Endocarditis

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Pathophysiology and Pharmacotherapy of Infectious Diseases Phar 6124

Objectives

• Overview endocarditis through definitions and epidemiology
• Link pathophysiologic considerations to clinical implications
• List implicated pathogens
• 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)
  - "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

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
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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
• 2-month mortality 15-20%
  – Despite advances in imaging, m/o identification, and antibiotic regimens
  • 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
  • 10^9-10^10 org per gram of tissue
  • Valvular tissue destruction

Clinical implications of pathophysiological considerations

Vegetation
  • Sheath covering
  • Bacterial inoculum
  • Growth phase
  • Metabolic rate

Therapeutic implication
  • Bactericidal agents and antibiotic penetration
  • MICs and resistance
  • Cell wall agent efficacy
  • Treatment duration

Etiology

<table>
<thead>
<tr>
<th>Bacteria Type</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>

Heartpoint.com

Rehm SJ IDCNA 12:879-901, 1998 (Adapted)
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 2nd 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
  - 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

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

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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)
  • Explain treatment failure
  • Validate therapeutic options
  • Confirm efficacy of simplified regimen
• Physical for classic findings of endocarditis
• Also consider: rh-factor and serology
General approach to treatment

- High dose
- Prolonged
- 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
  - "Non-groupable streptococci"
  - a-hemolysis
- Course typically sub-acute
- Most Viridans sensitive to PCN
  - Tolerant strains
  - Nutritionally deficient strains
- Short course therapy
  - Two-week AG+PCN therapy alone shown efficacious to four-week regimen (CID 1995 (21))
  - PCN-sensitive oral streptococcus or S. bovis
  - Native valve endocarditis
  - No heart failure, aortic insufficiency or conduction abnormalities
  - No evidence of extracardiac septic complications
  - Vegetation diameter ≤ 10 mm
  - Clinical response within 7 days (temperature)

Streptococci treatment

- PCN MIC ≤ 0.1 mg/L:
  - PCN G or ceftriaxone 4 weeks each
  - PCN G + gent. 2 weeks each
  - Vancomycin 4 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 / vancomycin sensitivity
    - MIC < 500 mg/L = gentamicin "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**
  - **Onset classification**
    - Early onset (< 1 year post-op)
    - Late onset (> 1 year post-op)
  - Non-prostheses cases in which surgical intervention is warranted, negative valve culture is treated for two-weeks post-op
- **Issues**
  - *S. epidermidis* possible contaminant
  - *S. aureus* typically invasive (ABE), typically involved with IVDA
  - Also central venous cath and valve replacement surgery contaminants

### 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
  - Data almost exclusively with right sided endocarditis, nafcillin, and *S. aureus*

### 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

### Investigator Antibiotic +BC Cure

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Antibiotic</th>
<th>+BC</th>
<th>Cure</th>
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</thead>
<tbody>
<tr>
<td>Korzeniowski</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 sterile 48hrs</td>
<td>47/50 (94%)</td>
</tr>
<tr>
<td></td>
<td>V+T</td>
<td>1 pt (BC 12/14d)</td>
<td>1/3 (33%)</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 cep + gent. 4-6 weeks + 3-5 days
    - Vancomycin 4-6 weeks
  - Methicillin-resistant Staphylococci
    - Vancomycin 4-6 weeks

### 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.
New Agents

- Quinupristin/dalfopristin (Synercid)
  - In-vitro activity MRSA, VRE, *Faecium*
  - In-vitro synergy with rifampin
    - *S. aureus* sensitive to quinupristin
  - Animal model synergy with doxycycline in *E. faecium* IE
  - Few cases of human *S. aureus* IE
  - Large, open trial showed Synercid cure rate < 54% in MRSA IE (as compared to 71% cure rate in aggregate infections)

- Linezolid (Zyvox)
  - Activity vs. MRSA, VRE, PRSP
  - Animal and in-vitro reports
    - Comparable activity to vancomycin
  - Limited human case reports
    - Prolonged use, concern for anemias

Unusual microorganisms

- 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
  - Both β-lactam producers and non-producers are susceptible to 3rd generation cephalosporins
    - First line treatment vancomycin + AG

- Fugal IE
  - *Candida* and *Aspergillus*
  - Typically IVDA, prosthesis, or long-term central venous catheters
    - Reference treatment remains with amphotericin B and flucytosine
    - Valve surgery always necessary

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

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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