Antibiotics 101: What Do I Need To Know?

Sloan B. Fleming, PharmD, BCPS
Clinical Pharmacist, Trauma Critical Care
Vanderbilt University Medical Center
April 21, 2010

Objectives

• Explain importance of Gram’s stain
• Distinguish between empiric, definitive, and prophylactic therapy
• Describe benefits & risks of common abx
• Discuss consequences of abx therapy
• Identify monitoring parameters

21 yo college student presents to ED with terrible HA and pain upon moving neck. VS: T 102.4, P 110, RR 18, BP 130/75. Labs wnl except WBC 22,500. Head CT nl. CSF gram stain shows gram-negative cocci. Which is the best empiric therapy?

(a) Penicillin G
(b) Ceftriaxone (Rocephin)
(c) Ceftriaxone plus dexamethasone
(d) Ceftriaxone plus vancomycin
Gram Stain

- Almost always the 1st test performed for identification of bacteria
- Differentiates bacteria into 2 groups: gram-positive and gram-negative
- Based on properties of bacterial cell wall (pos = purple/blue, neg = pink/red)
- Helps guide empiric therapy
3 Ways Antibiotics are Used

• **Empiric therapy** – given for proven or suspected infection, but *responsible organism(s) not yet identified*
• **Definitive therapy** – given for proven infection and *based on causative organism*
• **Prophylaxis** – given to *prevent* infection

Examples

• Transitioning from pip/tazo to ampicillin in patient with *Enterococcal* wound infxn susceptible to both
• Vancomycin + tobramycin + doripenem for ICU patient with probable VAP
• Cefazolin given before surgery to prevent *Staphylococcal* surgical site infxn

Getting Started

• Suspect an infection based on s/sx
• Obtain cultures
• Initiate *empiric* therapy
  – Based on likely pathogens, antibiogram, GS
  – Usually broad-spectrum
• Initiate *definitive* therapy when C&S known
  – Narrow spectrum
21 yo college student presents to ED with terrible HA and pain upon moving neck. VS: T 102.4, P 110, RR 18, BP 130/75. Labs wnl except WBC 22,500. Head CT nl. CSF gram stain shows gram-negative cocci. Which is the best empiric therapy?

(a) Penicillin G  
(b) Ceftriaxone (Rocephin®)  
(c) Ceftriaxone plus dexamethasone  
(d) Ceftriaxone plus vancomycin

**Antibacterial Drugs**

- Penicillins
- Cephalosporins
- Carbapenems
- Monobactams
- Glycopeptides
- Fluoroquinolones
- Aminoglycosides
- Tetracyclines
- Macrolides
- Oxazolidinones
- Sulfonamides
- Lincosamides

**Alteration of Cell Membrane**

- Polymyxins
- Bacitracin
- Neomycin

**DNA Replication**

- Ribosomes
- DNA Polymerase
- RNA Polymerase

**Protein Synthesis**

- tRNA
- mRNA
- rRNA
- Aminoacyl-tRNA
- Peptidyl-tRNA
- Eukaryotic initiation factor 2
- Elongation factor
- Translational factors

**Antimicrobials**

- Sulfonamides
- Dapsone
- Trimethoprim
- Pyrimethamine
- Pyrimethamine
- Dapsone
- Trimethoprim
- Chloroquine
- Chloroquine
- Sulfonamides
- Dapsone
- Trimethoprim
- Pyrimethamine
Beta-lactams

- Penicillins
  - Penicillin G, penicillin V
  - Nafcillin, oxacillin, dicloxacillin
  - Amoxicillin, ampicillin
  - Piperacillin, ticarcillin

- Cephalosporins

- Carbapenems

Penicillins

- Inhibit bacterial cell wall synthesis

- Penicillin G, penicillin V
- Nafcillin, oxacillin, dicloxacillin
- Amoxicillin, ampicillin
- Piperacillin, ticarcillin

Beta-lactamase

- Enzyme capable of destroying penicillins
- Breaks down the beta-lactam ring, making antibiotic ineffective
Beta-lactamase Inhibitor Combos

- Bind to beta-lactamase enzyme, protecting the beta-lactam ring
  - Amoxicillin/clavulanate (Augmentin®)
  - Ampicillin/sulbactam (Unasyn®)
  - Piperacillin/tazobactam (Zosyn®)
  - Ticarcillin/clavulanate (Timentin®)

Zosyn® Extended Infusion

- Retrospective cohort study in 194 patients with P. aeruginosa infection
  - Pip/tazo (Zosyn®)
    - 3.375g q4-6h (30 min)
    - 3.375g q8h (4 hour)

Lodise TP. Pharmacotherapy 2006;26:1320-32.

Why Extended Infusion?

VUMC Zosyn® Dosing Strategy

- CrCl > 20 = 3.375g q8h (4h infusion)
- CrCl < 20 = 3.375g q12h (4h infusion)
- Why?
  - Improved T > MIC
  - Reduced total daily dose
  - Cost savings
  - Circumvents practical limitations with CI

4-Hour Extended Infusion

Pipercillin/Tazobactam

Practical Considerations

- Administration timing
  - Use separate lines when possible
  - Use 4 hour antibiotic-free window
- Compatibility
  - Micromedex “IV Compatibility” feature
  - Contact pharmacy
EW is a 35yo F admitted to ortho service s/p MVC. Cefazolin 1g IV is ordered on call to OR for femur fx repair. Knowing that she is allergic to penicillin, what is the best initial action by the RN?

(a) Administer when OR calls for pt  
(b) Call MD to verify order accuracy  
(c) Administer following surgery  
(d) Ask patient about her rxn to penicillin

Cephalosporins

Inhibit bacterial cell wall synthesis

- Cefazolin, cephalexin
  - Gram-pos, skin infxns, surgical prophylaxis
- Ceftriaxone
  - Pneumonia, meningitis
- Cefepime
  - CAP/HAP, febrile neutropenia, *Pseudomonas*

Pre-op ABX: within 1h of Incision

<table>
<thead>
<tr>
<th>Measure Set ID</th>
<th>Performance Measure Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCP-Inf-1a</td>
<td>Prophylactic Antibiotic Received Within One Hour Prior to Surgical Incision - Overall Rate</td>
</tr>
<tr>
<td>SCP-Inf-1b</td>
<td>Prophylactic Antibiotic Received Within One Hour Prior to Surgical Incision - Ca/MO</td>
</tr>
<tr>
<td>SCP-Inf-1e</td>
<td>Prophylactic Antibiotic Received Within One Hour Prior to Surgical Incision - Other Cardiac Surgery</td>
</tr>
<tr>
<td>SCP-Inf-1d</td>
<td>Prophylactic Antibiotic Received Within One Hour Prior to Surgical Incision - Hip Arthroplasty</td>
</tr>
<tr>
<td>SCP-Inf-1e</td>
<td>Prophylactic Antibiotic Received Within One Hour Prior to Surgical Incision - Hip Arthroplasty</td>
</tr>
</tbody>
</table>
Abx received within 1h before incision: 98%

Concern for cross-reactivity

Penicillins

Cephalosporins

Penicillin Allergy

- Type 1 reactions
  - Mediated through IgE antibodies
  - Immediate
  - Anaphylaxis, urticaria (hives)

- Medical history taking is critical!
  - Distinguish allergic rxns from adverse rxns
  - Reaction?
**Are cephalosporins okay?**

- Cross-reactivity rate 5-10%
- Depends on reaction to penicillin
  - Not life-threatening – cephalosporins okay
  - Life-threatening – avoid cephalosporins
    - If no alternate abx – skin testing/desensitization
- Can order anaphylaxis kit
- Aztreonam is an option

**EW is a 35yo F admitted to ortho service s/p MVC. Cefazolin 1g IV is ordered on call to OR for femur fx repair. Knowing that she is allergic to penicillin, what is the best initial action by the RN?**

(a) Administer when OR calls for pt
(b) Call MD to verify order accuracy
(c) Administer following surgery
(d) Ask patient about her rxn to penicillin

**Carbapenems**

**Inhibit bacterial cell wall synthesis**

- Broadest-spectrum beta-lactam
- Imipenem/cilastatin
- Meropenem
- Ertapenem
- Doripenem

Stable against extended spectrum beta-lactamases (ESBLs)
A 50 yo F has been in the ICU x 2 weeks. Hospital course complicated by BSI and sepsis, requiring prolonged courses of abx. Her 10:00 meds include both vanc 1g IV and vanc 125mg PT. What is the best initial action by the RN?

(a) Administer meds as ordered  
(b) Ask Rx to change vanc IV to 12:00  
(c) Discontinue vanc PT in CPOE  
(d) Call MD to verify order accuracy

**Vancomycin**

- **MRSA, Enterococcus, Clostridium**  
  - *C difficile* – PO/PT  
  - Other infections – IV

- Infuse slowly to prevent red man syndrome  
  - 1000mg=60 min; 1500mg=90 min; 2000mg=120 min

- Bigger doses require bigger volumes

- May monitor trough levels (goal 15-20)
Aminoglycosides

<table>
<thead>
<tr>
<th>Inhibit protein synthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Gentamicin, tobramycin, amikacin</td>
</tr>
<tr>
<td>• Gram-positive + gram-negative infxns</td>
</tr>
<tr>
<td>• Usually in combo with 2nd drug</td>
</tr>
<tr>
<td>• Nephrotoxicity, ototoxicity</td>
</tr>
<tr>
<td>• Monitor levels</td>
</tr>
</tbody>
</table>

61 yo F with DM, ESRD, hep C cirrhosis. Admit for *Enterobacter* SBP + bacteremia. She was treated with levofloxacin IV until cx (-), and discharged on oral levofloxacin. Readmitted 15d later with s/sx SBP. Which of her home meds could have caused subtherapeutic abx concentrations?

(a) Insulin  
(b) Benazepril  
(c) Aluminum hydroxide  
(d) Metoprolol

Fluoroquinolones

<table>
<thead>
<tr>
<th>Inhibit DNA gyrase</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ciprofloxacin, Ofloxacin, Levofloxacin, Moxifloxacin, Gemifloxacin</td>
</tr>
<tr>
<td>• Resistance on the rise!</td>
</tr>
<tr>
<td>• Chelate cations – separate PO/PT by 2h</td>
</tr>
<tr>
<td>• May cause prolongation of QT interval</td>
</tr>
</tbody>
</table>
61 yo F with DM, ESRD, hep C cirrhosis. Admit for Enterobacter SBP + bacteremia. She was treated with levofloxacin IV until cx (-), and discharged on oral levofloxacin. Readmitted 15d later with s/sx SBP. Which of her home meds could have caused subtherapeutic abx concentrations?

(a) Insulin
(b) Benazepril
(c) Aluminum hydroxide
(d) Metoprolol

Tetracyclines

Inhibit protein synthesis

- Tetracycline, doxycycline, minocycline
- Bronchitis, sinusitis, tick-borne dz, malaria
- Chelate cations – separate PO by 2 hours
- N/V, photosensitivity, tooth discoloration
- Tigecycline (glycylcycline)
  - Broad-spectrum, IV only, N/V, restricted to ID

Macrolides

Inhibit protein synthesis

- Erythromycin, Clarithromycin, Azithromycin
- GI motility, respiratory, H Pylori, STDs
- N/V/D, metallic taste, QT prolong, drug ix
- Azithromycin – fewer drug ix, longer t\textsubscript{1/2}
58 yo F s/p abdominal surgery. Her meds include cefepime, metronidazole, lisinopril, and warfarin. You notice that during a.m. rounds, the medical team discontinues metronidazole. Which of the following lab abnormalities may have prompted this?

(a) SCr incr from 1.0 to 2.0
(b) K+ incr from 4.4 to 4.8 meq/L
(c) INR incr from 3.0 to 4.0
(d) Na+ decr from 140 to 135 meq/L

**Metronidazole**

- **Anaerobic infections**
- Intra-abdom, abscess, protozoa, H pylori
- N/V/D, significant drug ix with warfarin

Clinical Practice Guidelines for *Clostridium difficile*
Infection in Adults. 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA)

29. Metronidazole is the drug of choice for the initial episode of mild-to-moderate C. diff. The dosage is 500 mg orally 3 times per day for 10–14 days. (A-I)

**Clindamycin**

- Inhibits protein synthesis
- Anaerobes, *Staph, Strep*
- Alternative to penicillin in allergy
- Diarrhea (+/- *C difficile*)
- SSTI, infxs of oral cavity

**TMP/SMZ**

- Inhibits folic acid synthesis
- UTI, PCP, meningitis, MRSA
- GI, rash, bm suppression, hyperK
- Significant drug ix with warfarin
- Insoluble in IV solutions --- large volumes
- Short expiration --- call Rx for dose

**Linezolid**

- Inhibits protein synthesis
- MRSA, VRE
- Thrombocytopenia, peripheral neuropathy, optic neuropathy
- Watch for serotonin syndrome with SSRIs
- $$, resistance emerging
Daptomycin

Disrupts cell membrane

- MRSA, VRE
- Ineffective for pneumonia
- Muscle pain/weakness – monitor CK
- May falsely increase INR
  - Draw coag labs just prior to dapto dose
- $\$, restricted to ID

Antifungal Drugs

- Polyenes
- Azoles
- Echinocandins
- Antimetabolites

Amphotericin B

- Nephrotoxicity
  - NS before and after infusion
  - Potassium + magnesium supplementation
- Infusion-related reactions
  - Fever, chills, rigors
  - APAP, diphenhydramine, meperidine
- Lipid formulations are safer
Azoles

- **Fluconazole** – Candidiasis, QT prolong
- **Itraconazole** – Hepatotoxic, erratic absorp
- **Voriconazole** – Aspergillosis, visual effects
- **Posaconazole** – Prophylaxis in neutropenia, PO only, admin with meals
- Inhibit fungal cytochrome P450 --- drug ix

Echinocandins

- Caspofungin, **micafungin**, anidulafungin
- Invasive Candidiasis
- Fewer drug ix, excellent safety profile
- IV only
- $$

Adverse Consequences

- Allergy
- Superinfection
- Antibiotic resistance
- Toxicities
Resistant Strains

Resistant Strains Dominant

Antimicrobial Exposure

Resistant Strains Rare

Selection for abx-resistant Strains

Negative Impact of Resistance

- Risk of death
- Length of stay
- ICU transfer
- Cost of care
- Adverse events

- Safety of care
- Contact with HCP
Lifespan of new ABX?

Short-term success, but long-term treatment failure with linezolid for enterococcal endocarditis

Antibiotic Toxicities

- Gastrointestinal effects
- CNS toxicity
- Hematologic toxicity
- Renal toxicity
- Ototoxicity
- Photosensitivity
- Dermatologic

Monitoring Parameters

- Side effects
- Allergic reactions
- Signs/symptoms of infection
- Cultures
- Superinfection (e.g. *C difficile*)
- Drug levels
23 yo M admitted to BICU s/p electrocution. On hosp day 6, develops *Pseudomonas* pneumonia, treated with cefepime 2g q12h + amikacin 600mg q8h. P/T ordered for 3rd dose, due at 20:00. At 19:30, draw trough & hang dose. When should peak be drawn?

(a) 20:00  
(b) 20:30  
(c) 21:00  
(d) 21:30

**Therapeutic Drug Monitoring**

- Measurement of drug levels in the blood
- Used to determine most effective dose and to prevent toxicity
- Examples: anti-seizure drugs, lithium, antiarrhythmics, immunosuppressants, digoxin, aminoglycosides, vancomycin
- Goals differ with drug + site of infection
Timing of Specimen Collection

- **Single most important factor** in TDM
- **Peak** = highest drug concentration
  - 30 min after end of infusion
- **Trough** = lowest drug concentration
  - Immediately before next dose due

*Levels must be drawn appropriately in order to be accurately interpreted!*

---

23 yo M admitted to BICU s/p electrocution. On hosp day 6, develops *Pseudomonas* pneumonia, treated with cefepime 2g q12h + amikacin 600mg q8h. P/T ordered for 3rd dose, due at 20:00. At 19:30, draw trough & hang dose. When should peak be drawn?

(a) 20:00  
(b) 20:30  
(c) 21:00  
(d) 21:30

---

Don’t forget to check the ‘frig

- Vancomycin
- Aminoglycosides
- Cefazolin + other cephalosporins
- Piperacillin/tazobactam
- Penicillin G
- Nafcillin
“Call For” IV Antibiotics

- Must call pharmacy for each dose
  - Short expiration or $$$
- Tmp/Smz
- Daptomycin
- Rifampin
- Voriconazole
- Amphotericin B lipid formulations

Take Home Points

- Gram’s stain helps guide empiric therapy
- Infuse pip/tazo + doripenem over 4h
- Always obtain nature of allergic reactions
- Don’t forget to check the ‘frig
- Peak 30 min after end of infusion; trough immediately before next dose due
- Use abx wisely

Antibiotics 101:
What Do I Need To Know?

Sloan B. Fleming, PharmD, BCPS
Clinical Pharmacist, Trauma Critical Care
Vanderbilt University Medical Center
April 21, 2010