Bacterial Endocarditis

John C. Rotschafer, Pharm. D.
Professor
College of Pharmacy
University of Minnesota

Overview

• In pre-antibiotic era endocarditis was usually a fatal disease as a result of CHF
• Host defenses play minor role in disease
• Staphylococci and Streptococci usually responsible for >75% cases
• Changing spectrum of disease as results of indwelling prosthetic devices, illicit drug use, and an aging population

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

- “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

Pathogenesis

- Valve surface altered through trauma or blood turbulence eroding endothelial lining
  - Fibrin and platelets deposited at the damaged site forming nonthrombotic vegetative lesion
  - Transient bacteremia seeds vegetative lesion
  - Bacteria enter exponential growth protected from WBC in the confines of the vegetation
  - Bacteria can begin to damage valve and seed bloodstream with bacteria
Native Valve Endocarditis

- Right Sided
  - Tricuspid ≤ 6% (Most often IVDA)
  - Pulmonary < 1%
- Left Sided
  - Mitral 30 - 45%
  - Aortic 5 - 35%
  - Both valves ≤ 35%

Intravenous Drug Abuse (IVDA) Endocarditis

- Disease of the right side of the heart
- May present as pulmonary syndrome
  - Fever
  - Cough
  - Pleuretic chest pain
  - Hemoptysis
  - Pathogen a function of patient’s IV drug practices
    - Contaminated water, drugs, or equipment

Heart Valves & Blood Flow

- Venous: Right Atrium → Right Ventricle → Pulmonary Artery → Heart Valves → Lungs → Left Atrium
- Arterial: Left Atrium → Left Ventricle → Aortic Valve → Heart Valves → Lungs → Right Atrium
Pathogenesis

Conditions contributing to the development of endocarditis
- 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

Endocarditis

Common Bacterial Pathogens
- S. aureus (MRSA or MSSA)
- S. epidermidis (MRSE or MSSE)
- S. viridans
- Enterococci
- S. pneumoniae
- HACEK organisms
Endocarditis

- **Bacterial Pathogens**
  - HACEK Group
    - *Haemophilus* spp.
    - *Actinobacillus actinomycetemcomitans*
    - *Cardiobacterium hominis*
    - *Eikenella corrodens*
    - *Kingella kingae*
  
  *Slow growing, fastidious Gram negatives likely cause of Culture Negative Endocarditis*

Pathogens

- **Staphylococci**
  - *S. aureus* vs *S. epidermidis* (?contaminated B/C)
  - Methicillin sensitive vs resistant
- **Enterococci**
  - *E. faecalis* vs *E. faecium* vs other
  - Gentamicin &/or streptomycin sensitive
  - Ampicillin sensitive or resistant
  - Vancomycin sensitive or resistant

Enterococci

- **Enterococci naturally tolerant to aminoglycosides**
  - MIC < 500 mg/L = “sensitive” or synergy likely
  - MIC > 2000 mg/L = “resistant”
  - Gentamicin or Streptomycin aminoglycosides of choice
  - Resistance to gentamicin does not always mean resistance to streptomycin (reverse also true)
  - Tobramycin or amikacin not reliable choice
Culture Negative Endocarditis

- Misnomer as there may be a pathogen but organism recovery may not be possible with standard methods
  - Fungal
  - HACEK group
  - Rickettsiae
  - Chlamydiae
  - Anaerobes
  - Cysteine/Vitamin B6 dependent Streptococci
  - Brucella
  - Viral
  - Prior antibiotic therapy
  - Misdiagnosis

Diagnosis of Endocarditis

  - Definite Case of Endocarditis
    - Must have 2 major criteria or 1 major criteria & 3 minor criteria or 5 minor criteria
  - Possible Case of Endocarditis
    - Patient appears to have endocarditis but does not have the necessary number of major and minor criteria
  - Rejected Possibility of Endocarditis
    - While possibility considered initially an alternative diagnosis established or pathologic diagnosis not established
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

Diagnostic work-up

- CBC with differential, U/A, ESR
- > 3 sets of blood cultures drawn at different sites and times
- EKG & Echo
- Antibiotic sensitivity studies if +B/C’s
- Peak / trough serum inhibitory titer (SIT) & serum bactericidal titer (SBT)
- Physical for classic findings of endocarditis
**Echocardiography**

- Attempt to visualize vegetation’s on heart valve
  - Lesions must be > 2mm in size
- Negative test does not necessarily exclude endocarditis
  - Transesophageal (TEE)
    - Provides the most information but most invasive
      (approx 90% accurate in diagnosis)
  - Transthoracic (TTE)
    - Less invasive but harder to visualize valves

**Endocarditis Treatment**

- For left sided endocarditis generally 4 to 6 weeks of antibiotic therapy recommended
- For right sided endocarditis shorter courses of antibiotics may be considered

**Therapeutic Goals**

- Identify, if possible, the primary site of infection
- Identify infecting pathogen so as to direct therapy
- Sterilize the blood now and following therapy
- Prevent or limit valvular damage and resulting CHF
- Use a bactericidal antibiotic regimen
- Maintain optimal nutritional status of patient
- Prevent embolic disease
- Advise patient &/or family regarding future need for antibiotic prophylaxis
Treatment Considerations

- Large bacterial inoculum
- Pathogens not in exponential growth phase compromising the effect of antibiotics
- Platelet fibrin network prevents WBC from confronting bacteria
- Antibiotics and surgery only real treatment options

Staphylococci

- Methicillin Resistant
  - Vancomycin, Linezolid, Daptomycin or Q/D
- Methicillin Sensitive
  - Nafcillin
  - + Gentamicin
  - + Rifampin

Vancomycin vs. Nafcillin  S. aureus Endocarditis

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Antibiotic</th>
<th>+ BC</th>
<th>Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Korzeniowski</td>
<td>N</td>
<td>Mean 3.4d</td>
<td>22/35 (63%)</td>
</tr>
<tr>
<td>Chambers (1980)</td>
<td>N+T</td>
<td>19/20 sterile 48hrs</td>
<td>4750/94(%)</td>
</tr>
<tr>
<td></td>
<td>V+T</td>
<td>1 pt (+BC 12&amp;14d)</td>
<td>1/3 (33%)</td>
</tr>
<tr>
<td>Small (1980)</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>

Karchmer Ann Intern Med 1991
Adjunct Use of Gentamicin

- Data almost exclusively with right sided endocarditis, nafcillin, and S. aureus
- Data has been extrapolated to:
  - Left sided endocarditis
  - Bacteremia
  - S. epidermidis
  - Vancomycin
  - Other beta-lactam antibiotics

Adjunct Therapy of S. aureus
Nafcillin + Gentamicin

- Questionable practice
  - No difference in morbidity (other than duration of fever) or mortality
  - Addition of gentamicin reduces duration of bacteremia by approximately 1/2 day
- If decision is made to use gentamicin
  - Duration of therapy ≤ 5 days
  - Maintain Cpmax 3-5 mg/L & Cpmin < 1 mg/L
  - Present data would not support SDD

Adjunct Use of Rifampin

- Rifampin added for “synergy”
  - In-vitro data suggests possible synergy, antagonism, or indifference
- Levine suggests that the addition of rifampin to vancomycin offers no therapeutic advantage
- Drug might be useful in patients unable to lyse S. aureus inside WBC
Enterococci

• Beta-lactam sensitive
  – Ampicillin or Penicillin G (+ aminoglycoside if sensitive)

• Vancomycin Resistant
  – Chloramphenicol
  – Doxycycline/Minocycline
  – Investigational agent

• Aminoglycosides
  – Gentamicin or streptomycin if sensitive (+ cell wall agent)
  – Maintain gentamicin $C_{\text{max}}$ 3-5 mg/L & $C_{\text{min}} < 1$ mg/L
  – Maintain streptomycin $C_{\text{max}}$ approximately 20 mg/L

Aminoglycosides and Endocarditis

• Aminoglycosides are ototoxic and nephrotoxic

• Want to limit therapy to as short a period of time as possible to avoid toxicity
  – Staphylococci ≤ 5 days
  – Enterococci will require 4-6 weeks
  – Control peak and trough concentrations

• Elderly and/or renally impaired patients treated for extended periods of time are at greatest risk

Role of Anticoagulants in Endocarditis

• No anticoagulation if patient in NSR with uncomplicated endocarditis (native or bioprosthetic valve)

• Recommended long term in patients with PVE (mechanical) unless there are contraindications

• Embolism during therapy for native or bioprosthetic valve endocarditis uncertain & depend on circumstances
### Surgical Indications in Endocarditis

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

### Relative Indications for Surgery

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

### Endocarditis - Cause of Death

- CHF
- Embolic phenomena
- Mycotic aneurysm rupture
- Complications from cardiovascular surgery
- PVE
- Inadequate response to antibiotics
Antibiotic Prophylaxis
American Heart Assoc. JAMA 277:1794,1997

• 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

Conclusions

• Despite changing pathogen picture for endocarditis, >75% still caused by staphylococci & streptococci
• Increasing use of prosthetic devices increasing the prevalence of MRSE
• Changing patterns of IVDA may alter the spectrum of bacterial pathogens
• Resistance with Gram positive pathogens may make us more dependent on new drugs