UPDATES IN ANTIBIOTIC THERAPY FOR COMMON ILLNESSES

AMY BROOKS, PHARMD, BCPS
CLINICAL PHARMACIST
CONCORD HOSPITAL
CONCORD, NH
DISCLOSURES

I HAVE NO FINANCIAL RELATIONSHIPS TO DISCLOSE

I WILL BE DISCUSSING DOSING AND INDICATIONS OF ANTIBIOTICS THAT MAY NOT BE FDA APPROVED
OBJECTIVES

• Explain basic pharmacology of major antibiotic drug classes
• Develop an understanding of why certain antibiotics are used for certain disease states
• Discuss first-line antibiotic choices for common disease states
• Discuss circumstances in which alternative antibiotics would be necessary
BACKGROUND

• Studies have shown that up to 50% of all antibiotics prescribed are inappropriate.¹

• Leads to increased morbidity, mortality, cost, and bacterial resistance¹

• The spread of resistant bacteria can affect patients who were not even exposed to the antibiotics.²

• The CDC estimates that more than 2 million people are infected with antibiotic resistant bacteria yearly, leading to approximately 23,000 deaths each year.²
BACKGROUND

• 262.5 million antibiotics prescribed in the outpatient setting each year
• Outpatient prescribing practices affect local resistance patterns
• Prescribing practices vary by state and season
• Azithromycin and amoxicillin are the most commonly prescribed outpatient antibiotics
Community Antibiotic Prescribing Rates by State (2013/2014)*

50% of all antibiotics prescribed in U.S. health provider offices are either unnecessary or inappropriate

*Antibiotic prescriptions per 1000 persons
Prescribing data from 2014; population data from 2013
Source: IMS Health
ANTIBIOTIC DRUG CLASSES

• Penicillins
• Cephalosporins
• Carbapenems
• Fluoroquinolones
• Macrolides
• Clindamycin
• Glycopeptides (vancomycin)
• Daptomycin
• Linezolid
BASIC ANTIBIOTIC PRINCIPLES

• Dose matters (pharmacokinetics)
• The location of the infection in the body matters (pharmacodynamics)
• Every bug has a drug
  • There’s more to picking an antibiotic than “S” or “R”
• Much of antibiotic selection is risk vs benefit
  • Weighing out the seriousness of the infection with the seriousness of the antibiotic side effects
B-LACTAMS

- MOA: Inhibit cell wall synthesis
- Bactericidal time-dependent killing
- B-lactam ring is responsible for antibacterial activity, side chains responsible for spectrum of activity and pharmacologic properties
B-LACTAMS

• MOA: All β-lactams are cell wall active drugs that bind to penicillin-binding proteins (PBPs) and inactivate them, which leads to cell death.
  • Different bacteria have different types and varying amounts of PBPs
  • β-lactam antibiotics have varying degrees of affinity for binding and inactivating these different PBPs, which leads to differences in spectrum of activity.

• Major side effects
  • Hypersensitivity reactions (less common with newer agents)
  • Myelosuppression, interstitial nephritis, serum sickness, seizures (rare)
NATURAL PENICILLINS

- Penicillin G and penicillin V
- The MOST active against non β-lactamase producing gram positive bacteria
- Also cover some anaerobes (mouth anaerobes) and select gram negatives (*Neisseria*)
- Most commonly used for: Strep A, Syphilis, streptococcal endocarditis
- Available oral (PenV), IV, and IM depot
- Renally cleared, so need to be dose adjusted with renal failure
- Most common side effects: allergic reactions
  - Rare side effects: neutropenia, hemolytic anemia, seizure, serum sickness
AMINOPENICILLINS

- Ampicillin, amoxicillin
- Same spectrum of activity as penicillin G, but they have additional gram negative activity in Enterobacteriaceae that don’t produce β-lactamases.
- Drug of choice for enterococci
- Ampicillin and amoxicillin are considered interchangeable, except amoxicillin has much better oral absorption and less GI side effects
- Most common side effects: rash, GI upset, *C. diff*
- Renally cleared, requires dose adjustment in renal dysfunction
PENICILLINASE-RESISTANT PENICILLINS

- Methicillin (no longer available), nafcillin, oxacillin, dicloxacillin
- Drug of choice for MSSA
  - Also covers streptococcus species
- Major side effects: interstitial nephritis
- Renally cleared, requires dose adjustment with renal dysfunction
- Not used empirically, used as step-down therapy when culture results known
CARBOXYPENICILLINS/UREIDOPENICILLINS

- Carboxypenicillins: ticarcillin (no longer available in US)
- Ureidopenicillins: piperacillin
- These groups are referred to as the anti-pseudomonal penicillins
- Active against many resistant gram negative infections, including *Klebsiella*, *Citrobacter*, *Enterobacter*, *Serratia*, *Providencia*, and *P. aeruginosa*
- Gram positive activity of piperacillin considered equivalent to aminopenicillins
- Good anaerobe coverage (including *B. fragilis*)
- Most common side effects: rash, neutropenia, drug fever
- Renally cleared, requires dose adjustment in renal dysfunction
B-LACTAMASE INHIBITORS

- B-lactamases are also PBPs (binding target for penicillins), but they are smaller and not membrane bound.
  - When they bind to the drug, they are irreversible inhibitors of the drug, making them permanently inactive.
- B-lactamase inhibitors were created as “suicide substrates” of β-lactamases.
  - They bind to the β-lactamase and keep it from binding to the antibiotic
  - Antibiotic retains its activity against the organism
B-LACTAMASE INHIBITORS

• Clavulanic Acid, tazobactam, sulbactam, avibactam (new)
• Not available by themselves, only in combination with a β-lactam
• Active against Class A β-lactamases (penicillinases)
  • Produced by *S. aureus, H. influenzae, M. catarrhalis, Bacterioides, Enterobacteriaceae*
  • Do not inhibit cephalosporinases or carbapenemases (except avibactam)
• Augmentin (Amoxicillin/clavulanic acid), Unasyn (ampicillin/sulbactam), Zosyn (piperacillin/tazobactam)
CEPHALOSPORINS\textsuperscript{5}

- Contain the same \(\beta\)-lactam ring
- Spectrum of activity and pharmacologic properties (oral absorption, half-life) are changed by changing side chains.
CEPHALOSPORINS

- MOA: Disrupt cell wall synthesis by binding to PBPs
- Inactivated by AmpC cephalosporinases, ESBLs, and carbapenemases
  - Maintain stability in presence of many penicillinases
- All are renally cleared and must be dose adjusted **except** Ceftriaxone
- Side Effects
  - Very well tolerated
  - Hypersensitivity reactions most common, but less common than penicillins
1ST GENERATION CEPHALOSPORINS

- Cefazolin (IV), cephalexin (po)
- Cover most gram positives (except enterococcus and MRSA), especially effective against MSSA
- Used primarily for skin and soft tissue infections and peri-operative prophylaxis
- Cefazolin is a drug of choice for MSSA infections, including bacteremia and endocarditis
2\textsuperscript{ND} GENERATION CEPHALOSPORINS\textsuperscript{5}

- Cefuroxime (IV and po)
- Slightly improved gram negative coverage
  - \textit{E. coli, K. pneumoniae, Proteus mirabilis, H. influenzae, M. cattharalis}
  - Do not cover the more resistant gram negatives
- Used primarily for respiratory infections
3RD GENERATION CEPHALOSPORINS

- **Ceftriaxone**
  - “Workhorse”: used for many different infections
  - Dosed q24h, no renal adjustments needed
  - Drug of choice for *Streptococcus pneumoniae*
  - Commonly used for pneumonia, meningitis, UTI, cSSTI

- **Ceftazidime**
  - Only 3rd generation to cover *Pseudomonas aeruginosa*
  - Decreased coverage of gram positive organisms (MSSA, *S. pneumoniae*)
  - More of niche drug now, not used empirically as monotherapy due to increased resistance

- Oral 3rd generations: cefpodoxime (Vantin®, cefdinir (Omnicef®), cefixime (Suprax®)
4\textsuperscript{TH} GENERATION CEPHALOSPORINS\textsuperscript{5}

- Cefepime (IV)
- Widest spectrum of activity of all the cephalosporins
- Even better gram negative activity than 3\textsuperscript{rd} generation, including \textit{P. aeruginosa}, while maintaining gram positive activity
  - Zwitterion: crosses the outside membrane of gram negative bacteria rapidly, less likely to be inactivated by B-lactamases
- Does not cover MRSA, enterococcus, \textit{B. fragilis}
- Empiric treatment for hospital acquired pneumonia, sepsis, febrile neutropenia
5TH GENERATION CEPHALOSPORINS

- Ceftaroline (IV)
- First approved in 2010
- Effective against MRSA and ampicillin-sensitive Enterococcus faecalis
- Gram negative coverage similar to Ceftriaxone
CARBAPENEMS

- Similar structure and function to all other β-lactams, but with a few structural changes:
  - More stable in the presence of β-lactamases (less resistance)
  - Bind to a wide variety of PBPs in a lot of different organisms
  - Traverse the outer membrane of gram negatives using specific outer membrane proteins (OMPs)

- Spectrum of activity:
  - Meropenem, Imipenem, Doripenem: *P. aeruginosa*, *Enterobacteriaceae*, all gram + except MRSA and *E. faecium* (some *E. faecalis*), anaerobes
  - Ertapenem: doesn’t cover *Pseudomonas*
CARBAPENEMS

- **Resistance:**
  - Emergence of KPC-producing organisms and metallo B-lactamases
  - Not inactivated by ESBL, penicillinases, or carbapenemases

- **Side effects:** Very well tolerated.
  - Small increased incidence of seizures
    - Imipenem 1-2%
    - All others 0.1-0.3%
  - Much less hypersensitivity reactions than other β-lactams

- **Major Drug interactions:**
  - Depakote (Valproic acid): decreases VA levels by up to 50%
  - Renally cleared, must be dose adjusted in renal dysfunction
AZTREONAM

- Monobactam
- Least likely to cause an allergic reaction
- Covers ONLY gram negative organisms (including *P. aeruginosa*)
  - No gram positive coverage
  - No anaerobic coverage
- Used as a niche drug when culture results available and there is a documented gram negative infection.
B-LACTAM ALLERGIES

- The incidence of IgE mediated penicillin allergies is much less than originally reported
  - Large studies have found that only 10-15% of patient reported allergies to penicillin truly have an IgE mediated allergy when skin testing is done.
- Cross-reactivity to first and second generation penicillins originally stated to be as high as 10%, but newer studies have shown it is about 2% in patients with proven penicillin allergies.
  - 10-15% of reported penicillin allergies are IgE mediated, and of those there is a 2% risk of cross-reactivity with a cephalosporin.
- In a large scale study on carbapenem cross reactivity, 295 patients with confirmed penicillin allergies were given a carbapenem and only 1 patient had a possible IgE mediated reaction (0.3%).
- Aztreonam poses no risk of cross reactivity with penicillin allergy
FLUOROQUINOLONES

- Ciprofloxacin (IV and po), Levofloxacin (IV and po), Moxifloxacin (IV and po)
- MOA: Inhibit DNA gyrase and topoisomerase IV in bacteria, which rapidly inhibits bacterial DNA synthesis.
- Concentration dependent and bacteriocidal
- Major Side effects:
  - C. diff, N/V, CNS (headache, dizziness, delirium, hallucinations), QTc prolongation, hypersensitivity skin reactions
  - seizures (rare), arthropathy in adolescents (rare), tendon rupture (rare)
- Major drug interactions:
  - other QTc prolonging agents
  - CYP 1A2 inhibitor: Theophylline, caffeine, clozapine, methadone, tizanidine
  - Calcium/magnesium/aluminum/zinc: significantly bind the drug
- All have nearly 100% oral bioavailability
FLUOROQUINOLONES

• Ciprofloxacin:
  • Best **gram negative** fluoroquinolone
  • Covers *P. aeruginosa*
  • Less reliable gram positive coverage (NOT a respiratory fluoroquinolone)

• Moxifloxacin
  • Best **gram positive** fluoroquinolone
  • Drug of choice for multi drug resistant *Streptococcus pneumoniae*
  • Does NOT cover *P. aeruginosa*
  • Does NOT get appreciable drug concentration in the urine

• Levofloxacain
  • Coverage is in the middle of other 2 agents
  • Covers *P. aeruginosa* and *S. pneumoniae*
• Resistance
  • Most common type of resistance occurs spontaneously by chromosomal mutation
    • Occurs most often when there are large bacterial burdens and/or when the drug concentration at the site is less than the MIC of some of the more resistant organisms.
    • Most commonly seen with *S. aureus* and *P. aeruginosa*
  • Plasmid-mediated resistance that can be passed to other bacteria
  • Efflux pumps
MACROLIDES\textsuperscript{9}

• MOA: inhibit RNA-dependent protein synthesis
  • Bacteriostatic
• Major side effects:
  • Significant nausea/vomiting/diarrhea
  • QTc prolongation

\textbf{FIGURE 29-2} Azithromycin base.
MACROLIDES\(^9\)

- **Erythromycin**
  - No longer used as an antibiotic
  - Increased resistance, many side effects, dosed 4x/day
- **Azithromycin**
  - Improved gram negative coverage, notably *H. influenzae* and *M. catarrhalis*
  - Still associated with GI toxicity, but less than erythromycin
  - Significant tissue distribution
    - Exceeds serum concentrations 10-100 fold
    - Half life 2-4 days
- **Clarithromycin**
  - Improved gram positive coverage
  - Mainly used for *M. avium*
  - Significant GI upset, as well as tinnitus at higher doses
CLINDAMYCIN\textsuperscript{9}

- MOA: inhibits protein synthesis by binding to 50s ribosomal subunit
- Spectrum of activity: streptococcus, staphylococcus (including MRSA), anaerobes
  - Increasing \textit{S. pneumoniae} resistance
  - Inducible resistance in \textit{S. aureus} (D-test)
  - Covers all anaerobes, but resistance to \textit{B. fragilis} is now common and it is no longer recommended empirically
- Major side effects:
  - \textit{C. diff}
  - GI upset and diarrhea
  - Allergic reactions
VANCOMYCIN\textsuperscript{10}

- Covers all gram positive organisms
- MOA: Inhibits late stages of cell wall synthesis
  - Bacteriocidal with staph and strep, but bacteriostatic with enterococcus
- Metabolism: none
  - Excreted unchanged by the kidney
- Major side effects:
  - Red Man’s Syndrome (NOT an allergy!)
  - Nephrotoxicity (5%)
  - Ototoxicity (rare)
VANCOMYCIN$^{10}$

- Best described pharmacodynamic principle for efficacy is AUC/MIC ratio
  - This is estimated by measuring a trough
  - Serious infections (endocarditis, bacteremia, sepsis, pneumonia, etc): goal trough 15-20
  - All other infections goal trough 10-15
- Distribution into tissues is poor
  - Epithelial lining fluid (ELF) of lung: 16% serum concentration
  - CSF: 5-10% serum concentration
  - Soft tissue concentrations lower in diabetics than in non-diabetics
VANCOMYCIN\textsuperscript{10}

- Resistance
  - **Enterococcus (VRE)**
    - VanA gene most common cause
    - Causes formation of peptidoglycan precursors that have a lower affinity for vanco
    - Results in full vanco resistance (MIC $\geq$ 32)
  - **Staph aureus**
    - Caused by cell wall changes, most notably thickened cell wall
    - Causes ”MIC creep” (VISA, but no true VRSA)
    - hVISA: subpopulations of cells that can grow in the presence of vanco
    - Very recently, a few strains of VRSA have arisen that seem to have inherited the VanA enterococcus vancomycin resistance gene
DAPTOMYCIN

• Covers all gram positive organisms
• Concentration dependent, rapidly bacteriocidal
• MOA: interacts with and disrupts the cell membrane potential in a calcium-dependent manner
  • Not entirely understood
  • Does not cause cell lysis like most other antibiotics
• Metabolism: excreted unchanged in urine
• Major side effects: Increased CPK, skeletal muscle toxicity, eosinophilic pneumonia
DAPTOMYCIN

- Resistance
  - Rare true resistance, but there is some decreased susceptibility
  - Most often seen in patients with persistent bacteremia and/or undrained sources of infection
  - Isolates are susceptible initially, but after clinical failure they are cultured again and the organism is now resistant.
  - More commonly seen in enterococcus, but also seen in staph
LINEZOLID

• Member of new class of antibiotics entirely synthesized called oxazolidinones
• Covers all gram positive bacteria, but bacteriostatic
  • Also effective against *Mycobacterium tuberculosis* and *Mycobacterium avium* complex
• MOA: bind to 50s ribosome and inhibit protein synthesis
• Metabolism: oxidation (no CYP interactions)
• Available IV and po (100% bioavailable)
LINEZOLID

- Adverse drug reactions
  - Myelosuppression
    - Thrombocytopenia: 47% occurrence with >10 days therapy
  - Serotonin syndrome
    - It is a reversible nonselective monoamine-oxidase inhibitor
    - Seen with patients started on linezolid who are also on other serotonin agents
  - Peripheral neuropathy (more common than originally reported)
  - Optic neuropathy
    - Gradual onset of blurring
    - If continued, can lead to permanent vision loss
DISEASE STATES
PNEUMONIA

CAP\textsuperscript{13}
- Pneumonia in a patient who resides in the community
- Pneumonia occurring in a patient within the first 48 hours of hospital admission

HAP/HCAP\textsuperscript{14}
- HAP: pneumonia that occurs 48 hours or more after hospital admission
- VAP: pneumonia that occurs more than 48-72 hours after intubation
- HCAP: pneumonia in patients hospitalized for >2 days in the past 90 days, received abx in the past 30 days, reside in longterm care
PNEUMONIA

**CAP**
- Streptococcus pneumoniae
- Mycoplasma pneumoniae
- Haemophilus influenzae
- Chlamidophila pneumoniae
- Legionella

**HAP**
- Streptococcus pneumoniae
- Haemophilus influenzae
- Staphylococcus aureus
- Pseudomonas aeruginosa
- E. coli
- Klebsiella pneumoniae
- Enterobacter species
COMMUNITY ACQUIRED PNEUMONIA

Outpatient treatment

1. Previously healthy and no use of antimicrobials within the previous 3 months
   - A macrolide (strong recommendation; level I evidence)
   - Doxycycline (weak recommendation; level III evidence)

2. Presence of comorbidities such as chronic heart, lung, liver or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; or use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected)
   - A respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin [750 mg]) (strong recommendation; level I evidence)
   - A β-lactam plus a macrolide (strong recommendation; level I evidence)

3. In regions with a high rate (>25%) of infection with high-level (MIC >16 µg/mL) macrolide-resistant Streptococcus pneumoniae, consider use of alternative agents listed above in (2) for patients without comorbidities (moderate recommendation; level III evidence)
## COMMUNITY ACQUIRED PNEUMONIA

### Concord Hospital Laboratory

#### ANTIMICROBIAL SUSCEPTIBILITY SUMMARY

**JANUARY - DECEMBER 2014**

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<th>Amoxicillin/Clavulanate</th>
<th>Amikacin</th>
<th>Azithromycin</th>
<th>Chloramphenicol</th>
<th>Colistin</th>
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<td>84 23</td>
<td>100</td>
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<tr>
<td>Staphylococcus aureus, MRSA</td>
<td>459</td>
<td>48 64 100</td>
<td>99 15</td>
<td>99</td>
<td>49 100</td>
<td>98 70</td>
<td>99</td>
<td>96 100</td>
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<tr>
<td>Staphylococcus aureus, MSSA</td>
<td>1134</td>
<td>93 82 100</td>
<td>99 74</td>
<td>100</td>
<td>94 100</td>
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<tr>
<td>Staphylococcus Coag/Aggl Neg</td>
<td>240</td>
<td>58 69 100</td>
<td>93 49</td>
<td>92</td>
<td>58 100</td>
<td>99 76</td>
<td>55 100</td>
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<td>87 100</td>
<td>66 99</td>
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<tr>
<td>Staphylococcus lugdunensis</td>
<td>23</td>
<td>100 87 100</td>
<td>87</td>
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<tr>
<td>Streptococcus pneumoniae</td>
<td>58</td>
<td>38</td>
<td>97</td>
<td>98</td>
<td>72</td>
<td>98</td>
<td>72</td>
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</tr>
</tbody>
</table>
COMMUNITY ACQUIRED PNEUMONIA

- Inpatients, non-ICU treatment
  - A respiratory fluoroquinolone (strong recommendation; level I evidence)
  - A β-lactam plus a macrolide (strong recommendation; level I evidence)
- Inpatients, ICU treatment
  - A β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin (level II evidence) or a respiratory fluoroquinolone (level I evidence) (strong recommendation) (for penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended)
**HOSPITAL ACQUIRED PNEUMONIA**

### TABLE 4. INITIAL EMPIRIC THERAPY FOR HOSPITAL-ACQUIRED PNEUMONIA, VENTILATOR-ASSOCIATED PNEUMONIA, AND HEALTHCARE-ASSOCIATED PNEUMONIA IN PATIENTS WITH LATE-ONSET DISEASE OR RISK FACTORS FOR MULTIDRUG-RESISTANT PATHOGENS AND ALL DISEASE SEVERITY

<table>
<thead>
<tr>
<th>Potential Pathogens</th>
<th>Combination Antibiotic Therapy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogens listed in Table 3 and MDR pathogens</td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td><em>Antipseudomonal cephalosporin</em></td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em> (ESBL⁺)</td>
<td><em>(cefepime, ceftazidime)</em></td>
</tr>
<tr>
<td><em>Acinetobacter species</em>⁺</td>
<td>or</td>
</tr>
<tr>
<td><em>Antipseudomonal carbepenem</em></td>
<td><em>(imipenem or meropenem)</em></td>
</tr>
<tr>
<td>or <em>β-Lactam/β-lactamase inhibitor</em></td>
<td><em>(piperacillin–tazobactam)</em></td>
</tr>
<tr>
<td>plus</td>
<td></td>
</tr>
<tr>
<td><em>Antipseudomonal fluoroquinolone</em></td>
<td><em>(ciprofloxacin or levofloxacin)</em></td>
</tr>
<tr>
<td>or <em>Aminoglycoside</em></td>
<td><em>(amikacin, gentamicin, or tobramycin)</em></td>
</tr>
<tr>
<td>plus</td>
<td></td>
</tr>
<tr>
<td>Methicillin-resistant <em>Staphylococcus aureus</em> (MRSA)</td>
<td><em>Linezolid or vancomycin</em>⁺</td>
</tr>
<tr>
<td><em>Legionella pneumophila</em>⁺</td>
<td></td>
</tr>
<tr>
<td>Antibiotic</td>
<td>Dosage*</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>Antipseudomonal cephalosporin</td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td>1–2 g every 8–12 h</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>2 g every 8 h</td>
</tr>
<tr>
<td>Carbepenems</td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>500 mg every 6 h or 1 g every 8 h</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1 g every 8 h</td>
</tr>
<tr>
<td>β-Lactam/β-lactamase inhibitor</td>
<td></td>
</tr>
<tr>
<td>Piperacillin–tazobactam</td>
<td>4.5 g every 6 h</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>7 mg/kg per d†</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>7 mg/kg per d†</td>
</tr>
<tr>
<td>Amikacin</td>
<td>20 mg/kg per d†</td>
</tr>
<tr>
<td>Antipseudomonal quinolones</td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>750 mg every d</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>400 mg every 8 h</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>15 mg/kg every 12 h†</td>
</tr>
<tr>
<td>Linezolid</td>
<td>600 mg every 12 h†</td>
</tr>
</tbody>
</table>

* Dosages are based on normal renal and hepatic function.
† Trough levels for gentamicin and tobramycin should be less than 1 μg/ml, and for amikacin they should be less than 4–5 μg/ml.
‡ Trough levels for vancomycin should be 15–20 μg/ml.
DURATION OF TREATMENT FOR PNEUMONIA

**CAP**
- 5 days
  - Studies have proved as effective as 7-10 days
  - Patient should be stable and afebrile for 48-72 hours

**HAP/HCAP**
- De-escalation!!!
- 7 days
  - If empiric antibiotic appropriate and patient improving
  - Studies show as effective as 14-21 days therapy
- Exception: *P. aeruginosa* and *S. aureus*
  - Require more prolonged course
URINARY TRACT INFECTIONS
UNCOMPLICATED URINARY TRACT INFECTIONS

- Premenopausal, non-pregnant women with no urologic abnormalities
- Overwhelmingly caused by *E. coli* (75-90%)
- Guidelines put emphasis on “collateral damage”
  - “a term describing ecological adverse effects of antimicrobial therapy, such as the selection of drug-resistant organisms and colonization or infection with multidrug-resistant organisms”
  - Risk vs benefit of drug selection
UNCOMPPLICATED UTI

Level 1 Recommendations

- Nitrofurantoin 100mg po bid x5 days
- Bactrim DS (160/800) po bid x3 days
  - If local resistance does not exceed 20%
- Fosfomycin 3g po x1

Level 2 Recommendations

- Ciprofloxacin 250mg po bid x3 days or levofloxacin 250mg po daily x3 days
- Augmentin, cefaclor, cefdinir, cefpodoxime, cephalexin (x3-7 days)
  - NOT amoxicillin or ampicillin (unless known enterococcus)
ACUTE UNCOMPPLICATED PYELONEPHRITIS

- Still most commonly caused by *E.coli*, but culture and sensitivity is recommended for all cases
- Ciprofloxacin 500mg po bid x 7 days or Ciprofloxacin ER 1000mg po daily x7 days
- Levofloxacin 750mg po daily x 5 days
- Bactrim DS po bid x14 days (with initial 1g IM/IV ceftriaxone)
COMPLICATED UTI

- UTI in patients with an underlying condition that increases their likelihood of failing therapy
  - Diabetes, pregnancy, obstructing stone, hospital acquired, immunosuppression
- Still most commonly caused by *E. coli*, but other organisms as well such as proteus, klebsiella, serratia, enterococcus, staph, and pseudomonas.
- The organisms seen in complicated UTIs are often more resistant
  - ESBL-producing *E. coli*, *P. mirabilis*, and *K. pneumoniae*
  - Fluoroquinolone-resistant *E. coli*
  - VRE
COMPLICATED UTI<sup>16</sup>

- Because a broader range of organisms can cause complicated UTIs and these organisms tend to be more resistant, the empiric therapy is more broad spectrum than for uncomplicated UTI and the treatment is longer.
  - Ciprofloxacin 500mg po bid x 5-10 days
  - Levofloxacin 750mg po daily x 5-10 days
  - Ceftriaxone 1g iv q24h x 5-10 days
  - Ertapenem 1g IV q24h x 5-10 days
- Bactrim, macrobid, fosfomycin, and oral β-lactams not appropriate for empiric treatment.
  - Can be used if sensitive when culture results are available
UTI CLINICAL PEARLS

• Macrobid: CANNOT be used in patients with a CrCl < 60
  • Does not work
  • Increased risk of side effects
  • All risk, no benefit

• Bactrim: MUST be dose adjusted in patients with CrCl < 30
  • Causes crystallization in urine which leads to renal failure, hyperkalemia, and hypoglycemia
  • Use extreme caution in elderly patients (drink water!)
  • Should NOT be used with patients on warfarin

• Ciprofloxacin: MUST be dose adjusted in patients with CrCl < 30
  • Increased risk of side effects in elderly patients
SKIN AND SOFT TISSUE INFECTIONS
SKIN AND SOFT TISSUE INFECTIONS

MANAGEMENT OF SSTIs

NONPURULENT Nonosteocrine Infection/Cutaneous/Erysipelas

Severe

Moderate

Mild

INTRAVENTIOUS Rx

• Penicillin or
• Ceftriaxone or
• Cefazolin or
• Clindamycin

ORAL Rx

• Penicillin VK or
• Cephalosporin or
• Dicloxacillin or
• Clindamycin

I & D C & S

PURULENT Furuncle/Carbuncle/Abcess

Severe

Moderate

Mild

EMPIRIC Rx

• Vancomycin or
• Daptomycin or
• Linezolid or
• Telavancin or
• Ceftaroline

EMPIRIC Rx

• TMP/SMX or
• Doxycycline

Defined Rx

Necrotizing infections

Monomicrobial Streptococcus pyogenes
• Penicillin PLUS Clindamycin
• Clindamycin

Clostridial sp.
• Penicillin PLUS Clindamycin

Vibrio vulnificus
• Doxycycline PLUS Ceftazidine
• Aeromonas hydrophila
• Doxycycline PLUS Ciprofloxacin

Polymeric
• Vancomycin PLUS Piperacillin/Tazobactam

C & S

I & D

I & D

I & D

I & D

Since daptomycin and televancin are not approved for use in children, vancomycin is recommended; clindamycin may be used if clindamycin resistance is <10-15% at the institution.
CELLULITIS

• Nonpurulent cellulitis
  • Treatment should be directed towards covering streptococcus
  • MRSA is a very uncommon cause of nonpurulent cellulitis
    • One study showed treatment without MRSA coverage was 96% effective
  • Mild: cephalexin 500mg po q6h, clindamycin 300mg po q6h
  • Moderate: Ceftriaxone 1g IV q24h, Cefazolin 1g IV q8h
  • Severe: Zosyn 3.375g IV q6h + Vancomycin (goal tr 15-20)
    • Evaluation for necrotizing fasciitis
  • Treatment duration of mild to moderate is 5 days (if improved)
• In some instances, it is recommended to include *S. aureus* coverage
  • IVDU, penetrating trauma
CELLULITIS

- **Purulent SSTIs/Abscesses**
  - The initial treatment of all abscesses is appropriate incision and drainage.
  - Antibiotics not required unless patient has systemic signs and symptoms, is immunocompromised, or doesn’t improve despite adequate drainage.
  - If antibiotics are given, therapy is directed towards *S. aureus*, both MSSA and CA-MRSA.
    - Bactrim DS 1 tablet po bid
    - Doxycycline 100mg po bid
    - Vancomycin IV (goal tr 10-15)
    - Daptomycin 6mg/kg IV q24h
  - Antibiotics can be adjusted based on culture results when available.
  - Duration of treatment: 5-10 days.
# Diabetic Foot Infections

<table>
<thead>
<tr>
<th>Clinical Manifestation of Infection</th>
<th>PEDIS Grade</th>
<th>IDSA Infection Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms or signs of infection</td>
<td>1</td>
<td>Uninfected</td>
</tr>
<tr>
<td>Infection present, as defined by the presence of at least 2 of the following items:</td>
<td></td>
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<tr>
<td>- Local swelling or induration</td>
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<tr>
<td>- Erythema</td>
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<tr>
<td>- Local tenderness or pain</td>
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<tr>
<td>- Local warmth</td>
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<tr>
<td>- Purulent discharge (thick, opaque to white or sanguineous secretion)</td>
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<tr>
<td>Local infection involving only the skin and the subcutaneous tissue (without involvement of deeper tissues and without systemic signs as described below). If erythema, must be &gt;0.5 cm to ≤2 cm around the ulcer. Exclude other causes of an inflammatory response of the skin (eg, trauma, gout, acute Charcot neuro-osteoarthropathy, fracture, thrombosis, venous stasis).</td>
<td>2</td>
<td>Mild</td>
</tr>
<tr>
<td>Local infection (as described above) with erythema &gt;2 cm, or involving structures deeper than skin and subcutaneous tissues (eg, abscess, osteomyelitis, septic arthritis, fasciitis), and No systemic inflammatory response signs (as described below)</td>
<td>3</td>
<td>Moderate</td>
</tr>
<tr>
<td>Local infection (as described above) with the signs of SIRS, as manifested by ≥2 of the following:</td>
<td>4</td>
<td>Severe</td>
</tr>
<tr>
<td>- Temperature &gt;38°C or &lt;36°C</td>
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<tr>
<td>- Heart rate &gt;90 beats/min</td>
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<tr>
<td>- Respiratory rate &gt;20 breaths/min or PaCO₂ &lt;32 mm Hg</td>
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<tr>
<td>- White blood cell count &gt;12,000 or &lt;4000 cells/μL or ≥10% immature (band) forms</td>
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<td></td>
</tr>
<tr>
<td>Site of Infection, by Severity or Extent</td>
<td>Route of Administration</td>
<td>Setting</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Soft-tissue only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>Topical or oral</td>
<td>Outpatient</td>
</tr>
<tr>
<td>Moderate</td>
<td>Oral (or initial parenteral)</td>
<td>Outpatient/inpatient</td>
</tr>
<tr>
<td>Severe</td>
<td>Initial parenteral, switch to oral when possible</td>
<td>Inpatient, then outpatient</td>
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<tr>
<td>Bone or joint</td>
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<tr>
<td>No residual infected tissue (e.g., postamputation)</td>
<td>Parenteral or oral</td>
<td>...</td>
</tr>
<tr>
<td>Residual infected soft tissue (but not bone)</td>
<td>Parenteral or oral</td>
<td>...</td>
</tr>
<tr>
<td>Residual infected (but viable) bone</td>
<td>Initial parenteral, then consider oral switch</td>
<td>...</td>
</tr>
<tr>
<td>No surgery, or residual dead bone postoperatively</td>
<td>Initial parenteral, then consider oral switch</td>
<td>...</td>
</tr>
</tbody>
</table>
DIABETIC FOOT INFECTIONS

• Mild: can generally use narrow spectrum oral therapy targeted at gram positive organisms only
  • Clindamycin, cephalexin, Augmentin, Bactrim
  • Can combine 2 oral agents to maximize strep and staph coverage
    • Augmentin and Bactrim, cephalexin and Bactrim
• Treatment duration 1-3 weeks
DIABETIC FOOT INFECTIONS

• Moderate and Severe
  • Generally requires IV therapy at least initially
  • Empiric coverage should be broad spectrum
    • Gram positive organisms (including MRSA)
    • Gram negative organisms (pseudomonas not required to be covered)
    • Anaerobes
  • Cultures should be obtained and therapy should be changed as needed based on cultures results
    • Organisms often considered contaminants (CAN staph) can be pathogenic
    • Pseudomonas often not pathogenic
    • If patient improving on empiric treatment despite not covering an organism, recommend continuing current therapy.
    • If patient not improving, recommend broadening therapy to cover all organisms
DIABETIC FOOT INFECTIONS

- Moderate to Severe empiric treatment
  - Ceftriaxone 2g IV q24h + Vancomycin (if MRSA risk factors)
  - Ertapenem 1g IV q24h + Vancomycin (if MRSA risk factors)
  - Zosyn 3.375g IV q6h + Vancomycin (if MRSA risk factors)
- Treatment duration: 2-4 weeks
  - Patients often receive IV antibiotics for duration of treatment
  - OPAT use is increasing
C DIFF\textsuperscript{19}

- *C. difficile* is a toxin producing organism that can range from nonsymptomatic carrier to fulminant pseudomembranous colitis
- Studies have shown 85-96% of cases were associated with antimicrobial use in the past 14-28 days.
  - Duration of antibiotic and number of antibiotics are positively associated with *C. difficile* infection
- All antibiotics have been associated with development of CDI
  - Cephalosporins, clindamycin, and fluoroquinolones most highly associated
  - Aminoglycosides, bactrim, zosyn, vancomycin, tigecycline have low incidence
- Narrowing therapy when appropriate is good, but discontinuing antibiotics when no longer appropriate is most effective in preventing CDI.
<table>
<thead>
<tr>
<th>Clinical definition</th>
<th>Supportive clinical data</th>
<th>Recommended treatment</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial episode, mild or moderate</td>
<td>Leukocytosis with a white blood cell count of 15,000 cells/µL or lower and a serum creatinine level less than 1.5 times the premorbid level</td>
<td>Metronidazole, 500 mg 3 times per day by mouth for 10–14 days</td>
<td>A-I</td>
</tr>
<tr>
<td>Initial episode, severe*</td>
<td>Leukocytosis with a white blood cell count of 15,000 cells/µL or higher or a serum creatinine level greater than or equal to 1.5 times the premorbid level</td>
<td>Vancomycin, 125 mg 4 times per day by mouth for 10–14 days</td>
<td>B-I</td>
</tr>
<tr>
<td>Initial episode, severe, complicated</td>
<td>Hypotension or shock, ileus, megacolon</td>
<td>Vancomycin, 500 mg 4 times per day by mouth or by nasogastric tube, plus metronidazole, 500 mg every 8 hours intravenously. If complete ileus, consider adding rectal instillation of vancomycin</td>
<td>C-III</td>
</tr>
<tr>
<td>First recurrence</td>
<td>...</td>
<td>Same as for initial episode</td>
<td>A-II</td>
</tr>
<tr>
<td>Second recurrence</td>
<td>...</td>
<td>Vancomycin in a tapered and/or pulsed regimen</td>
<td>B-III</td>
</tr>
</tbody>
</table>
C DIFF CLINICAL PEARLS

- Metronidazole should not be used past a second recurrence due to increased risk for neurotoxicity
- Metronidazole can be used po or IV (po preferred) but vanco can only be used po
- Vancomycin taper can be very effective in patients who have recurrence
  - Example taper: vancomycin 125 mg po qid x10-14 days, then 125mg po bid x1 week, then 125mg po daily x1 week, then 125mg every 2-3 days for 2-8 weeks.
- If patient needs to continue on antibiotics for another infection, metronidazole or vancomycin should be continued through the course of therapy and then 7-10 days after other antibiotics stopped.
- Avoid imodium/lomotil in documented C. diff
- Cholestyramine is contraindicated with oral vancomycin
- There is some evidence that PPI use may be associated with increased risk of CDI, but evidence is not strong
- Fecal transplants!
CONTACT INFO:
AMY BROOKS
ABROOKS@CRHC.ORG
CONCORD HOSPITAL
CONCORD, NH