Antibiotic Management in Treating Special Care Patients

Solon Kao DDS FICD
Assistant Professor of Oral and Maxillofacial Surgery
Dental College of Georgia, Augusta University
Augusta, Georgia USA
Objectives

• The bugs
• Antibiotics associated with odontogenic infection
  • Drug interactions
• Antibiotics used in prophylaxis
• New Antibiotics and Summary

• *Bonus Lecture:*
  • *Post-Operative Analgesics*
Who are we dealing with?

Bacteria
Differentiation of Bacterial Species

• **Gram Staining**
  • Hans Christian Gram (1884)
    • Make bacteria visible in stained section of lung tissue
  • First step in identifying bacterial organism
  • 2 groups of bacteria
    • Gm+ and Gm-
  • How was it done
    • Crystal Violet
    • Iodine
    • Alcohol wash
    • Counterstaining with safranin
Types of Bacteria

• Gram Positive
  • Stain purple or blue

• Gram Negative
  • Stain pink or red

• Atypical
  • Properties of both gram positive and gram negative
Bacterial Cell Wall in Gm+ & Gm-
Anaerobe or Aerobe

- **Anaerobe**
  - Requires reduced oxygen for growth

- **Aerobe**
  - Requires oxygen for growth

- **Facultative**
  - Bacteria that can grow in the presence or absence of air
Where does the bacteria reside?

• Normal oral flora may be altered with
  • Tobacco use, pregnancy, diet, nutrition, age, oral hygiene, deciduous teeth eruption, caries, perio disease, abx, **hospitalization**

• Tongue, buccal mucosa and Saliva (Gm+)
  • Streptococcus Salivarius, Veillonella (Gm-)

• Tooth surfaces (Gm+)
  • Streptococcus Sanguinis(Gm+), mutans, mitis, and Actinomyces viscosus (fungus)
    • S Mutan is consistently isolated from decayed dental fissures and carious teeth.
Where does the bacteria reside?

• Gingival crevice (Gm-)
  • Anaerobes fusobacterium (Gm-), porphyromonas (Gm-), prevotella (Gm-), and anaerobic spirochetes

• Supragingival plaque
  • Gm+ facultative cocci and rods

• Subgingival plaque
  • Gm- anaerobic
Bacteria in Odontogenic Infection

• Gm+ facultative anaerobe cocci (68%)

• Gm- obligate anaerobe (30%)

• Gm+ facultative anaerobic Bacilli (2%)

Antibiotics
Timeline of Antibiotic

- Sulfa Drugs (1935)
- Penicillin (1941)
- Tetracyclines (1948)
- Erythromycin (1952)
- Clindamycin (1962)
Bacteriostatic or Bactericidal?

• Bacteriostatic
  • Antibiotics that inhibit replication of bacteria but depend on the immune system of the host to completely rid the body of the infection

• Bactericidal
  • Antibiotics that kill bacteria

1. Katzung BG
2. Rudolph AM, et. al.
Overall Summary of today’s lecture:
Bacteria in Odontogenic Infection

• Mostly involved anaerobic bacteria
• Abx effective against odontogenic infection
  • Amoxicillin, Amoxicillin / clavulanate, tetracycline, clindamycin, linezolid
• Amoxicillin is the treatment of choice for odontogenic infection
  • Despite of some resistance
  • Addition of clavulanic acid does not constitute *decisive* advantage
• Clindamycin is the other good alternative
• Abx with high bacteria resistance
  • Metronidazole, Erythromycin, Azithromycin

# Mechanism of Action of Antibiotics

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibition of cell-wall synthesis</td>
<td>Vancomycin, Penicillins, Cephalosporins, Aztreonam, Carbapenems</td>
</tr>
<tr>
<td>Inhibition of nucleic acid synthesis</td>
<td>Rifampin, Quinolones, Metronidazole</td>
</tr>
<tr>
<td>Inhibition of protein synthesis</td>
<td>Aminoglycosides, Tetracyclines, Erythromycin, Clindamycin</td>
</tr>
<tr>
<td>Inhibition of folate synthesis</td>
<td>Sulfonamides, Trimethoprim</td>
</tr>
</tbody>
</table>

Rudolph AM, et. al.
Bactericidal Cell Wall Synthesis Inhibitor
Penicillin Chemical Structure

- Basic chemical structure of penicillin consists of:
  - A) Thiazolidine Ring
  - B) β-Lactam Ring
  - C) Secondary amino group (RNH-)
Anatomy of Penicillin

• Cell wall synthesis inhibitor
  • Bacterialcidal

• Mech Action:
  • Beta-Lactam ring structure
  • Penetrate Transpeptidase (or Penicillin binding protein)
    • Bacterial use PBP for cell wall synthesis
    • Penetrate all cell layers in order to expose fragile inner membrane

• What can Bacteria do?
  • Penicillinase (beta-lactamase)
    • Staphylococcus Aureus (Gm +)
  • Alter transpeptidase such as MRSA
  • Gm – bacteria has Porins
    • Prevent PCN pass through
Penicillin and his friends

• Types of PCN
  • **Penicillin G** (1941 Fleming)
    • Pen V (oral) vs Pen G (IM or IV)
  
  • **Aminopenicillin** (better coverage for Gm -)
    • Ampicillin/Amoxicillin
  
  • **Penicillinase-Resistant PCN** (for MRSA)
    • Methicillin, Nafcillin, Oxacillin (IV)
    • Cloxacillin, Dicloxacillin (oral)
  
  • **Anti-Pseudomonal PCN** (expanded Gm – coverage)
    • Carboxypenicillins (Carbenicillin, ticarcillin)
    • Ureidopenicillins (Piperacillin, mezlocillin)
  
  • **Cephalosporins**
Amoxicillin (aminopenicillin)

- Enhanced intestinal absorption (particularly at mealtime)
- Middle ear fluid and serum level are higher when using Amoxicillin
- Increased incidence of drug hypersensitivity with rashes
Ticarcillin (3rd generation penicillin)

• Ticarcillin + clavulanate (Timentin)

• Broader spectrum against Pseudomonas aeruginosa

• Caution:
  • Volume overload (disodium salt)
  • Bleeding diathesis
    • Increase bleeding time
    • Interfere platelet function especially in renal failure patient
Penicillin and his friends

• Other Beta-Lactamase Inhibitors

• Clavulanic Acid
  • Discovered in 1974 by British scientist
  • Not effective by itself as antibiotic
  • Suicide inhibitor to B-Lactamase → form reactive material →...enzyme deactivated
  • Examples
    • Clavulanic Acid + Amoxicillin = Augmentin
    • Clavulanic Acid + Ticarcillin = Timentin

• Sulbactam
  • Bind to enzyme and protect degradation of antibiotic
  • Example
    • Sulbactam + Ampicillin = Unasyn

• Tazobactam
  • Sodium salt
  • Example:
    • Tazobactam + piperacillin = Zosyn
      • For Nosocomial pneumonia
Cephalosporins

• Second major group of β-lactam antibiotics
• Related chemically to penicillin
• Chemical structure consist of a four side β-lactam ring attached to a six side dihydrothiaside ring
Cephalosporin

• 1\textsuperscript{st} generation
  • Cefalexin (Keflex) Gm+
  • Cefazolin (Ancef) Commonly used in surgical prophylaxis for head and neck surgery that requires crossing the oropharyngeal mucosal barrier

• 2\textsuperscript{nd} generation
  • \textit{Broader Gm- coverage} with less Gm+ activity
    • Commonly used in GI or Pelvic infection

• 3\textsuperscript{rd} generation
  • Broad coverage, high potency, low toxicity, high level in CSF
  • Less activity with Gm+, \textit{More Gm- coverage}

• 4\textsuperscript{th} generation
  • Gm+ effect is similar to 3\textsuperscript{rd} generation
  • \textit{Better penetration} against Gm- than 3\textsuperscript{rd} generation
  • Crosses Blood brain Barrier \rightarrow Meningitis
Cross Sensitivity between Penicillin and Cephalosporins

• Can we use Cephalosporins for patient with Penicillin Allergy?
  • Answer: Depends on the condition

• If mild rashes associated PCN → OK

• If anaphylaxis, angioedema, urticaria, or asthma associated with PCN → NO
Cross Sensitivity between Penicillin and Cephalosporins

• Common Adverse reactions
  • Maculopapular skin rash, eosinophilia, drug fever and GI symptoms

• Anaphylactic reactions
  • Urticaria (hives), Laryngeal edema, angioedema, wheezing or hypotension.
  • IgE immune mediated reaction
    • Allergy Skin test can be helpful
      • Drawbacks: limited availability and additional cost
Cross Sensitivity between Penicillin and Cephalosporins

• How often does it occur?

  • Adverse reaction to PCN is 0.7% to 10%
    • Anaphylactic reaction 0.004% to 0.015%

  • Adverse reaction to Cephalosporins is 1% to 10%
    • Anaphylactic reaction in less than 0.02%
Cross Sensitivity between Penicillin and Cephalosporins

• **Common understanding**
  • Incidence of cross sensitivity has been reported to be as high as 10%

• **Cross-allergenicity**
  • between penicillin and cephalosporins is not exactly known
  • more likely with 1\textsuperscript{st} generation cephalosporins

• **Manufacturer statement**
  • Patient with previous hypersensitivity reaction to penicillin should be given cephalosporins cautiously as serious acute allergic reaction may occur
Cross Sensitivity between Penicillin and Cephalosporins

• Side-Chain Structure
  • Recent focus on Side-Chain structure to the Beta-Lactam Ring

• Miranda 1996 et al
  • Identical side chain → 38% has pruritus, erythema..
  • Different side chain → No reaction

• Novalbos 2001 et al
  • Different side chain -> No reaction
Cross Sensitivity between Penicillin and Cephalosporins

• Summary
  • If Cephalosporin is considered....
    • Obtained detailed hypersensitivity history
    • 2) Determine if reaction is life threatening or not
    • 3) Allergy Skin test if possible
    • 4) Choose a cephalosporins with different side chain
  Or

Use other Alternative Medicine
Clindamycin

New Antibiotics

Teixobactin

• Teixobactin (Jan, 2015)
  • Kill some bacteria by preventing them building their outer coats
  • Resistant to resistance!

• History:
  • Bacteria don’t grow in lab but in nature
  • Sample were collected from Grassy field in Maine
  • iChip (isolation chip): gather soil sample and isolate diff species of bacteria
  • Eleftheria Terrae: a new genus of a species that makes this antibiotics
    • Kills staph efficiently

New Antibiotics

Teixobactin

• Lab test:
  • Effective against staph aureus, anthrax, tuberculosis and clostridium difficile (bad diarrhea)
  • Resistant strain were none!

• How does it work?
  • Potent in vitro against Gm + bacteria
  • Cell wall synthesis inhibitor
  • Attack Lipid II and Lipid III (at an area that is CONSTANT across from diff species of bacteria)
    • Lipid II: needed to make wall around the cell
    • Lipid III: Maintain the wall around the cell
  • Similar to Vancomycin (Lipid II) (at an area that is variable across from diff species of bacteria)

• Limitation:
  • NOT active against outer membrane of Gm – pathogen

Boyhood home of President Woodrow Wilson. Built in 1859
Protein Synthesis Inhibitor
Anti-ribosomal Antibiotics

• Anti-ribosomal antibiotics (buy AT 30, CELL 50)
  • 30S: Aminoglycoside, Tetracycline
  • 50S: Chloramphenicol, Erythromycin, Lincomycin, Clindamycin

• Tetracycline
  • Chelate with milk/Ca/Mg: pass GI tract without absorption
  • Tetracyclin, Doxycycline demeclocycline, minocycline

• Erythromycin (Macrolide) (treat Legionnaire’s disease and Chlamydia)
  • Erythromycin, Clarithromycin, Azithromycin (Z pack)

• Clindamycin (for anaerobic coverage)
  • Pseudomembranous Colitis treat with Vancomycin or metronidazole
Macrolides

• Erythromycin
  • Naturally-occurring macrolide
  • Derived from Streptomyces erythreus
    • problems with acid lability, narrow spectrum, poor GI intolerance, short elimination half-life

• Clarithromycin and Azithromycin:
  • Broader spectrum of activity
  • Better bioavailability, better tissue penetration, prolonged half-lives
  • Improved tolerability
  • Azithromycin
    • Most prescribed outpatient antibiotic in 2010
    • Warning in 2013!!
Macrolide Spectrum of Activity

- **Gram-Positive Aerobes** –
  - Erythromycin and clarithromycin display the best activity
    (Clarithro>Erythro>Azithro)
  - Methicillin-susceptible Staphylococcus aureus
  - Streptococcus pneumoniae – resistance is developing
  - Group and viridans streptococci
  - Bacillus sp., Corynebacterium sp.
Macrolide Spectrum of Activity

- **Gram-Negative Aerobes** – newer macrolides with enhanced activity (Azithromycin, Clarithromycin, Erythromycin)
  - H. influenzae (not erythro), M. catarrhalis, Neisseria sp.
  - Do Not have activity against any Enterobacteriaceae
Macrolide Spectrum of Activity

• **Anaerobes** – activity against upper airway anaerobes

• **Atypical Bacteria** – all macrolides have excellent activity against atypical bacteria including:
  - Legionella pneumophila
  - Chlamydia sp.
  - Mycoplasma sp.
  - Ureaplasma urealyticum (GU disease)

• **Other Bacteria** –
  - Mycobacterium avium complex
  - Treponema pallidum, Campylobacter, Borrelia, Bordetella, Brucella. Pasteurella
Macrolides Pharmacology

• **Absorption**

  - Erythromycin – variable absorption (15-45%); food may decrease the absorption
    - Base: destroyed by gastric acid; enteric coated
    - Esters and ester salts: more acid stable

  - Clarithromycin – acid stable and well-absorbed (55%) regardless of presence of food

  - Azithromycin (Z pack) – acid stable acceptable absorption (38%), food decreases absorption of capsules
Macrolides
Drug Interactions

• Erythromycin and Clarithromycin ONLY— are inhibitors of cytochrome p450 system in the liver; may increase concentrations of:

• Theophylline
• Carbamazepine
• Cyclosporine
• Phenytoin
• Warfarin
• Digoxin, Disopyramide
• Valproic acid
• Terfenadine, Astemizole
• Cisapride
Macrolides
Adverse Effect

• In 2013, the FDA issued a warning that Azithromycin,

"can cause abnormal changes in the electrical activity of the heart that may lead to a potentially fatal irregular heart rhythm."

• Patient with preexisting conditions are at particular risk including
  • QT interval prolongation
  • Low blood levels of potassium or magnesium
  • Slower than normal heart rate, or those who use of certain drugs used to treat abnormal heart rhythms
Clindamycin

• Semisynthetic derivative of Lincomycin
• Isolated from Streptomyces lincolnensis in 1962
• Better absorption with broader spectrum
Clindamycin
Adverse Effects

• Gastrointestinal – 3 to 4 %
  • Nausea, vomiting, diarrhea, dyspepsia

• C. difficile colitis – one of worst offenders
  • Mild to severe diarrhea
  • Requires treatment with metronidazole

• Hepatotoxicity - rare
  • Elevated transaminases

• Allergy - rare
## Cost of Clindamycin

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Dosage</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>150mg</td>
<td>$1.20</td>
</tr>
<tr>
<td></td>
<td>300mg</td>
<td>$3.76</td>
</tr>
</tbody>
</table>
Newer Antibiotics
Streptogramins

• Synercid® is the first available agent which received FDA approval in September 1999

• Developed in response to need for agents with activity against resistant gram-positives
  • When other failed............

• Synercid® is a combination of two semi-synthetic pristinamycin derivatives: Quinupristin:Dalfopristin in a 30:70 ratio

• **IV administration**
• **Mechanism of Action**
  - Protein synthesis inhibitor
    - Each agent acts on 50S ribosomal subunits to inhibit early and late stages of protein synthesis

• **Bacteriostatic (bactericidal against some bacteria)**

• **Mechanism of Resistance**
  - Alterations in ribosomal binding sites
  - Enzymatic inactivation
Synercid®
Spectrum of Activity

- **Gm + Bacteria**
  - MRSA
    - Methicillin-Susceptible and Methicillin-Resistant Staph aureus and coagulase-negative staphylococci
  - Enterococcus faecium
  - *Many more*
    - Streptococcus pneumoniae, streptococcus viridans....
    - Corynebacterium, Bacillus. Listeria, Actinomyces
    - Clostridium sp. (except C. difficile), Peptococcus, Peptostreptococcus

- **Gram-Negative Aerobes**
  - Limited activity against Neisseria sp. and Moraxella

- **Atypical Bacteria**
  - Mycoplasma, Legionella
Synercid®
Adverse Effects

- Venous irritation – especially when administered in peripheral vein
- Gastrointestinal – nausea, vomiting, diarrhea
- Myalgias, arthralgias – 2%
- Rash
- ↑ total and unconjugated bilirubin

- Wallet wise......... Each Bottle of 500mg is about $425 (Walmart price)
  - Indicated for Staph aureus complicated skin infection
  - Adult dosage is 7.5mg/kg IV q 12 h for at least 7 days
    - Avg Adult is 70kg ➔ ~525mg IV each time.
    - One week supply of this med maybe ~$5950
Oxazolidinones

- Linezolid (Zyvox®) is the first available agent which received FDA approval in April 2000; available PO and IV
- Developed in response to need for agents with activity against resistant gram-positives (MRSA)
- Linezolid is a semisynthetic oxazolidinone which is a structural derivative of earlier agents in this class
Linezolid

• **Mechanism of Action**
  
  • **Protein Synthesis Inhibitor**
    
    • Binds to the 50S ribosomal subunit near to surface interface of 30S subunit – causes inhibition of 70S initiation complex which inhibits protein synthesis

• **Bacteriostatic (cidal against some bacteria)**

• **Mechanism of Resistance**
  
  • Alterations in ribosomal binding sites (RARE)
  
  • Cross-resistance with other protein synthesis inhibitors is unlikely
Linezolid
Spectrum of Activity

• **Gm + Bacteria**
  - Methicillin-Susceptible, Methicillin-Resistant AND Vancomycin-Resistant Staph aureus and coagulase-negative staphylococci
  - Streptococcus pneumoniae (including PRSP), viridans streptococcus, Group streptococcus
  - Enterococcus faecium AND faecalis
  - Bacillus. Listeria, Clostridium sp. (except C. difficile), Peptostreptococcus, P. acnes

• **Gram-Negative Aerobes – relatively inactive**

• **Atypical Bacteria**
  - Mycoplasma, Chlamydia., Legionella
Linezolid
Pharmacology

- Concentration-independent bactericidal activity
- Absorption – 100% bioavailable
- Distribution – readily distributes into well-perfused tissue; CSF penetration ≈ 30%
- Elimination – both renal and non-renal, but primarily metabolized; Half life is 4.4 to 5.4 hours; no adjustment for renal failure.
Linezolid
Adverse Effects

• Gastrointestinal – nausea, vomiting, diarrhea (6 to 8 %)
• Headache – 6.5%
• Thrombocytopenia – 2 to 4%
  • Most often with treatment durations of > 2 weeks
  • Therapy should be discontinued – platelet counts will return to normal

• Wallet
Linezolid (Zyvox)

- Treatment of complicated infection
  - 600mg p.o. b.i.d. X 10 days

- How does this mean to your wallet
  - Safeway Pharmacy price is...
    - $145.55 Generic (Safeway)
    - $2761.39 Brand-name (Walmart)
Home of George Walton (1749-1804), 1 of 3 GA Signer of Declaration of Independence
DNA Synthesis Inhibitor
Fluoroquinolones

- **Examples**
  - Levofloxacin (IV, oral), Ciprofloxacin (IV, oral)

- **Coverage**
  - Excellent coverage of gram negative and atypical bacteria; some gram positive coverage

- **Mechanism**
  - Inhibition of nucleic acid synthesis

- **Warnings**
  - Black Box
    - Reports of tendon inflammation and rupture
  - QT prolongation – use vasoconstrictors (epinephrine, mepivacaine) with caution
  - Photosensitivity
  - Caution in renal impairment
The Available FQs

• Older FQs
  • Norfloxacin (Noroxin®) – PO
  • Ciprofloxacin (Cipro®) – PO, IV

• Newer FQs
  • Levofloxacin (Levaquin®) – PO, IV
  • Gatifloxacin (Tequin®) – PO, IV
  • Moxifloxacin (Avelox®) – PO, IV

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-Life (h)</th>
<th>Oral Bioavailability (%)</th>
<th>Peak Serum Concentration (µg/mL)</th>
<th>Oral Dose (mg)</th>
<th>Primary Route of Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>3–5</td>
<td>70</td>
<td>2.4</td>
<td>500</td>
<td>Renal</td>
</tr>
<tr>
<td>Clinafloxacin</td>
<td>6</td>
<td>nd</td>
<td>2.5</td>
<td>200</td>
<td>Renal</td>
</tr>
<tr>
<td>Enoxacin</td>
<td>3–6</td>
<td>90</td>
<td>2.0</td>
<td>400</td>
<td>Renal</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>8</td>
<td>98</td>
<td>3.4</td>
<td>400</td>
<td>Renal</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>5–7</td>
<td>95</td>
<td>5.7</td>
<td>500</td>
<td>Renal</td>
</tr>
<tr>
<td>Lomefloxacin</td>
<td>8</td>
<td>95</td>
<td>2.8</td>
<td>400</td>
<td>Renal</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>9–10</td>
<td>&gt;85</td>
<td>3.1</td>
<td>400</td>
<td>Nonrenal</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>3.5–5</td>
<td>80</td>
<td>1.5</td>
<td>400</td>
<td>Renal</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>5–7</td>
<td>95</td>
<td>2.9</td>
<td>400</td>
<td>Renal</td>
</tr>
<tr>
<td>Sparfloxacin</td>
<td>18</td>
<td>92</td>
<td>2.2</td>
<td>200</td>
<td>Nonrenal</td>
</tr>
<tr>
<td>Trovafloxacin</td>
<td>11</td>
<td>88</td>
<td>1.5</td>
<td>50% renal, 50% fecal</td>
<td>Nonrenal</td>
</tr>
</tbody>
</table>
Fluoroquinolones

- Coverage
  - Excellent coverage of Gm- and atypical bacteria
    - Some Gm+ coverage
  - Urinary track infections
    - Norfloxacin or Ofloxacin 400mg BID
    - Ciprofloxacin 500 mg BID
  - Diarrhea caused by E. coli, salmonella or campylobacter
  - Gonococal infection, Ciprofloxacin and Ofloxacin
  - Prophylaxis for infection in neutropenic pts
Fluoroquinolones

• Drug Interactions
  • Binding agents (antacids, calcium, didanosine, iron, sucralfate, zinc) decrease absorption
  • Warfarin effect slightly increased (bleeding)
  • Ciprofloxacin:
    • Strong CYP 1A2 inhibitor: Additional interactions with theophylline, tizanidine, clozapine, olanzapine

• Common Side Effects
  • 3%-7% GI (nausea, diarrhea, constipation)
  • 6% headache
Fluoroquinolone

• Treat infection of respiratory, GI, and Urinary source
• Adverse effect
  • GI and CNS effect
  • Musculoskeletal and Cardiovascular

• So..... Why are you “wasting” my time telling me Fluoroquinolone....
  • Fluroquinolone may be indicated after you culture orofacial infection site
Metronidazole

- Metronidazole
  - Synthetic nitroimidazole antibiotic derived from azomycin
  - Effective against
    - Protozoa, and **anaerobes**
Metronidazole

• Mechanism of Action
  • Ultimately inhibits DNA synthesis
    • Enters bacteria or protozoan and is activated by reduction of the nitro group. Activated intermediates bind DNA and inhibit its synthesis
  • Metronidazole displays concentration-dependent bactericidal activity
Metronidazole

• Effective against clinically **anaerobes**
• Ineffective against all aerobic bacteria
• Treatment:
  • Sinusitis, anaerobic odontogenic infection, Pseudomembranous colitis
    • Odontogenic infection
      • Metronidazole (Flagyl) 500mg p.o. q.i.d. X 7~10 days
    • Pseudomembranous colitis
      • 500mg p.o. t.i.d X 10 days

• Caution:
  • Don’t take alcohol with metronidazole
    • Disulfuram-like reaction → nausea, vomiting, headache
Metronidazole
Adverse Effects

- **Gastrointestinal**
  - Nausea, vomiting, stomatitis, metallic taste

- **CNS – most serious**
  - Peripheral neuropathy, seizures, encephalopathy
  - Use with caution in patients with preexisting CNS disorders
  - Requires discontinuation of metronidazole

- **FDA Pregnancy category B**
  - Mutagenicity, carcinogenicity
    - Avoid during pregnancy and breastfeeding
Metronidazole
Drug Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin*</td>
<td>↑ anticoagulant effect</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>↑ phenytoin concentrations</td>
</tr>
<tr>
<td>Lithium</td>
<td>↑ lithium concentrations</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>↓ metronidazole concentrations</td>
</tr>
<tr>
<td>Rifampin</td>
<td>↓ metronidazole concentrations</td>
</tr>
</tbody>
</table>
Risk Factors / Adverse Effects
Antibiotic Resistance

How Antibiotic Resistance Happens

1. Lots of germs. A few are drug resistant.
2. Antibiotics kill bacteria causing the illness, as well as good bacteria protecting the body from infection.
3. The drug-resistant bacteria are now allowed to grow and take over.
4. Some bacteria give their drug-resistance to other bacteria, causing more problems.

http://www.cdc.gov/drugresistance/about.html
Antibiotic Resistance

• 30-65% of antibiotics prescribed in a hospital are found to be inappropriate

• Due to the widespread use of antibiotics, as well as the ability of the bacteria to acquire and spread resistance
Clostridium Difficile (C. Difficile)

• Gm+ bacteria that causes mild diarrhea to inflammation of colon

• Sign/ Symptom
  • Significant diarrhea
    • New onset of more than 3 partially formed or watery stool per 24 hours period
  • Recent antibiotic exposure
  • Abdominal pain
  • Fever
  • Distinctive foul stool odor

• Risk Factors
  • Antibiotics / Healthcare environment / Acid suppression medication
Clostridium Difficile (C. Difficile)

- Antibiotic associated
  - Fluoroquinolone
  - Cephalosporin
  - Carbapenem
  - Clindamycin

- What happened?
  - Disrupt normal intestinal flora
  - Overgrowth of C.Difficile

- Treatment
  - Metronidazole
    - 500mg p.o. t.i.d X 10 days
  - Vancomycin (pregnant women)
    - 125mg p.o. q.i.d X 10 days (maximum dose)
  - Probiotics
  - Fecal Bacteriotherapy
  - Colectomy
Considerations regarding treating Infection
Nature Of Infection

• Localized, slow progressing

• Diffuse cellulitis, progressing rapidly
Status Of Host Defenses

• Cancer chemotherapy
• Immunosuppression
• Severe Metabolic disease
• Myeloproliferative disease

• Use bactericidal drug in compromised patient
Duration Of Therapy

• Need 24 hours to get initial response
• Need 48-72 hours to see resolution of symptoms
• Want to continue therapy 48-72 hours after patient is asymptomatic
• Severe infection or lowered host resistance may require longer treatment
Odontogenic Infections

• When selecting abx and treating infection, remember

• Oral bugs consist of
  • Mixed  (70%)
  • Anaerobic (25%)
  • Aerobic  (5%)

• Infection Progress with regard to bacteria behavior
  • Cellulitis - Aerobic
  • Chronic Abscess - Anaerobic
Indications for Culture

• Treatment for three days without improvement
• Post-operative wound infection
• Recurrent infection
• Actinomyces is suspected
  • Evidence of sulfur granule
• Osteomyelitis is present
Choosing an antibiotic

• Host Factors
  • Severity of Infection
  • Co-morbidities and concomitant medications
  • Patient Allergies
  • Age

• Historical susceptibilities of organisms

• Cost

• Pharmacologic Factors
  • Half-life/duration of action
  • Penetration into tissue
  • Route of Elimination
  • Side Effects
  • Drug Interactions
  • Dosage Form
  • Spectrum of Action
## Cost of Oral Antibiotics

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Cost q wk</th>
<th>Pen V cost Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin V 500 qid</td>
<td>$10</td>
<td>1.0</td>
</tr>
<tr>
<td>Amoxicillin 500 tid</td>
<td>$4</td>
<td>0.4</td>
</tr>
<tr>
<td>Augmentin 875mg bid</td>
<td>$30</td>
<td>3</td>
</tr>
<tr>
<td>Ceftin 500 tid</td>
<td>$70</td>
<td>7</td>
</tr>
<tr>
<td>Clindamycin 300 qid</td>
<td>$15</td>
<td>1.5</td>
</tr>
<tr>
<td>Metronidazole 500 qid</td>
<td>$10</td>
<td>1</td>
</tr>
<tr>
<td>Moxifloxasin 400 qd</td>
<td>$80</td>
<td>8</td>
</tr>
<tr>
<td>Linezolid 600 bid (Zyvox)</td>
<td>$103.61 (generic)</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>$1036.55 (Brand-name)</td>
<td>103</td>
</tr>
</tbody>
</table>
Empiric ABX of choice

• No Allergies:
  • Penicillin
  • Clindamycin
  • Penicillin + Metronidazole
  • Clarithromycin / Azithromycin

• Penicillin Allergy:
  • Clindamycin
  • Clarithromycin / Azithromycin
Patient Education

• Administration of antibiotic
  • With food
    • Amox/Clav, Cefpodoxime, Clarithromycin
  • Without food
    • Pen VK, Dicloxacillin, Cefaclor, Tetracycline, Erythromycin
  • With full glass of water
    • Tetracyclines, Sulfonamides
  • 2 hours apart from milk/vitamins
    • Erythromycin, Quinolones, Tetracyclines

Gilbert DN, Moellering RC, Eliopoulos GM, et. al.
Common Errors in Antibiotic Therapy

• Viral infections can’t be treated with antibiotics.

• Ineffective levels are administered.

• A drug with no established specific effectiveness is prescribed.

• The infecting agent is not documented.
Common Errors in Antibiotic Therapy

• Abx therapy is changed to rapidly and incorrectly, assuming therapeutic failure prior to correcting all contributing factors.

• Cultures are not taken and susceptibility tests are not obtained

• Patients progress is not monitored

• Expensive drugs are prescribed when effective inexpensive agents would suffice
Antibiotic Premedication before Dental Procedures
Procedures with Bacteremic Dental Risk

• High Risk:
  • Intra-ligamentary and intra-osseous local anesthetics
  • Dental extractions
  • Periodontal procedures and / or prophylactic clear anticipated
Procedures with Bacteremic Dental Risk

• **High Risk:**
  
  • Endodontic instrumentation or surgery only beyond the apex
  
  • Dental implant placement and reimplantation of avulsed teeth
  
  • Initial placement of orthodontic bands but not brackets
Antibiotic Prophylaxis on Orthopaedic Implant Patient

• 2003 (AAOS/ADA) *advisory statement*
  • “The risk/benefit and cost/effectiveness ratios **fail to justify** the administration of routine ABX prophylaxis”

• 2009 AAOS *information statement*
  • Recommend **consider** ABX prophylaxis for **ALL** total joint patient for any possible procedure that may cause bacteremia
    • *Based on opinion of the authors*

• 2012 (AAOS/ADA) *Clinical Practice Guideline*

• 2014 ADA *Updated systematic review*
Antibiotic Prophylaxis on Orthopaedic Implant Patient

• 2012 (AAOS/ADA) **Clinical Practice Guideline (CPG)**
  • Discontinue routine ABX for prosthetic joint implant patient
    • Recommendation: Limited
    • *Patient preference should have substantial influence*

• Recommend for or against use of ABX for prosthetic joint implant patient undergoing dental procedure
  • Recommendation: Inconclusive/ lack of evidence
  • *Patient preference should have substantial influence*

• Patient with prosthetic joint implant maintain appropriate oral hygiene
  • Recommendation: Consensus
  • *Expert opinion supports the guideline recommendation*
Antibiotic Prophylaxis on Orthopaedic Implant Patient

• 2014 ADA Council on Scientific Affairs

• Prophylactic antibiotics prior to dental procedure are *NOT RECOMMENDED* for patients with prosthetic joint implants
Management of patients with prosthetic joints undergoing dental procedures

Clinical Recommendation:
In general, for patients with prosthetic joint implants, prophylactic antibiotics are not recommended prior to dental procedures to prevent prosthetic joint infection.

For patients with a history of complications associated with their joint replacement surgery who are undergoing dental procedures that include gingival manipulation or mucosal incision, prophylactic antibiotics should only be considered after consultation with the patient and orthopedic surgeon.* To assess a patient’s medical status, a complete health history is always recommended when making final decisions regarding the need for antibiotic prophylaxis.

Clinical Reasoning for the Recommendation:
- There is evidence that dental procedures are not associated with prosthetic joint implant infections.
- There is evidence that antibiotics provided before oral care do not prevent prosthetic joint implant infections.
- There are potential harms of antibiotics including risk for anaphylaxis, antibiotic resistance, and opportunistic infections like *Clostridium difficile*.
- The benefits of antibiotic prophylaxis may not exceed the harms for most patients.
- The individual patient’s circumstances and preferences should be considered when deciding whether to prescribe prophylactic antibiotics prior to dental procedures.

* In cases where antibiotics are deemed necessary, it is most appropriate that the orthopedic surgeon recommend the appropriate antibiotic regimen and when reasonable write the prescription.


Copyright © 2019 American Dental Association. All rights reserved. This page may be used, copied, and distributed for non-commercial purposes without obtaining prior approval from the ADA. Any other use, copying, or distribution, whether in printed or electronic format, is strictly prohibited without the prior written consent of the ADA.

ADA Center for Evidence-Based Dentistry™
Prophylaxis Recommendations: Infective Endocarditis (IE)

- Artificial Heart Valves
- History of infective endocarditis
- Certain congenital heart disease
  - Not properly treated cyanotic congenital heart disease
  - Prosthetic heart device related
    - < 6 months prosthetic device usage
    - Residual defect at/or near prosthetic device
- Cardiac transplant develops heart valve problem

AHA with input from ADA 2008 Recommendations
Prophylaxis Recommendations:
Infective Endocarditis (IE)

• Patients took prophylactic abx but
  **NO LONGER** needed includes:
  • Mitral Valve Prolapse
  • Rheumatic Heart Disease
  • Bicuspid Valve Disease
  • Calcified Aortic Stenosis
  • Congenital Heart Conditions
    • Ventricular Septal Defect, Atrial Septal Defect and
    • Hypertrophic Cardiomyopathy

AHA with input from ADA 2008 Recommendations
### Regimens for a dental procedure.

<table>
<thead>
<tr>
<th>SITUATION</th>
<th>AGENT</th>
<th>REGIMEN: SINGLE DOSE 30-60 MINUTES BEFORE PROCEDURE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Adults</td>
</tr>
<tr>
<td>Oral</td>
<td>Amoxicillin</td>
<td>2 grams</td>
</tr>
<tr>
<td></td>
<td></td>
<td>per kilogram</td>
</tr>
<tr>
<td>Unable to Take Oral Medication</td>
<td>Ampicillin OR Cefazolin or ceftriaxone</td>
<td>2 g IM* or IV†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 g IM or IV</td>
</tr>
<tr>
<td>Allergic to Penicillins or Ampicillin Oral</td>
<td>Cephalexin OR Clindamycin OR Azithromycin or clarithromycin</td>
<td>2 g</td>
</tr>
<tr>
<td></td>
<td></td>
<td>600 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>500 mg</td>
</tr>
<tr>
<td>Allergic to Penicillins or Ampicillin and Unable to Take Oral Medication</td>
<td>Cefazolin or ceftriaxone OR Clindamycin</td>
<td>1 g IM or IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>600 mg IM or IV</td>
</tr>
</tbody>
</table>

* IM: Intramuscular.
† IV: Intravenous.
‡ Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage.
§ Cephalosporins should not be used in a person with a history of anaphylaxis, angioedema or urticaria with penicillins or ampicillin.
We concluded that bacteremia resulting from daily activities is much more likely to cause infective endocarditis (IE) than bacteremia associated with a dental procedure.

We concluded that only an extremely small number of cases of IE might be prevented by antibiotic prophylaxis even if prophylaxis is 100 percent effective.

Antibiotic prophylaxis is not recommended based solely on an increased lifetime risk of acquisition of IE.

Limit recommendations for IE prophylaxis only to those conditions listed in Box 3.

Antibiotic prophylaxis is no longer recommended for any other form of congenital heart disease, except for the conditions listed in Box 3.

Antibiotic prophylaxis is reasonable for all dental procedures that involve manipulation of gingival tissues or periapical region of teeth or perforation of oral mucosa only for patients with underlying cardiac conditions associated with the highest risk of adverse outcome from IE (Box 3).

Antibiotic prophylaxis is reasonable for procedures on respiratory tract or infected skin, skin structures or musculoskeletal tissue only for patients with underlying cardiac conditions associated with the highest risk of adverse outcome from IE (Box 3).

Antibiotic prophylaxis solely to prevent IE is not recommended for gastrointestinal or genitourinary tract procedures.

Although these guidelines recommend changes in indications for IE prophylaxis with regard to selected dental procedures (see text), the writing group reaffirms that those medical procedures listed as not requiring IE prophylaxis in the 1997 statement remain unchanged and extends this view to vaginal delivery, hysterectomy, and tattooing. Additionally, the writing group advises against body piercing for patients with conditions listed in Box 3 because of the possibility of bacteremia, while recognizing that there are minimal published data regarding the risk of bacteremia or endocarditis associated with body piercing.
Infective Endocarditis Antibiotic Prophylaxis

• Additional Considerations

  • **Patient forget to premedicate!**

  “If the dosage of antibiotic is inadvertently no administered before the procedure, the dosage may be administered up to **two hours** after the procedure”

  • **Already taking antibiotic for another condition....**

  “Dentist select an antibiotic from a different class than the one the patient is already taking”
Downtown Augusta Savannah River Front
Post-Operative Analgesics
Pharmacy Law

• Medical use of drugs are affected by
  • Federal Trade Commission (FTC)
  • Food and Drug Administration (FDA)
  • Drug Enforcement Administration (DEA)
  • Individual states
Pharmacy Law

• FDA
  • If not approved, cannot be used in USA
  • Drug approved @ other country if FDA did not approve it → cannot use

• FDA + FTC
  • FDA approved drug + No physiological + psychological abuse potential
    • Rx drug
    • OTC drugs

• FDA + FTC + DEA
  • FDA approved drug + physiological & psychological abuse potential

• You are responsible for everything related to drugs

  Example:

  An office employee who lacks a license to prescribe drugs should never advise your patients to take any medication, including aspirin, acetaminophen, or even mouthwash without your knowledge and specific approval. You are legally responsible for any such advice given by your employees.
**FDA Pregnancy Categories**

- **Category A**
  - Without demonstrated risk

- **Category B**
  - Without risk with animal studies but no adequate well-controlled studies with human

- **Category C**
  - Adverse effect with animal studies and no human studies, but potential benefits may warrant use of Rx despite of risk

- **Category D**
  - Positive evidence of human fetal risk but potential benefits may warrant use of Rx despite potential risk

- **Category X**
  - Animal and humans have demonstrated fetal abnormalities and/or positive risk, Risk outweigh potential benefit.

Content and Format of Labeling for human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling (Federal Register/ Vol.73, No.104/Thursday, May 29,2008)
Pharmacy Law

• 5 Schedules based on abuse potential
  • 1) Schedule I
    • High abuse potential
    • No accepted medical use in USA
    • Simply **CANNOT** prescribe
    • Example: Heroin, LSD, Marijuana
  • 2) Schedule II
    • High abuse potential
    • Severe psychic /physical abuse liability
    • **Require WRITTEN Rx,** can be faxed & **NO REFILL**
    • Example: Oxycodone, Morphine, Fentanyl, Hydrocodone (along), Meperidine (Demerol)
  • 3) Schedule III
    • **Significant** abuse potential
    • Written Rx not required
    • Refill up to 5 times
    • Example: Hydrocodone combo (Vicodin, Norco), Codeine + Acetaminophen (Tylenol #3)
  • 4) Schedule IV
    • **Lower** abuse liability
    • Written Rx not required
    • 5 refills within 6 months
    • Example: Phenobarbital, Diazepam (Valium), Propofol (under proposal, Oct 2010), Tramadol (Ultram)
  • 5) Schedule V
    • **Very** low abuse potential
    • Written Rx not required
    • 5 refills within 6 months
    • Example: Robitussin

Analgesic Agents for Post-Operative Pain

- 3 major groups
  - 1) Non-opioid
  - 2) Opioid
  - 3) Combination (1+2)

- Non-opioids works at
  - Peripheral source of pain

- Opioid works at
  - Central nervous system
Non-Opioid Analgesics

• Used for most operative dental Pain

• Mechanism of action
  • Prostaglandin-mediated
  • Prevent sensitizing peripheral pain receptor
    • ↓ Action Potential impulse generating
    • “Insulate” peripheral pain receptor

• Other peripheral effect
  • Peripherally
    • Anti-inflammatory
    • Anti-rheumatic
  • Centrally
    • Antipyretic
Non-Opioid Analgesics

- Undesirable effects
  - Serious allergic reaction (Aspirin)
  - Gastrointestinal irritating, bleeding
  - ↑blood clotting time
  - Hepatic toxicity
  - Significant drug interaction

- Non-opioid analgesics
  - Non-steroidal anti-inflammatory drugs (NSAID)
    - Anti-inflammatory & anti-rheumatoid
    - Aspirin, Diflunisal, Ibuprofen
  - Antipyretic analgesics
    - Weak analgesic & antipyretic
    - **NOT anti-inflammatory agent!!!**
    - Acetaminophen
Control of Postoperative Sequelae

Pain and Discomfort

• Ibuprofen

  • Effective medication for post extraction pain management
  • Disadvantage
    • ↓ Platelet aggregation
    • ↑ bleeding time
      • not clinically important effect on normal patient
  • Maximum dose: 3200mg/day
Control of Postoperative Sequelae
Pain and Discomfort

• Acetaminophen
• Does NOT interfere
  • Post op bleeding
  • Platelet function
• Useful on patient with platelet defect
• Maximum dose: 4000 mg/day
Opioid Analgesics

- Morphine is the “gold standard” of all opioid analgesics
  - From opium
  - Name after Morpheus
    - Greek god of dreams
- Mechanism of action
  - Act on CNS, opioid receptor
    - \( \Delta \) perception of pain
    - \( \Delta \) emotional response
Opioid Analgesics

- All Opioid can elicit the following effects
  - 1) Psychological / physiological dependence
  - 2) Induce narcosis
    - Combination of analgesia, mood alteration, drowsiness, mental clouding
  - 3) ↓psychomotor skills
    - Not driving, using power tools
  - 4) Serious respiratory depression & Death
Combination of Opioid + Non-Opioid Analgesics

• Why Combo works well?
  • Peripheral acting med
    • ↓ # nerve impulses from surgery site
  •Centrally acting med
    • ↑ ability to disregard pain impulses coming to CNS

• Typical Peripheral med
  • Aspirin & Acetaminophen
Individual Non-Opioid Analgesics

- **Ibuprofen**
  - First Propionic acid derivative NSAID in USA from 70s
  - Antiarthritic, anti-inflammatory, & antipyretic
  - Adverse reaction
    - Nausea & vomiting
  - Mild to moderate pain
    - Example: Loading dose @800mg 1 hr prior surgery, 400mg post-op q4h (or higher time interval)
  - Other info
    - Take Ibuprofen with food or milk
      - ↓ GI problem
    - Drowsiness/blurred vision possible
    - ETOH will potentiate drowsiness
Individual Non-Opioid Analgesics

- Acetaminophen
  - No anti-inflammatory
  - Not cause GI bleeding, not effect platelet aggregation function
- Adverse reaction
  - Renal injury, hepatic necrosis & death
- Other info
  - Watch out for maximum dosage
Specific Opioid Analgesics

• Hydrocodone (Vicodin, Lortab)
  • Codeine congener
  • Moderate / severe pain

• Usual dosage
  • Adult
    • Hydrocodone 5mg + Acetaminophen 325mg
    • Take one cap p.o. q4-6h prn pain
  • Pediatric
    • Not recommended
Specific Opioid Analgesics

- **Oxycodone (Percocet)**
  - Semi-synthetic narcotic
  - Moderate / severe pain
  - ↑ analgesic potential than codeine
  - ↑ dependence liability

- **Usual dosage**
  - Adult
    - Oxycodone 5mg + Acetaminophen 325mg
    - Take one cap p.o. q4-6h prn pain
  - Pediatric
    - Not recommended for <6 y/o

---

<table>
<thead>
<tr>
<th></th>
<th>Oxycodone</th>
<th>Acetaminophen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percocet (5.0/7.5/10) /325</td>
<td>5.0mg/7.5mg/10mg</td>
<td>325mg</td>
</tr>
</tbody>
</table>
Guidelines for Analgesic Use

- Everyone is different on post-surgical perception
- Prescribe only enough analgesics to last for 2 days
  - If need more, examine the patient before doing so
- Analgesic Shifting technique
  - Example: for Severe pain
    - Mixture of opioid + non-opioid for first day or two
    - Gradually move to Non-opioid only

<table>
<thead>
<tr>
<th>Pain Level</th>
<th>Dental Procedure</th>
<th>Typical Analgesic used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Single, uncomplicated extraction</td>
<td>Weak analgesics: ASA, Acetaminophen, Ibuprofen</td>
</tr>
<tr>
<td>Moderate</td>
<td>Single extraction with flap reflection &amp; minor bone removal. Multiple extractions</td>
<td>Moderate analgesics: Ibuprofen 400mg Vidodin</td>
</tr>
<tr>
<td>Moderate / Severe</td>
<td>Extraction of impacted teeth with large flap and extensive bone removal and more</td>
<td>Strong Analgesics: Ibuprofen 800mg Percocet</td>
</tr>
</tbody>
</table>
Thank you everyone!

The only munitions factory remaining at the end of the American civil war