1. (Deya) Discuss the mechanism of action of Penicillins, Macrolides, Quinolones, and Aminoglycosides
   a. Penicillins: bind penicillin binding proteins and block transpeptidase cross-linking of cell wall. Bacteria cell walls contain peptidoglycan consisting of polysaccharides and a highly cross-linked polypeptide. Also works by removal or inactivation of an inhibitor of autolytic enzymes in the cell wall. Thus penicillins are bactericidal. Resistance to penicillins may be determined by the organism’s production of penicillin-degrading enzymes, β-lactamases, which open the β-lactam ring of penicillins (and cephalosporins). Clavulanic acid, sulbactam, and tazobactam are β-lactamase inhibitors that have a high affinity for and irreversibly bind some β-lactamases.
   b. Macrolides (i.e. erythromycin, azithromycin, clarithromycin): inhibit protein synthesis by blocking translocation (moving of tRNA from aminoacyl site to peptidyl site). Bind to the 23S rRNA of the 50S ribosomal subunit. Macrolides are bacteriostatic. Some macrolide-resistant bacteria lack the proper receptor on the ribosome (through methylation of the rRNA).
   c. Floroquinolones (i.e. cipro, ofloxacin, moxifloxacin): inhibit DNA gyrase (topoisomerase II), resulting in the breakage of the bacterial DNA structure. Floroquinolones are thus bactericidal. Floroquinolone resistant bacteria typically have point mutations in the bacterial DNA gyrase subunits.
   d. Aminoglycosides (i.e. gentamicin, neomycin, tobramycin, streptomycin): bind to 30S ribosomal subunit and inhibit formation of initiation complex and cause misreading of mRNA, thus inhibiting protein synthesis. Aminoglycosides are thus bactericidal. Of note, these drugs need oxygen for uptake and are thus ineffective against anaerobes. Also, these drugs are synergistic with β-lactam antibiotics (allow for diffusion of aminoglycosides across cell wall).

2. (Deya) What are the different classes of Cephalosporins? Tell us what they cover and give examples of each.
   a. First-generation cephalosporins include cefadroxil, cefazolin, cephalexin, cefaclor, and cephadine. These drugs are very active against gram-positive cocci, such as pneumococci, streptococci, and staphylococci. Although the first-generation cephalosporins are broad spectrum and relatively non-toxic, they are rarely the drug of choice for any infection. Oral drugs may be used for the treatment of urinary tract infections, for staphylococcal, or for streptococcal infections including cellulitis or soft tissue abscess. However, oral cephalosporins should not be relied on in serious systemic infections. Cefazolin penetrates well into most tissues. It is a drug of choice for surgical prophylaxis.
   b. Second-generation cephalosporins include cefaclor, cefamandole, cefonicid, cefuroxime, cefprozil, loracarbef, and ceforanide and the structurally related cephemycins cefoxitin, cefmetazole, and cefotetan, which have activity against anaerobes. In general, they are active against organisms inhibited by first-generation drugs, but in addition they have expanded gram-negative coverage. The oral second-generation cephalosporins are active against β-lactamase-producing H influenzae or Moraxella catarrhalis and have been primarily used to treat sinusitis, otitis, or lower respiratory tract infections, in which these organisms have an important role. Because of their activity against anaerobes (including B fragilis), cefoxitin, cefotetan, or cefmetazole can be used to treat mixed anaerobic infections such as peritonitis or diverticulitis. Cefuroxime is used to treat community-acquired pneumonia because it is active against β-lactamase-producing H influenzae or K pneumoniae and penicillin-resistant pneumococci. Although cefuroxime crosses the blood-brain barrier, it is less effective in treatment of meningitis than ceftriaxone or cefotaxime and should not be used.
   c. Third-generation agents include cefoperazone, cefotaxime, ceftazidime, ceftizoxime, ceftriaxone, cefixime, cefpodoxime proxetil, cefdinir, cefditoren pivoxil, cefdituben, and moxalactam. Compared with second-generation agents, these drugs have expanded gram-negative coverage, and some are able to cross the blood-brain barrier. Ceftazidime and cefoperazone are the only two drugs with useful activity against P aeruginosa.
   d. Fourth-generation cephalosporins include cefepime. They are more resistant to hydrolysis by chromosomal β-lactamases and have even better activity against P aeruginosa, Enterobacteriaceae, S aureus, and S pneumoniae. Clinical role is similar to that of third-generation cephalosporins.

3. Unasyn – Why do we use it? What does it cover? What doesn't it cover? What would you use (more than one please) in a penicillin allergic patient?

Unasyn contains ampicillin and sulbactam; the oral equivalent is amoxicillin/clavulanate. Amoxicillin is an amino-penicillin that is more active than penicillin against streptococci and pneumococci. It is also active against many gram negative organisms, although there is a high rate of resistance to Hemophilus influenzae and M. catarrhalis due to β-lactam production. Staph is resistant due to penicillinase production. Sulbactam is a beta-lactamase inhibiting compound that is used in combination with ampicillin to restore antimicrobial activity against resistant bacteria such as S. aureus, H. influenzae, Moraxella, B. fragilis, and other anaerobes. Unasyn covers the following bacteria:

**Gram-positive:**
- Aerobes: *S. aureus, S. epidermidis, S. pneumoniae, S. pyogenes, S.viridans, Enterococcus*
- Anaerobes: *Clostridium, Peptostreptococcus, Peptococcus*

**Gram Negative:**
Unasyn does not cover *Pseudomonas aeruginosa*. Clindamycin can be used in patients allergic to penicillin. Alternatively, drug combinations can be used (e.g., Vancomycin + levaquin/metronidazole). The specific antibiotics depend on the type of infection and coverage necessary.

4. (Amy) A patient presents with an odontogenic neck abscess. What bugs are you concerned about? How would you cover? Odontogenic infections tend to be polymicrobial with predominantly anaerobes. Anaerobic strep and staph, bacteroides species (Prevotella, Bacteroides fragilis), and veillonella are common. Aerobes include *Strep. viridans, Strep. pyogenes, S. aureues*, pneumococcus, *H. influenzae, H. parainfluenzae, E.coli*, and klebsiella. Clindamycin provides excellent anaerobic coverage and is also effective against streptococcus, most pneumococcus, and most staphlococcus (not MRSA). Alternative options are unasyn, or penicillin + flagyl.

5. (Dara) Tell us about the normal flora of the upper aerodigestive tract.

The upper aerodigestive tract contains a very diverse group of microorganisms (bacteria, fungi, mycoplasmas, protozoa, and possibly viral flora). Bacteria are the predominant group of microorganisms. There are over 350 different culturable species and a further proportion of unculturable flora, which can be identified using molecular techniques. The upper aerodigestive tract has a wide range of sites with different environmental conditions; each harboring a slightly different group of organisms. Some of the most common bacteria in each site follow:

<table>
<thead>
<tr>
<th>Oral cavity</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>teeth</td>
<td>streptococi, lactobacilli</td>
</tr>
<tr>
<td>mucous membranes</td>
<td>streptococi and lactic acid bacteria</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Upper respiratory tract</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>nares (nasal membranes)</td>
<td>staphylococci and corynebacteria</td>
</tr>
<tr>
<td>pharynx (throat)</td>
<td>streptococi, neisseria, Gram-negative rods and cocci</td>
</tr>
</tbody>
</table>

6. (Dara) What bugs are you concerned about in acute and chronic otitis Media? How will you cover and what are your choices?

**Acute OM:** Pathogenic bacteria are recovered from the middle ear effusion in at least half of children with AOM, and bacterial deoxyribonucleic acid (DNA) or cell wall debris is found in another quarter to third of specimens previously classified as sterile. Four species of bacteria (ie, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, and Streptococcus pyogenes), in this order, are responsible for the majority of AOM in patients over 6 weeks old. Other bacteria implicated in AOM include Staphylococcus aureus, Streptococcus viridans, and Pseudomonas aeruginosa.

Antimicrobial therapy is the mainstay of treatment, but there is no consensus on who should be treated, which abx should be used, or duration of therapy. Different studies support different options for the treatment of AOM, including a period of analgesics only followed by abx for patients with persistent symptoms, a single IM dose of abx, a 5-day course of PO abx, and a 10-14 day course of PO abx. Few large trials have shown improved efficacy of broad-spectrum abx over narrow spectrum. If decision is made to treat with PO abx, treat with 7 days high dose amoxicillin (alternatives for PCN allergic pts include cefuroxime or other second generation cephalosporin, azithromycin or ceftriaxone. In cases of resistant bacterial otitis, treat with augmentin (80-100mg/kg amox) or cefuroxime or ceftriaxone IM x3 days.

**Chronic OM(with effusiuon):** Eustachian tube dysfunction is a nearly universal finding in COME. Factors that may be involved include ciliary dysfunction, mucosal edema and hyperplasia, viscosity of secretion and possibly a middle-ear/nasopharyngeal pressure gradient. Bacterial exotoxin also may cause a reversible paralysis of middle ear cilia, and inflammatory edema can obstruct middle ear drainage. Main organisms include haemophilus influenza, streptococcus pneumoniae, branhamella catarrhalis, streptococcus pyogenes, staphylococcus epidermidis and other organisms.

Treatment of middle ear effusion should generally be considered for children with effusion of 3 months or longer. The decision to treat can be affected by the following – 1) hearing loss, 2) discomfort, 3) frequent OME episodes, 4) vertigo or unsteadiness, 5) TM changes, 6) middle ear pathology, and 7) associated upper respiratory tract disease. Among the medical options, only antimicrobial agents have been consistently shown to be of benefit. Antibiotics can be used here because there is evidence of persistent bacterial organism by both standard culture techniques and PCR, therefore, eradication of the organism may lead to resolution of the fluid. Antibiotic choices are similar to those for AOM, but a longer course should be given.
Organisms of acute sinusitis are similar to those of AOM. Drugs of choice include amoxicillin, augmentin, or erythromycin plus sulfonamide for PCN-allergic patients. Alternatives include second or third generation cephalosporins. Fluoroquinolones are highly effective second-line agents for adult sinusitis.

Chronic sinusitis can be caused by the same organisms as acute sinusitis. In quiescent stages, chronic sinus disease is caused by inadequate mucociliary function or obstruction. Chronic sinusitis is a polymicrobial infection involving both aerobes (S aureus, streptococci, H. flu, and M catarrhalis), anaerobes (peptostreptococcus, propionibacterium, prevotella and bacteroides), and fungus (aspergillus). The drug of choice is generally augmentin and treatment is for a longer period (ex- 6 weeks) as compared with acute sinusitis. Second line agents include clindamycin, cephalosporin plus metronidazole or fluoroquinolones.

8. (Josh) Otitis Externa and considerations for diabetic and immunocompromised patients.

Otitis external is an inflammatory (typically infectious) disorder of the external ear canal. Treatment requires debridement to facilitate clearance of infectious organisms and allow topical therapy to contact target tissue. Edematous canals require wicks. Acidification of the EAC is toxic to many bacterial (including pseudomonas) and fungal species (Domeboro, Vosol).

<table>
<thead>
<tr>
<th>OE Pathogenesis</th>
<th>Description</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial</td>
<td>Abrogation of hydrophobic ceruminous coating of the EAC, exposes underlying epithelium to trauma, water, contaminants, allowing for bacterial infection. Pseudomonas (40%), Staph (25%).</td>
<td>Cortisporin or polymyxin, neomycin, hydrocortisone (Good broad spectrum coverage, cheap, contact dermatitis, ototoxic if perf) Ophthalmic Gent/Tobra (Better tolerated, not as acidic, expensive, ototoxic) Floxin, Ciprodex (No contact dermatitis, no ototoxicity, expensive) Oral rx reserved for complications of OE</td>
</tr>
<tr>
<td>Fungal</td>
<td>Generally opportunistic, 2/2 to treatment of bacterial infections. Candida is superficial, commonly seen in pts with hearing aids. Aspergillus can be more aggressive, involving the epithelial and subcutaneous tissues. Only 2%, but more persistent in cases of chronic infection.</td>
<td>Clotrimazole/Nystatin (No aspergillus coverage) Genital violet/triple blue Oral itraconazole for resistant aspergillus</td>
</tr>
<tr>
<td>Chronic-Allergic</td>
<td>Resulting from topical allergy, usually neomycin, maculopapular eruption on the skin and conchal bowl and EAC</td>
<td>Elimination of offending agent, systemic control of primary process, debridement, topical corticosteroid solution or lotion</td>
</tr>
<tr>
<td>Chronic-contact dermatitis</td>
<td>Variety of causative agents, hairsprays, shampoos, hearing aid molds</td>
<td></td>
</tr>
<tr>
<td>Chronic-psoriasis</td>
<td>Systemic dermatitides such as seborrhea, results in hyperkeratosis and lichenification of the EAC</td>
<td></td>
</tr>
<tr>
<td>Chronic-granular</td>
<td>Thought to be from chronic infection by bacteria/fungi, manifested by granulation and excoriation of the EAC and TM, commonly seen in hearing aid dependency</td>
<td>Minimizing or alternating hearing aid use, culture, cautery of granulation, filling the EAC with topical antibiotic/antifungal creams, gentian violet as drying agent, surgery may be required</td>
</tr>
<tr>
<td>Malignant</td>
<td>Aggressive, potentially fatal, involves soft tissues and bone of skull base, eventual intracranial extension, rare, usually in diabetic and immunocompromised pts, mostly pseudomonas ans aspergillus but also staph and other exotic fungi</td>
<td>Culture guided. Early infections may be treated solely with oral cipro. More advanced requires IV abx. 6 week duration. HBO for more aggressive. Surgery reserved for cases where bone involvement is resistant to medical therapy.</td>
</tr>
</tbody>
</table>


**Fungal otitis media:** Fungal OE can be treated with meticulous debridement and acidification of the ear. Antifungal solutions or creams, such as clotrimazole or nystatin, may prove effective in candidal infections, but they do not cover Aspergillus well. Many infections will resolve with frequent debridement and administration of acetic acid drops, such as Vosol or Domeboro. An alternative is painting the EAC and TM with dyes with antifungal properties, such as gentian violet and triple blue dye. Persistent Aspergillus infections may require oral itraconazole.
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**Allergic fungal sinusitis**: AFS is believed to be an allergic reaction to aerosolized environmental fungi in an immunocompetent host. Treatment consists first of conservative, nonmutilating surgical removal of nasal polyps, inspissated allergic mucin, and fungal debris. The second part of therapy consists of immunomodulation. Adjunctive systemic steroids started perioperatively and tapered over a long period can result in cure; immunotherapy may also be beneficial. Systemic antifungal therapy may not be beneficial and has high associated costs and side effects. Finally, these patients can develop reinfection, so they may require repeat debridement and steroid/immunotherapy courses. Avoidance of known allergic molds is key to preventing recurrence.

**Aspergilloma of sinuses**: AKA fungus ball or mycetoma. Grow in sinuses irrespective of host immunocompetence. If host becomes immunocompromised, may become invasive. Treatment consists of conservative surgical debridement. No systemic antifungal therapy is needed once the fungus is surgically removed.

**Invasive fungal sinusitis**: Therapy requires reversal of underlying immunodeficiency (if possible), systemic antifungal therapy with amphotericin B or voriconazole, and radical surgical debridement of all necrotic tissue until normal tissue is reached. External approach may be necessary. Although it has not been proven in clinical trials, hyperbaric oxygen may also be helpful, since Mucor tends to thrive in acidic, ischemic environments. Close monitoring, especially during subsequent bouts of neutropenia, is important to diagnose recurrence early.

10. (Caroline) A patient presents with a post-traumatic CSF leak. Would you treat with antibiotics? What are the controversies regarding this? Does CSF otorrhea versus rhinorrhea influence you management? (Please read and photocopy the article by Julian Hoff).

*?julian Hoff article*

Yes.

Some say that by starting antibiotics in patients without symptoms of meningitis only selects out more resistant organisms. Others feel that the risks of potential irreversible effects of meningitis outweigh the risks of the use of antibiotics. The problem is that the low incidence of meningitis prevents studies from having adequate power.

Brodie HA et al. performed a meta-analysis of the literature and found that patients with posttraumatic rhinorrhea and a significantly decreased incidence of meningitis. (use abx, especially in patients whose CSF leaks don’t resolve in 24 hours).

Villalobos et al. also performed a meta-analysis and found no significant difference in incidence of meningitis.

No change in management between csf otorrhea versus rhinorrhea.

11. (Scott) Can you give PCN allergic patient cephalosporins? Initial cross-reactivity studies between cephalosporins and PCN come from the fact that certain 1st generation cephalosporins and PCN were made on similar equipment at the time. 15% of 1st generation cephalosporins cross-reacted with PCN. In a recent analysis, allergic reactions between cephalosporins and PCN were analyzed in 219 articles from 1960 to 2005. This included skin testing, monoclonal antibody studies. It was found that 1st generation cephalosporins have a modest cross-reactivity with PCN, but 2nd/3rd generation cephalosporins have a negligible cross-reactivity.

12. (Scott) Tell us about the bacteriology of necrotizing fascitis?

Mixed aerobic/anaerobic flora tend to be involved in necrotizing fascitis. A recent study of 83 patients showed 98% of patients with necrotizing fascitis had bacterial growth. 10% had aerobic bacteria only, 22% had anaerobic bacteria only, and 68% had mixed flora. On average there were 4.6 isolated bacteria per patient. Anaerobes tended to be in the buttocks, trunk, neck, inguinal regions. Clinical findings tended to associate with certain bacteria: edema with B. Fragilis, Clostridium spp., S. aureus, Prevotella spp., and group A strep; gas and crepitation with Enterobacter and Clostridium spp.; foul odor with Bacteroides spp. Certain predisposing conditions associate with certain bacteria: trauma with Clostridium spp.; DM with Bacteroides spp., Enterobacter, and S. Aureus; immunosuppression/malignancy with pseudomonas spp and Enterobacter.

*(Journal of Clinical Microbiology, Brook and Frazier, Sept. 1995: 33(9): 2382-2387.)*

13. (Tali) Toxic shock! You pack a nose for epistaxis and forget antibiotic RX. Are antibiotics indicated? What would you use? What are the signs and symptoms of TS? Treatment of TS?

Toxic shock syndrome (TSS) is caused by coagulase-positive staphylococci (s. aureus) and group A beta hemolytic streptococci (s. pyogenes). Exotoxin toxic shock syndrome toxin-1 (TSST-1) is the major toxin produced by strains of S aureus that are responsible for causing TSS. Streptococcus pyogenes exotoxin A (SPEA) and S pyogenes exotoxin B (SPEB) are the major toxins produced by group A beta-hemolytic streptococci. The toxins activate production of superantigens, such as tumor necrosis factor, interleukin-1, M protein, and gamma-interferon. TSS is an inflammatory response syndrome characterized by fever, rash, hypotension, constitutional symptoms, and multiorgan involvement. Todd first described it in 1978 in 7 children, aged 8-17 years, with Staphylococcus aureus
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infection. However, after an epidemic in 1981, TSS has been typically associated with tampon use in healthy menstruating women. Symptoms are similar for streptococcal TSS and staphylococcal TSS. The major difference is that a source of infection usually is identified with streptococcal TSS.

Risk Factors include: Use of superabsorbent tampons, postoperative wound infection, postpartum toxic shock, nasal packing, common bacterial infections, viral infection with influenza A or varicella, Diabetes mellitus, HIV, Chronic cardiac and/or pulmonary disease

Physical Exam
- Fever higher than 102°F
- Hypotension/Shock - Systolic BP less than 90 mm Hg or orthostatic decrease in systolic BP of 15 mm Hg
- Skin findings: diffuse rash, occasionally patchy and erythematous, with desquamation occurring approximately 1-2 weeks later. Rash initially appearing on trunk, spreading to arms and legs, and involving palms and soles.
- Signs of multiorgan involvement

Two infectious conditions pertain to nasal packing: toxic shock syndrome and bacterial rhinosinusitis. Absorbant nasal packing allows for colonization of staph aureus. Bacterial rhinosinusitis can develop as a result of blockage of the sinus ostia and mucosal edema caused by packing.

For TSS to occur after nasal surgery or with nasal packing, the individual must be colonized or infected with exotoxin producing staph and there must be a violation of the integrity of the mucosal membrane at the site of infection. The individual must also lack antibodies to the toxic shock toxin. TSS after nasal surgery was first reported in 1982. The first cases had nasal packing but others have reported it where no packing was used.

Prophylactic antistaph antibiotics appear to be ineffective in preventing TSS. This has been demonstrated by numerous case reports in which TSS occurred despite appropriate antibiotic treatment. Also, prospective analysis of prophylactic antibiotic treatment has shown to have no effect on the nasal carriage rate of staph aureus.

Treatment: Remove inciting agent, supportive care may include vigorous IV hydration and possible vasopressors for hypotension. Antistaph abx reduce risk of recurrence but don’t effect toxin already elaborated. Administration of steroids within 2-3 days of onset reduces severity of illness and duration of fever.