Endocarditis

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Image adapted from U Copenhagen Dept. Oral Surgery
Objectives

- Overview endocarditis though definitions and epidemiology
- Describe the pathophysiology, list implicated pathogens, and identify disease characteristics related to the specific types of endocarditis
- Identify the characteristic clinical, physical, and laboratory findings associated with endocarditis
- List workup considerations
- Identify empiric and definitive treatment modalities for each type of endocarditis
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)

“Infected 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
Definitions (cont.)

- “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
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

Rehm SJ  IDCNA 12:879-901,1998 (Adapted)
Narrowed Aortic Valve ("stenotic")

Vessels to and from the Lungs

Leaking Mitral Valve ("regurgitant")

Surface alteration

NBTE

Bacterial attachment

Sheath covering

Graphic adapted from Heartpoint.com
Pathophysiology

- Surface Alteration
- Non-Bacterial Thrombotic Embolism
  - Fibrin/Platelet deposition
- Bacterial attachment
  - Transient bacteremia
- Sheath covering
  - Fibrin/Platelets
  - Protective environment
  - Vegetation growth
    - $10^9$-$10^{10}$ org per gram of tissue
    - Valvular tissue destruction
<table>
<thead>
<tr>
<th>Etiology</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
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 Cx’s for 3 weeks
Laboratory findings (cont.)

- Echocardiography
  - Transthorasic 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

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


- **Definite Case of Endocarditis**
  - Pathologic (on open heart surg or autopsy)
    - M/o demonstrated by Cx or histology from vegetation or abscess
    - Pathologic lesion (vegetation/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
Duke criteria (cont.)

- 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

Nutritionally variant strains: See Enterococcus

Prosthetic valve: PCN G 4 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 MORTALITY
    - 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/ 3 (33% )</td>
</tr>
<tr>
<td></td>
<td>V+T</td>
<td>1 pt (+BC 12&amp;14d)</td>
<td></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 (cont.)

- Issues with vancomycin
  - Clinical and in-vitro experience suggest less effective anti-staph of vanco compared to β-lactams

- Issues with rifampin
  - In vitro data suggests possible synergy, antagonism, or indifference
  - In vivo data are highly variable
  - Routine clinical use NOT RECOMMENDED
  - Supplemental tx in non-responding cases
    - Might be useful to lyse *S. aureus* inside WBC
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.
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

*American Heart Assoc. JAMA 277:1794,1997*
Causes of death

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

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