Bacterial Endocarditis

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- Genentech – research grant

AHA Scientific Statement

Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications

A Scientific Statement for Healthcare Professionals From the American Heart Association

Circulation. 132:1435-86, 2015

Infective endocarditis: Outline

- Native valve endocarditis
- Prosthetic valve endocarditis
- Cardiac implantable device infections
- Unusual causes of endocarditis
- Prophylaxis (time permitting)
Native Valve Endocarditis

Which of the following is the most common bacterial etiology of infective endocarditis worldwide?

1. Streptococcus mutans
2. Streptococcus sanguis
3. Group A β-hemolytic streptococcus
4. Enterococcus faecalis
5. Staphylococcus aureus

When bacteremia is documented, which of the following is LEAST likely to be associated with endocarditis?

1. Streptococcus mutans
2. Streptococcus galloyticus
3. Streptococcus mitis
4. Enterococcus faecalis
5. Group A β-hemolytic streptococcus

Which of the following is NOT a HACEK Organism?

1. Haemophilus species
2. Acinetobacter species
3. Cardiobacterium hominis
4. Eikenella corrodens
5. Kingella species
6. Who gives a flying #%&$ anyway?
Etiology of Native Valve Endocarditis

<table>
<thead>
<tr>
<th>Organism</th>
<th>Percent of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td>27-35</td>
</tr>
<tr>
<td>Streptococci</td>
<td>33-35</td>
</tr>
<tr>
<td>Enterococci</td>
<td>8-10</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>4-9</td>
</tr>
<tr>
<td>HACEK/Gram-negative bacilli</td>
<td>3/4</td>
</tr>
<tr>
<td>Polymicrobial</td>
<td>2</td>
</tr>
<tr>
<td>Candida</td>
<td>1</td>
</tr>
<tr>
<td>Culture-negative</td>
<td>6</td>
</tr>
</tbody>
</table>

Etiology of Native Valve Endocarditis in Injection Drug Users

<table>
<thead>
<tr>
<th>Organism</th>
<th>Right-sided</th>
<th>Left-sided</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td>77%</td>
<td>23%</td>
</tr>
<tr>
<td>Streptococci</td>
<td>5%</td>
<td>15%</td>
</tr>
<tr>
<td>Enterococci</td>
<td>2%</td>
<td>24%</td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
<td>5%</td>
<td>12%</td>
</tr>
<tr>
<td>Candida</td>
<td>&lt;1%</td>
<td>12%</td>
</tr>
<tr>
<td>Culture-negative</td>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Definition of IE

- **Definite IE**
  - **Pathological criteria**: positive culture or histology of vegetation, embolus, intracardiac focus
  - **Clinical criteria**: 2 major **OR** 1 major + 3 minor **OR** 5 minor
- **Possible IE**: 1 major + 1 minor or 3 minor
- **Rejected**: alternative diagnosis, does not meet criteria for possible

Which of the following is NOT a major criterion in the Modified Duke Criteria for the Diagnosis of IE?

1. Typical organism consistent with IE from 2 separate blood culture in absence of a primary focus
2. Anti-phase 1 IgG antibody titer for Coxiella burnetii ≥ 1:800
3. Oscillating intracardiac mass on a valve or supporting structure on TTE
4. Worsening or changing pre-existing regurgitation murmur
Modified Duke Criteria for the Diagnosis of IE

1. Typical organism consistent with IE from 2 separate blood culture in absence of a primary focus
2. Anti-phase 1 IgG antibody titer for Coxiella burnetii > 1:800
3. Oscillating intracardiac mass on a valve or supporting structure on TTE, abscess, PVE dehiscence
4. New valvular regurgitation

Major Criteria for Diagnosis of IE

• Blood cultures
  – At least 3 sets from different sites with first and last at least 1h apart
• Echocardiography
  – Should be performed expeditiously in patients suspected of IE

Minor Criteria

• Predisposing heart condition, IDU
• Temperature > 38°C
• Vascular/immunologic phenomena: GN, Osler node, Janeway lesion, Roth spot, +RF, septic pulmonary emboli, systemic emboli, mycotic aneurysm
• Positive blood culture not meeting major criterion, positive serologic test
• ECHO minor criteria eliminated

Typical Organisms in Blood Cultures Consistent with IE

• Organisms*
  – Staphylococcus aureus
  – Viridans group streptococci
  – Strep. galolyticus (aka bovis)
  – Enterococcus (community-acquired)
  – HACEK
• In absence of primary focus
• Or persistently positive blood cultures
  – 2 cultures drawn > 12h apart positive
  – All 3 or majority of > 4 separate cultures with first and last drawn > 1h apart

* Coag-negative staph in patients with prosthetic valve
IE SUSPECTED

Low risk patient & low clinical suspicion

Neg

Pos

Rx

Low suspicion

High risk features on TTE

Yes

No

TEE

Look for other source

High risk patient or moderate to high clinical suspicion, difficult imaging candidate

TEE after TTE asap

Neg

Pos

Rx

Look for other source

What is High Risk?

- High risk patients (examples)
  - Prosthetic valve
  - Congenital heart disease
  - Previous endocarditis
  - New murmur, heart failure, heart block, stigmata of IE
- High risk TTE (examples)
  - Large or mobile vegetations, anterior MV leaflet veg
  - Valvular insufficiency, perivalvular extension, valve perforation
  - Ventricular dysfunction

“Acute” Community-acquired Native Valve Endocarditis

- A 63 y.o. man with no significant past medical history presents with a week of fever, rigors, and progressive dyspnea on exertion.
- Exam
  - T 39.5, BP 160/40, P110
  - Skin and conjunctiva (next slide)
  - JVD (+), rales ½ way up bilaterally.
  - Loud diastolic decrescendo murmur at the lower left sternal border.

Osler node

Janeway lesions

Conjunctival hemorrhage

Roth spots
Which of the following is the most appropriate empirical regimen for this patient?

1. Ampicillin + gentamicin
2. Cefazolin + gentamicin
3. Ceftriaxone + gentamicin
4. Nafcillin + vancomycin
5. Vancomycin + gentamicin

Septic Pulmonary Emboli, Staph endocarditis

Splinter Hemorrhage

Definitive Therapy – Native Valve Endocarditis
### Native Valve S. aureus IE

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nafcillin or oxacillin</td>
<td>6 wk</td>
<td>2 wk uncomplicated R-sided IE (IDU)</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>6 wk</td>
<td>Pen-allergic naf-intolerant patient (equivalent to naf)</td>
</tr>
<tr>
<td>MRSA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>6 wk</td>
<td>MSSA if beta-lactam hypersensitivity</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>6 wk</td>
<td>&gt; 8 mg/kg/day, vanco alternative</td>
</tr>
</tbody>
</table>

No gentamicin, no rifampin – both III/B

### Treatment of Viridans Group Streptococci and Strep. galolyticus IE
- **Pen MIC ≤ 0.12 μg/ml**
  - Penicillin, ceftriaxone, vancomycin x 4 weeks
  - Penicillin or ceftriaxone + gent x 2 weeks
- **Pen MIC > 0.12 μg/ml, < 0.5 μg/ml**
  - Penicillin or ceftriaxone (4 wk) + gent (2 wk)
  - Ceftriaxone or vancomycin (4wk)
- **Pen MIC ≥ 0.5 μg/ml**
  - Penicillin or ceftriaxone + gent
  - Vancomycin
  - Duration not defined (4 wk?)

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### Contraindications to Short Course Treatment of Endocarditis Caused by Penicillin-Susceptible Viridans Streptococci/Strep galolyticus
- Isolate with MIC Pen ≥ 0.1 μg/ml
- High level resistance gent
- Native valve with cardiac complications
  - Intra or extra cardiac abscess/local infection
- Native valve with CNS complications
- Yoyo Ma or Itzak Perlman

### Therapy of Endocarditis due to “Nutritionally Variant Streptococci”
- Abiotrophia and Granulicatella species
  - Susceptibility tests unreliable
  - Often penicillin tolerant, tendancy to relapse
- Therapy
  - Pen or amp 4 wks + gentamicin 2-4 wks (not β-lactam alone)
  - Or vancomycin alone (?)
### Enterococcal Endocarditis

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pen or amp + gent</td>
<td>4-6 wk</td>
<td>Pen S, Gent 1 mg/kg q8h, 6 wk for PVE, symptoms&gt;3 mo</td>
</tr>
<tr>
<td>Amp + Ceftriaxone</td>
<td>6 wk</td>
<td>Pen S, Aminoglycoside susceptible or resistant</td>
</tr>
<tr>
<td>Pen or amp + strep</td>
<td>4-6 wk</td>
<td>Gent resistant, Strep synergy, ClCr &gt; 50</td>
</tr>
<tr>
<td>Vanco + gent</td>
<td>6 wk</td>
<td>Pen resistant or beta-lactam intolerant (toxic!)</td>
</tr>
<tr>
<td>Linezolid or dapto</td>
<td>&gt; 6 wk</td>
<td>VRE: Dapto 10-12 mg/kg &amp; combo with amp or ceftaroline</td>
</tr>
</tbody>
</table>

### HACEK Organisms
- Haemophilus species
- Aggregatibacter species
- Cardiobacterium hominis
- Eikenella corrodens
- Kingella species

### Regimens Recommended for Treatment of IE Due to a HACEK organism

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>Avoid: assume amp or pen resistant unless MIC test confirmed susceptible</td>
</tr>
<tr>
<td>Amp + gent</td>
<td>NO GENT: nephrotoxic</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Regimen of choice</td>
</tr>
<tr>
<td>Ceftriaxone + gent</td>
<td>NO GENT: nephrotoxic</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Levo or FQ as single agent OK as alternative regimen</td>
</tr>
</tbody>
</table>

### Culture-Negative Endocarditis
- Prior antibiotics
- Fastidious organisms
  - HACEK
  - Abiotrophia defectiva, et al
  - Brucella sp.
- “Non-cultivable” organism
  - Bartonella quintana
  - Coxiella burnetii, Chlamydophila psittaci, Tropheryma whippelii, Legionella sp, Mycoplasma
- Fungi (molds)
- Not endocarditis
  - Libman-Sacks, myxoma, APLS, marantic, tumor
Surgical Management NVE/PVE

- Optimal timing of surgery not known
- Early surgery
  - Heart failure due to valvular dysfunction
  - IE from fungi or MDR organisms (i.e., VRE)
  - Presence of heart block, annular or aortic abscesses
  - Persistent bacteremia or fever > 5-7 days not attributable to another source
  - Emboli, large vegetations (> 10mm)

Prosthetic Valve Endocarditis

- A 70 y.o. male with fever, chills, and low back pain for 6 days.
- Bioprosthetic AVR 9 months previously for critical aortic stenosis.
- Exam
  - T 38, BP 104/70, P 110
  - Left conjunctival petechiae.
  - Rales 1/3 way up bilaterally.
  - Grade II/VI SEM
- Blood cultures: 3/3 positive at 18 hours for Gram-positive cocci

While awaiting TEE, which of the following antimicrobial regimens is most appropriate in this setting?

1. Vancomycin
2. Daptomycin
3. Vancomycin + rifampin
4. Vancomycin + gentamicin + rifampin
5. Daptomycin + linezolid + gentamicin
PVE versus NVE

- Similar presentations but ....
- Different microbiology
- More invasive infection, higher rates of
  - Heart failure
  - Conduction disturbances
  - New or changing murmurs
  - CNS events

Causes of Prosthetic valve endocarditis

**EARLY** (≤ 2 mo post op)
- Coag-neg Staph
- S. aureus
- Less common
  - Gram Neg bacilli
  - Enterococci
  - Fungi (Candida)
  - Diphtheroids

**LATE** (> 12 mo post op)
- Viridans streptococci
- S. aureus
- Coag-neg Staph
- Less common
  - Enterococci
  - Gram neg bacilli
  - Fungi
  - Diphtheroids

Therapy for PVE due to viridans streptococci or S. gallolyticus

<table>
<thead>
<tr>
<th>Regimen</th>
<th>24 h dose</th>
<th>Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pen or ceftriazone</td>
<td>24 mu/2g</td>
<td>6</td>
</tr>
<tr>
<td>+/- gentamicin*</td>
<td>3 mg/kg</td>
<td>2</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>30 mg/kg</td>
<td>6</td>
</tr>
</tbody>
</table>

*If pen MIC > 0.12 ug/ml add gent for 6 weeks or use ceftriazone or vancomycin

Therapy for Staphyloccocal PVE

<table>
<thead>
<tr>
<th>Methicillin sensitive</th>
<th>24 h dosage</th>
<th>Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>nafcillin/oxacillin</td>
<td>12 g</td>
<td>≥ 6</td>
</tr>
<tr>
<td>plus rifampin</td>
<td>900 mg</td>
<td>≥ 6</td>
</tr>
<tr>
<td>plus gentamicin</td>
<td>3 mg/kg</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Methicillin resistant or major pen allergy</th>
<th>24 h dosage</th>
<th>Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>vancomycin</td>
<td>30 mg/kg</td>
<td>≥ 6</td>
</tr>
<tr>
<td>plus rifampin</td>
<td>900 mg</td>
<td>≥ 6</td>
</tr>
<tr>
<td>plus gentamicin</td>
<td>3 mg/kg</td>
<td>2</td>
</tr>
</tbody>
</table>
Therapy for Enterococcal PVE

Same as for native valve endocarditis

Cardiac Implantable Device Infections
(permanent pacemakers, defibrillators)


Pacemaker Infection

• A 71 y.o. male, permanent pacemaker was implanted 2 months ago for sick sinus syndrome/syncope, presents subjective fever
• Exam:
  – T37.8°C, P78 (paced), R18, BP 122/80.
  – Generator pocket is slightly tender, swollen, with moderate warmth and erythema; otherwise WNL.
• Cultures
  – Pus aspirated from the pocket: MSSA
  – Blood cultures: negative

Which of the following is the best management?

1. Cefazolin + rif x 6 wks
2. Remove generator, then cefazolin + rif x10 days
3. Remove generator, then cefazolin + rif 6 wks
4. Remove entire device, then cefazolin + rif 6 wks
5. Remove entire device, then cefazolin x 10 days

rif = rifampin
Microbiology of Cardiac Implantable Device Infections

<table>
<thead>
<tr>
<th>Organism</th>
<th>% of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coag-neg staphylococi</td>
<td>42</td>
</tr>
<tr>
<td>S. aureus</td>
<td>29</td>
</tr>
<tr>
<td>Gram-neg bacilli</td>
<td>9</td>
</tr>
<tr>
<td>Polymicrobial</td>
<td>7</td>
</tr>
<tr>
<td>Culture-negative</td>
<td>7</td>
</tr>
<tr>
<td>Fungal</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
</tr>
</tbody>
</table>

Cardiac Implantable Device Infection Types

- Pocket site/generator only: ~ 60%
  - Blood culture positive <50%
  - Pocket infection or generator/lead erosion
- Occult bacteremia/fungemia: ~7-30%
- Lead infection +/- endocarditis: ~10-25%

Survival with and without Device Removal

[Graph showing survival rates with and without device removal]

Survival with and without Device Removal

[Graph showing survival rates with and without device removal]
AHA Guidelines for Management of Cardiac Implantable Device Infections

- Blood cultures before antibiotics
  - If positive, then TEE
- Gram stain, culture of pocket tissue, lead tips
- Device removal for all infections and occult staphylococcal bacteremia (consider for GNR bacteremia)
- Therapy (antibiotic based on susceptibility)
  - Pocket infection: 10-14 days
  - Bloodstream infection: > 14 days
  - Lead or valve vegetations: 4-6 weeks

Circ 2010;121:458-77

AHA Guidelines for Reimplantation

- Determine if reimplantation necessary
- New device on contralateral side
- >72h negative BC before reimplantation
- If IE: reimplant ≥ 14d after original removal
- Antibiotic prophylaxis: 1h before implantation, none thereafter
Weird Causes of Endocarditis

Case Presentation

• A 44 y.o man, subjective fever for 3 months, diarrhea x 1 year, 30 pound weight loss, intermittent arthralgias, mainly in his hands. No travel or animal exposures
• Vital signs: BP 172/52 P 92 R 24 T38C
• Exam: diastolic murmur at the lower left sternal border, and rales halfway up bilaterally.
• Blood cultures (6 sets) are drawn and remain negative after 21 days.
• Valvular tissue obtained at valve replacement reveals foamy macrophages by PAS stain.

Which of the following is the most likely etiologic agent?
1. A member of the HACEK group
2. Coxiella burnetii
3. Tropheryma whipplei
4. Chlamydia psittaci
5. Bartonella sp.

Tropheryma whipplei Infective Endocarditis

• Indolent with arthralgia, CHF, murmur, emboli
• Diarrhea and GI symptoms may be mild/absent
• Fever: not prominent
• Modest laboratory abnormalities: ESR, anemia, CRP
• Echocardiogram - vegetations, abscess, valve dysfunction
• Blood cultures negative, vegetations PCR positive
• Vegetations PAS positive foamy macrophages, bacteria on Warthin-Starry silver stain
• Rx: Surgery plus ceftriaxone (pen/gent) followed by doxycycline-hydroxychloroquine (> 1 year)

### Tools for Diagnosis of Culture-Negative Endocarditis

<table>
<thead>
<tr>
<th>Organism</th>
<th>Clinical clues</th>
<th>Serology</th>
<th>Specific PCR</th>
<th>Universal 16s/18s rRNA PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HACEK, strep, etc</td>
<td>Prior antibiotics</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Legionella</td>
<td>Immunocompromise</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>T. whipplei</td>
<td>Chronic illness</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Brucella</td>
<td>Travel</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Bartonella sp.</td>
<td>Cats, homeless, lice</td>
<td>X (≥1:800)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Mycoplasma</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Q fever</td>
<td>Animal contact, lab</td>
<td>X (≥1:800)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Chlamydia</td>
<td>Bird exposure</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

### Endocarditis Prophylaxis

63 year old female, no significant PMH except calcified aortic sclerosis; no prior history of IE, no known drug allergies.

The best recommendation for management prior to the extraction (all 30-60 minutes prior to the procedure) is:

1. No prophylaxis
2. Amoxicillin 2 gm p.o.
3. Clindamycin 600 mg p.o.
4. Azithro 500 mg p.o.
5. Ampicillin 1 gm i.v.

### Antimicrobial Prophylaxis for Endocarditis: Current AHA Recommendations

- List of cardiac conditions reduced
- List of procedures greatly reduced
- Regimens simplified
Rationale for Changes in Prophylaxis
IE Guidelines

• Bacteremia
  – Tooth brushing 154,000 times greater/yr than single extraction, daily activity possibly 5.6 x 10^6 greater/yr
• Antibiotics
  – do not eliminate bacteremia
  – not clear reduces IE
• No prospective studies supporting efficacy
• Case-control study: dental event not increased in IE
• If 100% effective, antibiotics prevent rare cases of IE

Cardiac Conditions Associated with High Risk for Adverse Outcome: Prophylaxis Advised with Dental Work

• Prosthetic cardiac valve
• Prior IE
• Congenital heart disease (CHD)
  – Unrepaired cyanotic CHD includes shunts/conduit
  – Repaired CHD with prosthetic material (within 6 mos)
  – Repaired CHD with residual defect
• Cardiac transplant with valvulopathy

AHA recommendations for prophylaxis of IE: Procedures

• Dental
  – involving gingival crevice
• Surgery
  – inside oral cavity
  – If bacterial infection present at the site
• GU
  – with bacterial infection

Regimines Recommendations for Prophylaxis of Endocarditis

<table>
<thead>
<tr>
<th>Preferred</th>
<th>30 – 60 min before</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Amoxicillin 2 gm</td>
</tr>
<tr>
<td>I.V.</td>
<td>Amp 2 gm or ceftriaxone 1 gm</td>
</tr>
<tr>
<td>Allergy to pcn-oral</td>
<td>Clinda 600 mg</td>
</tr>
<tr>
<td>Allergy to pcn- I.V.</td>
<td>Clinda 600 mg</td>
</tr>
</tbody>
</table>