Antibiotics and Infectious Disease in Otolaryngology-HNS

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Antibiotics

- Penicillins
- Cephalosporins
- Macrolides
- “Other” antibiotics
- Aminoglycosides
- Sulfonamides
- Flouroquinolones

Dr. Princy Kumar
Penicillins

- Fermentation products of Penicillium mold
  - B-lactam nucleus attached to thiazolidine ring
  - Changing the ring changes spectrum and resistance

- Mechanism of action
  - Interferes with final step of cell wall synthesis
  - Static or -cidal depending on bacterial enzymatic regulatory system (deregulated by penicillin)

- Clinical Pharmacology
  - Eliminated via kidney, almost unchanged--Probenecid
  - Stomach acid destroys most penicillins
  - Wider uptake with inflammation (CSF, Middle ear, etc)
Antistaphylococcal Penicillins

- Methicillin, Oxacillin, Cloxacillin, Dicloxacillin, Nafcillin
- Used for penicillin-resistant Staph infections.
- Dicloxacillin achieves the highest serum levels. All should be given in fasting state.
- Less efficacy than natural penicillins for PCN-sensitive microbes.
Amino-Penicillins

- Ampicillin, Amoxicillin, Bacampicillin
  - More rash (especially with Mono)
  - H. influenzae showing 5-55% resistance

- Spectrum
  - Strept., pneumococci (except highly-resistant), H. influenzae, Proteus, many E. Coli.
  - Inactivated by B-lactamases (including penicillinase) therefore less effective against Staph.
  - Ampicillin destroyed by acid, Amoxicillin and Becampicillin may be taken at mealtime—serum and middle ear levels higher than with Ampicillin.
Augmented Penicillins

- Amoxicillin + clavulanate, Ampicillin + sulbactam, Ticarcillin + clavulanate, Piperacillin + tazobactam
- Clavulanic acid irreversibly binds B-lactamase enzyme
- No change in effectiveness for pneumococci
Antipseudomonas Penicillins

- Ticarcillin, Mezlocillin, Piperacillin
- Less active than the amino-penicillins against gram positives
- Inactivated by B-lactamases therefore no advantage over other penicillins for nonpseudomonal infection.
- Synergistic against P. aeruginosa when combined with aminoglycosides (should always treat with two agents)
Penicillins

Toxicity:

- Rash (5%)—can be treated with antihistamines, but drug usually stopped. Recurs in only 50% with repeated exposure. PCN/Mono rash does not preclude future use. Only 5% cross reactive with Cephalosporins.

- Anaphylaxis (1/10,000)—more often with IV doses. Can desensitize. Do not use any B-lactam antibiotic (may use Azobactam).

- GI, Salt load, Platelet dysfunction (ticar)
Penicillins

**Resistance:**
- Intrinsic resistance (inability to bind or penetrate)
- β-lactamases & penicillinases hydrolyse β-lactam ring
  - H. influenza, M. catarrhalis, S. aureus, many anaerobes, gram negative organisms
- Either plasmid or chromosomally mediated
- S. aureus releases penicillinase into milieu destroying drug before contact with cell (doesn’t inactivate semisynthetic (oxacillin) or cephalosporins)
- S. pneumo resistance is entirely different – mediated by alterations in binding sites — moderate resistant strains still sensitive to higher doses.
Cephalosporins

- Semisynthetic β-lactam derived from Cephalosporium acremonium
- Mechanism: Same mechanism as PCN
- Resistance: Mediated by β-lactamase enzymes
- Clinical pharmacology: Wide distribution, but poor CSF penetration even with inflammation.
- Metabolism: Liver, Probenecid useful to increase levels.
- “Generations” groups according to spectrum
First Generation

- Cefadroxil (Duricef), Cefazolin (Ancef), Cephalexin (Keflex)
- Spectrum: Most gram positive cocci (GAS, S. pneumo, S. aureus (except MRSA—resistant to all cephalosporins), E. coli, Proteus, Klebsiella. Does not cover P. aeruginosa or H. influ.
- Use: S. aureus infection, surgical prophylaxis
Second Generation

- Cefuroxime (Ceftin/Zinacef) -- effective against common OM/sinusitis bacteria, including amp-resistant H. influ, good CSF penetration, active against intermediate-resistant S. pneumo
- 2\textsuperscript{nd} generation equivalents—Defpodoxime (Vantin), Defdinir (Omnicef) activity equal to Ceftin—used as alternative to Augmentin
- Spectrum: more gram negative coverage, valuable in treatment of H. influ. Not as effective against S. aureus as 1\textsuperscript{st} gen.
Third Generation

- Spectrum: gram negative > gram positive. Good for identified B-lactimase + H. influ., or M. cat., N. Gonorrhoeae, N. meningitidis

- Ceftriaxone (Rocephin), Cefotaxime (Claforan) effective against S. pneumo (even intermediate and high resistance), H. influ, N. mening. Used for high-level, multi-drug resistant pneumococcal infections with Vancomycin. Single dose IM can be effective for OM.

- Ceftazidime (Fortaz) has best effectiveness against Pseudo. of all B-lactams (alternative to Gent)
Cephalosporin toxicities

- Broad coverage leads to yeast/ fungus/ opportunistic bacterial overgrowth (candidiasis, C. diff)
- Diarrhea with 2\textsuperscript{nd} and 3\textsuperscript{rd} generation
Carbapenems

- Imipenem-Cilastin (Primaxin), Meropenem (Merrem)
- Broad spectrum. Do not cover MRSA, C. difficile
- Toxicities: persons allergic to PCN can react to these drugs. Seizures noted in Imipenem studies
Macrolides

- Produced by *Streptomyces erythreus* (erythromycin is natural product)
- Mechanism: bind to 50s subunit of bacterial ribosomes and block protein synthesis
- Resistance: target site alteration, antibiotic alteration, altered transfer
- Distribution: good penetration into oropharyngeal secretions.
Macrolides

- Spectrum: effective against atypicals (Chlamydia, Mycoplasma), Staph.(MRSA is resistant), Strep., Bordetella pertussis, H. influ, M. catarrhalis.
- ENT indications: Failed treatment of GAS in pharyngitis, resistant S. pneumo, H. influ., and M. catarrhalis in AOM (Bactrim/ Clarithromycin/ Azythromycin), Sinusitis (Clarithromycin equal to Augmentin, Azythromycin 500mg qDx3d =Augmentin x10 days)
- Toxicity: generally considered safe—side effects are rare. Ototoxicity (dose-dependant, peak)
Clindamycin

- Derived from *Streptomyces lincolnensis*
- Mechanism: Inhibits protein synthesis by binding to the 50s ribosome.
- Distribution: Poor CSF penetration, but excellent bone, oropharyngeal secretion levels.
- Spectrum: gram +, anaerobes. No activity against gram -.
- Resistance is mediated via decreased membrane permeability and alteration of 50s binding site.
- Toxicity: nausea/vomiting, C. difficile colitis
Vancomycin

- Glucopptide produced by *Streptomyces orientalis*
- Mechanism: bacteriocidal via inhibition of cell wall replication
- PO dosing has no systemic uptake
- Spectrum: gram +, MRSA. Vanc + Gent shows synergy against mixed infections.
- Toxicity: red man syndrome, phlebitis
- ENT uses: MRSA, severe infections with resistant gram + organisms
Metronidazole

- Bacteriocidal via production of DNA toxic substances within the cell
- Distribution: nearly all tissues, including CSF, saliva, bone, abscesses.
- IV=PO
- Spectrum: active vs. anaerobes, parasites
- ENT uses: C. difficile, anaerobic infections (abscesses)
- Toxicity: disulfram reaction, others are rare
Aminoglycosides

- Produced by Streptomyces and Micromonospora

Mechanism
- Bind to ribosomes and interfere with protein synthesis
- Bacteriocidal

Clinical pharmacology
- PO poor absorption; IM or IV best
- Distribution: hydrophilic, poor CSF, cross placenta

Metabolism
- Excreted unchanged, special dosing for renal failure
Aminoglycosides

- **Spectrum**
  - Gram-negative bacilli, P. aeruginosa (use with anti-pseudomonas penicillins)

- **Resistance**
  - Antibiotic modifying agents cause antibiotics to be unable to bind to the ribosome

- **Toxicity**
  - Nephrotoxic (trough)
  - Ototoxic (concentrated in perilymph, corresponds with prolonged therapy and peak levels)
  - Neuromuscular blockade (think of this in Myasthenia Gravis)
Sulfonamides

- Spectrum includes H. influenzae, M. catarrhalis. Generally not effective vs. other microbes.
- Mechanism: acts on protein synthesis chain
- Combined with erythromycin (Pediozole) it is as effective as ampicillin in treating AOM.
- Sulfonamide + Trimethoprim (Bactrim) is alternate 1st line agent for AOM. Both drugs act on protein chain—synergistic. Effective vs. beta-lactamase producing bacteria.
- Sulfa allergies can result in life-threatening TEN.
Flouroquinolones

- Derivative of previous earlier antibiotic (nalidixic acid)
- Mechanism of action: Inhibits DNA gyrase (bacteriocidal)
- Resistance is mediated by gyrase mutations and efflux mechanisms (drug permeation)
Flouroquinolones

Spectrum: Broad coverage. Effective vs. gram +, gram -, atypicals, and Pseudomonas.

- Respiratory quinolones (levofloxacin): active vs. GAS, S. pneumo (including penicillin-resistant forms), S. aureus (including MRSA), H. influ., and M. catarrhalis (including penicillin-resistant strains).
- Antipseudomonas quinolones (ciprofloxacin): effective vs. Pseudomonas and gram-negative bacteria.
- New floxins (Gati, Moxi, Gemi): similar to respiratory quinolones but less activity vs. Pseudomonas and addition of anaerobic activity.
Flouroquinolones

- Bioavailability: IV = PO. Once/day dosing. Wide distribution (CSF, saliva, bone, cartilage).
- Toxicities: drug interactions (cations), tendon toxicity, ?bone growth impairment. Ototopicals show no ototoxicity
- Gatifloxacin $2 cheaper/pill (retail) than Levo.
Flouroquinolones

- ENT uses: Necrotizing OE, Auricular perichondritis (or in procedures involving cartilage), Chronic ear disease, Sinusitis, Pharyngotonsillitis.
Infectious Disease

- Rhinitis/Sinusitis
- Pharyngitis/Tonsillitis
- Otitis Media
- Surgical wound infections
- Neck abscess
- Salivary gland infections
Rhinosinusitis

- Inflammation/infection of nasal and sinus tissues felt to be caused by stasis of secretions and superinfection often secondary to disease of the osteomeatal complex.

- Treatment recommendations (Acute):
  - 1\textsuperscript{st} line—amoxicillin/bactrim X10days
  - 2\textsuperscript{nd} line—augmentin, clarithromycin/azythromycin, cefuroxime, pediazole
  - Irrigation, Nasal steroids, Decongestants
  - Study looking at impact of 1\textsuperscript{st} line vs. 2\textsuperscript{nd} line showed the only difference in the two treatment groups was expense of therapy ($69 vs. $135).
Chronic Rhinosinusitis

- **Etiology**
  - Mixture of anaerobes and gram +, but is variable

- **Treatment**
  - Conflicting evidence on efficacy of antibiotic therapy
  - Clindamycin vs. Augmentin
  - Prolonged period (3-6 weeks) shown more effective than 10-14 day course
  - Nasal steroids with antibiotics most effective
  - Surgery
Polyposis/Fungal Sinusitis

- Polyposis: Cipro (polyps often seen with P. aeruginosa infections)
- Fungal: Itraconazole, Ampho B?
Recurrent Sinusitis after FESS

- **Organisms**
  - Gm + cocci—37.9% (normal incidence of resistant organisms)
  - Gm – rods—14.8% (90% of these in patients with h/o recurrent infxn) 7.2% P. aeruginosa (12% resistant to Cipro)
  - Fungal—1.7%, Sterile—30%

- **Treatment**
  - Culture-directed
  - Topical antibiotics
  - Irrigations
Recurrent Sinusitis after FESS

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  - Topical antibiotics
  - Irrigations
Pharyngitis

- Multiple etiologies
  - Streptococcal pharyngitis (GAS)
    - Most common bacterial cause (15-30% in children, 5-10% in adults)
    - Tonsillopharyngeal exudate + anterior cervical lymphadenitis
  - Diphtheria, other bacteria
  - Viral
    - Infectious mononucleosis
      - Epstein-Barr virus - 15-24 yo
      - Prodrome, then sore throat + high fever + lan
      - Splenomegaly (50%) - NO amoxicillin
## Causes of Pharyngitis

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Syndrome or Disease</th>
<th>Estimated Percentage of Cases†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viral</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinovirus (100 types and 1 subtype)</td>
<td>Common cold</td>
<td>20</td>
</tr>
<tr>
<td>Coronavirus (3 or more types)</td>
<td>Common cold</td>
<td>≥5</td>
</tr>
<tr>
<td>Adenovirus (types 3, 4, 7, 14, and 21)</td>
<td>Pharyngoconjunctival fever, acute respiratory disease</td>
<td>5</td>
</tr>
<tr>
<td>Herpes simplex virus (types 1 and 2)</td>
<td>Gingivitis, stomatitis, pharyngitis</td>
<td>4</td>
</tr>
<tr>
<td>Parainfluenza virus (types 1–4)</td>
<td>Common cold, croup</td>
<td>2</td>
</tr>
<tr>
<td>Influenzavirus (types A and B)</td>
<td>Influenza</td>
<td>2</td>
</tr>
<tr>
<td>Coxsackievirus A (types 2, 4–6, 8, and 10)</td>
<td>Herpangina</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Epstein–Barr virus</td>
<td>Infectious mononucleosis</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Infectious mononucleosis</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Human immunodeficiency virus type 1</td>
<td>Primary human immunodeficiency virus infection</td>
<td>&lt;1</td>
</tr>
<tr>
<td><strong>Bacterial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em> (group A β-hemolytic streptococci)</td>
<td>Pharyngitis and tonsillitis, scarlet fever</td>
<td>15–30</td>
</tr>
<tr>
<td>Group C β-hemolytic streptococci</td>
<td>Pharyngitis and tonsillitis</td>
<td>5</td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td>Pharyngitis</td>
<td>&lt;1</td>
</tr>
<tr>
<td><em>Corynebacterium diphtheriae</em></td>
<td>Diphtheria</td>
<td>&lt;1</td>
</tr>
<tr>
<td><em>Arcanobacterium haemolyticum</em></td>
<td>Pharyngitis, scarlatiniform rash</td>
<td>&lt;1</td>
</tr>
<tr>
<td><strong>Chlamydial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Chlamydia pneumoniae</em></td>
<td>Pneumonia, bronchitis, and pharyngitis</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Mycoplasmal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Mycoplasma pneumoniae</em></td>
<td>Pneumonia, bronchitis, and pharyngitis</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

*Adapted from Gwaltney and Bisno² with the permission of the publisher. The list is not exhaustive.†Estimates are of the percentage of cases of pharyngitis in persons of all ages that are due to the indicated organism.*
Pharyngitis

- Treatment
  - Traditionally 1\textsuperscript{st} line is penicillin or erythromycin X 10 days (still shown effective in patients >12 yo, or ill for >2 days).
  - Increasing incidence of treatment failure secondary to resistant organisms as well as compliance issues (taste/length of course) have some recommending 2\textsuperscript{nd} generation cephalosporins as first line.
    - Proliferation of enzymes by mixed infection prevents activity vs. GAS. (Cephalosporin not affected by penicillinase)
    - Normal flora decimated by penicillins, not by cephalosporins
Pharyngitis

- 2\textsuperscript{nd} line: Augmentin, Clindamycin (good abscess penetration, no rash, no beta-lactamase sensitivity), 2nd generation cephalosporin, Azithromycin—double dose (12mg/kg/day×5 days), IM Ceftriaxone X?days
- Timing of treatment: less recurrence, better response after 2-3 days; 9 days before carditis is a large risk
- No antibiotics at all?
Otitis Media

Microbiology

Treatment
- Amoxicillin/Bactrim
- 2\textsuperscript{nd} line/Areas of high resistance.
- Serious infections should be treated with Vancomycin (add cefotaxime or ceftriaxone if infected area has poor Vanco penetration)

**TABLE 2. Acute otitis media treatment recommendations for children who have not or have received antimicrobial therapy during the prior month**

<table>
<thead>
<tr>
<th>Antibiotics in Prior Month</th>
<th>Day 0 Cliniically Defined Treatment Failure on Day 3</th>
<th>Clinically Defined Treatment Failure on Days 10 to 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>High dose amoxicillin, usual dose amoxicillin</td>
<td>High dose amoxicillin/clavulanate; cefuroxime axetil; im ceftriaxone; clindamycin or tympanocentesis</td>
</tr>
<tr>
<td>Yes</td>
<td>High dose amoxicillin; high dose amoxicillin/clavulanate; cefuroxime axetil</td>
<td>High dose amoxicillin/clavulanate; cefuroxime axetil; im ceftriaxone; clindamycin or tympanocentesis</td>
</tr>
</tbody>
</table>

*Modified from Dowell et al., 1999.\textsuperscript{2}  \textsuperscript{†} Recommended drugs are those for which strong evidence of efficacy currently exists. Other drugs may also prove efficacious.  \textsuperscript{‡} High dose amoxicillin, 80 to 90 mg/kg/day. High dose amoxicillin/clavulanate, 80 to 90 mg/kg/day of the amoxicillin component, with 6.4 mg/kg/day of clavulanate (requires newer formulations, or combination with amoxicillin).  \textsuperscript{§} Documented efficacy in acute otitis media treatment failures if three daily doses are used.  \textsuperscript{¶} Clindamycin is not effective against *H*emophilus influenzae or *M*oraxella catarrhalis.*
Otitis Media

- **Resistance**
  - S. pneumo 5-61% resistant to penicillin
  - H. influenzae 5-55% resistance to ampicillin
  - M. catarrhalis >75% resistant to all penicillins
Suppurative Otitis

- Etiology (OE vs. Suppurative Otitis):
  - Chronic disease—P. aeruginosa (27%), S. aureus (24%)
  - Proteus, Fungal

- Treatment:
  - debridement + ototopicals
  - Antipseudomonas + S. aureus coverage (polymyxin (or gent) with neomycin, or cipro/ofloxacin if TM not intact)
  - Acetic acid (ototoxic), Boric acid, merthiolate, iodine, gentian violet (ototoxic) for aspergillus; Lotrimin (candidiasis)
Otitis Media-other issues

- Prophylaxis: decrease in MEE, AOM, OME without evidence of resistance. Theoretical risk of increased resistance
- Length of treatment
- Treatment of OME – PCR study.
Surgical Prophylaxis

Classification of Wounds
- Class I (thyroidectomy, otologic surgery)
- Class II (entry of aerodigestive tract)
- Class III (gross contamination, major head and neck surgery)
- Class IV (evidence of infection preop or preop exposure of tissues to contamination—trauma)

Prophylaxis:
- Incisions through skin -- Cephazolin
- Incisions through mucosa (anaerobic) – Clinda (+/- Gentamicin)
# Surgical Prophylaxis

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Antimicrobial Recommendation</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal surgery</td>
<td>None</td>
<td>Not needed if closed</td>
</tr>
<tr>
<td>Otology</td>
<td>None</td>
<td>Not needed for isolated anterior wall</td>
</tr>
<tr>
<td>Mandibular fracture</td>
<td>Cefazolin</td>
<td></td>
</tr>
<tr>
<td>Maxillary fracture</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Frontal sinus</td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td>Oral surgery</td>
<td>Penicillin or erythromycin</td>
<td></td>
</tr>
<tr>
<td>Orthognoptic surgery</td>
<td>None</td>
<td>Assume no contamination</td>
</tr>
<tr>
<td>Thyroidectomy</td>
<td>None</td>
<td>Perioperative administration</td>
</tr>
<tr>
<td>Salivary gland excision</td>
<td>None</td>
<td>Stop 24 hours after surgery</td>
</tr>
<tr>
<td>Radical neck dissection</td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td>Laryngectomy</td>
<td>Cefazolin</td>
<td></td>
</tr>
<tr>
<td>Major oral cavity</td>
<td>Moxalactam</td>
<td></td>
</tr>
<tr>
<td>Oropharyngeal resection</td>
<td>Clindamycin</td>
<td></td>
</tr>
<tr>
<td>Hypopharyngeal resection</td>
<td>Cefoperazone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cefotaxime</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ampicillin/sulbactam</td>
<td></td>
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<tr>
<td></td>
<td>Clindamycin/gentamicin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clindamycin/amikacin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ticarcillin/clavulanate</td>
<td></td>
</tr>
</tbody>
</table>
Surgical Wounds

- Prophylaxis not indicated for
  - Class I wounds
  - Uninfected sinonasal surgery

- Treatment timeline
  - No sooner than 2 hrs before surgery or 3 hrs after. Best if given one hour before skin incision and continued x24hrs or until period of contamination has passed.
Deep Neck Abscesses

- **Etiology**
  - Anaerobes, Staph., Strep., P. aeruginosa

- **Treatment**
  - Incision and drainage
  - Clindamycin + Gentamicin or Ceftazidime + Metronidazole
Acute Suppurative Sialadenitis

- Acute suppurative sialadenitis—anaerobic vs. Aerobic vs. mixed:
  - Parotid (41% vs. 34% vs. 25%)
  - Submandibular gland (33% vs. 44% vs. 22%)
  - Sublingual gland (33% vs. 33% vs. 33%)
  - S. aureus, H. influenzae (aerobes)
  - Gram negative bacilli (anaerobes)

- Treatment
  - Augmentin, clindamycin, or cephalosporin + flagyl
  - Siaologogues, massage, I&D
Drug Resistance

- Resistance to antibiotics:
  - inappropriate prescription
  - microbial evolution pressures
  - social pressures
  - poor compliance

- A grim future

- Delta, Utah – a new hope?
67 year old female 1 week s/p ORIF left hip now c/o left parotid swelling and pain. Pt reports symptoms began approximately two days after surgery. Also spiking fevers to 38.9 C.

PMHx: DM, HTN, CRI—pt noted to have acute on chronic renal failure after surgery—HD the day before you are called.
Case Report – Cont’d

PE: Older obese woman lying in bed. Obvious asymmetry of face with erythematous swelling over left preauricular/neck area. On palpation area is indurated, painful, and warm. No fluctuance. Purulent drainage expressed from Stenson’s duct. No stone palpated in duct. Oral mucosa is dry.