Antibiotic Prophylaxis in Dentistry

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Disclaimers

- Neither I nor my immediate family have any financial interests that would create a conflict of interest or restrict my independent judgment with regard to the contents of this course.
- Each participant should be aware of the potential risks of using limited knowledge about products and techniques that are discussed in this presentation.

Special Patient Care
This review will concentrate on two aspects of antibiotic prophylaxis

- Biological principles that guide its use
- Evolution of Antibiotic Protocols from the beginning to the present

Biological principles that guide its use

Various clinical situations where its use has been suggested needs to be judged according to current evidence

Antibiotic Prophylaxis

- The history of antibiotic prophylaxis is one of:
  - Substantial ignorance
  - Profound abuse

Antibiotic Prophylaxis is employed for three reasons

- Prevent surgical infections or their post-operative sequelae
- Prevent metastatic bacteremias (micro-organisms moving from one region of the body to the other)
- As "drugs of fear" to "prevent" any possible accusation that "all was not done for the patient"
  - i.e. "Malpractice prevention insurance"
Lawyers dictate much of the use (and abuse) of antibiotics with no shared legal responsibility for its untoward sequelae:
- Antibiotic-resistant organisms
- Increasing inability to treat these pathogens

The Need for Antibiotic Prophylaxis in Dentistry
- 1935, Okell and Elliot were first authors to detect bacteremia caused by streptococcus species (64%) after performing dental extractions


Development of antimicrobial prophylaxis protocols

First Infective Endocarditis Prophylaxis Protocol in History
- 1938 Feldman and Trace
  - Cleaning teeth before any manipulation of operative field
  - Extract on 1 or 2 teeth per session
  - Curettage and irrigation with antiseptics


1939 Elliot
- Peri- and intraoperative gingival prior to extraction
- Use of local anesthetic with epinephrine

1939 Long & Bliss

- Use of sulfamilamide, sulfaphyridine, and allied compounds
- Every six hours starting 2 days prior to procedure, and continuing 2-3 days afterward


1948 Hirsh

- 1948 Hirsh et al. first authors to investigate penicillin on the prevalence of post-dental extraction bacteremia


1955 AHA Committee on Prevention of Rheumatic Fever and IE

- 7 physicians developed prophylactic protocol for dental procedures


1955 AHA Recommendations

- Parenteral
  - 600,000 IU Aqueous PCN and 600,000 Procaine PCN administered 30 minutes prior to procedures

- Oral
  - 250,000 – 500,000 IU 30 minutes before each meal and before bedtime, starting 24 hours prior to procedure continuing five days after treatment with an extra dose immediately prior to procedure

* AHA has published 9 IE prophylaxis protocols between 1955 and 2007.
• For over seven decades, 1935 – 2007:
  • Bacteria from the oral cavity were considered a decisive factor in the pathogenesis of 10% - 15% of episodes of Infective Endocarditis (IE), and that
  • Dental procedures were a significant risk factor.

• There is little evidence on the genetic similarity with IE between bacteria isolated:
  • from the heart valve,
  • from the bloodstream, and
  • from the oral cavity

References

Very Healthy Mouth

Best case scenario
• Antibiotic prophylaxis may have prevented 10% of cases of B.E.

• Studies indicate antibiotic prophylaxis may prevent 5.7% of all native valve endocarditis and 3.8% of all prosthetic valve endocarditis

• Assuming prophylaxis were 49% effective would prevent 5 endocarditis cases annually in a population of 14.5 million


• B.E. prophylaxis may have prevented 240-280 of the annual 11,200 cases of B.E. per year


VGS

• If Viridans Group Streptococci (VGS) account for 25% of all endocarditis cases in the U.S. and dental procedures are responsible for 1% of those cases, (28 episodes)

• VGS-induced B.E. is less than 10% fatal, that is 2-3 cases annually

Risk for B.E. from a single dental treatment procedure:

• 1 in 14 million for general population
• 1 in 95,000 for highest risk, i.e. those in the past history of endocarditis


• Unresolved difficulties with antibiotic prophylaxis as they pertain to dentistry
- Lack of evidence antibiotic prophylaxis begun after the procedure is terminated is efficacious
- High financial costs of antibiotic prophylaxis
  - Hundreds of thousands to a million $$ to prevent a single case of endocarditis
- Documentation that the risk of an orally induced bacteremia is a thousand times greater from normal daily living activities (brushing, flossing, eating) than from dental treatment
- Extreme rarity of endocarditis caused by periodontal pathogens
  - Less than 150 cases in the literature
  - Most of them from a single microbe, Actinobacillus
- Probability that antibiotic prophylaxis does not reduce bacteremias significantly, making it either ineffective or having another mechanism of action

Contribution of antibiotic prophylaxis misuse to global epidemic of antibiotic-resistant bacteria
Possibility that death from penicillinaphylaxis may be greater than lives
saved by PCN prophylaxis against VGS

Microorganisms will always be with
us and we will always be trying to
stay ahead of them

Antibiotic Classification & Mechanism
Overview of By Mechanism

Author: Derek Moore

Bacterial Overview

Staphylococci
- Staph. aureus
- MSSA
- MRSA
- Staph. epidermidis
- Staph. saprophyticus

Streptococci
- Strp. pneumoniae
- Strp. pyogenes (Group A)
- Strp. agalactiae (Group B)
- Strp. viridans
- Strp. Bovis (Group D)

Enterococci
- E. faecalis (Group D strep)

Gram Positive Bacilli

<table>
<thead>
<tr>
<th>Spore Forming</th>
<th>Non-Spore Forming</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacillus anthracis</td>
<td>Corynebacterium diphtheriae</td>
</tr>
<tr>
<td>Bacillus cereus</td>
<td>Listeria monocytogenes</td>
</tr>
<tr>
<td>Clostridium tetani</td>
<td></td>
</tr>
<tr>
<td>Clostridium botulinum</td>
<td></td>
</tr>
<tr>
<td>Clostridium perfringens</td>
<td></td>
</tr>
<tr>
<td>Clostridium difficile</td>
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</tr>
</tbody>
</table>

Gram Negative Cocci

| Neisseria meningitidis | Neisseria gonorrhoeae |

Gram Positive Bacilli

| Bacillus anthracis | Streptococcus pneumoniae |
| Bacillus cereus | Strp. pyogenes (Group A) |
| Clostridium tetani | Strp. agalactiae (Group B) |
| Clostridium botulinum | Strp. viridans |
| Clostridium perfringens | Strp. Bovis (Group D) |
| Clostridium difficile | |

Gram Negative Bacilli

| E. coli | Salmonella typhi |
| Shigella flexneri | Shigella sonnei |
| Klebsiella pneumoniae | |
| Proteus | |
| Campylobacter jejuni | |
| Vibrio cholerae | Vibrio parahaemolyticus/vulnificus |
| Helicobacter pylori | |
| Pseudomonas aeruginosa | |
| Bacteroides fragilis | |

Respiratory bacilli

| Haemophilus influenzae | Neisseria meningitidis |
| Haemophilus ducreyi | Neisseria gonorrhoeae |
Antibiotic Resistance Mechanisms

- Bacteria develop the ability to hydrolyze these drugs using β-lactamase.
  - Confer resistance to penicillin.
  - e.g., E.coli, Staph epidermidis, Pseudomonas, aeruginosa, Klebsiella pneumonia.
  - Add β-lactamase inhibitor e.g., clavulanic acid in amoxicillin-clavulanate (Augmentin).
  - Genetic mutation of meCA - A bacterial gene encoding a penicillin-binding protein. New PBP has reduced affinity for antibiotics.
  - Confer resistance to methicillin, enoxacin, saufloxin.
  - e.g., MRSA.

Antibiotic Resistance Mechanisms

- Active efflux pumps.
  - Confer resistance to erythromycin and tetracycline.
  - e.g., marA gene in Staph.
  - Altered peptidoglycan subunit (altered D-alanyl-D alanine of NAM/NAG-peptide).
  - Confer resistance to vancomycin.
  - e.g., vancomycin-resistant enterococcus (VRE).

Antibiotic Resistance Mechanisms

- Ribosome alteration.
  - erm gene confer inducible resistance to MLS (macrolide-lincosamide-streptogramin) agents via methylation of 23s rRNA.
  - Demonstrate using D zone test.
  - For inducible clindamycin resistance in Staph and beta hemolytic Strep.
Antibiotics for Odontogenic Infections

1. PCN is the drug of choice
   • Effective against most gram positive aerobic and intraoral
     anaerobics found in alveolar abscess, peri and necrotic pulp
2. Penicillinase – resistant bacteria
   • Use Ampicillin / Amoxicillin or PCN with Clavulanic Acid
     (Augmentin)
3. Clindamycin
4. First Generation Cephalosporins

Antibiotic misuse in dentistry

• Primarily three ways:
  • Timing of administration and duration of administration is
    inappropriate
  • Substitute for incision and drainage — “the sun should never
    set on undrained pus”
  • Antibiotic prophylaxis to prevent or mitigate surgical
    infections or post-operative sequelae

• Antibiotic must be in the tissue before
  the bacteria enter the blood

*Stone, H & J. Basic principles in the use of prophylactic antibiotics. J.

• Beta-lactam antibiotics PCN and
  Cephalosporins prevent the final
  transpeptidation reaction necessary for
  the formulation of rigid bacterial cell wall

• Hopefully this presentation will reduce
  the use of antibiotics as “Drugs of Fear”

• Goal of prevention of infection by
  antibiotics due to blood-borne bacteria
  (bacteremia)
  • Kill bacteria in the blood before colonization of
    an organ or tissue
Macrolide antibiotics Clindamycin and Erythromycin act by inhibiting ribosomal protein synthesis.

The bacteria must be in the process of cell division for these antibiotics to be effective.

How can bacteria once incorporated into the cardiac valve vegetation with successive layering of platelets and fibrin be seriously affected by short-lived blood concentration of prophylactic antibiotics?

Bacterial endocarditis takes 4-6 weeks of antibiotic treatment.

The mechanism by which antibiotics prevent metastatic infection remains a mystery.

Complicating this already complex issue is increasing resistance.

Reduces our ability to:
- Treat acute infections
- Prevent metastatic bacteremias

Study in 2000

- 139 VGS cultures isolated from orofacial infections
  - 23% resistant to Pen G
  - 43% resistant to Erythromycin
  - 46% resistant to Clindamycin

Current standards of antibiotic prophylaxis in dentistry based upon review of:

- Prevention of Infective Endocarditis: Guidelines from the American Heart Association
- Prevention of orthopedic implant infection in patients undergoing dental procedures: Guidelines from the American Academy of Orthopedic Surgeons (AAOS), the American Dental Association (ADA) and the American Academy of Pediatric Dentistry
- Antibiotic prophylaxis only for those with underlying cardiac conditions with highest risk of adverse outcomes

Population based review of definitive and possible cases of I.E. demonstrated no increases in VGS I.E. after 2007 AHA Guidelines instituted


### Table 1: Cardiac Conditions Associated with the Highest Risk of Adverse Outcome from Endocarditis for Which Prophylaxis with Dental Procedures is Reasonable

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Prosthetic valve or prosthetic material used for cardiac valve repair</td>
</tr>
<tr>
<td>Previous infective endocarditis</td>
</tr>
<tr>
<td>Congenital heart disease (CHD)</td>
</tr>
<tr>
<td>Unrepaired cyanotic CHD, including palliative shunts and conduits</td>
</tr>
<tr>
<td>Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first six months after the procedure</td>
</tr>
<tr>
<td>Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which limits endothelialization)</td>
</tr>
<tr>
<td>Cardiac transplantation recipients who develop cardiac allograftopathy</td>
</tr>
</tbody>
</table>

* Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other forms of CHD.

† Prophylaxis is reasonable because endothelialization of prosthetic material occurs within six months after the procedure.

### Table 2: Dental Procedures for Which Endocarditis Prophylaxis is Reasonable for Patients in Table 1

- All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa
- The following procedures and events do not need prophylactic routine antibiotic injections through non-injected tissue, taking dental radiographs, placement of removable prosthetic or orthodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth, and bleeding from trauma to the lip or oral mucosa.

Acceptance by Dental Practitioners of 2007 AHA Guidelines

- 71% of dentists surveyed reported satisfaction with guidelines
- 70% of dentists reported most patients previously receiving antibiotics no longer required prophylaxis
- 70% of dentists reported significant number of patients still receiving antibiotic prophylaxis regardless of revised AHA guidelines


Antibiotic Prophylaxis for Non-valvular cardiovascular devices

- Pacemakers
- Implantable cardioverter defibrillators
- Coronary artery stents
- Prosthetic vascular grafts
- Dacron carotid patches
- Indwelling catheters

AHA has concluded

- No evidence oral microbes cause infection of these devices
- Antibiotic prophylaxis not recommended after device placement for dental procedures


Infection rate for these devices is very low
- All infections from these devices due to Staphylococci most likely from skin contamination at time of placement

Summary of Recommendations from the AAOS-ADA Clinical Practice Guidelines

RECOMMENDATION 1
The practitioner might consider discontinuing the practice of routinely prescribing prophylactic antibiotics for patients with hip and knee prosthetic joint implants undergoing dental procedures.

Grade of Recommendation: Limited

Description: Evidence from two or more “Low” strength studies with consistent findings, or evidence from a single Moderate quality study recommending for or against the intervention or diagnostic. A Limited recommendation means the quality of the supporting evidence is insufficient, or that well-conducted studies show little clear advantage to one approach versus another.

Implications: Practitioners should be cautious in deciding whether to follow a recommendation classified as Limited, and should exercise judgment and be alert to emerging publications that report evidence. Patient preference should have a substantial influencing role.
Summary of Recommendations from the AAOS-ADA Clinical Practice Guidelines

**RECOMMENDATION 2**
We are unable to recommend for or against the use of topical oral antimicrobials in patients with prosthetic joint implants or other orthopaedic implants undergoing dental procedures.

Grade of Recommendation: Inconclusive

Description: Evidence from a single low-quality study or conflicting findings that do not allow a recommendation for or against the intervention. An Inconclusive recommendation means that there is a lack of compelling evidence resulting in an unclear balance between benefits and potential harm.

Implications: Practitioners should feel little constraint in deciding whether to follow a recommendation labeled as Inconclusive and should exercise judgment and be alert to future publications that clarify existing evidence for determining balance of benefits versus potential harm. Patient preference should have a substantial influencing role.

Other considerations for antibiotic prophylaxis in dentistry
- Immuno-compromised patients
- Diabetes
- Splenectomy
- Hemodialysis
- Breast & Penile Implants

Immuno-compromised patients
- Cancer treatment / Chemotherapy & Radiology
- Leukemia / Neutropenia
- Hematopoietic stem cell transplant
- Solid organ transplant
- Autoimmune disease
  - Systemic Lupus Erythematosus
  - Sickle cell anemia
  - HIV / AIDS

Dental patients with suppressed granulocyte count (<500 – 1000)
- May be at risk of bacteremia
- No controlled studies to support this contention

→ Consult physician for antibiotic prophylaxis recommendation for dental patients

HIV / AIDS patients
- No greater risk for postoperative infection complication than patients without these disorders
- Should not receive antibiotic prophylaxis for dental procedures

Antibiotic prophylaxis for the diabetic dental patient

- Not indicated for well controlled non-kenotic diabetic
- No data support antibiotic prophylaxis for uncontrolled diabetic requiring emergency dental treatment


Antibiotic prophylaxis for dental patients on hemodialysis

- Virtually all infections with indwelling catheters are caused by staphylococci
- AHA advises against prophylaxis


Antibiotic prophylaxis for dental patients without spleens

- No data to support use of antibiotic prophylaxis
  - Consult physician

Antibiotic prophylaxis for placement of dental implants


Antibiotic prophylaxis for patients with breast or penile implants

- No scientific data support antibiotic prophylaxis
  - Consult physician

Antibiotic prophylaxis for the diabetic dental patient

- Only 2% of surveyed infectious disease specialists would recommend antibiotic prophylaxis in poorly controlled diabetics
  - Consult physician

Antibiotic prophylaxis for placement of dental implants
- Six trials included in study
- 1162 participants
- 18 years or older and healthy
- All used Amoxicillin only
- Follow-up 3 months or more

Key Results
- Oral administration of Amoxicillin one hour before placement of dental implants is effective in reducing implant failures.
- Giving antibiotics for 25 implants will reduce the loss of one early implant.

Key Results
- It is unclear whether post-operative antibiotics are useful.
- Unclear if other antibiotics are equally effective.
- No significant adverse events reported.

Conclusions
- 2 grams of Amoxicillin given orally as a single dose one hour pre-operatively significantly reduces failure of dental implants.

Fecal Microbiota Transplant (FMT)
- Fecal matter from a tested donor mixed with saline, strained and placed in a patient by Colonoscopy, Sigmoidoscopy, or Enema.

Now new therapy uses bacteria to treat disease.
FMT

- Used to replace good bacteria that has been killed or suppressed usually by use of antibiotics causing overgrowth of a bad bacteria like Clostridium difficile or C-diff
- D-diff can cause debility and sometimes fatal diarrhea
- Also used for IBS, Crohn's and UC/erative colitis

Interventive Use of Antibiotics in Dentistry

- Empiric Antibiotics of Choice for Odontogenic Infections
- See Table 1 and 2

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### Table 1. Empiric Antibiotics of Choice for Odontogenic Infections

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Antibiotic of Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early (first 3 days of infection)</td>
<td>Penicillin VK, amoxicillin Clavulanate, Cephalosporin (or other first generation cephalosporins)&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>No improvement in 24-36 hours</td>
<td>Beta-lactamase-stable antibiotics: Clindamycin or amoxicillin/clavulanic acid (Augmentin)&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Penicillin allergy</td>
<td>Clindamycin Clavulanate (if penicillin allergy is not anaphylactic type) Clarithromycin (Biaxin)&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Late (&gt;3 days)</td>
<td>Clindamycin Penicillin V/metronidazole, amoxicillin/metronidazole</td>
</tr>
</tbody>
</table>

<sup>1</sup> For better patient compliance, second generation cephalospors (cefalexin; cefuroxime) or twice daily dosing has been used.

<sup>2</sup> A macrolide useful in patients allergic to penicillin, given as twice daily dosing for better patient compliance.

Adapted from Drug Information Handbook for Dentistry, Richard Fenn, Timothy Miller, Harold Cralle, 12th Edition

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### Table 2. Empiric Antibiotics of Choice for Odontogenic Infections

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin VK</td>
<td>13 years: 25-50 mg/kg body weight in equally divided doses q6h for at least 7 days; maximum dose: 3 g/day</td>
</tr>
<tr>
<td>&gt;13 years: 500 mg q6h for at least 7 days</td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>90-200 mg/kg in 3-4 equally divided doses</td>
</tr>
<tr>
<td>&gt;10 kg: 10-20 mg/kg/day in divided doses q6h</td>
<td></td>
</tr>
<tr>
<td>&gt;2-10 kg: 15-30 mg/kg/day</td>
<td></td>
</tr>
<tr>
<td>&gt;2 kg: 150-500 mg q12h or 875 mg q24h for at least 7 days; maximum dose: 3 g/day</td>
<td></td>
</tr>
<tr>
<td>&gt;12 years: 500 mg q12h for at least 7 days</td>
<td></td>
</tr>
<tr>
<td>&gt;5-10 kg: 1.6 g/day</td>
<td></td>
</tr>
<tr>
<td>&gt;50 kg: 250-500 mg q12h or 875 mg q24h for at least 7 days; maximum dose: 3 g/day</td>
<td></td>
</tr>
<tr>
<td>Cefalexin (Keflex)</td>
<td>25-60 mg/kg/day in divided doses q6h</td>
</tr>
<tr>
<td>Severe infection: 10-100 mg/kg/day in divided doses q6h; maximum dose: 3 g/day</td>
<td></td>
</tr>
<tr>
<td>&gt;12 years: 1-2 g/day</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>&lt; 40 kg: 25-40 mg/kg/day in divided doses q6h</td>
</tr>
<tr>
<td>&gt;40 kg: 250-500 mg q8h or 875 mg q24h for at least 7 days; maximum dose: 3 g/day</td>
<td></td>
</tr>
<tr>
<td>&gt;40 kg: 250-500 mg q8h or 875 mg q24h for at least 7 days; maximum dose: 2 g/day</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin/clavulanic acid (Augmentin)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>45 kg: 180 mg q8h in divided doses</td>
</tr>
<tr>
<td>&gt;45 kg: 250-500 mg q8h or 875 mg q24h for at least 7 days; maximum dose: 2 g/day</td>
<td></td>
</tr>
<tr>
<td>Sub antimicrobial dose of Doxycycline: 20mg (Periostat)</td>
<td></td>
</tr>
<tr>
<td>Dose too low to affect bacteria</td>
<td></td>
</tr>
<tr>
<td>Low dose blocks matrix metalloproteinases (MMP's)</td>
<td></td>
</tr>
</tbody>
</table>

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JADA July 2015

- Non-surgical Treatment of Periodontitis with low dose Doxycycline
- Guidelines based on a systemic review and meta-analysis of treatment of periodontitis
Matrix Metalloproteinases (MMP’s)

- Enzyme that destroys connective tissue of periodontium

Periostat (Doxycycline 20mg)

- Taken p.o. twice daily
- Months duration
- Multiple 12 month studies report significant improvement in tooth attachment and decreased pocket depth with no significant side effects

Complications

Complications: What Can and Does Happen in Dentistry

"We look for medicine (& dentistry) to be an orderly field of knowledge and procedure. But it is not. It is an imperfect science, an enterprise of constantly changing knowledge, uncertain information, fallible individuals, and at the same time lives on the line. There is science in what we do, yes, but also habit, intuition, and sometimes plain old guessing. The gap between what we know and what we aim for persists. And this gap complicates everything we do."


Summary

- Of all medically abused drugs, antibiotic prophylaxis is likely only second to antibiotics employed for upper respiratory viral infections

Summary

- Guidelines for use of antibiotic prophylaxis have been available for over 40 years, but rarely consulted.
Summary

- Antibiotic prophylaxis still follows the path of “Drugs of Fear”
- Drugs employed to “prevent” malpractice allegations, allowing attorneys to dictate medical treatment

Summary

- Dental practitioners should exercise their clinical judgment in determining the duration and choices of antibiotics based upon evidence based knowledge.