I. Antibiotic Resistance

Development of resistance
- In individuals, sustained resistance can be induced in oral streptococci within a period of about 1 week after a short course of macrolide.

- Macrolide resistant *S pneumoniae*: <5% resistance in 1990’s and currently, many areas in the US have resistance rates higher than 30%.
- Fluoroquinolone-resistant *S pneumoniae*: first case of *S pneumoniae* resistant to levofloxacin documented in 2002
- There are now documented cases of carbepenem-resistant ESBL enteric pathogens.
Differences in local resistance patterns make it difficult to provide standard guidelines and call for antibiotic practices to be directed by local resistance patterns.

- **IDSA 2007** Community-Acquired Pneumonia guidelines recommend a macrolide for outpatient treatment of pneumonia for patients with no risk factors for drug-resistant *S. pneumoniae*. But be aware of caveats in these recommendations!
  
  "In regions with a high rate (>25%) of infection with high-level macrolide-resistant *S. pneumoniae*, consider the use of alternative agents..."

- Look out for increasing resistance of MRSA to clindamycin. Varies widely by region (MRSA now 41-66% sensitive to clindamycin in San Francisco, as low as 20-30% sensitive in parts of Chicago, Boston, and Minnesota). The resistance mechanism is through expression of a gene that changes the target site where the antibiotic normally binds. In this case, methylation of the bacterial ribosomal binding site confers resistance. Other alternatives are TMP/SMX +/- amoxicillin or a cephalosporin; doxycycline +/- amoxicillin or a cephalosporin; or linezolid.

**Strategies for preventing resistance**

- It helps to know and be on board with local and institutional strategies to reduce resistance. Use antibiograms, antibiotic formularies, and understand antibiotic restrictions.

### II. Side Effects from Antibiotics

**Statistics**

- A surveillance study found that 19% of ED visits for adverse drug events were attributable to antibiotics. Of these visits, 6% resulted in hospitalization. Penicillins and cephalosporins comprised half of these visits, though sulfonamides and clindamycin were had the highest rate of ED visits per prescription.

- A prospective observational study found that of all medication-related ED visits, antibiotics were related to 11.2% (same rate found for opiates).

**Penicillin allergy and cephalosporin cross reactivity**

- Originally, cross reactivity thought to be about 10%, based upon literature in the 60’s/70’s. In the initial studies, both types of antibiotics were manufactured via the same cephalosporium mold until 1980’s.

- 10-15% of those who state a PCN allergy are actually truly allergic to PCN (have an IgE-mediated allergy). 0.2-8% of those who state they have a PCN allergy (but not actually tested) will react to a cephalosporin. Less than 2% of those with skin-test proven PCN allergy will react to cephalosprins (thus 0.2-0.3% of those who state a PCN allergy). Frequency of anaphylaxis from cephalosporins is 0.0001 to 0.1%.

- While both PCN and cephalosporins have a similar molecular shape, the antigenic site is different for these drugs. The beta-lactam ring is the major player in PCN allergy. The R side chain off the beta lactam ring, not the ring itself, is the major antigenic site in cephalosporin allergic response.
Fluoroquinolones
- Achilles tendonopathy and rupture risk is higher in elderly and taking glucocorticoids (like COPD exacerbations). While not very common, patients should be made aware of this complication. Lawsuit 2 years ago accorded the prescribing physician some responsibility in a case of levofloxacin-induced Achilles tendon rupture, even though the physician was not a named defendant.

C. difficile diarrhea
- Fluoroquinolones and cephalosporin use are major risk factors now. Clindamycin use is still an important risk factor, but not as strong a risk factor now.
- Metronidazole may be used for initial treatment and first relapses if mild (no fever, no hypovolemia). Vancomycin should be reserved for more severe relapses and metronidazole intolerance.
Relapses are a clinical diagnosis (occurs in about 20% of cases) and it takes weeks for C. diff to clear from the stool, particularly for the newer, more sensitive PCR tox B assays. Do not send tests of cure to diagnose relapses.

Fidaxomycin – a new narrow spectrum antibiotic (taken BID) that only covers C. difficile. It is associated with less relapses compared to oral vancomycin (taken QID), but it is expensive (~$300/day of treatment).

Doxycycline

- Increase in use for outpatient PNA and CA-MRSA infections
- Most common documented side effects are esophageal ulcerations (so tell patients to take at dinner not at bedtime) and photosensitivity. Unlike tetracycline, cations won’t significantly decrease duodenal bioavailability so doxycycline may be taken with meals and milk. Photosensitivity will look like a sunburn and occurs minutes to hours afterwards. Sunscreen may be used to help prevent the phototoxic reaction. If the patient can avoid sunlight, use SPF, and the remaining course of doxycycline is short, the patient can continue doxycycline.

### III. Inadequate Treatment

Adequate dosing

- Vancomycin is actual weight based (15-20 mg/kg), not always a 1g dose (and adjust for renal function)
- Piperacillin-tazobactam (Zosyn) is not always dosed at 3.375g. If pseudomonas is suspected or severe sepsis/septic shock is present, then dose is 4.5g. The MIC for pseudomonas is higher than that for most other organisms. The risk factors for pseudomonas infection are structural lung disease (i.e. bronchiectasis), repeated exacerbations of COPD leading to frequent steroid and/or antibiotic use, recent mechanical ventilation, recent prior exposure to broad-spectrum antibiotics (within the last 30 days).
- Levofloxacin is dosed at 750 mg if pseudomonas is suspected. The newer 750 mg dose for other indications seems to be driven by competition with moxifloxacin (a more potent antimicrobial against pneumococcus) and azithromycin (Z-pack).
- 1 tab vs 2 tabs of DS TMP-SMX. Typically dosed 8-10 mg/kg/day of TMP for skin infections, thus 2 tabs of DS TMP-SMX. However, a recent (with some methodological flaws) study shows there might not be a difference.
- Nitrofurantoin is recommended for cystitis. However, it should not be used for upper urinary tract disease or in renal insufficiency (Cr>2.0). Nitrofurantoin is quickly cleared renally and concentrated in the tubules, thus it does not reach high blood levels.

Time to antibiotics in severe sepsis and septic shock

- Severe sepsis = SIRS + identified infection + evidence of end-organ dysfunction
- Septic shock = Severe sepsis + MAP <60-65 (or <80 with baseline HTN) or SBP <90 after fluid resuscitation AND/OR requiring vasopressors after fluid resuscitation
- Several studies document that time to antibiotics is one of the key factors in reducing mortality. Providing appropriate antibiotics within 1 hour of triage or qualification for EGDT reduces mortality. Delaying antibiotics, even as short as >1 hour is associated with increased mortality.
- Remember to add a macrolide (azithromycin or clarithromycin) for severe cases of PNA going to ICU (intubated). Macrolides were found to be superior to fluoroquinolones with respect to mortality. This is likely due to an immunomodulatory effect of macrolides, rather than solely an antibacterial property.

**IV. Adverse Drug Interactions**

Trimethoprim-sulfamethoxazole

- + ACEIs, ARBs, NSAIDs
  - hyperkalemia

- + warfarin
  - INR and hemorrhage risk

- + phenytoin
  - phenytoin toxicity

- + oral hypoglycemic
  - hyoglycemia

**Warfarin and antibiotics**

- The worse offenders are trimethoprim-sulfamethoxazole, fluoroquinolones, and metronidazole. A recent study documented TMP-SMX and ciprofloxacin associated with significant upper GI bleed in elderly patients on warfarin. 10% of those admitted with this complication died.
- Patients on warfarin should be told to follow-up in anticoagulation clinic in 1-2 days, call and obtain advise on warfarin adjustment from the anticoagulation clinic provider in 1-2 days, or have their warfarin dose adjusted and follow-up in anticoagulation clinic.
References
Last accessed 1/15/2012.
Kelkar et al. NEJM. 2001; 345: 804-809.
Ho et al. CMAJ. 2011; 183:1851-58.