Infected endocarditis

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Outline

• History
• Epidemiology
• Clinical manifestations
• Diagnosis
  - Criteria
  - Use of echocardiogram
  - Culture negative endocarditis
• Therapy
  - Specific antimicrobial therapy
  - Surgical issues
“…we must recognise that there are cases with the clinical history of the malignant form in which, post mortem, the valvular condition has been that of a severe vegetative or verrucose endocarditis. Such a case was a lad aged 11, a patient of Dr. Molson's[...]

He had chorea in July 1880, the second attack. Rapid improvement and recovery under Fowler's solution, [...] took place. There was a slight murmurous condition of the first sound. March 3rd, 1881, [...] he began to be feverish; had exacerbations each evening; temperature rising to 104°F. He became unconscious. There was slight paresis of the left side, and death took place on the 16th. [...]  

There were irregular, soft, greyish-white vegetations on the mitral valve, infarcts in the spleen and kidneys, and a small spot of red softening in the right corpus striatum.”
• **Definition**
  - infection of the endocardial surface of the heart (mural endocardium) or heart valves
  - infection can occur with bacterial or nonbacterial pathogens (fungi, Rickettsia, chlamydia)

• **Current term is Infective Endocarditis (IE)**
  - older expressions still in use are SBE (subacute bacterial endocarditis) or acute endocarditis
  - IE is usually divided into two groups
    • NVE: native valve endocarditis
    • PVE: prosthetic valve endocarditis
Epidemiology

- **Annual Incidence** in USA 10,000-20,000 new cases. 1 in 1000 admissions.

- Average age is in the high 50’s up from 30’s. (half the cases over 60 yrs old)

- **Mitral (40%) > Aortic (36%) > multivalve involvement**

- Tricuspid rarely except for IVDU

- **Mortality** remains 20% in spite of antibiotics and surgery (most of it due to CHF and mechanical failure) down from 45% in 1940s

- Mortality: Nosocomial >> community acq.
Risk factors

- Rheumatic valve disease - THE major risk historically; now only ~10-15% of NVE related to it
- MiV Prolapse (with regurgitation) - relative risk 3.5-8.2 accounts for 7-30% of community acquired NVE (not IVDU)
- Ao sclerosis, Bicuspid Ao, VSD
- Valve surgery - 1-3% get infected in the first year and ~1% / year thereafter
  - Mortality from early onset PVE has declined in the past 30 yrs (90% > 25%)
  - Late-onset (>1 yr after surgery) - usually with same organisms as native valve endocarditis; better prognosis
Risk factors

- Previous IE
- IVDU
- Chronic Hemodialysis - intravascular access, calcific valvular disease, immune impairment
- Cardiac devices
- Invasive medical procedures
- HIV - suggested, not confirmed as independent risk factor [unusual organisms - Listeria, Salmonella]
Other, less common risk factors

- Pregnancy
- Peritoneovenous shunts for the control of intractable ascites
- Ventriculoatrial shunts for the management of hydrocephalus
- Ulcerative lesions of colon 2° malignancy - *S. Bovis*
Particularities of IE in US

- Hemodialysis dependent
- Diabetes (independent risk factor for mortality)
- Presumed intravascular device source
- Receive vancomycin
- MRSA
- Persistent bacteremia
Pathogenesis

• Endocardial injury:
  - turbulent flow from acquired or congenital abn.
  - most common site = valve closure line
  - Catheter or another device > erosion
  - IVDU - contaminating debris

• Formation of sterile thrombus
Pathogenesis

- Transient bacteremia seeds the thrombus
  - Adhesion of bacteria to damaged endothelium depends on virulence factors - dextran, adhesins,
  - Host factors present at the damaged site - fibrinogen, laminin, and type 4 collagen

- “Maturation” - Further deposition of fibrin, plt., bacteria

- Vegetations have no vasculature!
Pathogenesis - where do the vegetations develop?

- atrial surface of Mi or Tr valve
- ventricular surface of incompetent Ao valve
- VSD - on the orifice of the defect, on the right ventricular side of the opening
- chordae tendineae of the anterior leaflet of the mitral valve in patients with aortic insufficiency.
- mitral regurgitation may develop vegetations (MacCallum's patch) on the wall of the left atrium where the regurgitant jet strikes the atrial wall and results in endocardial thickening
Venturi effect

Figure 1
Diagnosis

• Relatively straight forward when:
  - Numerous positive blood cultures in the presence of a well recognized predisposing cardiac lesion
  - Evidence of endocardial involvement

However:
• 25-30% of patients have no identifiable predisposing cardiac lesion at disease onset.
• Blood cultures may be often negative
• distinguish between IE and an alternate source of infection in a bacteremic patient with underlying heart disease.
Diagnosis

- careful history and physical examination
- blood culture and laboratory results
- electrocardiogram (ECG)
- chest radiograph
- echocardiogram
Duke Criteria

• Definite IE
  - Pathologic criteria
    • Microorganism: demonstrated by culture or histology in a vegetation, or in a vegetation that has embolized, or in an intracardiac abscess OR
    • Pathologic lesions: vegetation or intracardiac abscess, confirmed by histology showing active endocarditis
  - Clinical criteria
    • 2 major criteria OR
    • 1 major and 3 minor criteria OR
    • 5 minor criteria

• Possible IE
  - 1 major criterion and 1 minor criterion OR 3 minor criteria

• Rejected IE
  - Firm alternate diagnosis for manifestations of endocarditis OR
  - Resolution of manifestations of endocarditis, with antibiotic therapy for four days or less OR
  - No pathologic evidence of infective endocarditis at surgery or autopsy after antibiotic therapy for four days or less
  - Does not meet criteria for possible infective endocarditis, as above
Criteria - Major

- **Positive blood cultures for IE**
  
  - *Typical microorganism for infective endocarditis from two separate blood cultures*
    - Viridans streptococci
    - Streptococcus bovis, including nutritional variant strains
    - Staphylococcus aureus
    - Community-acquired enterococci, in the absence of a primary focus; OR
  
  - *Persistently positive blood culture, defined as recovery of a microorganism consistent with IE from:*
    - Blood cultures drawn more than 12 hours apart OR
    - All of three or a majority of four or more separate blood cultures, with first and last drawn at least one hour apart
  
  - *Single positive blood culture for Coxiella burnetii or antiphase I IgG antibody titer >1:800*
Criteria - Major

- Evidence of endocardial involvement
  - Positive echocardiogram for IE
    - TEE recommended in patients with prosthetic valves, rated at least "possible IE" by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients
    - Definition of positive echocardiogram
      - 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 anatomic explanation OR
      - Abscess OR
      - New partial dehiscence of prosthetic valve
  - New valvular regurgitation
    - Increase in or change in preexisting murmur not sufficient
Criteria - Minor

- **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
- **Immunologic phenomena** - glomerulonephritis, Osler's nodes, Roth spots, rheumatoid factor
- **Microbiologic evidence** - positive blood culture but not meeting major criterion as noted previously (excluding single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis) **OR** serologic evidence of active infection with organism consistent with IE

- Echocardiographic minor criteria eliminated
History and Physical

- risk factors
- murmurs
- classical stigmata
- complications
Splinter hemorrhages

- Nonblanching
- Distal nail bed (if entire length or proximal only, likely due to trauma)
Osler’s nodes

- Painful and erythematous nodules
- Located on pulp of fingers and toes
- ? Caused by immune complexes - vasculitis
Janeway lesions

- Erythematous, may be blanching macules, may be hemorrhagic
- Nonpainful
- Located on palms and soles
- Caused by emboli
Petechiae

- Often located on extremities or mucous membranes
Roth spots
Blood tests - nonspecific

- ESR, CRP
- normochromic normocytic anemia.
- Leukocytosis, thrombocytopenia - esp. with Staph; may be absent in subacute
- Hyperglobulinemia, cryoglobulins, circulating immune complexes, hypocomplementemia, +RF, false + RPR
Blood tests - specific

- Coxiella burnetii titer >1:800

- Blood cultures
  - minimum of three over 1h to 1 day depending on how sick the patient is
  - anaerobic cultures are very low yield
Organisms recovered from blood cultures

- **Typical:**
  - Staphylococcus aureus
  - Viridans streptococci and Streptococcus bovis
  - Enterococci
  - HACEK group organisms:
    - Haemophilus species (aphrophilus and paraphrophilus)
    - Actinobacillus actinomycetemcomitans
    - Cardiobacterium hominis
    - Eikenella corrodens
    - Kingella kingae

- **More likely than not:**
  - Group G streptococci >> group C or A
  - Streptococcus sanguis >> S. mitis

- **Unlikely, but possible:**
  - Propionibacterium spp., Corynebacterium spp., Bacillus spp., and coagulase-negative staphylococci
<table>
<thead>
<tr>
<th>Agent</th>
<th>Prevalence</th>
<th>Prosthetic Valve</th>
<th>Previous Valve Lesion</th>
<th>Clinical or Epidemiologic Features</th>
<th>Diagnostic Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual agent after antibiotic treatment</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Viridans streptococcus</td>
<td>Common</td>
<td></td>
<td></td>
<td>Poor dental status</td>
<td>PCR assay of valve</td>
</tr>
<tr>
<td>S. bovis</td>
<td>Common</td>
<td></td>
<td></td>
<td>Colonic lesion</td>
<td>PCR assay of valve</td>
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<tr>
<td>Fastidious bacteria</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Coxiella burnetii</td>
<td>Common (1–3%)</td>
<td>Rare</td>
<td>Common</td>
<td>Vegetation, contact with cats, neutropenia, fever may be absent, alcoholism rare</td>
<td>Specific serologic test, specific blood culture, PCR assay of blood or valve, test for antibodies to bartonella, test for antibodies to C. burnetii</td>
</tr>
<tr>
<td>Bartonella henselae</td>
<td>Common (0.5–12%)</td>
<td>Very rare</td>
<td>Rare</td>
<td>Vegetation, contact with cats rare, rural habitat, presence of body lice, fever may be absent, alcoholism common</td>
<td>Specific serologic test, specific blood culture, prolonged blood culture, PCR assay of valve, test for antibodies to bartonella, test for antibodies to C. burnetii</td>
</tr>
<tr>
<td>B. quintana</td>
<td>Common (0.5–12%)</td>
<td>Very rare</td>
<td>Rare</td>
<td>Vegetation, contact with cats rare, rural habitat, presence of body lice, fever may be absent, alcoholism common</td>
<td>Specific serologic test, specific blood culture, prolonged blood culture, test for antibodies to bartonella, test for antibodies to C. burnetii</td>
</tr>
<tr>
<td>Streptococci (granulicatella and abiotrophia species)</td>
<td>Common</td>
<td>Common</td>
<td>Very common</td>
<td>Vegetation, absence of fever rare, alcoholism rare</td>
<td>Use of cysteine-enriched medium for blood subculture, specific blood culture, PCR assay of valve, PCR assay of blood (if not tested)</td>
</tr>
<tr>
<td>Tropheryma whippelli</td>
<td>Very rare</td>
<td>Very rare</td>
<td>Very rare</td>
<td>Vegetation rare, alcoholism rare, chronic arthralgias preceding disease</td>
<td>Histologic examination of valve, PCR assay of valve, PCR assay of blood or blood, specific blood culture</td>
</tr>
<tr>
<td>Mycoplasma and ureaplasma species</td>
<td>Very rare</td>
<td></td>
<td></td>
<td></td>
<td>PCR assay of valve, specific culture of valve</td>
</tr>
<tr>
<td>Legionella species</td>
<td>Very rare</td>
<td></td>
<td></td>
<td></td>
<td>Serologic test, specific culture, PCR assay of valve</td>
</tr>
<tr>
<td>Finegoldia species</td>
<td>Very rare</td>
<td></td>
<td></td>
<td></td>
<td>PCR assay of valve, strict anaerobic culture</td>
</tr>
<tr>
<td>Brucella species</td>
<td>Rare in developed countries, common in developing countries</td>
<td></td>
<td></td>
<td></td>
<td>Serologic test, PCR assay of valve</td>
</tr>
<tr>
<td>Mycobacterium species</td>
<td>Very rare</td>
<td></td>
<td></td>
<td></td>
<td>PCR assay of valve</td>
</tr>
<tr>
<td>Fungi</td>
<td>Rare in general population</td>
<td>Very common</td>
<td>Very common</td>
<td>Vegetation, alcoholism (probable), absence of fever rare, intravenous drug use, valvular prosthesis</td>
<td>PCR assay of blood or of valve, specific blood culture, culture of emboli, specific serologic test</td>
</tr>
</tbody>
</table>

* Common denotes more than 100 cases reported in the literature, rare 50 to 100 cases, and very rare fewer than 50 cases. PCR denotes polymerase chain reaction. Data are from Brouqui and Raoult.⁶
ECG

- Rarely useful, but part of initial eval
- ischemia or infarction (thrombi in coronary circulation)
- New blocks or conduction delay -
  - New high degree AV block - suggestive - ring abscess
- Nonspecific ST-T changes suggestive of (purulent) pericarditis

- For passionate individuals and future cardiologists -
  “Electrocardiographic Findings in Infective Endocarditis” -
Echocardiography: TTE or TEE?

- TTE and TEE are complementary

- If there is any suspicion of IE, start with a TTE.
  Normal valves on TTE = unlikely IE
  Positive vegetation = no need for TEE if native valve
  Other abnormalities > go for TEE if high suspicion

- TEE should be used in patients with staph or fungal bacteremia, suspected PVE, concerns of intracardiac complications, high clinical suspicion and negative TTE
TTE vs TEE

- TEE has superior sensitivity (over 90% as opposed to 60%), however, it is significantly more expensive and invasive.

- NPV of TEE is 96-98%; if negative, repeat it in high risk patients if no improvement.

- Inter-reader variability

- Assess risk of embolization
  - large (if >10mm risk=57%; if <10mm, 22%)
  - mobile vegetations (48% as opposed to 9%)

Multislice CT

- Prelim data:
- identified 26 / 27 patients with vegetations and 9 / 9 patients with abscesses/pseudoaneurysms
- Missed all 4 valve perforations.
Complications

- **Renal** - diffuse glomerulonephritis with uremia, renal infarction with hematuria

- **Neurologic** - strokes, encephalopathy, mycotic cerebral aneurysms; pts may present with visual changes, headache, change in mental status

- **Cardiac** - CHF, arrhythmias, pericarditis

- **Vertebral osteomyelitis and septic arthritis** (esp multiple joints and axial skeleton joints)
High mortality predictors

- Infection with S. aureus, while mortality is lower with streptococcal infection (8 versus 33 percent with S. aureus in one series)
- Heart failure
- Diabetes mellitus
- Embolic events
- Perivalvular abscess
- Larger vegetation size
- Female gender
- Contraindication to surgery
- Low serum albumin
- Persistent bacteremia
- Abnormal mental status
- Poor surgical candidacy
Treatment
General principles

• use intravenous antibiotics
• use bactericidal as opposed to static antibiotics
• Review carefully the susceptibilities for the isolated organism
• generally, long duration of therapy is needed (> 4 weeks)
<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Native valve</th>
<th>Prosthetic Valve</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Therapy</td>
<td>Duration</td>
</tr>
<tr>
<td>Prosthetic Valve</td>
<td>Therapy</td>
<td>Duration</td>
</tr>
<tr>
<td>Viridans streptococci or</td>
<td>PCN G 12-18 million units IV / 24h in 4-6 divided</td>
<td>4 wks</td>
</tr>
<tr>
<td>Streptococcus bovis</td>
<td>doses or Ceftriaxone 2gm IV q24h OR Ceftriaxone</td>
<td>PCN G 24 million units IV in 4-6 divided doses OR</td>
</tr>
<tr>
<td></td>
<td>2gm IV q24h in one dose or penicillin G as above</td>
<td>ceftriaxone 2gm IV q24h +/- gentamicin* IV OR</td>
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<tr>
<td></td>
<td>OR Severe b-lactam allergy: Vancomycin IV</td>
<td>Severe b-lactam allergy: Vancomycin IV</td>
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<tr>
<td></td>
<td>2 wks</td>
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<tr>
<td></td>
<td>2 wks (gent)</td>
<td>6 wks (vanco)</td>
</tr>
<tr>
<td></td>
<td>4 wks</td>
<td></td>
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<tr>
<td></td>
<td>Penicillin G 24 million units IV q24h in 4-6</td>
<td>Penicillin G 24 million units IV in 4-6 divided doses</td>
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<td></td>
<td>divided doses OR ceftriaxone 2gm IV q24h PLUS</td>
<td>or ceftriaxone 2gm IV q24h +/- gentamicin* IV OR</td>
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<tr>
<td></td>
<td>gentamicin* IV OR</td>
<td>Severe b-lactam allergy: Vancomycin IV</td>
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<td></td>
<td>OR Severe b-lactam allergy: Vancomycin IV</td>
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<tr>
<td></td>
<td>6 wks</td>
<td>6 wks (for b-lactam and gent)</td>
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<tr>
<td></td>
<td>4 wks</td>
<td>6 wks (vanco)</td>
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<td></td>
<td>Staph (MSSA or MSSE)</td>
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<tr>
<td></td>
<td>Nafcillin 1 12gm IV in 4-6 divided doses OR</td>
<td>Nafcillin 2gm IV q4h PLUS rifampin 300mg IV/PO q8h</td>
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<tr>
<td></td>
<td>Cefazolin 2gm IV q8h* (for non-severe PCN allergy)</td>
<td>PLUS gentamicin* IV</td>
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<tr>
<td></td>
<td>Either of the above PLUS gentamicin 3-5 days OR</td>
<td>(goal vancomycin trough = 10-15mcg/ml)</td>
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<td></td>
<td>OR Severe b-lactam allergy: Vancomycin IV</td>
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<tr>
<td></td>
<td>6 wks</td>
<td>≥ 6 wks (naf and rif)</td>
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<td></td>
<td>6 wks</td>
<td>2 wks (Gent)</td>
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<td></td>
<td>6 wks</td>
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<tr>
<td></td>
<td>Staph (MRSA)</td>
<td></td>
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<tr>
<td></td>
<td>Vancomycin (goal trough 10-15mcg/ml)</td>
<td>Vancomycin IV PLUS rifampin 300mg IV/PO q8h PLUS</td>
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<tr>
<td></td>
<td>6 wks</td>
<td>gentamicin* IV</td>
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<td></td>
<td></td>
<td>(goal vancomycin trough = 10-15mcg/ml)</td>
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<td></td>
<td>≥ 6 wks (vanco and rif)</td>
<td>2 wks (Gent)</td>
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<tr>
<td></td>
<td>Enterococci</td>
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<td></td>
<td>Ampicillin 2gm IV q4h PLUS gentamicin* IV OR</td>
<td>Ampicillin 2gm IV q4h PLUS gentamicin* 3 IV OR</td>
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<td></td>
<td>OR Severe b-lactam allergy: Vancomycin IV PLUS</td>
<td>OR Severe b-lactam allergy: Vancomycin IV PLUS</td>
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<td></td>
<td>gentamicin* IV OR</td>
<td>gentamicin* 4 IV</td>
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<td></td>
<td>4-6 wks (both)</td>
<td>6 wks (both)</td>
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<td>6 wks (both)</td>
<td>6 wks (both)</td>
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<td></td>
<td>HACEK</td>
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<td></td>
<td>Ceftriaxone 2gm IV q24h OR Severe b-lactam allergy:</td>
<td>Same as native valve</td>
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<tr>
<td></td>
<td>ciprofloxacin 400mg IV q12h</td>
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<td></td>
<td>4 wks</td>
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<td></td>
<td>4 wks</td>
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<td></td>
<td>Culture negative 4</td>
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<tr>
<td></td>
<td>Amp-sulbactam 12g / 24h IV in 4 divided doses OR</td>
<td>(≤ 1yr from valve repl.)</td>
</tr>
<tr>
<td></td>
<td>PLUS gentamicin IV OR</td>
<td>Vancomycin PLUS gentamicin* IV PLUS cefepime 2gm IV q8h</td>
</tr>
<tr>
<td></td>
<td>OR Vancomycin IV + Gentamicin IV + Ciprofloxacin</td>
<td>PLUS rifampin 300mg IV/PO q8h</td>
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<td></td>
<td>PO/IV OR</td>
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<td></td>
<td>4-6 weeks (both)</td>
<td>6 wks (ceft and doxy)</td>
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<td></td>
<td>4-6 weeks (all three)</td>
<td>2 wks (gent)</td>
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</table>
Prevention

• 1997 guidelines stratified pts into risk categories and recommended prophylaxis to high and moderate risk

• 2007 guidelines limit prophy to **highest risk pts:**
  - Prosthetic cardiac valves
  - Previous history of IE
  - Unrepaired or recently repaired (w/in 6 Mo) cyanotic congenital heart disease or residual defects
  - Cardiac transplant recipients with valvulopathy
Prevention

• **Procedures** for which prophylaxis is indicated:
  - Dental procedures that involve manipulation of periapical region or perforation of oral mucosa
  - Invasive procedures of respiratory tract with biopsy or drainage of an infective focus (abscess, empyema)
  - Surgical procedures that involve infected skin, skin structures and musculoskeletal tissue

• **Abx of choice:** amoxicillin PO, ampicillin IV, cefazolin IV/IM, clindamycin PO/IV/IM, macrolide, all in single dose 30-60 min prior to procedure
Surgical therapy for IE

- 1961 - first valve repair for a patient with fungal endocarditis
- Thought to reduce mortality in selected cases, in conjunction with medical therapy; no prospective studies
- Greatest benefit in patients with CHF