, 10 mg/kg; erythromycin ethylsuccinate or erythromycin stearate, 20 mg/kg; gentamicin, 2.0 mg/kg; and vancomycin, 20 mg/kg. Follow-up doses should be one-half the initial dose. **Total pediatric dose should not exceed total adult dose.**

†Generally recommended for patients at highest risk including those with prosthetic heart valves; physician may elect more vigorous regimens.

Adapted from Dajani AS, Bisno AL, Chung KJ, et al: Prevention of bacterial endocarditis: Recommendations of the American Heart Association. JAMA 264:2919, 1990. Copyright 1990 American Medical Association.

TABLE 58–16 Regimens for Prophylaxis Against Endocarditis: Use with Genitourinary and Gastrointestinal (Except Esophageal) Procedures

Setting	Antibiotic	Regimen*
High-risk patients	Ampicillin plus gentamicin	Ampicillin 2.0 gm IV/IM plus gentamicin 1.5 mg/kg within 30 min of procedure, repeat ampicillin 1.0 gm IV/IM or give amoxicillin 1.0 gm PO 6 hr later
High-risk, penicillin-allergic patients	Vancomycin plus gentamicin	Vancomycin 1.0 gm IV over 1-2 hr plus gentamicin 1.5 mg/kg IM/IV infused or injected 30 min before procedure. No second dose recommended
Moderate-risk patients	Amoxicillin or ampicillin	Amoxicillin 2.0 gm PO 1 hr before procedure or ampicillin 2.0 gm IM/IV 30 min before procedure
Moderate-risk, penicillin-allergic patients	Vancomycin	Vancomycin 1.0 gm IV infused over 1-2 hr and completed within 30 min of procedure

*Dosing for children: ampicillin 50 mg/kg IV/IM, vancomycin 20 mg/kg IV, gentamicin 1.5 mg/kg IV/IM (children's doses should not exceed adult doses).

Adapted from Dajani AS, Taubert KA, Wilson W, et al: Prevention of bacterial endocarditis: Recommendations by the American Heart Association from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young. JAMA 277:1794-1801, 1997.

Prognosis

- Untreated, infective endocarditis is uniformly fatal. Aggressive medical and surgical management, however, has dramatically improved the outcome.
- Mortality overall from both native and prosthetic valve endocarditis remains fairly high, ranging from 17 to 36%.
- Certain subgroups carry a lower risk of death (endocarditis related to viridans streptococci); endocarditis due to *S. aureus,* fungal endocarditis, and zoonotic endocarditis have higher mortalities.
- Heart failure and CNS events are the most frequent causes of death.
- Endocarditis recurs in 12 to 16% of patients and is more common in injection drug users, elderly people, and patients with prosthetic valves.

ΕΥΧΑΡΙΣΤΩ