ACUTE BACTERIAL ENDocarditis

Michelle Paulson
Morning Report: 2/18/04
Endocarditis:

- Vegetation of platelets, fibrin, organisms, inflammatory cells
- Affects valves, septal defects, chordae tendinae, and mural endocardium
Endocarditis Epidemiology:

- Incidence 1.7-6.2 cases / 100,000 person years; 10,000-15,000 new cases per year
- Incidence in IVDU 150-2000 cases / 100,000 person years
- Over 1/2 of cases are in people aged 60+
- Male to female ratio of 2:1-9:1
Endocarditis Epidemiology:

- **RISK FACTORS:**
  - IVDU (biggest risk factor for right-sided endocarditis, but most IVDUers have left-sided endocarditis)
  - Prosthetic heart valves (occurs in 1-4% on recipients during the first year post-op, then at a rate of 1% per year)
  - Structural heart disease (now mostly mitral valve prolapse with mitral regurgitation—the risk is 5-8X that of normal population; formerly, rheumatic heart disease was biggest cause)
  - Nosocomial endocarditis (from a procedure or vascular device)
Organisms involved:

- Staphyloccocal--*aureus, coag negative*
- Streptococcal--*bovis, viridans, sanguis, mutans, mitis, lugdunensis*
- Enterococcus
- Gram negative
- Fungi
- Culture negative and HACEK--*Bartonella, Coxiella burnetii, Chlamydia, Tropheryma whippiei, Legionella, Brucella and HACEK=* (Haemophilus species, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corroden, Kingella kingae)*

***Staph aureus is leading cause***

**THINK ACUTE and AGGRESSIVE**
Staphylococcus aureus:

- In one study of 103 patients with *S. aureus* bacteremia, all underwent both TTE and TEE, endocarditis found in 25%.
- In another study of 262 patients with *S. aureus* bacteremia, 34% were found to have endocarditis.
- In yet another study of 505 patients with *S. aureus* bacteremia, 13% had endocarditis.
Signs and Symptoms:

- Fever
- Anorexia
- Weight loss
- Malaise
- Night sweats

- Heart murmur
- Splenomegaly
- Petechiae
Skin manifestations of endocarditis:

- Splinter hemorrhage
- Osler’s nodes
- Conjunctival petechiae
- Janeway lesion
Ocular manifestations of endocarditis:

Roth spot
Other laboratory data:

- Leukocytosis, abnormal UA, elevated C-reactive protein or erythrocyte sedimentation rate
Defining Endocarditis:

MODIFIED DUKE CRITERIA

- **Major Criteria**
  - Positive Blood Cultures
    - Positive Blood Cultures with organism typical for ID or persistently positive blood cultures drawn more than 12 hours apart or 3/3 or majority of 4 or more blood cultures with 1st and last set one hour apart minimum
    - Single + blood culture for *Coxiella burnetti* or antiphase 1 IgG antibody titer > 1:800
  - Evidence of Endocardial Involvement
  - Positive Echocardiogram
    - Mass on valve or supporting structure, abscess or new dehiscence of a prosthetic valve
  - New Valve Regurgitation
Defining Endocarditis:

MODIFIED DUKE CRITERIA

- Minor Criteria
  - Predisposing heart condition or IVDU
  - Fever > 38.0° C
  - Vascular phenomena--emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, Janeway lesions
  - Immunologic phenomena--glomerulonephritis, Osler’s nodes, Roth spots, rheumatoid factor
  - Microbiologic evidence--positive blood cultures that did not meet major criteria
Defining Endocarditis:

- MODIFIED DUKE CRITERIA
  - Requires 2 major criteria or 1 major and any 3 minor or 5 minor
Diagnosis:

- Draw at least 3 blood cultures from separate sites
- TTE all suspected cases of IE (do a TEE first if patient has a prosthetic valve)
- Thorough clinical exam looking for stigmata of IE (heart, neuro, skin, and ocular exams in particular)
- EKG (new heart block common if perivalvular disease)
Echocardiography:

- One study of 114 cases of suspected IE evaluated TTE vs. TEE
  - Change in diagnosis in 25 of 114 cases with a TEE (11% in native valves vs. 34% in prosthetic valves)  
    Roe et al. American Heart Journal 2000
  - TEE had PPV or 90% and NPV or 100% for native valve endocarditis
Echocardiography

- TEE sensitivity 92% vs. 62% in one review of seven studies (but no difference in specificity)
- The ACC/AHA make a class I recommendation for TEE in bacteremic patients, esp. if it’s staphylococcus and fungemia if TTE is equivocal or there is no known source of bacteremia
Complications:

- **Cardiac**: CHF, paravalvular abscess, pericarditis, intracardiac fistulas, aortic valve dissection
- **Neuro**: encephalopathy, meningitis, embolic CVA, cerebral hemorrhage, brain abscess, seizure
- **Embolization**: (reported in 1/6-1/3 of all cases) CVA, blindness, ischemic extremities
- **Mycotic Aneurysms**: septic emboli destroy muscular layer of artery, leading to dilation and aneurysm and therefore bleeding risk
- **Renal**: renal infarction, interstitial nephritis, glomerulonephritis or abscess
- **Vertebral Osteomyelitis**: especially with *Staph aureus*
Treatment of endocarditis:

## Table 4. Usual Antimicrobial Therapy for Common Causes of Infective Endocarditis.*

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Native-Valve Endocarditis</th>
<th>Prosthetic-Valve Endocarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Penicillin-susceptible viridans streptococci,</strong></td>
<td>Penicillin G or ceftriaxone for 4 wk†</td>
<td>Penicillin G for 6 wk and gentamicin for 2 wk†</td>
</tr>
<tr>
<td><em>Streptococcus viridans</em> and other streptococci with MIC of penicillin &lt;0.1 ( \mu g/mL )</td>
<td>A 2-wk regimen of penicillin G (or ceftriaxone) and gentamicin can be used in some cases,‡ but it is not recommended for patients with myocardial abscess, endocardial fistula, or other streptococci with MIC of penicillin &gt;0.1 ( \mu g/mL ).</td>
<td>Shorter duration of treatment with an aminoglycoside (2 wk) is usually appropriate for prothetlic valve endocarditis. Penicillin G or ceftriaxone may be substituted for penicillin-susceptible viridans streptococci, S. bovis, or other streptococci with MIC of penicillin &gt;0.1 ( \mu g/mL ).</td>
</tr>
<tr>
<td>Relatively penicillin-resistant streptococci with MIC of penicillin &gt;0.1 to 0.5 ( \mu g/mL )</td>
<td>Penicillin G for 6 wk and gentamicin for 4 wk†</td>
<td>Penicillin G for 6 wk and gentamicin for 2 wk†</td>
</tr>
<tr>
<td><em>Streptococcus species</em> with MIC of penicillin &gt;0.5 ( \mu g/mL )</td>
<td>Penicillin G (or ampicillin) and gentamicin for 4-6 wk‡</td>
<td>Penicillin G (or ampicillin) and gentamicin for 6 wk‡</td>
</tr>
<tr>
<td><em>Staphylococci</em></td>
<td>6 wk of therapy is recommended for patients with symptoms lasting longer than 3 mo, myocardial abscess, or selected other complications.</td>
<td>It may be prudent to delay initiation of rifampin for 1 or 2 days, until therapy with two other effective antistaphylococcal drugs has been initiated.</td>
</tr>
<tr>
<td>Methicillin-susceptible staphylococci</td>
<td>Nafcillin or oxacillin for 4-6 wk, with or without addition of gentamicin for the first 2–3 days of therapy</td>
<td>Nafcillin or oxacillin with rifampin for 6 wk and gentamicin for 2 wk‡</td>
</tr>
<tr>
<td>Methicillin-resistant staphylococci</td>
<td>Nafcillin or oxacillin with rifampin for 6 wk and gentamicin for 2 wk‡</td>
<td>Vancocin with or without addition of gentamicin, for the first 2–5 days of therapy</td>
</tr>
<tr>
<td>Right-sided staphylococcal native-valve endocarditis in selected patients</td>
<td>Nafcillin or oxacillin with gentamicin for 2 wk</td>
<td>Vancocin with or without addition of gentamicin, for the first 2–5 days of therapy</td>
</tr>
<tr>
<td>HACEK organisms</td>
<td>Ceftriaxone for 4 wk</td>
<td>Ceftriaxone for 6 wk</td>
</tr>
<tr>
<td><em>Corynebacterium diphtheriae</em></td>
<td>Ampicillin and gentamicin for 4 wk as an alternative regimen, but some isolates may produce beta lactamase, thereby reducing the efficacy of this regimen.</td>
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</table>

*Data are from Bayer et al.,** Working Party of the British Society for Antimicrobial Chemotherapy,** and Wilson et al.** MIC denotes minimal inhibitory concentration; HACEK organisms, haemophilus species (*Haemophilus parainfluenzae*, *H. influenzae*, and *H. paragallinarum*), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, and Kingella kingae; and HIV, human immunodeficiency virus.

†Vancocin therapy is indicated for patients with confirmed immediate hypersensitivity reactions to beta-lactam antibiotics.

‡For patients who have infective endocarditis due to methicillin-susceptible staphylococci and who are allergic to penicillins, a first-generation cephalosporin or vancocin can be substituted for nafcillin or oxacillin. Cephalosporins should be avoided in patients with confirmed immediate-type hypersensitivity reactions to beta-lactam antibiotics.
Treatment:

For *Staph aureus* infections:

- Oxacillin resistant *staph aureus*
  - vancomycin 1 gram q 12 hours +/- gentamicin for initial 3-5 days

- Oxacillin sensitive *staph aureus*
  - oxacillin 2 grams q 4-6 hours (or nafcillin) for duration of 4-6 weeks
Treatment:

- Medically treated patients with moderate to severe CHF have a mortality rate of 56-86%.
- Combining surgery and medical treatment has been shown in uncontrolled studies to decrease mortality (one grouped analysis of retrospective studies of patients with CHF and endocarditis showed combined treatment decreased mortality to 29% vs. 60% with medical treatment alone (p<0.001)--however, some patients in the medical group had comorbidities that would not have allowed surgery).
- One small study of endocarditis and acute aortic regurgitation showed 7/8 patients with moderate to severe CHF died suddenly during medical treatment vs. 1/5 with surgical treatment.
- *There are no prospective trials!!!*
### Indications for surgery:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Acute aortic regurgitation (AR) or mitral regurgitation (MR) with heart failure</td>
<td>I</td>
</tr>
<tr>
<td>2. Acute AR with tachycardia and early closure of the mitral valve on echocardiography</td>
<td>I</td>
</tr>
<tr>
<td>3. Fungal endocarditis</td>
<td>I</td>
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<tr>
<td>4. Evidence of annular or aortic abscess, sinus or aortic true or false aneurysm</td>
<td>I</td>
</tr>
<tr>
<td>5. Evidence of valve dysfunction and persistent infection after a prolonged period (7 to 10 days) of appropriate antibiotic therapy, as indicated by presence of fever, leukocytosis, and bacteremia, provided there are no noninfectious causes for infection.</td>
<td>I</td>
</tr>
<tr>
<td>6. Recurrent emboli after appropriate antibiotic therapy</td>
<td>IIa</td>
</tr>
<tr>
<td>7. Infection with gram-negative organisms or organisms with a poor response to antibiotics in patients with evidence of valve dysfunction</td>
<td>IIa</td>
</tr>
<tr>
<td>8. Mobile vegetations &gt; 10 mm on echocardiography</td>
<td>IIb</td>
</tr>
<tr>
<td>9. Early infections of the mitral valve that can likely be repaired</td>
<td>III</td>
</tr>
<tr>
<td>10. Persistent pyrexia and leukocytosis with negative blood cultures</td>
<td>III</td>
</tr>
</tbody>
</table>

*Criteria also apply to repaired mitral and aortic homograft or autograft valves. Endocarditis defined by clinical criteria with or without laboratory verification; there must be evidence that function of a cardiac valve is impaired.

**ACC/AHA classification**

- **Class I**: Conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective.
- **Class II**: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
  - **Class IIa**: Weight of evidence/opinion is in favor of usefulness/efficacy.
  - **Class IIb**: Usefulness/efficacy less well established by evidence/opinion.
- **Class III**: Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful and in some cases may be harmful.

Increased surgical risk:

- Risk factors for mortality after valve surgery
  - NYHA class IV heart failure
  - Cardiogenic shock
  - Older age
  - Preoperative acute renal failure
  - Staphylococcus infection
Does valve surgery actually decrease mortality in IE?:

- Recently published retrospective study examined 513 patients who met Duke criteria and had left sided native valvular disease and a complication for which valve surgery is considered (eg. CHF, regurgitation, persistent infection, systemic emboli to vital organs, or vegetation on valve) from 1990-2000

- Primary outcome was all-cause mortality at 6 months

- Of the 513 patients, 97% fulfilled Duke criteria

- Of the 513 patients, 230 had valve surgery--47% had mechanical valves, 44% had bioprosthetic, and 9% had valve repair
Results:

- Valve surgery was associated with a reduced 6 month mortality when compared with medical treatment: 16% vs. 33% (CI, 0.29-0.63, P<0.001)

- Propensity-matched group (n=218), valve surgery still remained associated with a reduced mortality: 15% vs. 28%, P=0.01
Results with heart failure:

- In no to mild congestive heart failure, there was no reduction in mortality HR, 1.04, CI 0.43-2.48, P=0.93

- In moderate to severe heart failure, there was a significant reduction in mortality as compared to medical therapy HR, 0.22, CI 0.08-0.53, P=0.01
Does an aspirin a day keep the vegetation away?

- A randomized, double-blinded, placebo-controlled study of aspirin 325 mg daily in infective endocarditis for duration of 4 weeks was studied to see if there was a lower rate of embolization; n=115; embolic rates were 28.3% with aspirin vs. 20% with placebo, p=0.29; therefore aspirin had NO effect in this study on vegetation embolization reduction.
Does size matter?:

- There is no definitive studies to suggest that the size of the vegetation is correlated to heart failure, mortality, or need for surgery; small trials suggest that vegetations larger than 10 mm were associated with more embolic events, but these results have yet to be validated.
Fungal Endocarditis

- No clinical trials of appropriate therapy, surgery vs. medical treatment
- One review article summarized all case reports between 1995-2000 for total of 152 cases
  - Yeasts--94.1% were *Candida*
  - Molds--71.8% were *Aspergillus*
  - 78 of 118 pts had surgery went on to surgery (65.5%--no data on 33 pts)
  - Mortality with mold (82.1% compared with 40.3% with yeast, p<0.001)
References:

References:

- Up to Date: topics: (1) Treatment of Staphylococcus aureus bacteremia, (2) Infective Endocarditis: case definitions and criteria for diagnosis, (3) Complications of Infective Endocarditis, (4) Indications for surgery in Infective Endocarditis (5) Role of Echocardiography in infective endocarditis (6) Infective endocarditis: epidemiology and risk factors