USE AND MISUSE OF ANTIBIOTICS:
A FOCUS ON ANTIMICROBIAL STEWARDSHIP
SATURDAY/4:30-5:30PM

ACPE UAN: 0107-9999-17-007-L01-P 0.1 CEU/1.0 hr

Activity Type: Application-Based

Learning Objectives for Pharmacists: Upon completion of this CPE activity participants should be able to:
1. Evaluate a patient with a beta-lactam allergy and describe the clinical impact of antibiotic allergies
2. Review risk factors for and the appropriate diagnosis of C. difficile infection
3. Describe the clinical impact of antimicrobial resistance
4. Discuss the role of antimicrobial stewardship programs and outline essential antimicrobial stewardship activities
5. Select and dose antimicrobials with the goal of improving patient outcomes and reducing unintended consequences associated with antimicrobial therapy.

Speaker: Brett Heintz, B.S., PharmD, BCPS (AQ-ID), AAHIVE
Dr. Brett Heintz received his B.S. in cell and molecular biology at San Diego State University and his PharmD from the University of California, San Francisco. He completed residencies in pharmacy practice and infectious diseases at the University of California, Davis Medical Center. Dr. Heintz, a Pharmacy Specialist in Infectious Diseases and Internal Medicine, joined the Iowa City VA Health Care System in September 2012. As Clinical Associate Professor at the University of Iowa College of Pharmacy, he precepts pharmacy students, delivers didactic lectures and coordinates a pharmacotherapy course. His primary research and clinical interests include antimicrobial dosing in special populations, including renal failure, dialysis, hepatic failure and obesity and management of outpatient delivery of antimicrobial therapy. He has authored several articles and book chapters related to antimicrobial therapy and has presented at local, state, national, and international level meetings. He is also the recipient of several teaching awards.

Speaker Disclosure: Brett Heintz reports no actual or potential conflicts of interest in relation to this CPE activity. Off-label use of medications will be discussed during this presentation.
Use and Misuse of Antibiotics: A Focus on Antimicrobial Stewardship

Brett Heintz, B.S., PharmD, BCPS (AQ-ID), AAHIVE
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Iowa City Veterans Affairs Medical Center
Clinical Associate Professor of Pharmacy
University of Iowa College of Pharmacy

Disclosure

• No actual or potential conflicts of interest associated with this presentation

• Off-label use of medications will be discussed during this presentation
Learning Objectives

• Upon successful completion of this activity, participants should be able to:
  1. Be able to describe the clinical impact of antimicrobial resistance.
  2. Review common risk factors, in particular antimicrobial agents, associated with *Clostridium difficile* colonization and infection.
  3. Discuss the role of antimicrobial stewardship programs and outline some essential antimicrobial stewardship activities.
  4. Be able to appropriately select and dose antimicrobials with the goal of improving patient outcomes and reducing unintended consequences associated with antimicrobial therapy.
  5. Be able to appropriately evaluate a patient with a beta-lactam allergy & describe the clinical impact of antibiotic allergies.

Review: Antimicrobial Agents

• Spectrum of activity
  • Narrow-spectrum (limited range of bacteria)
    • Gram-positive, Gram-negative or anaerobes only
  • Broad-spectrum (wide range of bacteria)
    • Gram-positive, Gram-negative, and anaerobes
      • Carbapenems, β-lactam + BL inhibitors, moxifloxacin

• The concept of broad-spectrum can have different meanings based on practice environment and evaluation of resistance
Review: Antimicrobial Agents

• **Bacteriostatic**
  - Slow / inhibit growth by interfering with bacterial protein production without killing the bacteria\(^1\)

• **Bactericidal**
  - Ability to directly kill the bacteria by affecting cell-wall or cell-membrane structure OR DNA synthesis\(^1\)

• **Does it really matter: bactericidal vs. static?**
  - **NO**: if not deep infection in immunocompetent patient\(^1\)-\(^2\)

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The Blame Game: Definitions

- **Overuse**
  - Overall number of antibiotic prescriptions compared to benchmark

- **Misuse**
  - The specific antibiotic used is not optimal in the given setting
  - Broad-spectrum regimen to cover community-acquired infection
  - Treatment of a positive clinical culture/lab in absence of infection
  - Treatment of a presumed viral infection with an antibacterial agent
  - Failure to de-escalate to narrow-spectrum agent(s), when appropriate

- **Abuse**
  - Preference based on non-medical influences (financial, industry)

- **Inappropriate**
  - Suboptimal antimicrobial selection/dose/route/duration

Risks of Antimicrobials

- **Global Effects**
  - Remote / intangible to the patient & prescriber
  - Future loss of effectiveness
    - Promotion of resistance & more virulent pathogens

- **Individualized Effects**
  - More immediate and tangible
  - Drug safety & adverse drug reaction profile
    - Selection of resistance & *Clostridium difficile*
Relationship between antibiotic use, resistance, treatment failure and overall healthcare burden

- Increase in antibiotic use
- Increase in resistant strains
- Limited treatment alternatives
  - more antibiotics
  - increased resistance
  - Increased C. difficile
  - increased mortality
- Ineffective empiric therapy
  - increased morbidity
  - more antibiotics
  - increased resistance
- Increased use of healthcare resources
- Increased hospitalization
  - more antibiotics
  - increased resistance
  - Limited treatment alternatives
  - more antibiotics
  - increased resistance

Inadequate empiric therapy (selection\textsuperscript{1-5}, dosing\textsuperscript{6-10}) increases mortality and driven by resistance

![Graph showing mortality rates for Adequate and Inadequate therapy]

Clinical Impact of Antimicrobial Resistance

- Resistance is increasing at an alarming rate
  - Resistance is leaking out into the community
    - MRSA resistant to clindamycin and other oral antibiotics
    - *E. coli* resistance to TMP/SMX (Bactrim®), Cipro common
  - >50% of 2 million nosocomial infections in USA annually are caused by antibiotic-resistant bacteria

- Resistance is associated with worse outcomes
  - Morbidity & Mortality
  - Health-care Costs

Epidemiology of antibiotic resistance

Antibiotic Resistance* – A Global Problem

MRSA PRP ESBL VRE MBL VISA VRSA


Penicillin Vancomycin Carbapenem Vancomycin & teicoplanin Daptomycin Telavancin

Emergence → Spread

* ESCAPE: Enterococcus faecium (VRE), Staphylococcus aureus (MRSA), Clostridium difficile, Acinetobacter (MBL), Pseudomonas (MBL), Enterobacteriaceae (ESBL)

Antimicrobial Resistance Varies Globally1-7

United States/North America

<table>
<thead>
<tr>
<th>Strain</th>
<th>Resistance Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA1</td>
<td>59.5%</td>
</tr>
<tr>
<td>Pseudomonas/cefepime2</td>
<td>16.8%</td>
</tr>
<tr>
<td>Pseudomonas/PIP-TAZ2</td>
<td>10.3%</td>
</tr>
<tr>
<td>VRE1</td>
<td>29.5%</td>
</tr>
<tr>
<td>ESBL (Klebsiella pneumoniae)2</td>
<td>14.9%</td>
</tr>
<tr>
<td>Strap pneumonia/penicillin4</td>
<td>40.3%</td>
</tr>
</tbody>
</table>

Europe

<table>
<thead>
<tr>
<th>Strain</th>
<th>Resistance Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA3</td>
<td>28.8%</td>
</tr>
<tr>
<td>P aeruginosa/cefepime2</td>
<td>12.4%</td>
</tr>
<tr>
<td>P aeruginosa/PIP-TAZ2</td>
<td>14.0%</td>
</tr>
<tr>
<td>VRE3</td>
<td>4.4%</td>
</tr>
<tr>
<td>ESBL (K pneumoniae)3</td>
<td>17.3%</td>
</tr>
<tr>
<td>S pneumoniae/penicillin4</td>
<td>36.9%</td>
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Latin America

<table>
<thead>
<tr>
<th>Strain</th>
<th>Resistance Rate</th>
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</thead>
<tbody>
<tr>
<td>MRSA4</td>
<td>35.3%</td>
</tr>
<tr>
<td>P aeruginosa/cefepime2</td>
<td>13.9%</td>
</tr>
<tr>
<td>P aeruginosa/PIP-TAZ2</td>
<td>23.5%</td>
</tr>
<tr>
<td>VRE4</td>
<td>5.6%</td>
</tr>
<tr>
<td>ESBL (K pneumoniae)4</td>
<td>36.8%</td>
</tr>
<tr>
<td>S pneumoniae/penicillin4</td>
<td>40.3%</td>
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</table>

Asia Pacific

<table>
<thead>
<tr>
<th>Strain</th>
<th>Resistance Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA5</td>
<td>52%-67%</td>
</tr>
<tr>
<td>P aeruginosa/cefepime2</td>
<td>6.5%</td>
</tr>
<tr>
<td>P aeruginosa/PIP-TAZ2</td>
<td>10.8%</td>
</tr>
<tr>
<td>VRE5</td>
<td>1.9%-3%</td>
</tr>
<tr>
<td>ESBL (K pneumoniae)5</td>
<td>24.8%</td>
</tr>
<tr>
<td>S pneumoniae/penicillin4</td>
<td>60.4%</td>
</tr>
</tbody>
</table>

*Resistance rates for bloodstream infection isolates.
†Includes Japan, Taiwan, Hong Kong, and Singapore.

MRSA=Methicillin-resistant Staphylococcus aureus; PIP-TAZ=piperacillin-tazobactam; VRE=Vancomycin-resistant Enterococci; ESBL=extended-spectrum beta-lactamase

Methicillin-Resistant *S. aureus* (MRSA) Among Intensive Care Unit Patients, 1996-2015


Extended Spectrum Beta-lactamases (ESBLs)

Source: National Nosocomial Infections Surveillance (NNIS) System
Fluoroquinolone-Resistant 
*Pseudomonas aeruginosa*, 1996-2015

Source: National Nosocomial Infections Surveillance (NNIS) System

USA – New Antibacterial Agents Available

<table>
<thead>
<tr>
<th>Year</th>
<th>No. Approved</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>20</td>
<td>Multiple agents</td>
</tr>
<tr>
<td>1992</td>
<td>3</td>
<td>Cefpodoxime, lomefloxacin, temafloxacin</td>
</tr>
<tr>
<td>1993</td>
<td>1</td>
<td>Piperacillin/tazobactam</td>
</tr>
<tr>
<td>1994</td>
<td>0</td>
<td>Lowest number of agents since 1988</td>
</tr>
<tr>
<td>1995</td>
<td>2</td>
<td>Cefditoren, dirithromycin</td>
</tr>
<tr>
<td>1996</td>
<td>4</td>
<td>Cefepime, levofloxacin, meropenem, sparfloxacin</td>
</tr>
<tr>
<td>1997</td>
<td>2</td>
<td>Grepafloxacin, trovafloxacin</td>
</tr>
<tr>
<td>1998</td>
<td>0</td>
<td>Rivaled 1994</td>
</tr>
<tr>
<td>1999</td>
<td>3</td>
<td>Dalfopristin/quinupristin, gatifloxacin, moxifloxacin</td>
</tr>
<tr>
<td>2000</td>
<td>1</td>
<td>Linezolid</td>
</tr>
<tr>
<td>2001</td>
<td>2</td>
<td>Cefditoren, ertapenem</td>
</tr>
<tr>
<td>2002</td>
<td>0</td>
<td>Repeat of 1994 and 1998</td>
</tr>
<tr>
<td>2003</td>
<td>2</td>
<td>Daptomycin, gemifloxacin</td>
</tr>
<tr>
<td>2004</td>
<td>4</td>
<td>Nitazoxanide, rifaximin, tinidazole, telithromycin</td>
</tr>
<tr>
<td>2005</td>
<td>1</td>
<td>Tigecycline</td>
</tr>
<tr>
<td>2006-2016: doripenem, ceftaroline, telavancin/dalbavancin/oritavancin, fidaxomicin, tedizolid, ceftolozane/tazobactam, ceftazidime/avibactam</td>
<td>NO new MOA</td>
<td></td>
</tr>
</tbody>
</table>

Today’s Antibiotic Dilemma

BAD BUGS, NO DRUGS

As Antibiotic Discovery Stagnates ...
A Public Health Crisis Advances

Factors Affecting Emergence of Resistance

• Selective pressure
  • Conditions enhancing bacterial ability to develop resistance
    • *Biggest driver of resistance is antibiotic overuse or misuse*
  • Poor infection control

• Proliferation of resistant clones (multi-drug resistant)
  • *Sub-optimal dosing* promotes (selects for) resistance

• Inability to detect emerging phenotypes

• Nonhuman use: antibiotics in agriculture, livestock
  • Approximately 40% of all antibiotics are for animal use

Mechanisms of Antimicrobial Resistance

- **Innate resistance mechanisms** (*intrinsic resistance*)
- **Acquired from other sources** (*acquired resistance*)
  - Spontaneous mutations: changes in bacterial DNA
    - Structural genes
      - enzymatic activity, target-site/transport modification
    - Regulatory genes
      - increased expression or de-repression of regulator
  - Addition of new DNA:
    - Encoding inactivating enzymes, modified targets, regulatory
    - Plasmids, transfer of genes between bacteria

Emergence of Antimicrobial Resistance

* Acquisition of resistance genes (acquired resistance) accounts for most antimicrobial resistance among bacteria
Emergence of Antimicrobial Resistance

Resistant Strains
Rare

Antimicrobial Exposure

Resistant Strains
Dominant

VIDEO https://www.youtube.com/watch?v=yybsSqcB7mE
https://www.youtube.com/watch?v=plVkJV5lh

Antibiotic Use Drives Resistance

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Drugs shown to drive resistance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCN-Resistance Pneumococcus (PRP or PRSP)</td>
<td>Ampicillin, TMP-SMX, 1st G. Cephalosporins</td>
</tr>
<tr>
<td>Methicillin resistant S. aureus (MRSA)</td>
<td>Cephalosporins, β-lactams, Clindamycin, FQs</td>
</tr>
<tr>
<td>Vancomycin-resistant Enterococci (VRE)</td>
<td>Vancomycin, cephalosporins, β-lactams, Clindamycin, Metronidazole (anti-anaerobics)</td>
</tr>
<tr>
<td>Extended spectrum beta-lactamase (ESBL) enteric Gram-negative bacilli</td>
<td>3rd Generation cephalosporins, aztreonam, Anti-anaerobics: clindamycin, metronidazole, fluoroquinolones, ± carbapenems</td>
</tr>
<tr>
<td>Multi-drug resistant plasmid</td>
<td>Fluoroquinolones</td>
</tr>
</tbody>
</table>

* Not all inclusive – shown for example only – most referenced examples
**Beta-lactamases (Ambler Classification)**

<table>
<thead>
<tr>
<th>Active Site</th>
<th>Group</th>
<th>Gene(s)</th>
<th>Characterization</th>
<th>Substrate</th>
<th>Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serine-enzymes</td>
<td>A</td>
<td>TEM, SHV, CTX-M; KPC*</td>
<td>Penicillinases (Broad Spectrum and Extended Spectrum β-lactamases – ESBL)</td>
<td>Pen / Amp / Pip</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cephalosporins*</td>
<td>S-R</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Carbapenems*</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+ Clavulanic Acid</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>OXA</td>
<td>Oxacilllases</td>
<td>All Penicillins</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cephalosporins</td>
<td>S-R</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Carbapenems</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+ Clavulanic Acid</td>
<td>S-R</td>
</tr>
<tr>
<td>Zinc-enzyme</td>
<td>C</td>
<td>CMY, FOX, MIR</td>
<td>Cephalosporinases (Amp C Producers)</td>
<td>All Penicillins</td>
<td>R</td>
</tr>
<tr>
<td>(Metallo-protease)</td>
<td></td>
<td></td>
<td></td>
<td>Cephalosporins*</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Carbapenems</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+ Clavulanic Acid</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>IMP, VIM</td>
<td>Carbapenemases</td>
<td>All Penicillins</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cephalosporins</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Carbapenems</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+ Clavulanic Acid</td>
<td>R</td>
</tr>
</tbody>
</table>

* Broad spectrum BL renders 1st generation cephalosporins resistant. ESBLs render 3rd generation cephalosporins (oxymino-cefs) resistant.

**Clostridium difficile**

Associated Disease (CDAD)

What's the Link of Antibiotics and CDAD?
**C difficile: Risk Factors & Causes**


**C difficile: Antimicrobial Associations**

- Many antimicrobials associated with CDAD
  - High risk: **fluoroquinolones**, clindamycin, ceftriaxone
  - Length of antibiotic therapy is often a factor
  - Total usage is often a factor for driving local risks
  - Ability to alter GI flora & achievable GI concentrations
- Assess generalizability & clinical impact of studies
  - Some studies restricted or excluded various agents
  - Some studies assessed risk for colonization, not infection

**Clostridium difficile Colonization**

- Time-series analysis have shown antibiotics increase risk for *C. difficile* gut colonization.

<table>
<thead>
<tr>
<th>Strain</th>
<th>Log $^{10}$ CFU/mL of cecal contents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strain 1</td>
<td>3</td>
</tr>
<tr>
<td>Strain 2</td>
<td>4</td>
</tr>
<tr>
<td>Strain 3</td>
<td>5</td>
</tr>
</tbody>
</table>

**Restricted Antimicrobial agents**

- Pip/tazo
- Cefepime
- Aztreonam
- Metronidazole
- Ciprofloxacin

**Deplete gut flora**

- Clindamycin
- Aminoglycoside
- Penicillins
- TMP/SMX
- Vancomycin


**Clostridium difficile Infection - CDI**

- **CDI risk factors:** antibiotics & cumulative exposure
- **Multicenter retrospective cohort study**
  - 10,154 patients, 241 CDI cases: evaluated antibiotic exposure

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CDI +</th>
<th>CDI --</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI procedure</td>
<td>79 (33)</td>
<td>1360 (14)</td>
<td>2.6 (2.0-3.5)</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>8 (3)</td>
<td>174 (2)</td>
<td>2.1 (1.1-4.2)</td>
</tr>
<tr>
<td>Previous CDI</td>
<td>5 (2)</td>
<td>51 (1)</td>
<td>4.5 (1.8-11.2)</td>
</tr>
<tr>
<td>ICU Admission</td>
<td>104 (43)</td>
<td>2907 (29)</td>
<td>3.1 (2.1-4.7)</td>
</tr>
<tr>
<td>PPI/H2A</td>
<td>208 (86)</td>
<td>6757 (68)</td>
<td>2.8 (1.9-4.6)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>26 (11)</td>
<td>520 (5)</td>
<td>1.9 (1.3-2.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of Antibiotics</th>
<th>CDI +</th>
<th>CDI --</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31 (13)</td>
<td>3744 (38)</td>
<td>Reference</td>
</tr>
<tr>
<td>2</td>
<td>54 (22)</td>
<td>2507 (25)</td>
<td>2.5 (1.6-4.0)</td>
</tr>
<tr>
<td>3-4</td>
<td>70 (29)</td>
<td>2505 (25)</td>
<td>3.3 (2.5-5.2)</td>
</tr>
<tr>
<td>≥ 5</td>
<td>86 (36)</td>
<td>1157 (12)</td>
<td>9.6 (6.1-15.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antibiotic Class</th>
<th>CDI +</th>
<th>CDI --</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycoside</td>
<td>22 (9)</td>
<td>837 (8)</td>
<td>0.9 (0.3-3.0)</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Gen Ceph</td>
<td>94 (39)</td>
<td>3883 (39)</td>
<td>2.4 (1.4-4.1)</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; Gen Ceph</td>
<td>74 (31)</td>
<td>1527 (15)</td>
<td>3.1 (1.9, 5.2)</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>34 (14)</td>
<td>876 (9)</td>
<td>1.9 (0.8-4.4)</td>
</tr>
<tr>
<td>Macrolides</td>
<td>48 (20)</td>
<td>1266 (13)</td>
<td>1.5 (0.7-3.1)</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>37 (15)</td>
<td>981 (10)</td>
<td>0.3 (0.1-0.9)</td>
</tr>
<tr>
<td>PPI/H2A</td>
<td>208 (86)</td>
<td>6757 (68)</td>
<td>2.8 (1.9-4.6)</td>
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<td>CDI +</td>
<td>CDI --</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>-----------------------</td>
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<td>86 (36)</td>
<td>1157 (12)</td>
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</tr>
</tbody>
</table>

*All hazard ratios for time-dependent variables reflect comparisons between individuals with and without exposure at each event time.*

*Observed dose dependent increases in CDI risk with increasing cumulative dose, number of antibiotics, and days of antibiotic exposure.*

**Clostridium difficile infection - CDI**

- # of patients needed to be treated → CDI episode
  - Fluoroquinolones: 28 patients
  - Broad-spectrum cephalosporins: 37 patients
  - Amoxicillin-clavulanate: 94 patients

<table>
<thead>
<tr>
<th>Very High Risk</th>
<th>High Risk</th>
<th>Medium Risk</th>
<th>Low Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolones (moxi &gt; levo &gt; cipro)</td>
<td>3rd Generation Cephalosporins</td>
<td>Amoxicillin-clavulanate</td>
<td>Piperacillin-tazobactam</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>1st Gen. Ceph</td>
<td>Carbenems</td>
<td></td>
</tr>
<tr>
<td>2nd Gen. Ceph</td>
<td>Vancomycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macroldes</td>
<td>Metronistale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMP/SMX</td>
<td>Amoxicillin</td>
<td>Gentamcinc</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tetracyclines</td>
<td>Linzolid</td>
</tr>
</tbody>
</table>

Note: Restricted agents in study

Activity vs. C diff

No anaerobic activity (gut flora retained)

* Generally antibiotics with activity against gut/anaerobic flora associated with CDI

**Fluoroquinolone Use and CDAD**

- New endemic *C. difficile* strain (B1/NAP1) of great concern
  - More drug resistant, virulent and toxic with increased transmission
  - Fluoroquinolones significantly increase risk for B1/NAP1 strain
  - Recent retrospective cohort study found quinolones independently associated with B1/NAP1 upon multivariate analysis (OR 3.2, P< 0.001)

**Resistance of *C. difficile* isolates to various antimicrobial agents: risk for B1/NAP1**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Current B1/NAP1 Isolates, N=24 (%)</th>
<th>Current Non-B1/NAP1 Isolates, N=24 (%)</th>
<th>P-value</th>
<th>Historic B1/NAP1 Isolates, N=14 (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>19 (79)</td>
<td>19 (79)</td>
<td>1.0</td>
<td>10 (71)</td>
<td>0.7</td>
</tr>
<tr>
<td>Amox/clav</td>
<td>24 (100)</td>
<td>23 (96)</td>
<td>1.0</td>
<td>14 (100)</td>
<td>1.0</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>24 (100)</td>
<td>10 (42)</td>
<td>&lt; 0.001</td>
<td>0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>24 (100)</td>
<td>10 (42)</td>
<td>&lt; 0.001</td>
<td>0</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>


Toward Optimal Use:
Antimicrobial Stewardship

Antimicrobial Stewardship

• Definition
  • “The optimal selection, dosage, route, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity & impact on subsequent resistance.”

• The 4 D’s
  • Right Drug
  • Right Dose
  • Right Duration
  • De-escalation to pathogen directed therapy

Antimicrobial Stewardship

- Goals of antimicrobial stewardship
  - Optimize antimicrobial use: *right dose, route, interval, duration*
  - Increase clinical efficacy & outcomes
  - Decrease antimicrobial toxicity, cost, resistance and CDI

- Interventions by Antimicrobial Stewardship Programs
  - Prospective audit with intervention & feedback
  - Formulary restriction, preauthorization, order forms
  - Educate house staff & guideline development
  - Dose optimization, de-escalation, IV-PO protocols

- Monitoring
  - Resistance trends, antimicrobial usage, *C. difficile* rates

Antimicrobial Stewardship

New Drugs / Vaccine Development

Reduced Resistance

Antimicrobial Stewardship

Improved Diagnostics

Infection Control / Prevention

Education / Benchmark

Optimize Antimicrobial Selection / Dosing


Strategies to Prevent Antimicrobial Resistance

12 Break the chain
11 Isolate the patient
10 Stop treatment when cured
9 Appropriate selection and dosing
8 Treat infection, not colonization
7 Treat infection, not contamination
6 Use local & patient specific micro data
5 Practice infection and antimicrobial control
4 Access the experts
3 Target the pathogen
2 Get the catheters out
1 Vaccinate

Prevent Transmission

Use Antibiotics Wisely

↑ Efficacy (cost-efficacy)
↓ Resistance / Toxicity

Diagnose/Tx Effectively

Prevent Infections

Center of Disease Control (CDC)
Resistance: Key Prevention Strategies

**Susceptible Pathogen**

Prevent Infection

Effective Diagnosis & Treatment

Antimicrobial Resistance

Antimicrobial Use

Center of Disease Control (CDC)

---

**Antimicrobial Stewardship:**
Beyond the Restriction & Review

<table>
<thead>
<tr>
<th>Goal</th>
<th>Antimicrobial Stewardship Strategies / Resources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treat infected patients (not colonization)…</td>
<td>Improved diagnostic technologies</td>
</tr>
<tr>
<td>…with antimicrobial regimens…</td>
<td>Define &amp; implement formal risk algorithms</td>
</tr>
<tr>
<td>…at the dose…</td>
<td>Understand spectrum of activity</td>
</tr>
<tr>
<td>…and duration…</td>
<td>Understand effects on normal flora &amp; resistance</td>
</tr>
<tr>
<td></td>
<td>Identify regimens balance of risk vs. benefits</td>
</tr>
<tr>
<td></td>
<td>Safe and effective dosing recommendations</td>
</tr>
<tr>
<td></td>
<td>Understand &amp; identify PK/PD targets: utilization of MIC</td>
</tr>
<tr>
<td></td>
<td>Clinical implementation of PK/PD (dose optimization)</td>
</tr>
<tr>
<td></td>
<td>Understand duration-resistance relationships</td>
</tr>
<tr>
<td></td>
<td>Head-to-head trials of durations of therapy</td>
</tr>
<tr>
<td></td>
<td>Biomarker-guided (procalcitonin) duration of therapy</td>
</tr>
<tr>
<td></td>
<td>…most likely to minimize risk of emergence of resistance with acceptable risks.</td>
</tr>
</tbody>
</table>

**ASP Goals:** optimize dose & outcomes; reduce resistance, toxicity & cost
Evolution of Antimicrobial Dosing

Basic
Clinicians select dosing from own resources (PI, Sanford, etc)

Intermediate
Institutional dosing guidelines
Institutional dosing guidelines, traditional patient-specific pharmacist assisted dose individualization

PK-PD based institutional dosing guidelines
PK-PD based institutional dosing guidelines and patient specific PK/PD based individualization

Advanced

Antimicrobial Stewardship Levels

<table>
<thead>
<tr>
<th>Program Level</th>
<th>Review</th>
<th>Restriction</th>
<th>Dose Optimization</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beginner</td>
<td>List of monitored antibiotics</td>
<td>None</td>
<td>Institutional dosing guidelines</td>
<td>Clinician judgment</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Rules-based flagging of drug alerts</td>
<td>Formulary + restriction to ID consult</td>
<td>Institution guidelines &amp; target drug individualization</td>
<td>Evidence based guidance on duration</td>
</tr>
<tr>
<td>Futuristic</td>
<td>Expert system point-of-case patient-specific drug selection assistance and dose individualization with real-time antimicrobial stewardship alerts</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Prescribing Principles 1

• Important factors to consider
  • Determine the site of infection
    • Composition of local bacterial flora and likely pathogens
    • Achievable concentration of antimicrobial (moxifloxacin & UTI)
    • Activity of antimicrobial at infection site (daptomycin & pneumonia)
  • Define the host
    • Immune status
    • Extremes of age
  • Obtain a detailed exposure history (epidemiology)
  • Establish a microbiologic diagnosis (when possible)

Prescribing Principles 1

• Important factors to consider (continued)
  • Evaluate for risk factors for resistance

<table>
<thead>
<tr>
<th>Pseudomonas</th>
<th>MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known colonization</td>
<td>Known colonization</td>
</tr>
<tr>
<td>Prolonged hospitalization (nosocomial)</td>
<td>Recent admission or nursing home</td>
</tr>
<tr>
<td>Medical devices</td>
<td>Mechanical devices or surgery</td>
</tr>
<tr>
<td>Recent antibiotics active vs. gut flora</td>
<td>Recent antibiotics within 90 days</td>
</tr>
<tr>
<td>Structural lung disease</td>
<td>Critical illness</td>
</tr>
<tr>
<td>Significant exposure: standing water</td>
<td>Other: male gender, IVDU, exposure</td>
</tr>
</tbody>
</table>

* Possible risk factors, by association: immunocompromised, critically ill, recent admission, diabetes, SNF

Prescribing Principles 2

- Obtain a clinical diagnosis
  - Syndromic
    - Sepsis, pneumonia, fever of unknown origin
  - Etiologic
    - Enterococcal endocarditis, pneumococcal pneumonia

- Without a diagnosis, important questions on antimicrobial therapy can’t be answered (4 D’s)
  - Drug, Dose, Duration, and De-escalation

Prescribing Principles 3

- Timely administration of antimicrobial therapy
  - Perform microbiologic workup first, if possible
    - Administer antimicrobials immediately for high risk patients (critically ill, severe immune compromise, CNS infections)

- Deliberate delay in therapy for indolent infections
  - To establish a microbiology/etiologic diagnosis first
    - Subacute bacterial endocarditis (blood culture)
    - Osteomyelitis (bone/tissue culture): consider "washout" period

“In more stable clinical situations, antimicrobial therapy should be deliberately withheld until after collection of the appropriate diagnostic specimens.”

Antimicrobial Stewardship Treatment Guidelines. Clinical Infectious Diseases 2007; 44:159-77
Prescribing Principles 4

- Know your practice environment
  - Local antibiogram and prescribing patterns

- Explore patient’s exposures to guide selection
  - Allergy or intolerances (clarify nature of allergy)
  - Recent antimicrobial use within last 3 months
  - Recent culture/susceptibility data
  - Prior contact or colonization with MDR organisms


Antibiogram

- List of bacteria/antibiotics & corresponding susceptibilities

<table>
<thead>
<tr>
<th>Category</th>
<th>Data-lactams</th>
<th>B-lactam/ Beta-lactamase Inhibitor Combination</th>
<th>Fluoroquinolones</th>
<th>Aminoglycosides</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram Negative Organism (6)</strong> - All Sources (excluding Urine)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antimicrobial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acinetobacter baumannii (33)</td>
<td>8 8 8 8 8 8 8 16 16 16 4 8 16 16 8 8 16 2/32</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citrobacter freundii (31)</td>
<td>90 100 77 77 77 77 77 50 50 50 100 80 80 10 10 10 10 10 10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterobacter aerogenes (53)</td>
<td>91 100 100 91 91 88 100 90 90 90 100 90 90 80 80 100 80 80 80</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escherichia coli (293)</td>
<td>91 91 91 91 91 91 91 91 91 91 91 91 91 91 91 91 91 91 91 91 91</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klebsiella oxytoca (39)</td>
<td>100 87 100 100 100 100 100 50 50 50 100 100 100 100 100 100 100 100 100 100 100 100 100 100 100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Klebsiella pneumoniae (119)</td>
<td>94 94 94 94 94 94 94 94 89 89 89 94 94 94 94 94 94 94 94 94 94 94 94 94 94 94</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa (292)</td>
<td>73 92 92 92 92 92 92 92 92 92 92 92 92 92 92 92 92 92 92 92 92 92 92 92 92</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus mutans (62)</td>
<td>55 55 55 55 55 55 55 55 55 55 55 55 55 55 55 55 55 55 55 55 55 55 55 55 55</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>streptococcus pneumoniae</em> (217)</td>
<td>85 85 85 85 85 85 85 85 85 85 85 85 85 85 85 85 85 85 85 85 85 85 85 85 85</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Clinical Impact & Evaluation of Antimicrobial Allergies

A Primer on Antibiotic Allergies

<table>
<thead>
<tr>
<th>Coombs</th>
<th>Mechanism</th>
<th>Examples</th>
<th>Time of Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>IgE-mediated</td>
<td>Anaphylaxis, Angioedema, SOB</td>
<td>Minutes-hours</td>
</tr>
<tr>
<td>II</td>
<td>IgG, IgM</td>
<td>Hemolytic anemia, thrombocytopenia, Interstitial nephritis</td>
<td>&gt; 3 days</td>
</tr>
<tr>
<td>III</td>
<td>Immune Complex</td>
<td>Serum sickness, cutaneous eruptions, drug fever, nephritis, vasculitis</td>
<td>7-10 days</td>
</tr>
<tr>
<td>IV</td>
<td>Cell mediated</td>
<td>Contact dermatitis, Rash/Hives, Morbilliform eruptions</td>
<td>7-20 days (initial) 8-120 h (reexposure)</td>
</tr>
</tbody>
</table>
Antibiotic Allergies

• 10% patients report a penicillin allergy, but often unreliable
  • > 90% of “allergies” can be ruled out by objective measures
  • > 95% of patients with an “penicillin allergy” tolerate a penicillin

• “Beta-lactam allergy” is a significant healthcare problem
  • Associated with increased healthcare costs¹
  • Associated with increased resistance & worse patient outcomes²
    • Length of stay ……………….. Increased by 1.2 days
    • ICU admission ………………. 1.4 times more likely
    • In-hospital death …………….. Increased risk (OR 1.6)
    • More than 1 antimicrobial…. Higher odds (OR 1.8)
    • Resistance & C. difficile…….. Increased risk

² Charneski L, et al. Impact of Antimicrobial Allergy Label in the Medical Record on Clinical Outcomes in Hospitalized Patients. Pharmacotherapy 2011;31:742-4

Antibiotic Allergies

• Limitations to evaluation of a drug allergy
  • Often over reported, poorly documented & subjective
  • Presentation heterogeneous & many factors involved
  • Several drugs are often taken simultaneously
  • Sensitivity can be lost over time, especially > 10 years
  • There is a lack of consensual diagnostic procedures
    • Consider skin testing: > 90% sensitivity
      • > 95% negative predictive value for type 1 mediated reactions
      • Less predictive for non-IgE mediated reactions (type 2, 3, 4)
Antibiotic Allergies and Intolerances

• Reviewing and appropriately de-labeling allergies has antimicrobial stewardship implications
  • Clarify nature of reaction: intolerance vs. allergy
  • If allergy has been ruled out remove it from the profile
  • If allergy has not been ruled out consider alternatives
    • If alternative antimicrobial therapy is not an option consider:
      • Skin testing or oral re-challenge to clarify allergy
      • Prophylaxis/treatment of suspected reaction
      • Rapid desensitization if type 1 reaction and skin testing not feasible


Antibiotic Allergies and Intolerances

• Penicillin Allergy History: What Questions to Ask
  • How long ago was the reaction?
  • Does the patient recall the reaction?
    • If not, who informed them of it?
  • How long after starting penicillin did the reaction begin?
  • What were the characteristics of the reaction?
  • Has the patient taken similar antibiotics* before, in particular after the reaction? If yes, what was the result?

* amoxicillin, ampicillin, cephalosporins, cephalexin, Keflex®, etc.
Antibiotic Allergies

- Cross-reactivity of PCNs & cephalosporins < 5%
  - < 1% for PCNs and 3rd or 4th generation cephalosporins
- Side chain important in predicting risk for reaction
  - Penicillin & aminopenicillins have R group side chains identical to side chains of various cephalosporins

| Penicillin & Corresponding Cephalosporins with Similar Side Chains |
|---------------------|---------------------|---------------------|
| **PENICILLIN**     | **Amoxicillin / Ampicillin** | **Penicillin G** |
| **CEPHALOSPORIN**  | Cephalexin (1st generation) | Cephalothin (1st generation) |
|                     | Cefadroxil (1st generation) | Cefoxitin (2nd generation) |
|                     | Cefaclor (2nd generation)  |                     |
|                     | Cefprozil (2nd generation) |                     |

β-Lactams: Allergy – Cross Reactivity

- Penicillin Allergy
  - ≈ 0%
  - 1-5%
- Cephalosporin Allergy
  - 5-10%
  - <1%
- Monobactam Allergy
  - ? ≈ 0%
- Carbapenem Allergy
  - ? ≈ 0%

References:
Penicillin Allergy: Is it safe to use a Cephalosporin?

**Patient with past reaction to penicillin requires a cephalosporin**

**Skin testing to penicillin**

- **NOT AVAILABLE**
  - **Risk Stratification**
    - **Low Risk**
      - Reaction > 10 years ago
      - Previously tolerated cephalosporin
      - Non IgE-mediated reaction
      - **Give cephalosporin directly**: Reaction within 24 hours occurs in < 1%, but risk for anaphylaxis is very low
    - **Moderate Risk**
      - Reaction within past 10 years
      - Possible IgE-mediated reaction
      - **Give low risk cephalosporin**: Reaction within 24 hours occurs in < 1%, but risk for anaphylaxis is low
    - **High Risk**
      - **Desensitize to cephalosporin** or use alternative therapy

- **AVAILABLE**
  - **Risk Stratification**
    - **Low Risk**
      - Reaction > 10 years ago
      - Previously tolerated cephalosporin
      - Non IgE-mediated reaction
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    - **High Risk**
      - **Desensitize to cephalosporin** or use alternative therapy

---

American Academy of Allergy & Immunology 2010, Romano A. et al. JACI 2010
Prescribing Principles 5

• Let the microbiology results guide you
  • Example: A negative MRSA nasal swab has a very high NPV for MRSA infection and can guide de-escalation

<table>
<thead>
<tr>
<th>MRSA culture site</th>
<th>Results of analysis to predict a MRSA-positive culture for patients tested for nasal colonization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
</tr>
<tr>
<td>Bloodstream</td>
<td>0.74</td>
</tr>
<tr>
<td>Respiratory</td>
<td>0.75</td>
</tr>
<tr>
<td>SSTI: Extremity</td>
<td>0.61</td>
</tr>
<tr>
<td>SSTI: Ulcer</td>
<td>0.70</td>
</tr>
<tr>
<td>Urine</td>
<td>0.77</td>
</tr>
<tr>
<td>Other</td>
<td>0.60</td>
</tr>
<tr>
<td>Total</td>
<td>0.67</td>
</tr>
</tbody>
</table>

PPV = positive predictive value, NPV = negative predictive value


Prescribing Principles 5 (cont)

• Let the microbiology results guide you
  • Adjust therapy based on Gram stain results
    • Ex: Non-fermenting GNR implies *Pseudomonas*
  • Adjust therapy based on culture results
    • Ex: *Pseudomonas* on culture, but lack of antipseudomonal
  • Adjust therapy based on antimicrobial susceptibility results
    • Use minimum inhibitory concentration (MIC) to guide agent/dosing
    • De-escalate to the most narrow/potent antimicrobial, if possible
    • “S” does NOT always = Success
    • Lowest MIC does NOT always imply the best therapeutic option
Interpretation of an MIC

• Does a lower MIC imply better?
  • NO – it’s relative to the “breakpoint” for susceptibility

• Breakpoint
  • Highest MIC that is considered to be “susceptible” for a given antimicrobial (varies by antimicrobial class)
  • Determined by FDA & CLSI: guided by in-vitro/vivo data
    • MIC distributions, PK/PD modeling, animal models, outcome data
    • May change based on clinical data to optimize patient outcomes

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Beta-lactams</th>
<th>Carbapenem</th>
<th>BLI</th>
<th>FQ</th>
<th>Aminoglycoside</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent</td>
<td>Amp</td>
<td>Aztreonam</td>
<td>Ceph</td>
<td>Pip</td>
<td>Pip-tazo</td>
<td>Gipro</td>
</tr>
<tr>
<td>Breakpoint (mg/L)</td>
<td>8</td>
<td>8</td>
<td>8*</td>
<td>16</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>16</td>
<td></td>
<td></td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>2/38</td>
<td>2/38</td>
<td></td>
<td></td>
<td>2/38</td>
<td></td>
</tr>
</tbody>
</table>

MIC: Minimum Inhibitory Concentration, CLSI: Clinical / Laboratory Standards Institute, FQ = fluoroquinolone
* Cefazolin non-urinary breakpoint = 2mg/L & cephalosporin urinary breakpoint = 16mg/L (CLSI 2015). ^ revised in 2010: 4 to 1mg/L

Bacterial Killing as a Function of MIC

MIC: Minimum Inhibitory Concentration
MIC 50: MIC Required To Inhibit The Growth Of 50% Of Organisms
MIC 90: MIC Required To Inhibit The Growth Of 90% Of Organisms
MPC = Mutant Prevent Concentration = 10-100 X MIC
Get the Right Dose Up Front!

Underdosing selects for resistance

Aggressive empiric dosing may prevent resistance & optimizes outcomes

“Dead bugs don’t mutate”
Assess Risk (toxicity) vs. Benefit (efficacy) Ratio

The Relationship Between Drug, Bug, & Host

Drug

Bacteria

Effect of antibiotic at the site of infection (dose-effect relationship)

Pharmacodynamics

Resistance

Pharmacokinetics

Toxicity

Absorption
Distribution
Metabolism
Elimination

Infection

Host Defenses

Host

Antimicrobial Selection & Dosing

Patient Factors
- Patient age
- Patient size
- Infection site
- Infection severity
- Immunologic status
- Foreign bodies
- Acute vs. Chronic
- ABX history (susceptibility)
- Drug Allergies, ADRs
- Renal / Metabolic Function
- Renal Replacement Therapy

Drug/Bug Factors
- Pathogen
- Drug PK/PD
- Drug plasma Conc
- [Drug]: Infection site
- Post ABX effect
- Protein binding
- Resistance / Susceptibility
- Safety

Evaluation of Potentially Infected Patient

Is the patient infected?
S/O evidence of infection (fever, WBC, micro, imaging)

Does the patient have risk factors for resistance?*
(recent antibiotics/hospitalization, nosocomial, colonization...)

What is the likely site/source of infection?
What are the likely organisms for the site?
What antimicrobials provide adequate coverage?*

Daily reassessment of clinical status, labs, micro, etc.^
(Provide Antimicrobial Stewardship Interventions as appropriate)
Recommend Empirc Antibiotic Selection & Dosing

* What patient and/or disease state factors affect decision (allergies, comorbidities, past micro, organ dysfunction)?
^ If NOT responding assess 1) correct diagnosis, 2) need for source control, 3) drug/dose/concentration, 5) microbiology

Antibiotic Prescribing Process/Decisions

Pre-Prescribing Decision Making
• Q1: Do I test/evaluate?
• Q2: Do I treat?
• Q3: How do I treat?

Post-Prescribing Decision-Making
• Q4: Can I stop?
• Q5: Can I narrow?
• Q6: How long to treat?

Case 1
JG is a 62 YOM with multiple medical problems, including ongoing urinary retention and presence of indwelling Foley, who presents to his PCP for a follow-up appointment. JG denies other urinary symptoms. Cipro 500mg PO q12h to complete 14 days is ordered as urinalysis suggests "UTI."

- Vitals/labs
  - Tmax 36.6C, HR 68, RR 16, BP 122/68, WBC 5.2, Scr 2.9mg/dL
  - Urinalysis: WBC 15-20, moderate leukocyte esterase, few bacteria
  - Urine culture: $10^3$ Enterococcus faecalis, E. coli (MIC pending)

- Identify potential problems with this case.
Case 2

- JR is a 73 yo F who presents foot pain, fever, chills, lethargy & syncope. On exam she is found to have evidence of a “limb threatening” diabetic foot ulcer with necrotic tissue & exposed bone. She is deemed a poor surgical candidate and is started on moxifloxacin given her penicillin allergy.

- **PMH**
  - DM-2 & history of *S. aureus* diabetic foot ulcer, CKD-2, hypertension, chronic UTIs (recently *Pseudomonas* treated with cipro 3 weeks ago)
  - Allergies: penicillin (historical – 48 years ago)

- **Vitals/Labs**
  - WBC 18.2, Scr 2.9, T 39.2, BP 92/60, HR 120, RR 24, MRSA + (nares)

- Identify potential problems with this case.

Case 3

- SD is a 48 year old morbidly obese male (152kg) with no other significant medical problems who is presenting from the community with dyspnea, low grade fever, productive cough and radiographic evidence of pneumonia. He is initiated on vancomycin 1g IV q12h, pip/tazo 3.375g IV q8h and levofloxacin 500mg IV q24h. The patient has NKDA.

- **Vitals/Labs**
  - WBC 13.2, Scr 1.1mg/dL, T 38.1C, BP 138/82, HR 88, RR 24

- **Microbiology**
  - MRSA nares (negative), sputum (Gram stain): GPC pairs/chains

- Identify potential problems with this case.
Case 4

- RJ is a 80 year old female with MMPs, including recurrent UTIs, recently treated ciprofloxacin x 4 over the past year who now presents with profound diarrhea and leukocytosis. Upon review of the case the patient grew out *Klebsiella* x many previously pan-susceptible, but most recently MDR.

- **Vitals/Labs**
  - WBC 23.2, Scr 1.6mg/dL, T 38.3C, BP 118/62, HR 96, RR 22

- **Microbiology**
  - Urine: *Klebsiella* (MDR, except carbapenems), stool: *C difficile* (NAP-1)

- What most likely contributed to CDI (NAP-1) & MDR GNR?
- How could this have been prevented?

Clinical Summary

- Selecting the most appropriate antibiotic should be based on patient, epidemiologic & bacterial findings
  - Right indication, right selection, right dose, right duration
  - Use susceptibilities to guide antimicrobial dose / selection
  - Appreciate that prior antimicrobial use drives resistance!!!

- Resistance is increasing, but can be minimized
  - Appropriate antimicrobial use is vital to combat resistance
  - Need to control antimicrobial use through stewardship
  - Use local antimicrobial resistance profiles (antibiograms)
Questions

SUPPLEMENTAL SLIDES
Treatment Options For Resistant Pathogens

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>First Choice(s)</th>
<th>Alternative Choice(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRSP</td>
<td>Vancomycin, ceftiraxone</td>
<td>Moxifloxacin, linezolid, cefepime</td>
</tr>
<tr>
<td>MRSA (hospital-acquired)</td>
<td>Vancomycin</td>
<td>Daptomycin, linezolid, D/Q, TMP/SMX</td>
</tr>
<tr>
<td>MRSA (community-acquired)</td>
<td>Linezolid, daptomycin, D/Q</td>
<td>TMP/SMX, doxycycline, ± clindamycin</td>
</tr>
<tr>
<td>VRE</td>
<td></td>
<td>UTI: NTF, doxycycline, fosfomycin</td>
</tr>
<tr>
<td>P. aeruginosa (PA)</td>
<td>AP-BL ± AG or FQ</td>
<td>AG or FQ or Colistin alone</td>
</tr>
<tr>
<td>ESBL Klebsiella, E. coli</td>
<td>Systemic: Carbapenem Urine/biliary: pip-tazo, cefepime</td>
<td>Systemic: AG, FQ, aztreonam Cystitis: fosfomycin, TMP/SMX, NTF</td>
</tr>
<tr>
<td>Carbapenem-resistant Enterobacteriaceae (CRE)</td>
<td>Varies based on susceptibilities &amp; site/severity of infection: colistin, tigecycline, aminoglycosides, ± fosfomycin, ± aztreonam, ± FQs</td>
<td></td>
</tr>
<tr>
<td>Carbapenem-resistant P. aeruginosa</td>
<td>Novel BL dosing strategy * AG/FQ or Colistin</td>
<td>Systemic: colistin, aztreonam Cystitis: ciprofloxacin, fosfomycin</td>
</tr>
<tr>
<td>Enterobacter (risk for Amp C Producer)</td>
<td>Severe: Carbapenem (CP), cefepime? Moderate: CP, cefepime, FQ</td>
<td>Mid/UTI: Ceftepoxinor, TMP/SMX, Fluoroquinolone</td>
</tr>
<tr>
<td>Acinetobacter</td>
<td>Carbapenem</td>
<td>Tigecycline, TMP/SMX, colistin</td>
</tr>
<tr>
<td>Acinetobacter or PA resistant to BL/AG/FQ</td>
<td>Colistin, aggressive/novel β-lactam dosing strategies</td>
<td>Tigecycline (Acinetobacter)</td>
</tr>
</tbody>
</table>

PRSP= penicillin resistant S. pneumoniae, D/Q=dalfopristin/quinupristin, CP=carbapenem, AP = antipseudomonal, BL=beta-lactam, AG=aminoglycoside, FQ=fluoroquinolone, TMP-SMX (and T/S)=trimethoprim-sulfamethoxazole, NTF = nitrofurantoin

* Pip/tazo (Zosyn®) can be used for ESBL producing Enteric Gram negative rods, but not AMP-C producing strains (Enterobacter)

CDI: Over diagnosis in Molecular Era

- **Design**
  - Prospective observational cohort study including 1416 hospitalized patients with stool samples tested for *Clostridium difficile* toxin ≥72 hours after admission

- **Objective**
  - To determine the natural history and impact of treatment of patients who are toxin immunoassay negative (Tox-) or polymerase chain reaction positive (PCR+) for CDI

- **Inclusion Criteria**
  - Diarrhea with ≥ 3 unformed bowel movements OR ≥ 600 mL of rectal or colostomy output within 24 hours

**CDI: Over diagnosis in Molecular Era**

**Results**
- Tox+/PCR+ had a longer duration of diarrhea vs. Tox-/PCR+ & Tox-/PCR- (< 0.001) and greater risk of recurrent diarrhea
- Tox-/PCR+ & Tox-/PCR- patients had a similar risk of diarrhea
- Nearly all CDI related complications/deaths occurred in Tox+
- Treatment had NO impact on outcomes among Tox- patients

<table>
<thead>
<tr>
<th>Test Results</th>
<th>Interpretation</th>
</tr>
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<tbody>
<tr>
<td>GDH (+), Toxin (+)</td>
<td>Patient has CDI – Treatment and isolation indicated</td>
</tr>
<tr>
<td>GDH (-), Toxin (-)</td>
<td>Patient does NOT have CDI – Search for alternative diagnosis</td>
</tr>
<tr>
<td>GDH (+), Toxin (-), PCR (+)</td>
<td>Patient is colonized with nontoxigenic C. difficile – Search for alternative diagnoses</td>
</tr>
<tr>
<td>GDH (+), Toxin (-), PCR (-)</td>
<td>Possible infection (likely colonized with toxigenic C. difficile) – Isolate &amp; consider alternative diagnoses. Treat if suspect CDI.</td>
</tr>
<tr>
<td>GDH (-), Toxin (+)</td>
<td>Discordant results – Recollect sample for repeat testing.</td>
</tr>
</tbody>
</table>

Polage CR, et al. Over diagnosis of Clostridium difficile Infection in the Molecular Test Era. JAMA, 2015; 175(11)