Not too much, not too little, but just right

Pearls and pitfalls of antibiotic use by primary care for the adult patient

Objectives

• Describe current antibiotic regimens recommended for use in common infections found in the primary care settings (both inpatient and outpatient) for adult patients

• Describe practical pearls for the use of common antibiotics

• Be aware of changes in prescribing recommendations including black box warnings and regional sensitivity patterns of common antibiotics

How to think about antibiotic use...

Mind Map

Data Conflicts

Public Health Recs

Insurance Rules

Patient Requests

Specialist Recs
And to make it even more difficult...

- Guidelines are constantly changing
- Resistance patterns are changing
- Drugs can become temporarily unavailable
- Local culture can be a strong influence – may be positive or negative
- Current local resistance patterns may be difficult to obtain

Keeping the drugs all straight - when to use what?

- Have an idea of what bugs cause which infections
- Have an idea of which of your drugs have good coverage for which bugs
- Simplify your list - you don't need to use all drugs in all categories
- Tailor the drug characteristics to the patient
- Be aware of possible adverse reactions, sensitivities, contraindications
- Look at drugs, bugs, and infection locations from multiple directions - develop a mind map
- Review, review, review - you won't remember it if you don't use it or talk about it or just think about it
- Learning is best if it is meaningful, graphic, and messy

Categorize your bacteria

<table>
<thead>
<tr>
<th>Gram positive</th>
<th>Gram negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobic</td>
<td>Anaerobic</td>
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</table>

Additional detail and special cases

- Morphology
  - Gram-positive cocci: staph aureus, streptococcus, enterococcus
  - Gram-negative bacilli: e. coli, shigella, pseudomonas, in other use beta-lactamase pen, or clb
  - SACE and pseudomonas
  - Gram-negative coccobacilli: haeccoccus influenzae, st. pneumoniae
  - Anaerobic: slow (anaerobic, pseudomonas enterobacteriaceae)
  - Others: - BTO (infections specific to - rod)
- Space organisms plus pseudomonas (gram neg bacilli)
  - Serratia, proteus, acinetobacter, cimribacter, enterobacter
  - Have inducible, chromosomal beta-lactamase (ampc) that may not be detected on initial susceptibility testing, but can lead to resistance while on therapy to all beta-lactams except carbapenems
  - Coagulase-negative staph – are generally resistant to drugs that have activity against other staph

Infections

- Upper respiratory
- Lower respiratory
- Skin & soft tissue
- Urine
- Blood
- Intra-abdominal/GI
- Pelvic
- Bone
- CNS
- Systemic

Antibiotics

- Beta-lactams
  - Penicillins
  - Cephalosporins
  - Macrolides
  - Tetracyclines
  - Sulfa (TMP/SMX)
  - Fluoroquinolones
- Vancomycin
- Metronidazole
- Clindamycin
- Carbapenems*
- Aminoglycosides*
- Nitrofurantoin
- Linezolid*
Respiratory Infections

- URI
- AOM
- Sinusitis
- Pharyngitis
- Acute bronchitis
- Pneumonia
- S. pneumo
- H. flu
- Moraxella
- Strept species
- Anaerobes (ATD)

A woman died in early September in Reno, NV of sepsis due to Klebsiella pneumoniae. What was notable about this case?

a. She had previously had a prolonged overseas stay
b. She had been hospitalized multiple times over the previous two years
c. The specimen was obtained from a wound
d. The isolate was resistant to 26 antimicrobials
e. All of the above

Overuse of antibiotics is a driver of resistance

- Increased efforts for education to avoid antibiotics when not needed
- New studies looking at decreasing duration of treatment
- Attempts to limit broad spectrum antibiotics such as fluoroquinolones (new black box warning)

Do you really need to prescribe that antibiotic?

When are antibiotics not required?*

- Viral infections (URI: 70)
- Acute sinusitis
- Acute OM
- Acute bronchitis
- Asymptomatic bacteriuria
- Mild diverticulitis

* Special situations exist where antibiotics are recommended – know the exceptions
Let's get things organized...

**Antibiotics: Beta-Lactams -- Penicillins**

- Original natural penicillins
  - Penicillin G – IV form
  - Penicillin V – oral form
- Anti-staphylococcal penicillins
  - Nafcillin, dicloxacillin
  - Good: MSSA, streptococci
  - Poor activity against staph
  - Short half-life; needs frequent dosing
  - Frequently causes phlebitis with IV use

**Spectrum**
- Good: treponema pallidum, most streptococci (including S. pneumo), ATD anaerobes
- Moderate: enterococci, N. Meningitidis (Pen G)
- Poor: everything else
- Short half-life; needs frequent dosing

**Aminopenicillins**
- Oral – amoxicillin
  - Better bioavailability, better tolerated, less frequent administration
  - May use high dose to overcome some S. pneumo resistance
  - Use in treat outpatient enterococcus (UTI)
  - Be careful using amoxicillin as empiric tx for UTIs due to increasing resistance to E.coli. Check cultures.
- IV – ampicillin
  - Ampicillin is the drug of choice for susceptible enterococcus
  - For severe enterococcal infections (endocarditis) – generally combined with aminoglycoside in order to achieve bactericidal activity

- Anti-pseudomonal penicillins
  - Piperacillin, ticarcillin
  - Active against pseudomomas and other resistant GNRs
  - Same spectrum as amoxicillin/empicillin plus above
  - Generally not used alone
Antibiotics: Beta-Lactams -- Penicillins

- Beta-lactamase inhibitor combos: The beta-lactamase inhibitor only freez up the beta-lactam to kill the organism—it doesn’t enhance the activity
  - Ampicillin/sulbactam – Unasyn
  - Amoxicillin/clavulanate – Augmentin: the only oral formulation
  - Piperacillin/tazobactam – Zosyn
  - Pip/taz = Amp/sub plus better gram negative activity including pseudomonas and SPACE
  - Used for many purposes: HAP, severe skin/soft tissue infections, infected diabetic ulcers, intra-abdominal infections
  - Good anaerobic coverage (above and below the diaphragm)

- Gram positive cocci
  - Staph (MSSA)
    - Nafcillin
  - Staph (MRSA)
  - Strept
  - All penicillins
  - Enterococcus
  - Amox/ampicillin

- Anaerobes
  - Above the diaphragm
  - Pip/taz

Antibiotics: Beta-Lactams -- Cephalosporins

1st generation
- Cefazolin (IV)
- Cephalexin (oral)
- Mostly gram positive coverage, some GNR
- Used for:
  - Skin and skin structure infections
  - Surgical prophylaxis
  - MSSA bacteremia and endocarditis
  - Good alternatives to the anti-staphylococcal penicillins; less phlebitis and given less frequently

2nd generation
- Cefuroxime (po), cefoxitin (IV), cefotetan (IV)
- Somewhat weaker GP (reasonable strept and staph coverage)
- ATD anaerobes
- Improved GNR coverage – E.coli, Klebsiella, H.flu, Neisseria, SPACE
- Cefotetan is one of a handful of cephalosporins which have a side-chain MTT (N-methylthiotetrazole).
- Can inhibit vitamin K production and prolong bleeding
- Can cause a disulfiram like reaction when patient drinks alcohol
- Cefotetan & cefoxitin are cephamycins. This subgroup has activity against may anaerobes in the GI tract and therefore is used as surgical prophylaxis for abdominal surgery

3rd generation – ceftriaxone, cefotaxime, ceftazidime*, cefpodoxime, cefixime
- Spectrum – good GNR coverage, decent GP, strept
- 3rd generation cephalosporins have a strong association with C.diff - associated diarrhea
- Cefotaxime (po)
- useful as a step-down to oral IV Ceftriaxone, but like all beta lactams risks poor serum bioavailability (so not as suitable for bacteremia, deep seated or serious infections)
- Has the MTT sidechain that can inhibit vitamin K production
- As a group, no coverage of enterococcus, pseudomonas, anaerobes

- Ceftazidime is different than the others
  - No clinically useful gram positive activity
  - Does have activity against pseudomonas
  - Historical choice for treatment of neutropenic fever when coupled with vancomycin for gram positive coverage

4th generation
- Cefepime
- Expanded gram negative coverage but also has better gram positive coverage compared with 3rd generation
- Think of it as a combination of cefazolin and ceftazidime

Antibiotics: Atypicals

- Pseudomonas, Pip/taz
- Amoxicillin/sulbactam – Unasyn
- Used for skin and soft tissue infections of head and neck
- Amoxicillin/clavulanate – Augmentin
- Amp/ampicillin

Questions:

- What is at least one difference between amoxicillin and cephalexin?
- Which would you use to treat a typical case of acute bronchitis?
- Which would you use to treat a dental infection?
- Which would you use empirically to treat cystitis in a young woman?
- Would this drug be appropriately used for CAP? Does it treat enterococcus? Does it treat anaerobes?
Antibiotics: Beta-Lactams -- Cephalosporins

- 5\textsuperscript{th} generation -- ceftaroline
  - Acitivity against MRSA, trade-off - lost some gram-negative activity
  - Think of it as vancomycin plus ceftriaxone with a little Enterococcus faecalis coverage thrown in

Macrolides -- azithromycin, clarithromycin

- Broad coverage but not great depth as resistance (especially to S. Pneumoniae) is becoming an increasing issue. Spotty GNR coverage.
- Apprx 35\% of S. pneumoniae is resistant to azithromycin, so combine with ceftriaxone for patients sick enough to hospitalize with community-acquired pneumonia (or recent use)
- QT prolongation: Caution with patients with heart disease
- Many drug interactions - use your favorite drug interaction app
- Azithromycin is the drug of choice for most atypical infections
  - Hospital use:
    - Excellent bioavailability: po equals IV
    - Duration: three days of 500 mg daily or typical "Z-pack" dose is adequate

Question: mycoplasma pneumoniae and chlamydia pneumoniae are potential causes of acute bronchitis. Is treating them with a macrolide appropriate?

Fluoroquinolones

- Clinicians LOVE fluoroquinolones. That’s probably why the FDA issued a black box warning last summer. Directives: save them for when you really need them
- Adverse reactions:
  - QT prolongation, possible increased risk of CV death (levo), tendon rupture (especially if on steroids), diarrhea, cartilage damage, dysglycemias (particularly if on insulin), dizziness, HA, rash, teratogenicity, transaminitis, increased risk of retinal detachment, high rate of c.diff.
- Class characteristics
  - Excellent bioavailability. Use po whenever possible
  - Good coverage of atypicals (cipro relatively weaker)
  - Excellent TB coverage -- do not use for pneumonia if you suspect TB at the same time (monotherapy for TB drives resistance)
  - Chelating agents - less effective when taken orally with sucralfate, iron, MVI with zinc, antacids containing aluminum or magnesium (separate by two hours)

Fluoroquinolones

- Ciprofloxacin
  - Best GNR coverage; little GP coverage (not good coverage for S. pneumo)
  - Covers pseudomonas
  - No anaerobic coverage
  - Twice daily dosing

- Levofloxacin
  - "Respiratory FQ" - better GP coverage, very good GNR coverage
  - Good strep coverage, sstaph
  - Pseudomonas coverage but less reliable than cipro - UMass data (2014) showed 35\% resistance rate
  - Good urine penetration
  - Once daily dosing

- Moxifloxacin
  - Best GP and anaerobic coverage
  - No anaerobic activity
  - No pseudomonas activity
  - Once daily dosing

TMP/SMX

- Wide spectrum including coverage of staph -- both MSSA and MRSA-CA, not great against strept, good GNR coverage but not pseudomonas
- Also covers pneumocystis, respiratory tract, Listeria, and more
- Good for skin infections except weak for strept -- add cephalexin to it
- Approx 90\% bioavailability (use po)
- First line agent for empiric treatment of cystitis if local E.coli resistance is <20\%
  - UMass resistance rate 24\% (inpatient sampling)
  - State average: 25\% with one SD range approx 20-30\%
- Adverse reactions: hypersensitivity and rashes, GI effects, dose-dependent bone marrow suppression, increased creatinine (both pseudo-C increase, about 20\%, and true AKI from interstitial nephritis and ATN), hyperkalemia
Question

What are risk factors for TMP/SMX-induced hyperkalemia?

- Older age
- Diabetic
- ACE inhibitors
- OID
- Potassium-sparing diuretics
- NSAIDs

Nitrofurantoin

- Broad spectrum but only used for lower tract UTI (cystitis)
- Poor kidney tissue penetration – DO NOT use for pyelonephritis
- Generally given for 7 days but recent study indicated that 5 days is likely adequate
- Avoid long-term use due to potential pulmonary side effects: hypersensitivity pneumonia and chronic pulmonary fibrosis
- Contraindicated with decreased renal function CrCl < 50
- May cause diarrhea
- Decreased CrCl decreases excretion of drug so serum levels can rise causing increased adverse reactions and toxicity
- Common side effects: nausea, HA
  - Can turn the urine brown
  - Macrobid (crystalline form) – name implies: Macro BID
  - Macrodantin (crystalline form is shorter acting and needs to be taken QID)

Tetracyclines

- Spectrum: Fairly broad spectrum with some Staph and MRSA coverage, some gram negative coverage, and atypicals. Has activity for unusual pathogens including: Rickettsia, Lyme disease, Tularemia, Vario, Brucella, Q fever, Anthrax
  - Good choice for mild-moderate skin/soft tissue infections due to community-acquired MRSA infection, but has poor deep coverage so often combined with beta lactam like cephalaxin.
  - Doxycycline is the preferred tetracycline in most cases due to convenient BID dosing, and lack of food-drug interactions.
  - Tetracyclines chelate cations therefore the oral bioavailability is significantly decreased when administered with calcium, iron, antacids, or multivitamins:
    - Be sure to ask about supplements!
    - Watch for esophageal irritation. Take pills with water, standing up if possible. Never swallow dry.
    - Sun sensitivity with doxy is real. This means a sunburn.

Vancomycin

- Insusceptible for gram-positive activity
- Considered the gold standard for MRSA infections.
- No gram negative coverage
- Many enterococci (especially E. faecium) have become resistant (VRE)
- Considered a slowly cidal drug (compared to beta-lactams), but toxic if dosed incorrectly
  - Not as effective as nafcillin against MSSA, due to slowly cidal nature; increased treatment failure/relapse when used for MSSA bacteremia/endocarditis
  - Red man syndrome
    - Histamine-mediated reaction; not a true allergy
    - Patient may feel warm, flushed, and may be hypertensive
    - Prevent the reaction by slowing the infusion rate
    - Antihistamines can ameliorate the reaction
  - Dosing: typical is 15-20 mg/kg ideal body weight; max 8 gm/24 hrs, can load 25-30 mg/kg intravascularly in critically ill patients. The typical is 2 gm qds dosing is inadequate for most patients. For severe renal failure, cut dose to 10 mg/kg – i.e. load 15 mg/kg, then check daily levels and reduce when levels >15.
  - 10 mg/kg q12 hrs for severe infections or those with unstable renal function. Good troughs 5-10 for prevent bacterial MRSa infections >20 for CII infections, >50 for less severe infections (e.g. routine cellulitis, easy negative staph, etc.). Some experts will even check troughs in non-severe, non-MRSA infections in patients with stable renal function.

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**Metronidazole**

- **Anaerobic niche player:** provides good coverage for both gram-positive and gram-negative anaerobes in the gut and pelvis but doesn’t work as well with anaerobes in the mouth (actinomyces, propionibacteria).
- Effective against protozoa such as trichomonas, entamoeba, and giardia.
- Think of it as a tool for abdominal and pelvic anaerobes and protozoa.
- Common side effects: nausea, vomiting, diarrhea, metallic taste in mouth, yeast.
- Excellent bioavailability: PO essentially equals IV.
- Black box warning: carcinogenic in rats and mice (but not hamsters).
- Disulfiram-like reaction with alcohol.
- Psychosis with disulfiram.

**Clindamycin**

- Think of it as a mixture of vancomycin and metronidazole but not quite as good as either alone.
- It is an alternative when treatment requires gram-positive activity (as when a patient has a beta-lactam allergy).
- Be aware that it has more activity against pathogens such as MRSA and S. pyogenes.
- If MRSA (or MSSA) appears susceptible – always do lab check a “D-test” which looks for inducible resistance to clindamycin in strains that are resistant to erythromycin. If D-test positive, do not use clindamycin.
- Covers many anaerobic organisms but there is a higher level of resistance among the gram-negative anaerobes than with metronidazole.
- Traditionally causes highest rate of C. diff among all abs (~10%).
- Carries a black box warning regarding propensity to induce C. diff.
- Also can cause a relatively benign, self-limited diarrhea.
- Clindamycin is nearly 100% orally bioavailable, but oral doses are generally lower than IV doses in order to improve GI tolerance.

**Scratch Pad - Summary**

**Gram positive cocci**
- **Staph (MSSA):** nafcillin, cephalaxin, cefuroxime, (ceftriaxone), ceftepime, (cephalosporins, TMP), vanco, clinda, doxy
- **Staph (MRSA):** cephalaxin, TMP/SMX, vanco, clinda, doxy
- **Strep:** all penicillins, all cephalosporins except cefuroxime, macrolides, lev, aes, nitrofurantoin, vanco, clinda

**Anaerobes**
- **Above the diaphragm:**
  - All penicillins except nafcillin group
  - Cefuroxime, cefotetan, cefazolin, moxifloxacin
  - Metronidazole (less good)
  - Clindamycin
- **Below the diaphragm:**
  - Pip/taz
  - Cefotetan, cefazolin
  - Moxifloxacin
  - Metronidazole
  - Clindamycin (less good)