Infective Endocarditis

Jessica Barrett, DO
OPG Infectious Diseases
Licking Memorial Hospital Grand Rounds
12/9/19

Introduction

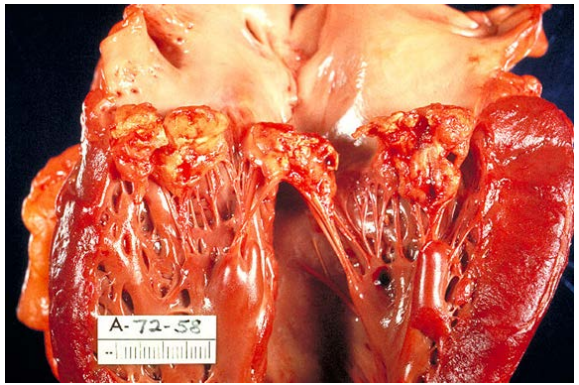
- Jessica Barrett, DO
- Undergraduate: Miami University
  - Microbiology, Molecular Biology
- Medical School: TouroCOM NYC
- Residency: Riverside Methodist Hospital
- Fellowship: Ohio State University

Objectives

- Diagnosis of infective endocarditis and common causative organisms
- Medical therapy for infective endocarditis
- Surgical indications for infective endocarditis

Infective Endocarditis (IE)

- Infection of the endocardial surface of the valve and implies physical presence of microorganisms on the surface.
  - Valves
  - Septal defects
  - Mural endocardium



Modified Duke's Criteria

- Definite IE
  - Pathological criteria
  - Clinical criteria
    - 2 major criteria
    - 1 major criteria and 3 minor criteria
    - 5 minor criteria
- Possible IE
  - 1 major Criterion and 1 minor criterion
  - 3 minor criteria
- Rejected

Criteria

- Major
  - Blood culture positive for typical microorganism
  - Single positive blood culture positive for *Coxiella burnetii* (or anti-phase I IgG Ab >1:800)
  - Evidence of endocardial involvement
  - Echocardiogram positive
- Minor
  - Predisposition
  - Fever (>38℃)
  - Vascular phenomena
  - Immunological phenomena
  - Microbiological evidence

Typical Microorganisms

- *Strep viridans*
- *Strep bovis*
- HACEK group
  - *Haemophilus*, *Aggregatibacter*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella*
- *Staph aureus*
- Community acquired *Enterococcus*

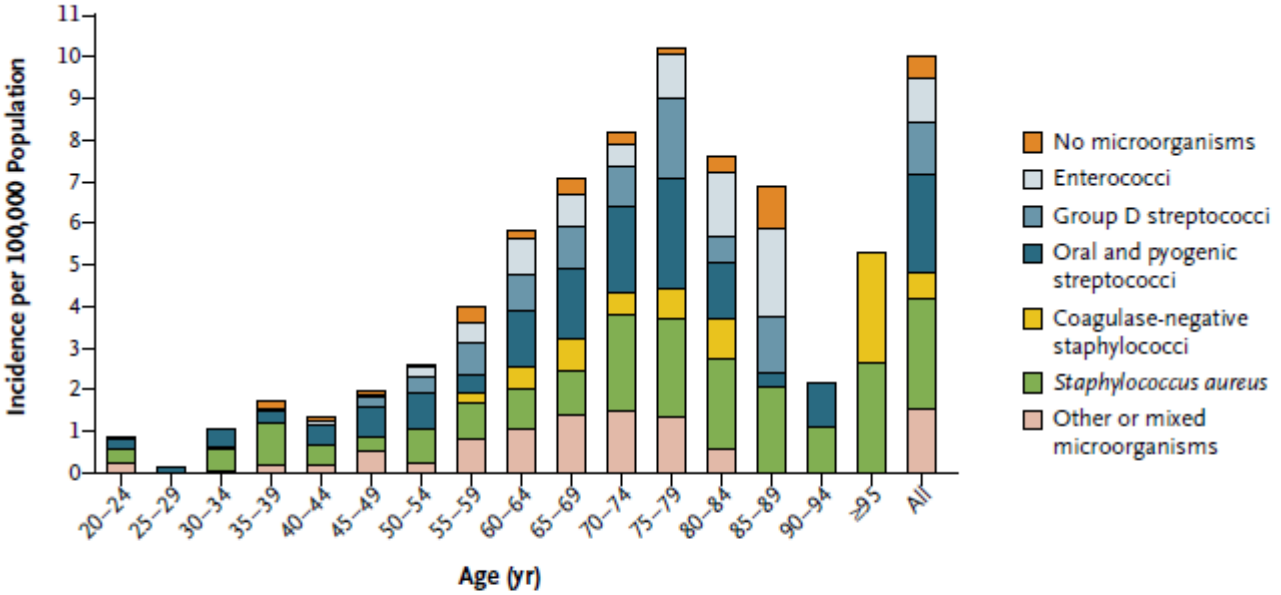


Figure 1. Incidence of Definite Infective Endocarditis, According to Age and Microorganism.

Streptococci and staphylococci account for 80% of cases of infective endocarditis, with proportions varying according to valve (native vs. prosthetic), source of infection, patient age, and coexisting conditions. The clustering of various predisposing factors with age probably explains the higher incidence of infective endocarditis in persons 65 years of age or older. Adapted from Selton-Suty et al.[7]

Positive Echocardiogram

- Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternate anatomic explanation
- Abscess
- New partial dehiscence of a prosthetic valve
- New valvular regurgitation

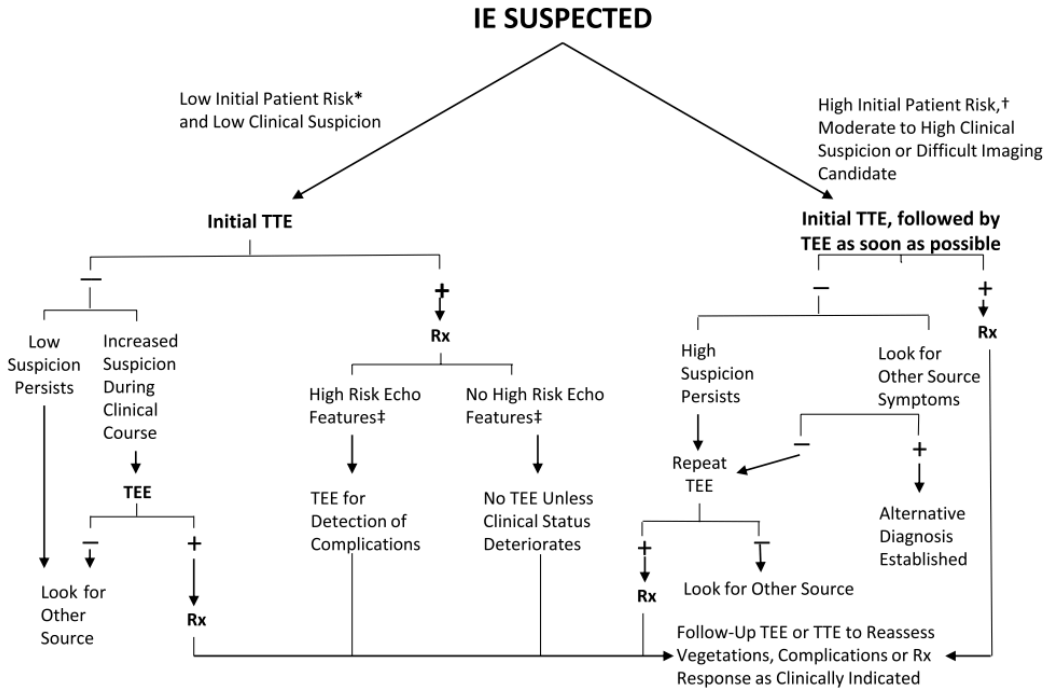
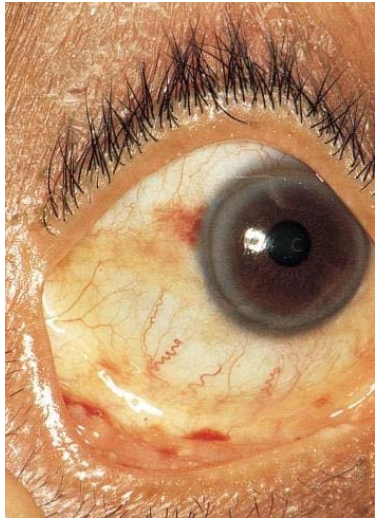
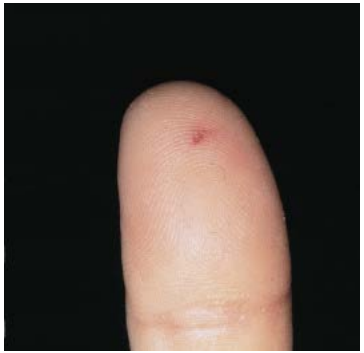


Figure. An approach to the diagnostic use of echocardiography (echo). Rx indicates prescription; TEE, transesophageal echocardiography; and TTE, transthoracic echocardiography. *For example, a patient with fever and a previously known heart murmur and no other stigmata of infective endocarditis (IE). †High initial patient risks include prosthetic heart valves, many congenital heart diseases, previous endocarditis, new murmur, heart failure, or other stigmata of endocarditis. ‡High-risk echocardiographic features include large or mobile vegetations, valvular insufficiency, suggestion of perivalvular extension, or secondary ventricular dysfunction (see text). Modified from Baddour et al.[12]

Vascular Phenomena

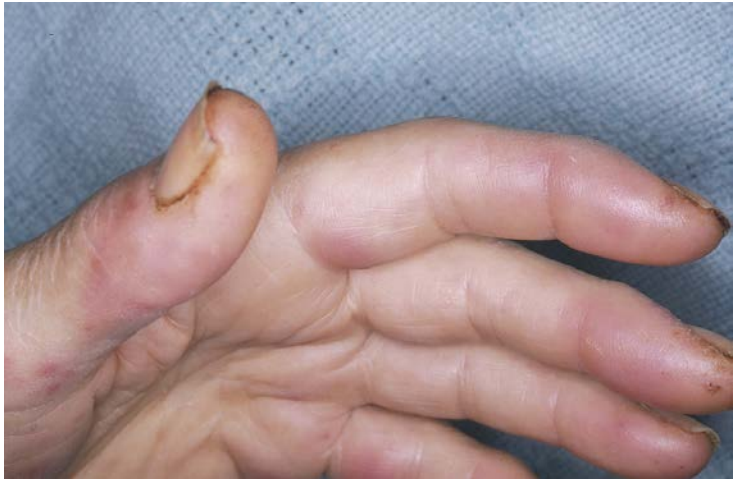
- Major arterial emboli
- Septic pulmonary infarcts
- Mycotic aneurysm
- Intracranial hemorrhage
- Conjunctival hemorrhage
- Janeway lesions

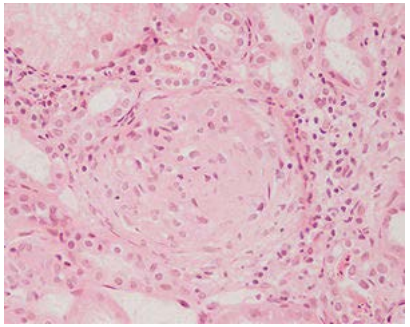




Immunological Phenomena

- Glomerulonephritis
- Osler nodes
- Positive rheumatoid factor





Epidemiology

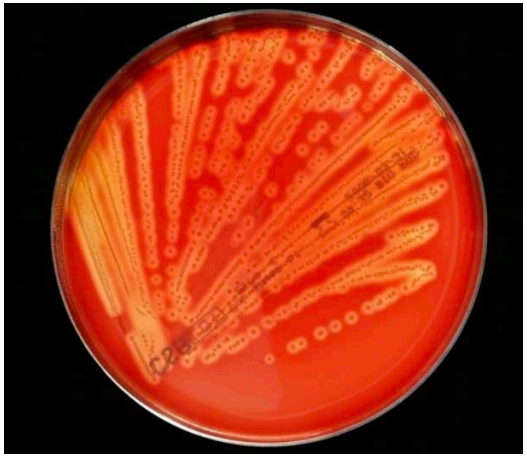
- AHA estimates USA annual incidence 10,000-20,000 new cases a year.
- Incidence of 3-9 cases per 100,000 persons in industrialized countries
- Mean age > 50 years
- Male to female 1.7:1
- Sites:
  - Mitral valve alone 28-45%
  - Aortic valve alone 5-36%
  - Aortic + mitral 0-35%
  - Tricuspid valve 0-6%
  - Pulmonic valve <1%

Medical Therapy

- Documenting clearance of blood cultures is imperative, as the first set of negative blood cultures marks day one of therapy.
- Antibiotic therapy should be intravenous.
- In most cases, six weeks of IV therapy is indicated.
- At the end of medical therapy, a repeat or “exit” echo is very important to document a new “baseline”.

Medical Therapy

- Selection of antibiotic therapy is dependent upon the organism and, often, MICs as well.



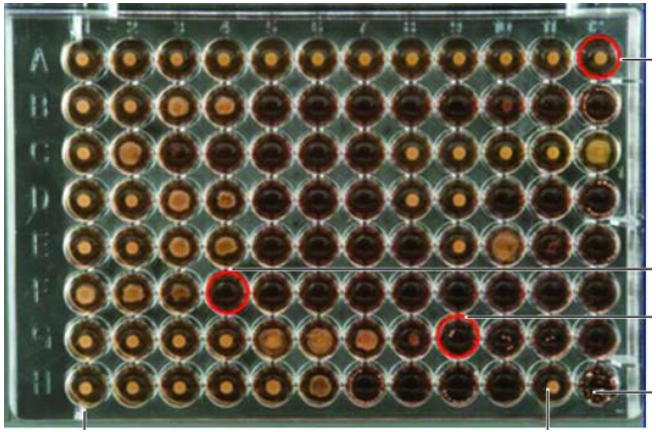


Table 7. Therapy of NVE Caused by Highly Penicillin-Susceptible VGS and *Streptococcus gallolyticus (bovis)*

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Aqueous crystalline penicillin G sodium	12–18 million U/24 h IV either continuously or in 4 or 6 equally divided doses	4	*Class IIa; Level of Evidence B*	Preferred in most patients >65 y or patients with impairment of eighth cranial nerve function or renal function.
Or				Ampicillin 2 g IV every 4 h is a reasonable alternative to penicillin if a penicillin shortage exists.
Ceftriaxone sodium	2 g/24 h IV/IM in 1 dose	4	*Class IIa; Level of Evidence B*	
Aqueous crystalline penicillin G sodium	12–18 million U/24 h IV either continuously or in 6 equally divided doses	2	*Class IIa; Level of Evidence B*	2-wk regimen not intended for patients with known cardiac or extracardiac abscess or for those with creatinine clearance of <20 mL/min, impaired eighth cranial nerve function, or *Abiotrophia, Granulicatella,* or *Gemella* spp infection; gentamicin dose should be adjusted to achieve peak serum concentration of 3–4 µg/mL and trough serum concentration of <1 µg/mL when 3 divided doses are used; there are no optimal drug concentrations for single daily dosing.†
Or				
Ceftriaxone sodium	2 g/24 h IV or IM in 1 dose	2	*Class IIa; Level of Evidence B*	
Plus				
Gentamicin sulfate‡	3 mg/kg per 24 h IV or IM in 1 dose	2		
Vancomycin hydrochloride§	30 mg/kg per 24 h IV in 2 equally divided doses	4	*Class IIa; Level of Evidence B*	Vancomycin therapy is reasonable only for patients unable to tolerate penicillin or ceftriaxone; vancomycin dose should be adjusted to a trough concentration range of 10–15 µg/mL.

IM indicates intramuscular; IV, intravenous; NVE, native valve infective endocarditis; and VGS, viridans group streptococci. Minimum inhibitory concentration is ≤0.12 µg/mL. The subdivisions differ from Clinical and Laboratory Standards Institute–recommended break points that are used to define penicillin susceptibility.

*Doses recommended are for patients with normal renal function.

†Data for once-daily dosing of aminoglycosides for children exist, but no data for treatment of IE exist.

‡Other potentially nephrotoxic drugs (eg, nonsteroidal anti-inflammatory drugs) should be used with caution in patients receiving gentamicin therapy. Although it is preferred that gentamicin (3 mg/kg) be given as a single daily dose to adult patients with endocarditis caused by viridans group streptococci, as a second option, gentamicin can be administered daily in 3 equally divided doses.

§Vancomycin dosages should be infused during the course of at least 1 hour to reduce the risk of histamine-release "red man" syndrome.

Table 8. Therapy of NVE Caused by Strains of VGS and *Streptococcus gallolyticus (bovis)* Relatively Resistant to Penicillin

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Aqueous crystalline penicillin G sodium	24 million U/24 h IV either continuously or in 4–6 equally divided doses	4	*Class IIa; Level of Evidence B*	It is reasonable to treat patients with IE caused penicillin-resistant (MIC ≥0.5 μg/mL) VGS strains with a combination of ampicillin or penicillin plus gentamicin as done for enterococcal IE with infectious diseases consultation (*Class IIa; Level of Evidence C*). Ampicillin 2 g IV every 4 h is a reasonable alternative to penicillin if a penicillin shortage exists.
Plus				
Gentamicin sulfate†	3 mg/kg per 24 h IV or IM in 1 dose	2		Ceftriaxone may be a reasonable alternative treatment option for VGS isolates that are susceptible to ceftriaxone (*Class IIb; Level of Evidence C*).
Vancomycin hydrochloride‡	30 mg/kg per 24 h IV in 2 equally divided doses	4	*Class IIa; Level of Evidence C*	Vancomycin therapy is reasonable only for patients unable to tolerate penicillin or ceftriaxone therapy.

IE indicates infective endocarditis; IM, intramuscular; IV, intravenous; MIC, minimum inhibitory concentration; NVE, native valve infective endocarditis; and VGS, viridans group streptococci. MIC is >0.12 to <0.5 μg/mL for penicillin. The subdivisions differ from Clinical and Laboratory Standards Institute–recommended break points that are used to define penicillin susceptibility.)

*Doses recommended are for patients with normal renal function.

†See Table 7 for appropriate dose of gentamicin. Although it is preferred that gentamicin (3 mg/kg) be given as a single daily dose to adult patients with endocarditis caused by viridans group streptococci, as a second option, gentamicin can be administered daily in 3 equally divided doses.

‡See Table 7 for appropriate dosage of vancomycin.

Table 10. Therapy for NVE Caused by Staphylococci

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Oxacillin-susceptible strains				
Nafcillin or oxacillin	12 g/24 h IV in 4–6 equally divided doses	6	*Class I; Level of Evidence C*	For complicated right-sided IE and for left-sided IE; for uncomplicated right-sided IE, 2 wk (see text).
For penicillin-allergic (nonanaphylactoid type) patients				Consider skin testing for oxacillin-susceptible staphylococci and questionable history of immediate-type hypersensitivity to penicillin.
Cefazolin*	6 g/24 h IV in 3 equally divided doses	6	*Class I; Level of Evidence B*	Cephalosporins should be avoided in patients with anaphylactoid-type hypersensitivity to β-lactams; vancomycin should be used in these cases.
Oxacillin-resistant strains				
Vancomycin§	30 mg/kg per 24 h IV in 2 equally divided doses	6	*Class I; Level of Evidence C*	Adjust vancomycin dose to achieve trough concentration of 10–20 μg/mL (see text for vancomycin alternatives).
Daptomycin	≥8 mg/kg/dose	6	*Class IIb; Level of Evidence B*	Await additional study data to define optimal dosing.

IE indicates infective endocarditis; IV, intravenous; and NVE, native valve infective endocarditis.
*Doses recommended are for patients with normal renal function.
§For specific dosing adjustment and issues concerning vancomycin, see Table 7 footnotes.

Table 13. Therapy for Endocarditis Involving a Native or Prosthetic Valve or Other Prosthetic Material Resulting From *Enterococcus* species Caused by a Strain Susceptible to Penicillin and Resistant to Aminoglycosides or Streptomycin-Susceptible Gentamicin-Resistant in Patients Able to Tolerate β-Lactam Therapy*

Regimen	Dose† and Route	Duration, wk	Strength of Recommendation	Comments
Double β-lactam			*Class IIa; Level of Evidence B*	Double β-lactam is reasonable for patients with normal or impaired renal function abnormal cranial nerve VIII function or if the laboratory is unable to provide rapid results of streptomycin serum concentration; native valve infection with symptoms of infection <3-mo duration may be treated for 4 wk with the streptomycin-containing regimen. PVE, NVE with symptoms >3 mo, or treatment with a double β-lactam regimen require a minimum of 6 wk of therapy.
Ampicillin	2 g IV every 4 h	6		
Plus				
Ceftriaxone	2 g IV every 12 h			
Alternative for streptomycin susceptible/gentamicin resistant				
Either		4–6	*Class IIa; Level of Evidence B*	Use is reasonable only for patients with availability of rapid streptomycin serum concentrations. Patients with creatinine clearance <50 mL/min or who develop creatinine clearance <50 mL/min during treatment should be treated with double–β-lactam regimen. Patients with abnormal cranial nerve VIII function should be treated with double–β-lactam regimen.
Ampicillin sodium	2 g IV every 4 h			
Or				
Aqueous penicillin G sodium	18–30 million U/24 h IV either continuously or in 6 equally divided doses			
Plus				
Streptomycin sulfate‡	15 mg/kg ideal body weight per 24h IV or IM in 2 equally divided doses			

IM indicates intramuscular; IV, intravenous; NVE, native valve infective endocarditis; and PVE, prosthetic valve infective endocarditis.
*For patients unable to tolerate a β-lactam, see Table 14.
†Doses recommended for patients with normal renal and hepatic function.
‡Streptomycin dose should be adjusted to obtain a serum peak concentration of 20 to 35 μg/mL and a trough concentration of <10 μg/mL.

Table 14. Vancomycin-Containing Regimens for Vancomycin- and Aminoglycoside-Susceptible Penicillin-Resistant *Enterococcus* Species for Native or Prosthetic Valve (or Other Prosthetic Material) IE in Patients Unable to Tolerate β-Lactam

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Unable to tolerate β-lactams				
Vancomycin†	30 mg/kg per 24 h IV in 2 equally divided doses	6	*Class IIa; Level of Evidence B*	
Plus				
Gentamicin‡	3 mg/kg per 24 h IV or IM in 3 equally divided doses	6		
Penicillin resistance; intrinsic or β-lactamase producer				
Vancomycin	30 mg/kg per 24 h IV in 2 equally divided doses	6	*Class IIb; Level of Evidence C*	For β-lactamase–producing strain, if able to tolerate a β-lactam antibiotic, ampicillin-sulbactam§ plus aminoglycoside therapy may be used.
Plus				
Gentamicin‡	3 mg/kg per 24 h IV or IM in 3 equally divided doses	6		

IE indicates infective endocarditis; IM, intramuscular; and IV, intravenous.
*Doses recommended are for adults with normal renal function.
†Dose of vancomycin should be adjusted to obtain a serum trough concentration of 10 to 20 μg/mL.
‡Dose of gentamicin should be adjusted to obtain serum peak and trough concentrations of 3 to 4 and <1 μg/mL, respectively.
§Ampicillin-sulbactam dosing is 3 g/6 hour IV.

Table 15. Therapy for Endocarditis Involving a Native or Prosthetic Valve or Other Prosthetic Material Resulting From *Enterococcus* Species Caused by Strains Resistant to Penicillin, Aminoglycosides, and Vancomycin

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Linezolid Or	600 mg IV or orally every 12 h	>6	*Class IIb; Level of Evidence C*	Linezolid use may be associated with potentially severe bone marrow suppression, neuropathy, and numerous drug interactions. Patients with IE caused by these strains should be treated by a care team including specialists in infectious diseases, cardiology, cardiac surgery, clinical pharmacy, and, in children, pediatrics. Cardiac valve replacement may be necessary for cure.
Daptomycin	10–12 mg/kg per dose	>6	*Class IIb; Level of Evidence C*	

IE indicates infective endocarditis, and IV, intravenous.
*Doses recommended are for patients with normal renal and hepatic function.

Table 16. Therapy for Endocarditis Involving a Native or Prosthetic Valve or Other Prosthetic Material Caused by HACEK Microorganisms

Regimen	Dose and Route	Duration, wk	Strength of Recommendation	Comments
Ceftriaxone sodium*	2 g/24 h IV or IM in 1 dose	4, NVE; 6, PVE	*Class IIa; Level of Evidence B*	Preferred therapy: cefotaxime or another third- or fourth-generation cephalosporin may be substituted.
Or				
Ampicillin sodium	2 g IV every 4 h		*Class IIa; Level of Evidence B*	Ampicillin sodium may be an option if the growth of the isolate is sufficient to permit in vitro susceptibility results.
Or				
Ciprofloxacin†	1000 mg/24 h orally or 800 mg/24 h IV in 2 equally divided doses		*Class IIb; Level of Evidence C*	Fluoroquinolone therapy‡ may be considered for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin or moxifloxacin may be substituted; fluoroquinolones generally is not recommended for patients <18 y old. Treatment for 6 wk is reasonable in patients with PVE (*Class IIa; Level of Evidence C*).

HACEK indicates *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species; IM, intramuscular; IV, intravenous; NVE, native valve infective endocarditis; and PVE, prosthetic valve infective endocarditis.

*Patients should be informed that intramuscular injection of ceftriaxone is painful.

†Dose recommended for patients with normal renal function.

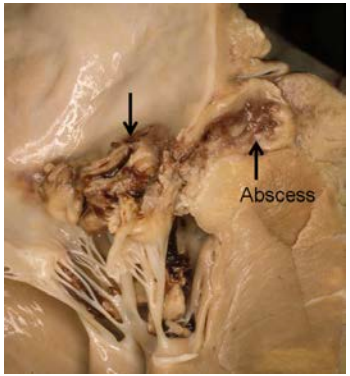
‡Fluoroquinolones are highly active in vitro against HACEK microorganisms. Published data on the use of fluoroquinolones for endocarditis caused by HACEK are minimal.

Special Circumstances

- Prosthetic Valve Endocarditis
  - Treatment is still organism-dependent, but empiric therapy includes:
    - Vancomycin
    - Cefepime or Carbapenem
    - Gentamicin
- Culture-Negative Endocarditis
  - Goal is to cover the most likely organisms
    - Vancomycin
    - Ceftriaxone or Amp-Sulbactam

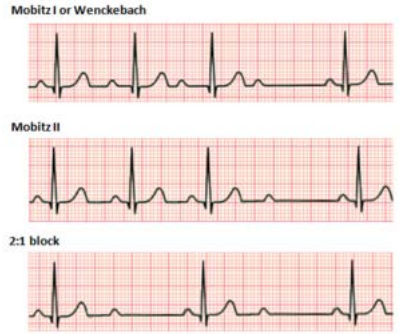
Surgical Indications Based on Echo

- Persistent vegetation after systemic embolization
- Anterior mitral leaflet vegetation, particularly with size >10 mm
- ≥1 Embolic events during first 2 weeks of antimicrobial therapy
- Increase in vegetation size despite appropriate antimicrobial therapy
- Valvular dysfunction
- Valve perforation or rupture
- Perivalvular extension
- Valvular dehiscence, rupture, or fistula
- Large abscess or extension of abscess despite appropriate antimicrobial therapy



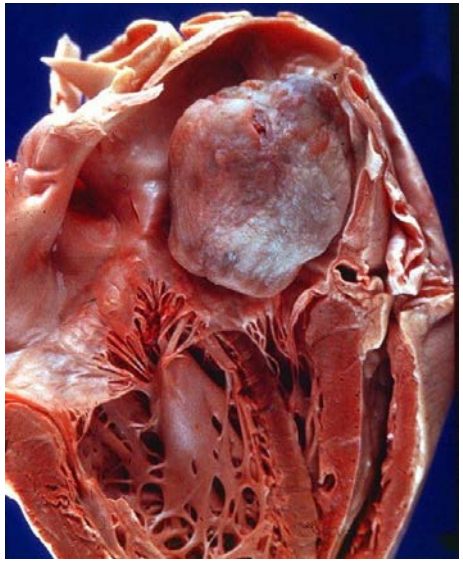
Clinical Surgical Indications

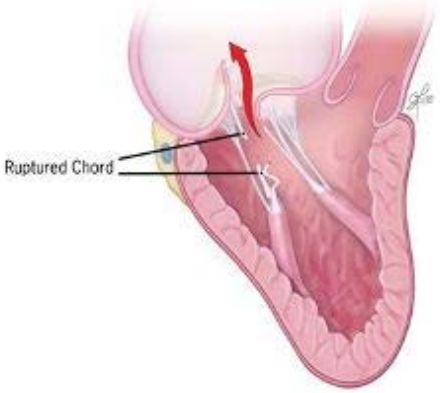
- Acute aortic or mitral insufficiency with signs of ventricular failure
- Heart failure unresponsive to medical therapy
- New heart block



Noninfectious Mimickers

- Antiphospholipid Antibody Syndrome
- Atrial Myxoma
- Carcinoid
- Rheumatic Carditis
- SLE
- Polyarteritis Nodosa
- Behcet's
- Post-Valvular Surgery
- Eosinophilic Heart Disease
- Ruptured Mitral Chordae
- Myxomatous Degeneration





Epidemiologic Clues

- IVDU: *S aureus*, fungi, *Pseudomonas*
- Poor dental health: Viridans group *Strep*, nutritionally variant *Strep*, HACEK
- Homeless, body lice: *Bartonella* species
- Dog-Cat exposure: *Bartonella* species, *Pasteurella* species, *Capnocytophaga* species
- Contaminated/nonpasteurized milk or farm animals - *Brucella* species, C*oxiella burnetii, Erysipelothrix* sp

Epidemiologic Clues

- Solid organ transplantation: *S aureus, Aspergillus fumigatus, Enterococcus* species, *Candida* species
- Early (≤1 y) prosthetic valve placement: Coagulase-negative *Staph, S aureus*, Aerobic Gram-negative bacilli, Fungi, *Corynebacterium* species, *Legionella* species
- Late (>1 y) prosthetic valve placement: Coagulase-negative *Staph*, *S aureus*, Viridans group *Strep*, *Enterococcus* species, Fungi, *Corynebacterium* species

Key Clinical Points

- *Staph and Strep* account for 80% of cases of infective endocarditis, with *Staph* currently the most common pathogens.
- Cerebral complications are the most frequent and most severe extra-cardiac complications. Vegetations that are large, mobile, or in the mitral position and infective endocarditis due to *Staph aureus* are associated with an increased risk of symptomatic embolism.

Key Clinical Points

- Identifying the causative microorganism is central to diagnosis and appropriate treatment; two or three blood cultures should routinely be drawn before antibiotic therapy is initiated.
- When infective endocarditis is suspected, echocardiography should be performed as soon as possible.
- Indications for surgery include heart failure, uncontrolled infection, and prevention of embolic events.

THANK YOU!

References

- Baddour L, et al. Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications. *Circulation.* 2015;132:1435-1486.
- Hoen B, et al. Infective Endocarditis. *NEJM*. 2013;368;15.


BELIEVE IN WE™
OhioHealth