BASIC KNOWLEDGE ABOUT INFECTIVE ENDOCARDITIS FOR CLINICIAN

When should I suspect infective endocarditis?

Antibiotic regimen

Patient care after completion of treatment

Prophylactic Regimens

Prosthetic Valve Endocarditis (PVE)

Health Care Associated Endocarditis (HAE)

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When should I suspect infective endocarditis?

1. Sepsis of unknown origin
2. New valve lesion / regurgitant murmur
3. Arterial Emboli (limb, stroke, kidney)
4. Hematuria, glomerulonephritis
5. Peripheral abscess (spleen, spine, …)
6. Fever plus:
   - Cardiac prostheses
   - New CHF
   - Heart disease (Valve, congenital, pace maker)
   - Skin (Osler, Janeway ) lesions
   - New conduction defects
   - Multifocal/rapid changing pulmonic infiltrations
   - IV drug abuse

What should be done once endocarditis is suspected?
1. Delay antibiotics until 3 sets (3 aerobic + 3 anaerobic) of blood cultures (BC) are taken, each of the six bottles should contain 8-10 ml of blood (Figure).
2. Order basic lab: CBC, ESR, CRP, Urinalysis, Rheumatoid factor, Urea/creatinine & Liver function tests.
3. Order Echo ASAP. Order TEE from the start if there is: prosthesis, progressive valve insufficiency, suspected valve ring abscess or Staph aureus infection.

What are the criteria for diagnosis of endocarditis?

**Major criteria**

1. **Positive Blood culture for IE**
   - At least 2 positive BC drawn 12 h apart; or all of 3 BC for typical microorganisms consistent with IE: Viridans streptococci, Streptococcus bovis, HACEK group, Staphylococcus aureus; or enterococci.
   - Single positive BC for Coxiella burnetii (or C. burnetii anti–phase 1 IgG antibody titer >1:800)
2. **Positive Echo**: vegetation, abscess, or dehiscence of prosthetic valve
3. **New valvular regurgitation** (worsening of preexisting murmur not enough)

**Minor criteria**

1. Predisposing heart condition, pace maker lead, or IV drug abuse
2. Fever, temperature >38°C for at least 6D
3. Vascular phenomena: arterial emboli, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway’s lesions
4. Immune phenomena: glomerulonephritis, Osler’s nodes, Roth’s spots, and positive rheumatoid factor
5. Microbiological evidence: positive BC but does not meet a major criterion as noted above or positive serology for typical micro-organism.

**Definitive IE is diagnosed if there are**
- 2 major criteria; or
- 1 major criterion and 3 minor criteria; or
- 5 minor criteria

**Possible IE is diagnosed if there is**
- 1 major criterion and 1 minor criterion; or
- 3 minor criteria

**Reject the diagnosis of IE if there is**
- Firm alternative diagnosis explaining the clinical findings
- Resolution of IE syndrome with antibiotic therapy for <4 days
- No pathological evidence of IE at surgery with antibiotic therapy for <4 days
- Does not meet criteria for possible IE as above

**Causes of negative blood cultures?**
- Most common: antibiotic use before collecting blood or sending inadequate blood volume for culture.
- Other reasons: atypical pathogens (Bartonella, Chlamydia, Coxiella, Brucella, Legionella, fungi & HACEK)
- History: contact with Birds (Chlamydia), Cats & Dogs (Bartonella), Goat, row meet & cattle (Coxiella, Brucella)
- Guided by the clinical history, order special culture media or serologic tests (see table).

What if the Echo is negative despite strong clinical suspicion?
If the initial TTE is negative à order TEE. If the initial TEE is negative à repeat TEE after one W
Consider differential diagnosis Consider second opinion

### Antibiotic regimen for culture negative IE (or pending BC results)?

**Native valves:** Ampicillin-sulbactam 12 g/24 h IV in 4 equally divided doses plus Gentamicin 3 mg/kg QD IV/IM in 3 equal doses for 4-6 weeks

**Prosthetic valve endocarditis:** Vancomycin 30 mg/kg per 24 h IV in 2 equally divided doses plus Gentamicin sulfate 3 mg/kg per 24 h IV/IM in 3 equally divided doses + Rifampicin

<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>Common organisms</th>
<th>Clinical condition</th>
<th>Common organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection drug use</td>
<td><em>S. aureus</em> Coagulase-negative staph β-Hemolytic strept Fungi Gram-negative bacilli Polymicrobial</td>
<td>Genitourinary disorders, (eg. pregnancy, delivery, and abortion)</td>
<td><em>Enterococcus</em> Group B streptococci <em>Listeria monocytogenes</em> Gram-negative bacilli <em>Neisseria</em></td>
</tr>
<tr>
<td>Indwelling vascular devices</td>
<td><em>S. aureus</em> Coagulase-negative staph Fungi Aerobic Gram-negative bacilli <em>Corynebacterium</em></td>
<td>Chronic skin disorders</td>
<td><em>S. aureus</em> β-Hemolytic streptococci</td>
</tr>
<tr>
<td>Alcoholism, cirrhosis</td>
<td><em>Bartonella</em> <em>Aeromonas</em></td>
<td>Poor dental health, dental procedures</td>
<td>Viridans streptococci Nutritionally variant streptococci <em>Abiotrophia</em> HACEK organisms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diabetes mellitus</td>
<td><em>S. aureus</em> β-Hemolytic strept <em>S. pneumoniae</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Burn patients</td>
<td><em>S aureus</em> Gram-negative bacilli,</td>
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</tbody>
</table>
Anticoagulation policy with systemic emboli, prosthetic valves or AF?
- In Valve prosthesis, warfarin, a target INR: 2.
- Stop all anticoagulation with \textit{S. aureus} prosthetic valve IE complicated by recent CNS emboli for at least the first 2 weeks of antibiotic therapy.

When to consider referral to surgery?
- Heart failure (NYHA III-IV) not responsive to medical treatment
- Acute aortic or mitral insufficiency with signs of ventricular failure
- Valve perforation or rupture
- Fungal endocarditis
- New heart block
- Large abscess or extension of abscess despite appropriate antimicrobial therapy
- Persistent vegetation after systemic embolization
- Anterior mitral leaflet vegetation, particularly with size $\geq$10 mm
- $\geq$1 embolic events during first 2 wk of antimicrobial therapy
- Increase in vegetation size despite appropriate antimicrobial therapy

**Patient care after completion of treatment:**

1. **Before or at completion of therapy**

   Obtain TTE to establish new baseline
   Educate patient about signs of endocarditis, need for antibiotic prophylaxis for dental/surgical procedures
   Thorough dental evaluation and treatment if not performed earlier in evaluation
   Prompt removal of IV catheter at completion of antimicrobial therapy
   Drug rehabilitation referral for patients who use illicit injection drugs

2. **Follow-up**

   1. Obtain at least 3 sets of BC from separate sites for any unexplained fever & before initiation of antibiotic therapy
   2. Evaluation of valvular and ventricular function (echocardiography)
4. Scrupulous oral hygiene and frequent dental professional office visits

Procedures that require endocarditis prophylaxis:

1. Dental procedures
2. Tonsillectomy and/or adenoidectomy
3. Bronchoscopy (rigid bronchoscope)
4. Sclerotherapy for esophageal varices
5. Esophageal dilation
6. ERCP
7. Biliary tract surgery
8. Surgical operations that involve intestinal mucos
9. Prostatic surgery
10. Cystoscopy

Procedures that don’t require endocarditis prophylaxis:

1. Endotracheal intubation
2. Bronchoscopy (flexible bronchoscope)
3. Tympanostomy tube insertion
4. TEE
5. Endoscopy
6. Cardiac catheterization, including PTCA, stents

Prophylactic Regimens

Prophylactic Regimens for Dental, Oral, Respiratory, or Esophageal Procedures

<table>
<thead>
<tr>
<th>Situation</th>
<th>Agent</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard general prophylaxis</td>
<td>Amoxicillin</td>
<td>Adults: 2.0 g; children: 50 mg/kg orally 1 h before procedure</td>
</tr>
<tr>
<td>Unable to take oral medications</td>
<td>Ampicillin</td>
<td>Adults: 2.0 g IM or IV; children: 50 mg/kg IM or IV within 30 min before procedure</td>
</tr>
<tr>
<td>Allergic to penicillin</td>
<td>Clindamycin or</td>
<td>Adults: 600 mg; children: 20 mg/kg orally 1 h before procedure</td>
</tr>
<tr>
<td></td>
<td>Cephalexin or</td>
<td>Adults: 2.0 g; children: 50 mg/kg orally 1 h before procedure</td>
</tr>
<tr>
<td></td>
<td>Cefadroxil or</td>
<td>Adults: 2.0 g; children: 50 mg/kg orally 1 h before procedure</td>
</tr>
<tr>
<td></td>
<td>Azithromycin or</td>
<td>Adults: 500 mg; children: 15 mg/kg orally 1 h before procedure</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin</td>
<td>Adults: 600 mg; children: 20 mg/kg IV within 30 min before procedure</td>
</tr>
<tr>
<td>Allergic to penicillin and unable</td>
<td>Clindamycin or</td>
<td>Adults: 600 mg; children: 20 mg/kg IV within 30 min before procedure</td>
</tr>
<tr>
<td>to take oral medications</td>
<td>Cefazolin</td>
<td>Adults: 1.0 g; children: 25 mg/kg IM or IV within 30 min before procedure</td>
</tr>
</tbody>
</table>

Prophylactic Regimens for Genitourinary/GIT procedures
<table>
<thead>
<tr>
<th>Situation</th>
<th>Agents</th>
<th>Regimen</th>
</tr>
</thead>
</table>
| High-risk patients                    | Ampicillin plus gentamicin | Adults: ampicillin 2.0 g IM or IV plus gentamicin 1.5 mg/kg (not to exceed 120 mg) within 30 min of starting procedure; 6 h later, ampicillin 1 g IM/IV or amoxicillin 1 g orally  
Children: ampicillin 50 mg/kg IM or IV (not to exceed 2.0 g) plus gentamicin 1.5 mg/kg within 30 min of starting the procedure; 6 h later, ampicillin 25 mg/kg IM/IV or amoxicillin 25 mg/kg orally |
| High-risk patients allergic to ampicillin/amoxicillin | Vancomycin plus gentamicin | Adults: vancomycin 1.0 g IV over 1-2 h plus gentamicin 1.5 mg/kg IV/IM (not to exceed 120 mg); complete injection/infusion within 30 min of starting procedure  
Children: vancomycin 20 mg/kg IV over 1-2 h plus gentamicin 1.5 mg/kg IV/IM; complete injection/infusion within 30 min of starting procedure |
| Moderate-risk patients                | Amoxicillin or ampicillin | Adults: amoxicillin 2.0 g orally 1 h before procedure, or ampicillin 2.0 g IM/IV within 30 min of starting procedure  
Children: amoxicillin 50 mg/kg orally 1 h before procedure, or ampicillin 50 mg/kg IM/IV within 30 min of starting procedure |
| Moderate-risk patients allergic to ampicillin/amoxicillin | Vancomycin | Adults: vancomycin 1.0 g IV over 1-2 h complete infusion within 30 min of starting procedure  
Children: vancomycin 20 mg/kg IV over 1-2 h; complete infusion within 30 min of starting procedure |

PROSTHETIC VALVE ENDOCARDITIS
Infective endocarditis on top of prosthetic material; mechanical or tissue valves, valve rings, pacemaker or defibrillation leads and synthetic shunts represents approximately 25% of endocarditis cases. The incidence is expected to increase as the number of invasive cardiac procedures continues to rise.

The risk of prosthetic valve endocarditis (PVE) is not uniform. The risk is greatest during the first 6 months after surgery (particularly during the initial 5-6 weeks) and thereafter declines to a lower risk. Patients operated for native valve endocarditis are at special risk for PVE. Mechanical prostheses are more liable to infection than tissue valves, but after 12 months, the risk of infection of Bioprothesis exceeds that of mechanical valves. The risk of infection on a pacemaker/defibrillator lead is higher for repeat procedures rather than initial implantations.

There are two forms of PVE; early and late. The arbitrary cutoff between the two is one year. PVE within 12 months after valve surgery is likely to be derived from events during the surgical admission. On the other hand, late PVE is more likely to be community acquired. This difference explains the causative microbiology in the two situations. In early PVE, the commonest organisms are those originating in the hospital environment: Coagulase negative staphylococci, Staphylococcus aureus, gram negative bacilli and fungi. In late PVE, the predominant pathogens are streptococci, enterococci followed by staphylococci.

The mere presence of prosthetic material endangers the integrity of the natural body defenses against microbial invasion. The normal laminar flow is replaced by eddies which favor deposition of fibrin on adjacent endothelial surfaces which may form a nidus for infection. Migration of polymorphs, lymphocytes to the site of infection is markedly hampered by a prosthetic surface. This explains why the pathology of PVE differs from the “leaflet-limited” form seen in native valves. Infection on mechanical prostheses commonly extends beyond the valve ring to the annulus, periannular tissue as well as the fibrous trigone between the aortic and mitral valves. The consequences are usually drastic with valve dehiscence, severe paravalvular regurgitation, ring abscess, fistulous tracts and conduction disturbances. Because of the aggressive underlying infection, systemic complications are more frequent in PVE than in native valve IE. CHF, cerebrovascular complications, and sepsis may be encountered separately or combined in up to one fourth of patients with PVE. The first manifestation of PVE may be a fatal prosthetic valve dehiscence or obstruction.

The clinical picture and the diagnosis of PVE can be deceptive but nevertheless more complicated. A high index of suspicion is necessary. Fever in the perioperative period is commonly ascribed to wound infection, pneumonia or transfusion reactions. Embolization can be attributed to inadequate anticoagulation. Even blood cultures may be rendered non-diagnostic by the frequently prescribed parenteral antibiotics. The dense shadows of metallic leaflets usually mask any vegetation in transthoracic echocardiograms. That’s why transesophageal echocardiography (TEE) is preferred as an initial imaging method in suspected PVE. Even by TEE it may be difficult to discern small vegetations from suture material.

Penetration of antimicrobials from the blood stream to the site of infection is also markedly limited by the presence of prosthetic material. The choice of the initial empirical regimen is based on the most commonly cultured organisms in early PVE;
staphylococci. The most effective combination for methicillin resistant Staphylococci is Vancomycin, gentamycin and rifampicin. The value of rifampicin is in its unique antistaphylococcal activity on prosthetic surfaces. For methicillin susceptible Staphylococci, vancomycin is replaced by nafcillin or large dose cefazolin. A quinolone may be used as an alternative in gentamycin resistant strains.

Surgery stands a very important role in the management of PVE. Some authorities consider the mere presence of prosthetic endocarditis an indication for redo surgery. A homograft represents the best option to replace an infected metallic prosthesis with. In real life, one must balance the risk of a redo valve replacement with extensive debridement as well as the availability of homografts on one hand and the high risk of progressive uncontrollable infection and systemic complications on the other hand. An unstable prosthesis with >40% dehiscence of the circumference is a clear indication of emergency surgery.

HEALTH CARE ASSOCIATED ENDOCARDITIS (HAE)

This is a relatively new term that has replaced the old one, nosocomial endocarditis. It applies to the following situations:

1. Endocarditis diagnosed > 72 hr from hospital admission, provided there is evidence that endocarditis was not present on admission
2. Endocarditis diagnosed within 60 days (some may extend this period up to 6 months) from a previous hospital admission
3. Early post operative Prosthetic Valve Endocarditis (PVE)
4. Risk procedure of bacteremia was performed (the risk procedure may be as simple as inserting a cannula or as invasive as cardiac surgery)

Patients with HAE share common and serious features:

1. Virulent type of pathogens (Methicillin Resistant Staphylococci, Gram negative bacilli and fungi)
2. Poor prognosis: higher rates of complications and mortality (mortality rates approaching 40% in our series and some of the European series)
3. Poor response to medical treatment and frequent need for cardiac surgery

HAE occurs mainly as a result of a breakdown in the chain of infection control in hospitals. Such a difficult, costly problem with poor outcome could be prevented by following strict rules of hospital infection control.

HAE should be dealt with as preventable rather than a curative disease.