Introduction

Endocarditis: inflammation of the endocardium
- Implies bacterial presence in the lesion
- Can be within septal defects or mural endocardium

Classification
- Native Valve Endocarditis
- Prosthetic Valve Endocarditis (PVE)
- Endocarditis due to intravenous drug abuse (IVDA)

“Infective Endocarditis” vs “Bacterial Endocarditis”
- SBE
- ABE

Definitions

Acute Bacterial Endocarditis (ABE):
- Fulminating infection
- High fever
- Systemic toxicity
- Death in < 6 weeks

Subacute Bacterial Endocarditis (SBE):
- Indolent infection
- Prior to valvular disease
- Death in 6 weeks - 3 months

“Left-sided” endocarditis
- Mitral valve

“Right-sided” endocarditis
- Involvement of the tricuspid valve
- Related to IVDA and indwelling pacemakers

“Native-valve” endocarditis
“Prosthetic-valve” endocarditis

“Culture-Negative” endocarditis
- Bad isolation/identification technique
- Fastidious isolate
- Non-bacterial culprit
- Antibiotics administration pre-culture

Definitions (cont.)
Epidemiology
- Less than 5 cases per 100,000
- Approximately 1 case per 1000 admissions
- Unchanged for 30 years
- Greater than 50% patients over age 50
- Unusual in children
- Overall mortality 16-27%
  - Age
  - Aortic valve involvement
  - CHF
  - CNS complications

Epidemiology (cont.)
- > 75% IE patients have evidence of endocarditis risk factors
  - History of IV drug abuse
  - History of rheumatic heart disease
  - Congenital heart disease or malformations
  - Mitral valve prolapse or valvular insufficiency
  - Ventral septal defect
  - Valvular stenosis
  - Prosthetic valve

Pathophysiology
- Surface Alteration
- Non-Bacterial Thrombotic Embolism
  - Fibrin/Platelet deposition
- Bacterial attachment
  -Transient bacteremia
- Sheath covering
  - Fibrin/Platelets
  - Protective environment
- Vegetation growth
  - $10^7-10^{10}$ org per gram of tissue
  - Valvular tissue destruction

Etiology

<table>
<thead>
<tr>
<th>Organism</th>
<th>Percentage of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococci</td>
<td>60-80</td>
</tr>
<tr>
<td>Viridans streptococci</td>
<td>30-40</td>
</tr>
<tr>
<td>Enterococci</td>
<td>5-18</td>
</tr>
<tr>
<td>Other streptococci</td>
<td>15-25</td>
</tr>
<tr>
<td>Staphylococci</td>
<td>20-35</td>
</tr>
<tr>
<td>Coagulase-positive</td>
<td>10-27</td>
</tr>
<tr>
<td>Coagulase-negative</td>
<td>1-3</td>
</tr>
<tr>
<td>Gram-negative aerobic bacilli</td>
<td>1.5-13</td>
</tr>
<tr>
<td>Fungi</td>
<td>2-4</td>
</tr>
<tr>
<td>Miscellaneous bacteria</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Mixed infections</td>
<td>1-2</td>
</tr>
<tr>
<td>Culture-negative</td>
<td>&lt;5-24</td>
</tr>
</tbody>
</table>

Clinical presentation
- Variable – ABE with sepsis-like presentation
- Vague symptoms
  - Fever
  - Anorexia and weight loss
  - Malaise/weakness
  - Chills
  - Diaphoresis
  - Dyspnea
  - Cough
- Focal neurologic complaints (20% cases)
- Embolic phenomenon

Rehm SJ | IDCNA 12:879-901,1998 (Adapted)
Physical findings
- Low grade fever (90% cases)
- Cardiac examination (85% cases)
  - Murmur
  - Change in murmur (10%): Likely 2º CHF
- Classic symptoms (>1 in IE)
  - Petechiae
  - Splinter hemorrhages
  - Osler nodes
  - Janeway lesions
  - Roth Spots

Laboratory findings
- Hematologic
  - Often abnormal but not diagnostic
  - Anemia/pancytopenias
  - ESR / CRP
  - Rh-factor / circulating immune complexes
- Blood culture
  - Single most important lab test
  - Continuous / low grade bacteremia
  - Minimum of 3 sets (different sites) in first 24 h
  - May require >3 if previous abx administered
  - Hold Ct's for 3 weeks

Laboratory findings (cont.)
- Echocardiography
  - Transthoracic echocardiography (TTE)
    - Rapid
    - Non-invasive
    - 98% specificity, 60 % sensitivity
    - Views obstructed by obesity, COPD, chest-wall deformities
  - Transesophageal echocardiography (TEE)
    - Higher ultrasonic frequency
    - 88-100% specificity, 86-94% sensitivity

Diagnosis
- Straightforward if oslerian manifestations present
  - Bacteremia/fungemia
  - Evidence of active valvulitis
  - Peripheral emboli**
  - Immunologic phenomenon**

**Typically evident for acute (not R. sided)
- Duke Criteria

Note: Negative TTE or TEE do not rule out vegetative IE
**Duke criteria**

- **Definite Case of Endocarditis**
  - Pathologic (on open heart surgery or autopsy)
  - Microscopic evidence of vegetation or abscess
  - Clinical (Duke Criteria)
    - 2 major criteria
    - 1 major criteria & 3 minor criteria
    - 5 minor criteria
- **Possible Case of Endocarditis**
  - Findings consistent with IE, but not qualified as “definite” or “rejected” according to Duke criteria

- **Rejected Possibility of Endocarditis**
  - Pathologic
    - No evidence of IE at surgery/autopsy after antibiotic therapy < 4 days
  - Clinical
    - Firm alternate diagnosis
    - Resolution of manifestations (with therapy) < 4 days

**Duke Major criteria**

- Positive blood cultures
  - Typical pathogen frequently associated with endocarditis
  - Multiple positive cultures (75-100% of cultures positive)
  - Positive cultures obtained throughout the day
- Evidence of endocardial involvement
  - New evidence of valve regurgitation
  - Echocardiogram positive
    - Vegetation present
    - Evidence of intra-cardiac abscess
    - Dehiscence of prosthetic valve

**Duke Minor criteria**

- Fever >38 C (100.4 F)
- History of IVDA or predisposing heart disease
- Positive Blood culture but not typical pathogen
- Echo not meeting major criterion
- Immune
  - +RF, Osler Node, Roth Spot, or Glomerulonephritis
- Vascular
  - PE, mycotic aneurysm, Janeway lesion, arterial emboli, intracranial hemorrhage, Flame hemorrhage

**Workup**

- CBC with differential, U/A, ESR
- ≥ 3 sets of blood cultures drawn at different sites and times
- EKG & Echo
  - CXR + V/Q if R. sided involvement suspected
  - Antibiotic sensitivity studies if BCxs positive
- Peak / trough serum inhibitory titer (SIT) & serum bactericidal titer (SBT)
- Physical for classic findings of endocarditis
- Also consider: rh-factor and serology

**General approach to treatment**

- High dose, prolonged therapy
- Bactericidal
- Bacteriostatic agents combination
Treatment issues
- Hold antibiotics before Cx?
- Abx reduce recovery by 35-40%
- If patient does not have 1) toxic appearance 2) clinical or EEG evidence of severe or progressive valve regurgitation or CHF
- If initial BCx (-), delay 2-4 days
- Use of aminoglycosides (AG)
  - Oto- and Nephro-toxic
  - Duration of therapy
  - Desired levels

Streptococci
- Issues
  - Most common cause of IE (especially Native valve)
  - Common inhabitants of oral cavity/gingiva
  - Course typically sub-acute
  - Most Viridans sensitive to PCN
    - Tolerant strains
    - Nutritionally deficient strains

Streptococci treatment
- PCN MIC $\leq 0.1$ mg/L:
  - PCN G or ceftriaxone: 4 weeks each
  - PCN G + gent.: 2 weeks each
  - Vancomycin: 4 weeks
  - Nutritional variant strains: See Enterococcus

  Prosthetic valve: PCN 6 weeks + AG 2 weeks
- PCN MIC $> 0.1$ mg/L and $< 0.5$ mg/L
  - PCN G + gent: 4 weeks and 2 weeks
  - Vancomycin: 4 weeks
- PCN MIC $> 0.5$ mg/L
  - See Enterococcus

Enterococci
- Issues
  - No bactericidal agent
    - PCN MICs elevated
    - Resistant to all cephalosporins
    - Possible Vanco resistance: Synercid / Linezolid / Chloramphenicol / Doxycycline
  - Typically indolent infections (SBE)
  - Test ampicillin / vanco sensitivity
  - Test gentamicin / streptomycin sensitivity
  - MIC $< 500$ mg/L = gent “sensitive”
  - MIC $< 2000$ mg/L = streptomycin “sensitive”
  - No tobramycin or amikacin

Enterococci treatment
- Enterococci
  - PCN G + gent: 4-6 weeks each
  - Ampicillin + gent: 4-6 weeks each
  - Vancomycin + gent: 4-6 weeks each

  Prosthetic valve: 6 week treatment
  Pre-treatment infection $> 3$ months: 6 wk tx

Note: Gentamicin / Streptomycin resistance encoded by separate genes.
AG resistant isolate may require extended (8-12 week) β-lactam Tx.

Staphylococci
- Treatment stratification based on prosthesis presence
  - Issues
    - S. epidermidis possible contaminant
    - S. aureus typically invasive (ABE), typically involved with IVDA
    - Also central venous cath and valve replacement surgery contaminants
    - Test methicillin sensitivity
Staphylococci (cont.)

- Issues with AG
  - In vitro data and experimental cardiac vegetation data: accelerated kill
  - Clinical effects
    - Reduced duration of fever
    - Reduced duration of bacteremia (1/2 day)
    - NO DIFFERENCE IN MORBIDITY
    - NO DIFFERENCE IN MORTALITY
  - Data almost exclusively with right sided endocarditis, nafcillin, and S. aureus

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Antibiotic</th>
<th>+BC</th>
<th>Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Korzeniowski (1982)</td>
<td>N</td>
<td>Mean 3.4d</td>
<td>22/35 (63%)</td>
</tr>
<tr>
<td>Chambers</td>
<td>N+T</td>
<td>19/20</td>
<td>47/50 (94%)</td>
</tr>
<tr>
<td></td>
<td>V+T</td>
<td>sterile @48hrs</td>
<td>1 pt (+BC 12&amp;14d)</td>
</tr>
<tr>
<td>Small (1990)</td>
<td>V</td>
<td>2Pt(+BC 7-16d)</td>
<td>8/13 (62%)</td>
</tr>
<tr>
<td>Levine (1991)</td>
<td>V</td>
<td>Median 7d</td>
<td>18/22 (82%)</td>
</tr>
<tr>
<td></td>
<td>V+R</td>
<td>Median 9d</td>
<td>18/20 (90%)</td>
</tr>
</tbody>
</table>

Staphylococci treatment (no prosthesis)

- Staphylococci in absence of prosthesis
  - Methicillin-susceptible Staphylococci
    - Nafcillin + gent. 4-6 weeks + 3-5 days
    - 1st gen ceph + gent. 4-6 weeks + 3-5 days
  - Vancomycin 4-6 weeks
  - Methicillin-resistant Staphylococci
    - Vancomycin 4-6 weeks

Limited data suggesting IVDA with MSSA infecting R. sided valves can be tx’d with 2-weeks β-lactam course effectively.

Staphylococci treatment (prosthesis present)

- Staphylococci in the presence of prosthesis
  - Methicillin-susceptible Staphylococci
    - Nafcillin + rifampin + gent. >6 weeks, 2 weeks for gent.
  - Methicillin-resistant Staphylococci
    - Vanco + rifampin + gent. >6 weeks, 2 weeks for gent.

HACEK

- Slow growing, fastidious gram-negatives likely not to result in positive culture (culture-negative)
  - Haemophilus spp.
  - Actinobacillus actinomycetemcomitans
  - Cardiobacterium hominis
  - Eikenella corrodens
  - Kingella kingae
- Issues
  - Typically sub-acute
  - Large vegetations / common emboli
HACEK treatment
- Should be considered ampicillin-resistant
- Both β-lactam producers and non-producers are susceptible to 3rd generation cephalosporins
  - Ceftriaxone sodium 4 weeks
  - Amp + gent. 4 weeks each

Role of anticoagulation
- ? Contraindication
  - Intracerebral hemorrhage
  - Pts with prosthesis who normally maintained (without evidence of cerebral events)

Surgical indications
- Definite
  - Hemodynamically unstable
  - New or worsening CHF
  - Valvular dysfunction
  - Uncontrolled infection
    - + Blood cultures > 3 days
    - Fungal endocarditis
    - Perivalvular or myocardial abscess
  - Eliminate primary site of infection

Surgical indications (cont.)
- Relative
  - Vegetation >10mm
  - Recurrent systemic emboli (> 2)
  - Mitral valve preclosure
  - Ruptured chordae tendineae, papillary muscle, ventricular septum
  - Heart block
  - Infection relapse

Antibiotic prophylaxis
- One hour prior to procedure:
  - 2 Gm Amoxicillin orally or
  - 600 mg Clindamycin orally or
  - 2 Gm Cephalexin orally or
  - 500 mg Clarithromycin orally or
  - 2 Gm Ampicillin intramuscularly

Causes of death
- CHF
- Embolic phenomena
- Mycotic aneurysm rupture
- Complications from cardiovascular surgery
- PVE
- Inadequate response to antibiotics
Summary

- Cardio/infectious diseases
- RF → pathophysiology
- Streptococci, Staphylococci, Enterococci
- Vegetations → lab, clinical, physical findings
- Empiric treatment (prolonged, high dose) tailored to native or prosthetic valve, or IVDA
- Definitive therapy for each pathogen