Antibiotic Prophylaxis for Dental Treatment of Patients with Cardiovascular Disease: When and Why?

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Introduction

Antibiotic prophylaxis

- Patients with heart conditions → Infective Endocarditis
- Patients with total joint replacement → Prosthetic Joint Infections
Infective Endocarditis

Definition

▶ Endocarditis: inflammation of the endocardial surfaces
▶ Infective endocarditis (IE): microbial infection of endocarditis lesions ("vegetations")
Infected Endocarditis

Epidemiology

- Incidence: 1-5 cases in 100,000 persons/year
- Overall mortality rate: ~20%
- Men more susceptible than women (1.2 to 3 times)
- Median age: over 55 years
  - Reduced incidence of rheumatic heart disease
  - Increased rates of cardiac damage and repair with age
- Increased incidence in patients with no known previous cardiac disease
  - Young children (up to the age of 2 years)
  - Intravenous drug users
Infective Endocarditis

Pathogenesis

- Formation of non-bacterial thrombotic vegetations (NBTV)
- Endocardial lining damaged by certain pre-existing heart conditions (e.g. congenital or acquired valvular dysfunction, history of previous IE, prosthetic heart valves, etc.)
- Deposition of fibrin and platelets
- Adherence of circulating microorganisms (during an episode of bacteremia) to NBTV
- Conversion of the NBTV to IE
Infected Vegetations

- microorganisms
- fibrin
- platelets
- inflammatory infiltrate
Infected Vegetations

- Heart valves
- Endocardium
Infected Vegetations

- Embolize and occlude blood vessels and valvular orifices
- Decrease cardiac output
- Induce congestive cardiac failure
Conditions associated with risk of Infective Endocarditis (American Heart Association (AHA) Guidelines, 1997)

**High-risk category**
- Prosthetic cardiac valves
- History of previous IE
- Complex cyanotic congenital heart disease
- Surgically constructed shunts/conduits

**Moderate-risk category**
- Most other congenital cardiac malformations
- Acquired valvular dysfunction
- Hypertrophic cardiomyopathy
- Mitral valve prolapse (MVP) with valvular regurgitation and/or thickened leaflets

PROPHYLAXIS RECOMMENDED
Conditions associated with risk of Infective Endocarditis (American Heart Association (AHA) Guidelines, 1997)

**Negligible-risk category**
- Isolated secundum atrial septal defect
- Surgical repair of atrial or ventricular septal defect
- Patent ductus arteriosus of more than 6 months duration
- Previous coronary artery bypass graft surgery
- Physiological or functional heart murmur
- Previous Kawasaki disease without valvular dysfunction
- Cardiac pacemakers
- Implanted defibrillators

PROPHYLAXIS NOT RECOMMENDED
Conditions associated with risk of Infective Endocarditis (British Society for Antimicrobial Chemotherapy (BSAC) Guidelines, 2006)

- History of previous IE
- Prosthetic cardiac valves
- Surgically constructed shunts/conduits
- Complex congenital heart disease
- Complex LV outflow abnormalities (aortic stenosis, bicuspid aortic valves)
- Acquired valvulopathy and MVP with substantial leaflet pathology and regurgitation

**PROPHYLAXIS RECOMMENDED**

**NON-DENTAL PROCEDURES**
Infective Endocarditis

Microbiology

- Streptococci: recognized etiological agents of IE (Bayliss et al, 1983; Douglas et al, 1993)
- *Staphylococcus aureus*: leading cause of IE (Fowler et al, 2005; Miro et al, 2005; Cabell et al, 2002)
  - Overall worsening of the clinical course
  - Increased number of serious complications
  - Higher mortality rates
Infective Endocarditis

Microbiology

- HACEK group bacteria (*Haemophilus* spp., *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella* spp.): 5-10% cases
- Fungi, *Mycobacterium* spp., chlamydiae, and *Mycoplasma* spp.: low frequency
Bacterial Virulence Factors

➔ Adherence to the vegetations
Bacterial Virulence Factors

- Adherence to the vegetations
- Promotion of thrombus formation
  - *S. sanguinis*: Platelet aggregation-associated protein (PAAP)

![Diagram of bacterial virulence factors](image)

**Nat Rev Microbiol. 2006**
Bacterial Virulence Factors

- Adherence to the vegetations
- Promotion of thrombus formation
- Resistance to phagocytosis and killing by PMNs
  - *S. gordonii*
  - *A. actinomycetemcomitans*

A. actinomycetemcomitans highly leukotoxic strain

A. actinomycetemcomitans low leukotoxic strain

Johansson *et al.,* 2000
Prevention of Infective Endocarditis by Antibiotic Prophylaxis

- The exact mechanisms behind antibiotic prophylaxis are unknown
- Efficacy of antibiotic prophylaxis: animal studies and clinical experience
Prevention of Infective Endocarditis by Antibiotic Prophylaxis

Mechanisms of Antibiotic Prophylaxis (animal models)

I. Reduction of the incidence and magnitude of bacteremia

II. Prevention of adherence to the vegetations

III. Inhibition of bacterial growth on the vegetations
Bacteremia after Antibiotic Prophylaxis in Humans

➡️ Conflicting results
Bacteremia after Antibiotic Prophylaxis in Humans

- Investigated the incidence and magnitude of postextraction bacteremia
- Healthy patients randomly assigned to receive active drug or placebo
- Test groups: Penicillin V, Amoxicillin, Erythromycin, Clindamycin and Cefaclor
- Blood samples: lysis-filtration technique
- Antibiotic prophylaxis did not reduce the incidence or magnitude of bacteremia after dental extraction
- The absence of reduction in bacteremia in the prophylaxis was not due to high bacterial resistance
The protective effect of prophylaxis must be the result of interference with crucial steps in the development of IE.
Prevention of Infective Endocarditis by Antibiotic Prophylaxis

Mechanisms of Antibiotic Prophylaxis (humans)

I. Reduction of the incidence and magnitude of bacteremia
II. Prevention of adherence to the vegetations
III. Inhibition of bacterial growth on the vegetations
Oral Bacteria, Dental Treatment and Infective Endocarditis

- Oral bacteria and IE: a century of association
- Bacteremia of oral origin
  - Transient type
  - Various magnitudes
### Table I. Prevalence of bacteremia after various types of dental procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Extractions</strong></td>
<td></td>
</tr>
<tr>
<td>• single</td>
<td>51%</td>
</tr>
<tr>
<td>• multiple</td>
<td>68-100%</td>
</tr>
<tr>
<td><strong>Periodontal surgery</strong></td>
<td></td>
</tr>
<tr>
<td>• flap procedure</td>
<td>36-88%</td>
</tr>
<tr>
<td>• gingivectomy</td>
<td>83%</td>
</tr>
<tr>
<td><strong>Scaling and root planing</strong></td>
<td>8-80%</td>
</tr>
<tr>
<td><strong>Periodontal prophylaxis</strong></td>
<td>0-40%</td>
</tr>
<tr>
<td><strong>Endodontics</strong></td>
<td></td>
</tr>
<tr>
<td>• intracanal instrumentation</td>
<td>0-31%</td>
</tr>
<tr>
<td>• extracanal instrumentation</td>
<td>0-54%</td>
</tr>
<tr>
<td><strong>Endodontic Surgery</strong></td>
<td></td>
</tr>
<tr>
<td>• flap reflection</td>
<td>83%</td>
</tr>
<tr>
<td>• periapical curettage</td>
<td>33%</td>
</tr>
<tr>
<td><strong>Toothbrushing</strong></td>
<td>0-26%</td>
</tr>
<tr>
<td><strong>Dental flossing</strong></td>
<td>20-58%</td>
</tr>
<tr>
<td><strong>Interproximal cleaning with toothpicks</strong></td>
<td>20-40%</td>
</tr>
<tr>
<td><strong>Irrigation devices</strong></td>
<td>7-50%</td>
</tr>
<tr>
<td><strong>Mastication</strong></td>
<td>17-51%</td>
</tr>
</tbody>
</table>

Seymour et al, 2000
Oral Bacteria, Dental Treatment and Infective Endocarditis

Are dentists the real culprits for IE?

- A number of studies reporting IE after dental procedures
- High frequency of bacteremia after oral invasive procedures
- High recovery rate of oral streptococci in IE cases
Oral Bacteria, Dental Treatment and Infective Endocarditis

Are dentists the real culprits for IE?

- Bacteremia from dental procedures: low intensity compared to $1 \times 10^9$
- Bleeding is a poor predictor of dental-induced bacteremia
- Dental procedures: no risk of cumulative bacteremia
- Cumulative exposure to bacteremia from daily activities may be up to $10^6$ greater than operative dental procedures (Roberts, 1999)
- Less than 4% of all IE cases are related to dental treatment-induced bacteremia (Guntheroth, 1984; Strom et al, 1998)
Dental Procedures Considered for Antibiotic Prophylaxis in Risk Patients (AHA, 1997)

- Dental extractions
- Periodontal procedures, including surgery, scaling, root planing and probing
- Dental implant placement, reimplantation of avulsed teeth
- Endodontic instrumentation or surgery only beyond the apex
- Subgingival placement of antibiotic fibers or strips
- Initial placement of orthodontic bands
- Intraligamentary local anesthetic injections
- Prophylactic cleaning of teeth or implants with anticipated bleeding
- Incision and drainage or other procedures involving infected tissues
**Table II. AHA Guidelines for Antibiotic Prophylaxis**

<table>
<thead>
<tr>
<th>Situation</th>
<th>Agent</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard general prophylaxis</strong></td>
<td>Amoxicillin</td>
<td>Adults: 2.0 g; children: 50 mg/kg Orally 1 hour before procedure</td>
</tr>
<tr>
<td><strong>Unable to take oral medications</strong></td>
<td>Ampicillin</td>
<td>Adults: 2.0 g; children: 50 mg/kg Intramuscularly (IM) or intravenously (IV) within 30 min before procedure</td>
</tr>
<tr>
<td><strong>Allergic to penicillin</strong></td>
<td>Clindamycin</td>
<td>Adults: 600 mg; children: 20 mg/kg Orally 1 hour before procedure</td>
</tr>
<tr>
<td><strong>OR</strong></td>
<td>Azithromycin or clarithromycin</td>
<td>Adults: 500 mg; children: 15 mg/kg Orally 1 hour before procedure</td>
</tr>
<tr>
<td><strong>Allergic to penicillin and unable to take oral medications</strong></td>
<td>Clindamycin</td>
<td>Adults: 600 mg; children: 50 mg/kg IV within 30 min before procedure</td>
</tr>
</tbody>
</table>

Dajani *et al*, 1997
Dental Procedures Not Recommend for Antibiotic Prophylaxis (AHA, 1997)

- Restorative dental procedures with or without retraction cord
- Intracanal endodontic procedures, post placement and buildup
- Local anesthetic injections
- Placement of rubber dams
- Postoperative suture removal
- Placement of removable prosthodontic or orthodontic appliances, and orthodontic appliance adjustment
- Taking oral impressions
- Fluoride treatments
- Taking oral radiographs
- Shedding of primary teeth
Endodontics

- Pulp and periapical disease: microbial infection (Kakehashi et al, 1965; Sundqvist, 1976; Möller et al, 1981)

- Polymicrobial
Endodontics

- Pulp and periapical disease: microbial infection (Kakehashi et al, 1965; Sundqvist, 1976; Möller et al, 1981)

- Polymicrobial

- Bacteremia
  - Non-existent (Bender et al, 1960 and 1963; Baumgartner et al, 1976)
  - Sampling, transport and culture methods ???
Teeth with asymptomatic apical periodontitis

Bacteremia
- Intracanal instrumentation: 31%
- Instrumentation beyond the apex: 54%

Endodontic therapy

Application of rubber dam

Antibiotic Prophylaxis for Dental Procedures in High-Risk Patients (BSAC, 2006)

**Dental procedures requiring antibiotic prophylaxis**
- All dental procedures involving dento-gingival manipulation
- Endodontics

**High-risk cardiac conditions requiring antibiotic prophylaxis**
- History of previous IE
- Prosthetic cardiac valves
- Surgically constructed shunts/conduits
Table II. Antibiotic Prophylaxis for Dental Procedures (BSAC)

<table>
<thead>
<tr>
<th>Population</th>
<th>&gt;10 years</th>
<th>≥5 to &lt;10 years</th>
<th>&lt;5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Amoxicillin 3 g</td>
<td>Amoxicillin 1.5 g</td>
<td>Amoxicillin 750 mg</td>
</tr>
<tr>
<td></td>
<td>1 h pre-procedure</td>
<td>1 h pre-procedure</td>
<td>1 h pre-procedure</td>
</tr>
<tr>
<td>Allergic to penicillin</td>
<td>Clindamycin 600 mg</td>
<td>Clindamycin 300 mg</td>
<td>Clindamycin 150 mg</td>
</tr>
<tr>
<td>Allergic to penicillin and unable to swallow capsules</td>
<td>Azithromycin 500 mg oral suspension</td>
<td>Azithromycin 300 mg oral suspension</td>
<td>Azithromycin 200 mg oral suspension</td>
</tr>
<tr>
<td>Intravenous regimen expedient</td>
<td>Amoxicillin 1 g IV</td>
<td>Amoxicillin 500 mg IV</td>
<td>Amoxicillin 250 mg IV</td>
</tr>
<tr>
<td></td>
<td>just before procedure</td>
<td>just before procedure</td>
<td>just before procedure</td>
</tr>
<tr>
<td>Intravenous regimen expedient and allergic to penicillin</td>
<td>Clindamycin 300 mg IV at least 10 min before procedure</td>
<td>Clindamycin 150 mg IV at least 10 min before procedure</td>
<td>Clindamycin 75 mg IV at least 10 min before procedure</td>
</tr>
</tbody>
</table>

Gould et al, 2006
Reasons to promote the use of prophylactic regimens for IE prophylaxis

- IE results in high morbidity and mortality
- Prophylaxis is a long-standing medical practice
- IE prophylaxis follows logical principles (limited targeted population/procedures, limited pathogens, short-course regimens, reasonably safe and inexpensive)
- Animal models support prophylaxis
- Medico-legal concerns
Reasons for challenging the use of prophylactic regimens for IE prophylaxis

- IE prophylaxis has not resulted in a decreased incidence of the disease
- No published, controlled clinical trials in humans
- Transient bacteremias are common events
- Individuals at-risk for IE are not easily identified
- False sense of security for patient and healthcare provider
- Potential for increasing antimicrobial resistance and adverse effects of antibiotics
- Poor compliance by patient and healthcare provider
Conclusions

• The use of antibiotics does not guarantee prevention of IE in all cases

• Prevention of IE by antibiotic prophylaxis has been proven to be effective in experimental animal models, but not always in humans

• Antibiotic prophylaxis prior to dental treatment in high-risk patients remains reasonable and prudent, although evidence for its efficacy is currently lacking

• Greater emphasis should be placed on improving oral health, especially in high-risk patients