Infective Endocarditis

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- Definition
- Epidemiology
- Pathogenesis
- Clinical manifestations
- Diagnosis
- Treatment

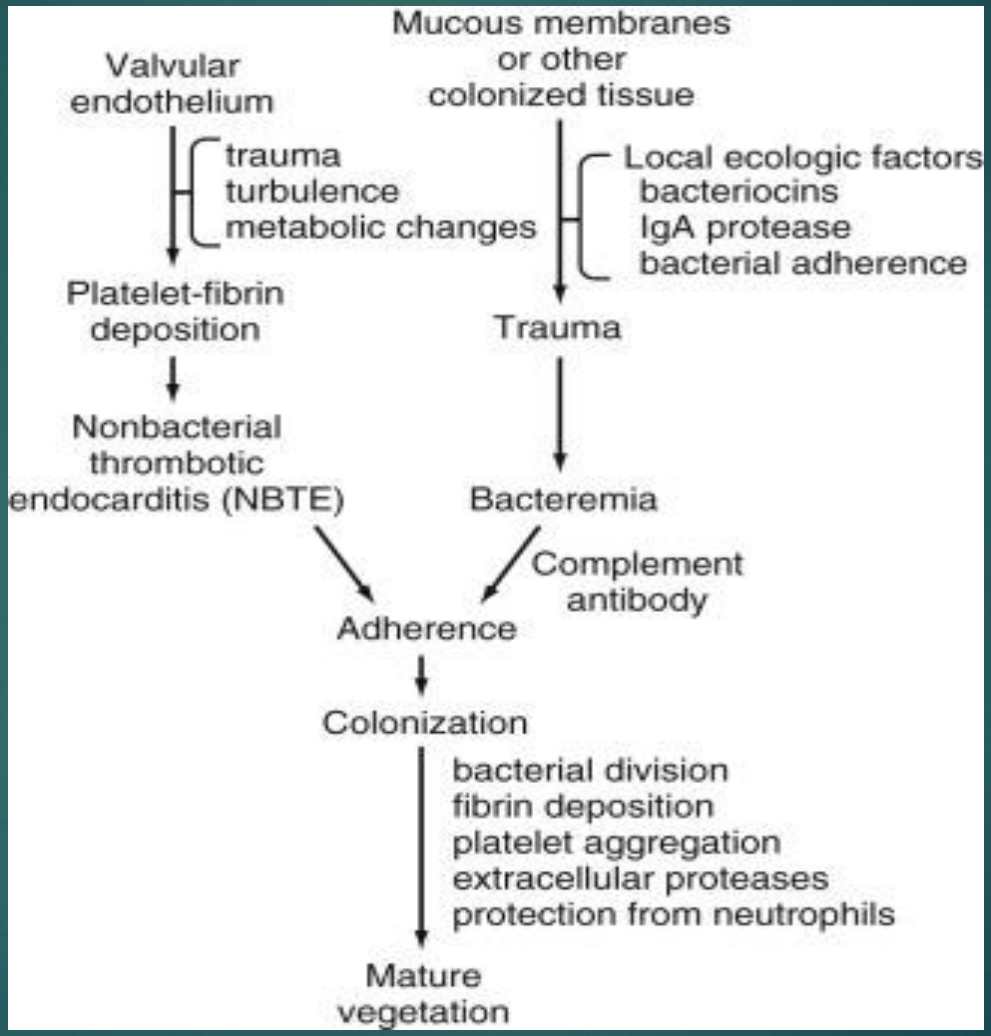
Introduction

- Bacterial or fungal infection of the endocardium, including native or prosthetic valves, the endocardial surface, or an implanted cardiac device.
- Bacteremia with adherence of bacteria to a preexisting valvular lesion.
- Whereas streptococcal infection was the predominant cause in earlier eras, staphylococcal infection is now the leading cause of native valve, prosthetic valve, and cardiac device infections,.
- Despite advancements in the diagnosis and therapy for endocarditis, the in-hospital mortality rate remains high, at nearly 20%.

epidemiology

- Approximately 10,000 to 15,000 new cases of infective endocarditis (IE) are diagnosed in the United States each year
- The mean age of patients with IE:
- In 1926 <30
- In 1943 39
- Currently >50% of patient are >50 years of age
- men are affected more commonly (54% to 69% of cases)
- It is traditionally associated with heart valves damaged by rheumatic heart disease
- In the current era, health care contact and injection drug use are the primary risk factors

Pathogenesis



Pathogenesis

Nonbacterial thrombotic Endocarditis:

- Valvular surface need to be perturbed
- Cardiac valvular vegetations were found in 19% of 200 nonselected ambulatory patients with solid tumors undergoing prospective echocardiographic screening.
- Valvular lesions were most common among patients with carcinoma of the pancreas or lung or lymphoma.

Hemodynamic factors:

- Valvular insufficiency
- Pacemakers, ICD
- Hyperdynamic circulation eg: Fistulas and shunt in HD
- Lesions with high degree of turbulence (eg, small VSD, valvular stenosis resulting from insufficient valves

Transient Bacteremia

- The bacteremia usually is low grade <10 colony-forming units (CFU/mL) and transient; bloodstream is usually sterile in <15 to 30 minutes

Microorganism- NBTE interaction

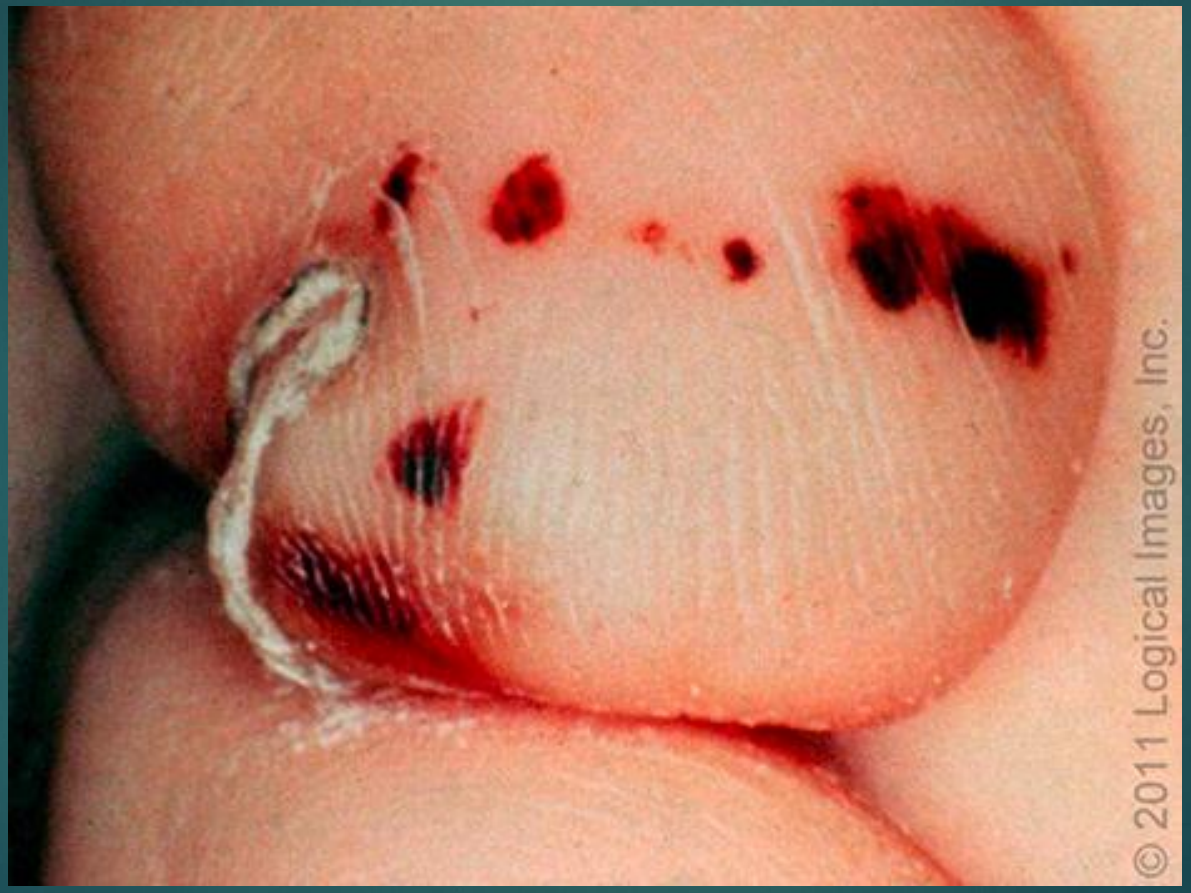
- That organisms commonly associated with IE (enterococci, viridans streptococci, *S. aureus, S. epidermidis, P. aeruginosa*) adhered more avidly to normal canine aortic leaflets in vitro than organisms uncommon in IE *(Klebsiella pneumoniae, E. coli)*

PROCEDURE/MANIPULATION	% POSITIVE BLOOD CULTURES
Dental	
Dental extraction	18-85
Periodontal surgery	32-88
Chewing candy or paraffin	17-51
Tooth brushing	0-26
Oral irrigation device	27-50
Upper Airway	
Bronchoscopy (rigid scope)	15
Tonsillectomy	28-38
Nasotracheal suctioning/intubation	16
Gastrointestinal	
Upper gastrointestinal endoscopy	8-12
Sigmoidoscopy/colonoscopy	0-9.5
Barium enema	11
Percutaneous needle biopsy of liver	3-13
Urologic	
Urethral dilation	18-33
Urethral catheterization	8
Cystoscopy	0-17
Transurethral prostatic resection	12-46
Obstetric/Gynecologic	
Normal vaginal delivery	0-11
Punch biopsy of the cervix	0
Removal/insertion of intrauterine (contraceptive) device	0

ORGANISM	ENDOCARDITIS : NONENDOCARDITIS RATIO
Streptococcus mutans	14.2 : 1
Streptococcus bovis I	5.9 : 1
Dextran-positive *Streptococcus mitior*	3.3 : 1
Streptococcus sanguinis	3 : 1
S. mitior	1.8 : 1
Unclassified viridans streptococci	1.4 : 1
Enterococcus faecalis	1 : 1.2
Miscellaneous streptococci	1 : 1.3
S. bovis II	1 : 1.7
Streptococcus anginosus	1 : 2.6
Group G streptococci	1 : 2.9
Group B streptococci	1 : 7.4
Group A streptococci	1 : 32

Clinical manifestations

- Any organ system may be involved
- Fever 95%
- Heart murmer 85%
- New murmer 48%
- Changing murmer 20%
- Petechiae 20-40% usually appear in crops in the conjunctiva, buccal mucosa, palate and extremities
- Osler's nodes 10-25% of subacute cases
- Janeway lesions
- Splenomegaly 11%, splenic infarct, if persistent fever do CT abdomen
- it is often associated with chills, anorexia, and weight loss.
- Other common symptoms of IE include malaise, headache, myalgias, arthralgias, night sweats, abdominal pain, dyspnea, cough, and pleuritic pain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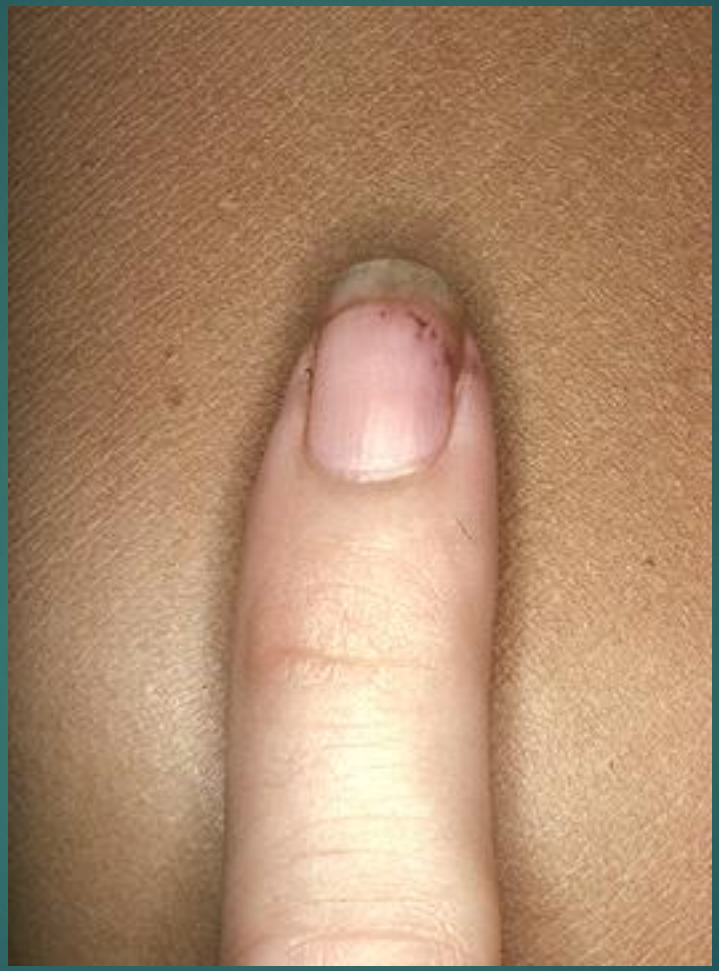

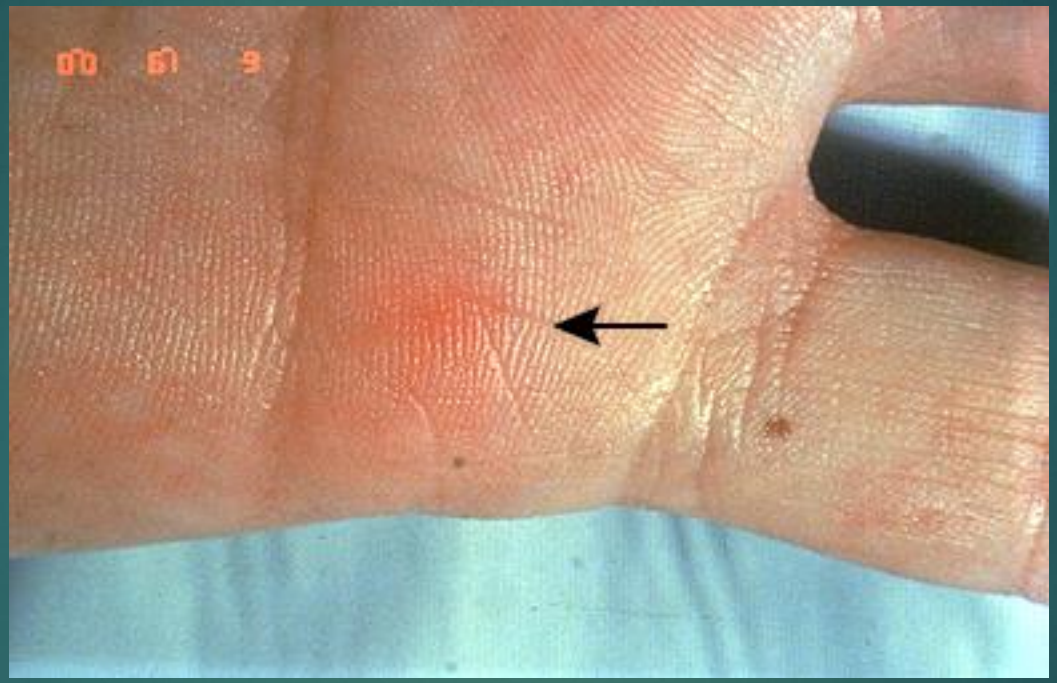

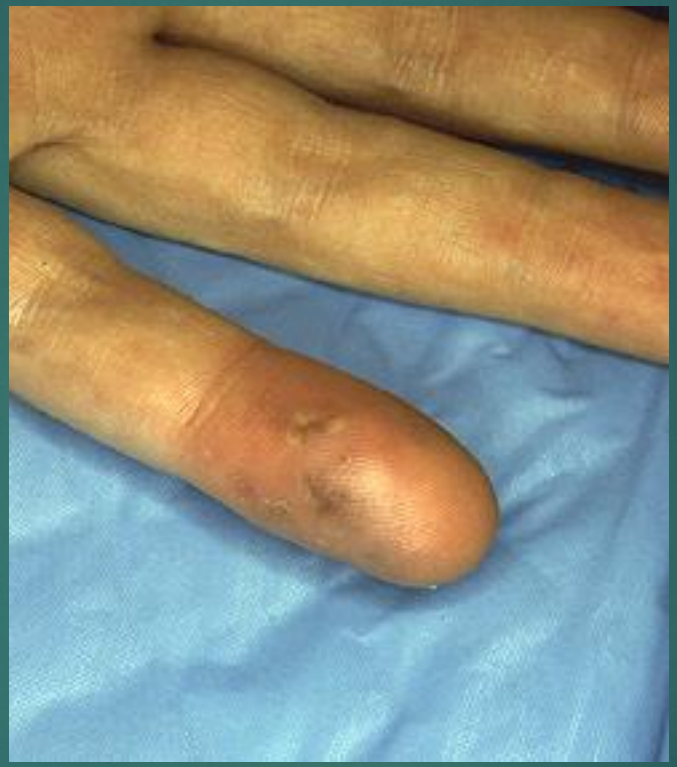

Complications as presenting symptoms

- Cardiac (up to 50% of patients) – Valvular insufficiency, heart failure, and others
- Neurologic (20-40%) – Embolic stroke, intracerebral hemorrhage, brain abscess, and others
- Septic emboli (up to 25%) – Infarction of kidneys, spleen, and other organs.
- In right-sided endocarditis, septic pulmonary emboli may be seen.

- Metastatic infection (such as vertebral osteomyelitis, septic arthritis, psoas abscess)
- Systemic immune reaction (eg, glomerulonephritis)
- A thorough investigation of extracardiac manifestations is particularly important in the setting of *Staphylococcus aureus* bacteremia given the virulence of this organism

Laboratory findings

- Blood culture
- Most important lab test in diagnostic workup
- Bacteremia is usually continuous and low grade (<100 CFU/ml in 80% of cases)
- When bacteremia present, the first 2 blood cultures yield the etiologic agent more than 90% of the time (decrease if patient received antibiotic)

- At leas 3 sets of blood culture should be obtained in the first 24 hrs, more if patient received antibiotic in the prior 2 weeks
- Repeat blood culture every 48-72 hrs

Other laboratory findings

- Nonspecific findings:
- Elevated ESR 60%
- Elevated CRP
- Normochromic-normocytic anemia 70-90%
- Positive rheumatoid factor 40-50%
- Hyperglobulinemia, cryoglobulinemia, circulating immune complexes, hypocomplementemia

- False-positive serologic tests for syphilis occur in some patients.
- Urinalysis may demonstrate microscopic hematuria 30-60%, proteinuria 50-65%, and/or pyuria.
- RBC casts on urinalysis is generally indicative of glomerulonephritis, which is a minor diagnostic criterion for IE.

- EKG may demonstrate new or evolving conduction disease (first-degree atrioventricular block, bundle branch block, or complete heart block), reflecting paravalvular or myocardial extension of infection

Special diagnostic tests

- The incidence of so-called blood culture–negative endocarditis has ranged from 2.5% to 31% in published series.
- Specialized methods and not extended incubation times are recommended for recovery of fastidious organisms (HACEK)
- Serologic studies (Q fever, murine typhus, psittacosis endocarditis, bartonella)

- Culture of the valve tissue or the vegetation that embolized may help (microscopy help for intracellular or fastidious organisms), fungal stain.
- PCR may be useful in difficult to grow organisms
- Test for mannan antigenemia help in the diagnosis of disseminated candidiasis

Diagnosis

Infective endocarditis should be suspected in any patient with :

- A new or increased regurgitant heart murmur along with signs or symptoms of infection or bacteremia.
- Fever (with or without bacteremia)
- Relevant cardiac risk factors (prior IE, presence of a prosthetic valve or cardiac device, history of valvular or congenital heart disease)

- (Intravenous drug use, indwelling intravenous lines, immunosuppression, or a recent dental or surgical procedure).

- TTE has less than optimal sensitivity (50%-80%)
- TEE has very high sensitivity and specificity

Diagnosis

- Additional diagnostic evaluation for patients with suspected or known IE includes
- Electrocardiography
- CXR
- Computed tomography (CT) of the spine

Major criteria
Positive blood cultures for IE (one of the following):
Typical microorganisms consistent with IE from two separate blood cultures:
Staphylococcus aureus
Viridans streptococci
Streptococcus gallolyticus (formerly *S. bovis*), including nutritional variant strains (*Granulicatella* spp and *Abiotrophia defectiva*)
HACEK group: *Haemophilus* spp, *Aggregatibacter* (formerly *Actinobacillus actinomycete comitants*), *Cardiobacterium hominis*, *Eikenella* spp, and *Kingella kingae*
Community-acquired enterococci, in the absence of a primary focus; **OR**
Persistently positive blood culture:
For organisms that are typical causes of IE: At least two positive blood cultures from blood samples drawn >12 hours apart
For organisms that are more commonly skin contaminants: Three or a majority of ≥4 separate blood cultures (with first and last drawn at least one hour apart)
Single positive blood culture for *Coxiella burnetii* or phase I IgG antibody titer >1:800*
Evidence of endocardial involvement (one of the following):
Echocardiogram positive for IE:
Vegetation (oscillating intracardiac mass on a valve or on supporting structures, in the path of regurgitant jets, or on implanted material, in the absence of an alternative anatomic explanation) **OR**
Abscess **OR**
New partial dehiscence of prosthetic valve
New valvular regurgitation
Increase in or change in preexisting murmur not sufficient
Minor criteria
Predisposition: Intravenous drug use or presence of a predisposing heart condition (prosthetic heart valve or a valve lesion associated with significant regurgitation or turbulence of blood flow)
Fever: Temperature ≥38.0°C (100.4°F)
Vascular phenomena: Major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, or Janeway lesions
Immunologic phenomena: Glomerulonephritis, Osler nodes, Roth spots, or rheumatoid factor
Microbiologic evidence: Positive blood cultures that do not meet major criteria **OR** serologic evidence of active infection with organism consistent with IE
(Echocardiographic minor criteria eliminated)*

diagnosis

Modified Duke criteria for diagnosis of infective endocarditis - Table A

Definite IE is established in the presence of any of the following:
Pathologic criteria
Pathologic lesions: vegetation or intracardiac abscess demonstrating active endocarditis on histology **OR**
Microorganism: demonstrated by culture or histology of a vegetation or intracardiac abscess
Clinical criteria
Using specific definitions listed in **Table B:**
2 major clinical criteria **OR**
1 major and 3 minor clinical criteria **OR**
5 minor clinical criteria
Possible IE*
Presence of 1 major and 1 minor clinical criteria **OR** presence of 3 minor clinical criteria
Rejected IE
A firm alternate diagnosis is made **OR**
Resolution of clinical manifestations occurs after ≤4 days of antibiotic therapy **OR**
No pathologic evidence of infective endocarditis is found at surgery or autopsy after antibiotic therapy for four days or less
Clinical criteria for possible or definite IE not met

IE: infective endocarditis.

* The category of possible IE represents a modification from the previous published Duke criteria.

Etiologic agents

Among 2781 patients with IE in a large cohort, the distribution of pathogens was as follows:

- ●*Staphylococcus aureus* – 31%
- ●Viridans group streptococci – 17%
- ●Enterococci – 11%
- ●Coagulase-negative staphylococci – 11%
- ●*Streptococcus bovis* – 7%
- ●Other streptococci – 5%
- ●Non-HACEK gram-negative bacteria – 2 %
- ●Fungi – 2 %

- ●**HACEK – 2 %; organisms in this category include a number of fastidious gram-negative bacilli:**
- ***H****aemophilus aphrophilus*
- ***A****ctinobacillus actinomycetemcomitans*
- ***C****ardiobacterium hominis*
- ***E****ikenella corrodens*
- ***K****ingella kingae*
- Culture-negative endocarditis 8%
- Polymicrobial 1%
- Other organisms 3%

Etiology of IE in injection drug users

- In Detroit 1990
- S. Aureus 60.8%
- Streptococci 16.2%
- Pseudomonas aeruginosa 13.5
- Polymicrobial 8.1%
- Corynbacterium JK 1.4%

Therapy for Infective Endocarditis

- Initiation of empiric antibiotic therapy is appropriate after multiple blood cultures have been drawn when clinical suspicion for endocarditis is intermediate or high.
- Tailored antibiotic therapy is guided by the causative organism and its microbiologic susceptibilities.
- In addition to IV antibiotic therapy, upto 50% of patients with valvular infective endocarditis might need surgery
- In patients with endocarditis with complications, surgery has been found to improve mortality compared with antibiotic therapy alone.

Therapy for Infective Endocarditis

- Parenteral antibiotics are recommended over oral drugs in most circumstances because of the importance of sustained antibacterial activity.
- Erratic absorption with many classes of agents makes oral drugs less desirable.

- Short-term therapy has been associated with relapse, and most current recommendations emphasize extended drug administration.

- Antibiotic combinations should produce a rapid bactericidal effect. This is seen with synergistic combinations, such as penicillin plus an aminoglycoside effective against most viridans streptococci or enterococci.

Therapy for Infective Endocarditis

- The selection of antibiotics should be based on antimicrobial susceptibility tests
- Treatment should be monitored clinically
- Antimicrobial blood levels
- Blood cultures
- To ensure eradication of the bacteremia
- In patients with persistent or recurrent fever during therapy.

Therapy for Infective Endocarditis

- Causes of persistent or recurrent fever despite appropriate antimicrobial
- pulmonary or systemic emboli
- Drug hypersensitivity
- The most common cause is extensive valve ring or adjacent structure infection or metastatic infection

- Approximately one third of patients with left-sided IE require surgery during the acute stages of infection for either valve replacement or metastatic infection.
- Close monitoring and early surgical consultation of patients with IE, particularly those with signs of heart failure or persistent fever, are essential.

Tests Useful for Antimicrobial Treatment Monitoring

- MIC
- Aminoglycosides have a low toxic-to-therapeutic ratio, especially in elderly patients and in patients with renal disease, need to monitor level
- If synergy with another agent is demonstrable, serum concentrations of the aminoglycosides lower than those generally considered "therapeutic" may be adequate

Staphylococcus aureus

Native Valve		
Methicillin-susceptible	Nafcillin or oxacillin, 2 g IV q4h × 4-6 wk *Optional:* gentamicin, 1 mg/kg IV q8h × 3-5 days	Use of gentamicin in native valve *S. aureus* IE is associated with significant nephrotoxicity without clear clinical benefit and therefore is not encouraged
	Cefazolin, 2 g IV q8h × 4-6 hr *Optional:* gentamicin, 1 mg/kg IV q8h × 3-5 days	Acceptable in setting of penicillin allergy other than immediate hypersensitivity. See above cautions about gentamicin use.
Methicillin-resistant	Vancomycin, 15-20 mg/kg IV q8-12h × 6 wk	Also acceptable in setting of immediate hypersensitivity or anaphylaxis to penicillin; goal vancomycin trough level 15-20 µg/mL is recommended
Prosthetic Valve		
Methicillin-susceptible	Nafcillin or oxacillin, 2 g IV q4h × ≥6 wk, *plus*gentamicin, 1 mg/kg IV q8h × 2 wk, *plus*rifampin, 300 mg PO/IV q8h × ≥6 wk	
Methicillin-resistant	Vancomycin, 15-20 mg/kg IV q8-12h × ≥6 wk *plus* gentamicin, 1 mg/kg IV q8h × 2 wk,*plus* rifampin, 300 mg PO/IV q8h × ≥6 wk	Goal vancomycin trough level 15-20 µg/mL is recommended
Injection Drug Use		
Methicillin-susceptible	Nafcillin or oxacillin, 2 g IV q4h × 2 wk; *plus*gentamicin, 1 mg/kg IV q8h × 2 wk	Two-week regimen only for use in injection drug users with infection limited to tricuspid valve, no renal insufficiency, and no extrapulmonary infection. Two weeks of monotherapy with antistaphylococcal penicillin has also been successfully used in these patients.
Methicillin-resistant	Vancomycin, 15-20 mg/kg IV q8-12h × 4 wk	Use of gentamicin in this setting is not recommended. Goal vancomycin trough level 15-20 µg/mL is recommended.
	Daptomycin, 6 mg/kg IV qd × 4-6 wk	Daptomycin is U.S. Food and Drug Administration–approved for treatment of right-sided *S. aureus* IE; for adults, some experts recommend 8-10 mg/kg IV

Coagulase-Negative Staphylococci		
Native Valve		
Methicillin-susceptible	Nafcillin or oxacillin, 2 g IV q4h × 4-6 wk *Optional:* gentamicin, 1 mg/kg IV q8h × 3-5 days	
Methicillin-resistant	Vancomycin, 15-20 mg/kg IV q8-12h × 6 wk	Also acceptable in setting of immediate hypersensitivity or anaphylaxis to penicillin. Goal vancomycin trough level 15-20 µg/mL is recommended.
Prosthetic Valve		
Methicillin-susceptible	Nafcillin or oxacillin, 2 g IV q4h × ≥6 wk, *plus*gentamicin, 1 mg/kg IV q8h × 2 wk, *plus*rifampin, 300 mg PO/IV q8h × ≥6 wk	
Methicillin-resistant	Vancomycin, 15-20 mg/kg IV q8-12h × ≥6 wk, *plus* gentamicin, 1 mg/kg IV q8h × 2 wk,*plus* rifampin, 300 mg PO/IV q8h × ≥6 wk	Goal vancomycin trough level 15-20ug/mL is recommended

Penicillin-Susceptible Viridans Streptococci (MIC ≤0.1 µg/mL) and *Streptococcus bovis (S. gallolyticus)*		
	Penicillin, 2-3 million units IV q4h × 4 wk, *or*ampicillin, 2 g IV q4h × 4wk	Also effective for other penicillin-susceptible nonviridans streptococci (e.g., group A streptococci)
	Ceftriaxone, 2 g IV qd × 4 wk	For penicillin allergy; patients with uncomplicated viridans streptococcal IE are candidates for outpatient therapy
	Penicillin, 2-3 million units IV q4h × 2 wk, *plus*gentamicin, 1 mg/kg IV q8h × 2 wk	Uncomplicated native valve IE only; not acceptable for nutritionally variant streptococci
Nutritionally variant strain	Penicillin, 2-4 million units IV q4h × 4 wk, *plus*gentamicin, 1 mg/kg IV q8h × 2 wk	For prosthetic valve IE, give 6 wk of penicillin. Nutritionally variant streptococci are often penicillin tolerant.
	Vancomycin, 15-20 mg/kg IV q8-12h × 4 wk	For penicillin allergy
Relatively Penicillin-Resistant Viridans Streptococci (MIC 0.12-<0.5 µg/mL)		
	Penicillin, 4 million units IV q4h × 4 wk, *plus*gentamicin, 1 mg/kg IV q8h × 2 wk	
	Vancomycin, 15-20 mg/kg IV q8-12h × 4 wk	For penicillin allergy or to avoid gentamicin

Enterococci [c] and Penicillin-Resistant Viridans Streptococci (Penicillin MIC >0.5 µg/mL)		
Penicillin-susceptible, aminoglycoside-susceptible enterococci	Penicillin [d] 3-5 g IV q4h × 4-6 wk, *plus* gentamicin, 1 mg/kg IV q8h × 4-6 wk;*or* Ampicillin, 2 g IV q4h,*plus* gentamicin, 1 mg/kg IV q8h × 4-6 wk	Increase duration of both drugs to 6 wk for prosthetic valve infection or for enterococcal IE with symptoms >3 mo. For older patients and those with underlying renal disease, can consider shortening the duration of gentamicin to 2 wk.
Penicillin-resistant, vancomycin-susceptible, aminoglycoside-susceptible enterococci	Vancomycin, 15-20 mg/kg IV q8-12h × 6 wk, *plus* gentamicin, 1 mg/kg q8h × 6 wk [e]	Also for patients with penicillin allergy. This regimen is associated with enhanced risk of nephrotoxicity. Penicillin desensitization should be considered as an alternative to this regimen when possible.
Penicillin-susceptible, aminoglycoside-resistant enterococci	Ampicillin, 2 g IV q4h,*plus* ceftriaxone, 2 g IV q12h	Useful for patients with significant underlying renal disease
Penicillin-resistant, vancomycin-resistant enterococci	No standard therapy; daptomycin, linezolid, and quinupristin-dalfopristin have been used	Consult infectious diseases specialist

HACEK Strains		
	Ceftriaxone, 2 g IV qd × 4 wk	Increase duration to 6 wk for infections involving prosthetic valves
	Ampicillin-sulbactam, 3 g IV q6h × 4 wk (if β-lactamase producing strain) [g]	Increase duration to 6 wk for infections involving prosthetic valves
Non-HACEK Gram-Negative Bacilli [f]		
Enterobacteriaceae	Extended-spectrum penicillin (e.g., piperacillin-tazobactam) or cephalosporin plusaminoglycosides for susceptible strains	Treat for a minimum of 6-8 wk. Some species exhibit inducible resistance to third-generation cephalosporins. Valve surgery is often required for patients with left-sided IE caused by gram-negative bacilli, especially for prosthetic valve IE. Consultation with an infectious diseases specialist is recommended.
Pseudomonas aeruginosa	Antipseudomonal penicillin (e.g., piperacillin) plus high-dose tobramycin, 8 mg/kg/day IV or IM in once-daily doses; or High-dose ceftazidime, cefepime, or imipenem	Goal tobramycin peak and trough concentrations of 15-20 µg/mL and ≤2 µg/mL, respectively. Treat for a minimum of 6-8 wk. Early valve surgery usually required for left-sided Pseudomonas IE; consultation with a specialist in infectious diseases is recommended.
Fungi [f]		
	Treatment with a parenteral antifungal agent (usually an amphotericin B–containing product) is usually recommended as initial therapy	Fungal endocarditis is usually an indication for valve replacement surgery. Long-term/lifelong suppressive therapy with oral antifungal agents is often required. Consultation with a specialist in infectious diseases is recommended.

Surgical Therapy

- ***Patients with IE and CHF should be immediately evaluated for potential surgical therapy.***
- indications for potential surgical intervention during active IE:
- (1) more than one serious systemic embolic episode
- (2) uncontrolled infection
- (3) ineffective antimicrobial therapy (e.g., in fungal IE)
- (4) resection of mycotic aneurysms

- (5) most cases of prosthetic valve IE caused by more antibiotic-resistant pathogens (e.g., staphylococci, enteric gram-negative bacilli)
- (6) local suppurative complications, including perivalvular or myocardial abscesses.

Surgical Therapy

- ***Echocardiographic features associated with a potential increased need for surgical intervention:***
- (1) persistent vegetations after a major systemic embolic episode
- (2) large (>1 cm) anterior mitral valve vegetations
- (3) increase in vegetation size after appropriate antibiotic therapy
- (4) acute mitral insufficiency
- (5) valve dehiscence, perforation, or rupture

- (6) periannular extension of infection (e.g., paravalvular abscess or fistula).
- early valve surgery is associated with increased survival in patients with IE.
- early surgical intervention may improve survival in CHF.

Surgical Therapy

- Indication for surgery in Rt sided IE
- persistent infection is the indication for surgery in more than 70% of patients

- Most patients are injection drug users, with IE caused by organisms that are difficult to eradicate with antimicrobial therapy alone (e.g., fungi, GNB)
- Tricuspid valvulectomy or vegetectomy with valvuloplasty is the procedure of choice for refractory right-sided IE.
- Valve replacement at a second operation is advised only if medical management fails to control the hemodynamic manifestations and the patient has ceased using illicit drugs.

references

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- IDSA guidelines, cardiovascular, endocarditis management
- Uptodate, clinical manifestations of infective endocarditis, algorithms, pictures

Thank you