Antimicrobial Stewardship 101:
*Tips and Tricks for Changing Your Practice*

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Clinical Pharmacy Specialist
Infectious Diseases and Antimicrobial Stewardship

October 4, 2019
*Nothing to Disclose*
Objectives

• Report increased knowledge of how antimicrobial stewardship improves outcomes

• Identify a role for advanced practice providers (APP) within antimicrobial stewardship

• Optimize personal antibiotic prescribing within the four moments of antibiotic decision making
Stewardship is “the responsible overseeing and protection of something considered worth caring for and preserving.”

How does this apply to antimicrobials?
History of Antimicrobials

• Penicillin discovered in 1928

• Improvement in survival and advances in modern medicine

• 1/3 of antibiotics are prescribed inappropriately
  • Wrong agent, dose, duration, frequency, or indication
  • Large percentage of pediatric antibiotics
Consequences of Inappropriate Antimicrobial Use

Patient:
- Resistance
- Adverse Effects
- Limited treatment options
- Hospital acquired conditions
- Cost burden
- Missed days at work or school
- Prolonged hospital admissions

Healthcare System:
- Cost burden
- Waste of antimicrobials
- Drug shortages
- Infection control concerns

Community:
- Resistance
- Cost burden
Antimicrobial Resistance

- Antimicrobials = “community resource”
  - Effectiveness decreases overtime and with overuse

Image Source: CDC
Bad Drugs, Few New Drugs

- ~50 antibiotics in development
- Limited dosing or safety information in pediatric patients

Image Source: Economist, IDSA
Patient Case

- Presented with signs and symptoms of pyelonephritis
- Urine culture with >100K of *E. coli*
- 14 days of IV antibiotics + inpatient admission
- Age of this patient???

### Escherichia coli (ESBL positive)

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC Interp</th>
<th>MIC Dilution</th>
<th>MIC Interp</th>
<th>MIC Dilution</th>
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<tbody>
<tr>
<td>Amikacin</td>
<td></td>
<td>S</td>
<td></td>
<td>4</td>
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<td>Ampicillin</td>
<td>R</td>
<td>&gt;=32</td>
<td>R</td>
<td>&gt;=32</td>
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<td>R</td>
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<td>&gt;=64</td>
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<td>Cefoxitin</td>
<td>R</td>
<td></td>
<td>S</td>
<td>&lt;=4</td>
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<td>Cefazidime</td>
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<td>&gt;=4</td>
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<td>Ertapenem</td>
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<td>S</td>
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<td>&lt;=0.5</td>
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<tr>
<td>ESBL</td>
<td></td>
<td>Pos</td>
<td></td>
<td>Pos</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>R</td>
<td>&gt;=16</td>
<td>R</td>
<td>&gt;=16</td>
</tr>
<tr>
<td>Meropenem</td>
<td>S</td>
<td></td>
<td>S</td>
<td>&lt;=0.25</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>S</td>
<td>&lt;=16</td>
<td>S</td>
<td>&lt;=16</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>R</td>
<td>&gt;=16</td>
<td>R</td>
<td>&gt;=16</td>
</tr>
<tr>
<td>Trimethoprim/ Sulphamethoxazole</td>
<td>R</td>
<td>&gt;=320</td>
<td>R</td>
<td>&gt;=320</td>
</tr>
</tbody>
</table>
Antimicrobial Resistance in Pediatrics

- Increasing both nationally and globally
- *Staphylococcus aureus*
  - Increase in clindamycin resistance for both MSSA and MRSA
  - Guidelines recommend avoid if resistance rates >10% for certain infections

| Children’s Mercy Clindamycin Susceptibility Rates (% susceptible) |
|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
|                   | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 |
| MSSA              | 85   | 84   | 81   | 84   | 85   | 77   |
| MRSA              | 88   | 88   | 82   | 83   | 79   | 82   |

MSSA = methicillin susceptible S. aureus; MRSA = methicillin resistant S. aureus

“Super Bugs” in Pediatrics

• Extended-spectrum beta-lactamases (ESBLs)
  • Resistance to most beta-lactam antibiotics

• Carbapenem-resistant Enterobacteriaceae (CRE)
  • Resistance to carbapenem antibiotics (e.g. meropenem)

Cost Burden of Resistance

- $20,000 = average cost for treatment of multidrug resistant infection
  - Amounts to $20 billion nationally

- Additional costs:
  - Additional microbiology tests to determine treatment options
  - Prolonged hospital stay
  - Missed days of work or school
  - Additional tests, admissions, and treatments for adverse drug reactions

Patient Safety with Antimicrobials

Adverse Effects of Fluoroquinolones: Where Do We Stand?

George Sakoulas, MD

Melanoma Associated With Long-term Voriconazole Therapy
A New Manifestation of Chronic Photosensitivity

Severe Acute Respiratory Failure in Healthy Adolescents Exposed to Trimethoprim-Sulfamethoxazole

Jenna D. Miller, MD, FAAP, Jane Taylor, MD, MS, Jennifer L. Goldman, MD, MS

Patient Safety with Antimicrobials

- 5-year review ED visits for antibiotic adverse drugs events (ADE)
- ~70,000 visits/year
  - 46.2% of ED visits for drug-related ADE
- 40.7% in children ≤ 2 years

Conserving for the Right Patients

- Significant amount of antimicrobial waste hospital-wide
  - Inappropriate use
  - Doses prepared, but not administered (i.e. discontinued or discharged)
    - $250,000/year
    - 50 wasted doses/day
Conserving for the Right Patients

• Significant antimicrobial drug shortages
  • Recent antibiotic shortages:
    • Cefotaxime, ampicillin/sulbactam, cefazolin, metronidazole, cefoxitin, meropenem, cefepime
  • Lead to use of suboptimal or 2nd line agents

• Important role of stewardship in conservation and allocation
Consequences of Inappropriate Antimicrobial Use

Patient
- Resistance
- Adverse Effects
- Limited treatment options
- Hospital acquired conditions
- Cost burden
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Healthcare System
- Cost burden
- Waste of antimicrobials
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- Infection control concerns

Community
- Resistance
- Cost burden
Antimicrobial Stewardship Program (ASP) Requirements

Executive Order -- Combating Antibiotic-Resistant Bacteria

EXECUTIVE ORDER

Core Elements of Antibiotic Stewardship

SECOND REGULAR SESSION

SENATE BILL NO. 579

98TH GENERAL ASSEMBLY

APPROVED: New Antimicrobial Stewardship Standard

The Joint Commission recently announced a new Medication Management (MM) standard for hospitals, critical access hospitals, and nursing care centers. Standard MM.09.01.01 addresses antimicrobial stewardship and becomes effective January 1, 2017.
Antimicrobial Stewardship

“Optimizing clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, selection of pathogenic organisms, and the emergence of resistance.”
A patient presented with an intraabdominal infection after a bowel perforation. The patient was receiving a lower dose of an antibiotic at a twice daily frequency. ASP recommending **increasing the antibiotic dose and administering it once daily**, thereby **minimizing line entries and CLABSI risk**.

ASP reviewed a patient receiving IV antibiotics for a urinary tract infection. The team was planning to discharge the patient on a broad-spectrum antibiotic associated with many side effects. ASP recommended transitioning the patient to a **more narrow-spectrum, well-tolerated oral antibiotic** administered once daily. The patient was **discharged on this antibiotic**.
Antimicrobial Stewardship Interventions

- Selecting the **right antibiotic** at the **right dose** for the **right indication** and **duration**

<table>
<thead>
<tr>
<th>Stewardship Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimize therapy (IV to PO, dosing)</td>
</tr>
<tr>
<td>Modify therapy (duration, broaden/narrow coverage)</td>
</tr>
<tr>
<td>Discontinue therapy</td>
</tr>
<tr>
<td>ID Specialist Consultation</td>
</tr>
<tr>
<td>Clinical practice guideline implementation</td>
</tr>
<tr>
<td>Antimicrobial restriction</td>
</tr>
<tr>
<td>Quality and cost utilization analyses</td>
</tr>
<tr>
<td>Education and resource development</td>
</tr>
<tr>
<td>Appropriate testing</td>
</tr>
</tbody>
</table>
Children’s Mercy ASP

- Review of inpatient antibiotic orders at 48 hours
- Antibiotic “time-outs”
- Nursing antibiotic engagement tool
- Guideline development
- Quality improvement projects pharyngitis and otitis media
- Outpatient Handbook
  - Children’s Mercy Evidence Based Practice Website
  - Care Process Models
  - Acute Otitis Media
  - Outpatient Antibiotic Handbook
- Penicillin allergy clarification and testing
Multidisciplinary Approach to ASP

- **Hospital Administration**
  - Provide formal and financial support for ASP

- **Prescribers**
  - Prescribe appropriate antibiotics (right drug, dose, indication, and duration)
  - Reassess antibiotic appropriateness during treatment
  - Provide education to families and patients

- **Pharmacy**
  - Optimize antibiotic use by recommending appropriate drugs and doses
  - Perform 48-hour timeouts to assess continued need for antibiotics
  - Assess for eligibility for IV to PO conversion for antibiotics

- **Nursing**
  - Obtain cultures prior to antibiotics if feasible
  - Recognize opportunities for IV to PO conversion for antibiotics
  - Identify and thoroughly document antibiotic adverse reactions
  - For more ways nurses serve as members of the ASP team [click here](#)

- **Microbiology**
  - Supply patient-specific culture/sensitivity data & hospital antibiogram
  - Provide useful testing methods (i.e. rapid diagnostic tests)

- **Infection Control**
  - Monitor/prevent the spread of multidrug resistant organisms
  - Promote proper hygiene practices

- **Data Analyst**
  - Gather meaningful antibiotic use data to disseminate
APPs and ASP

Large contributor to outpatient prescribing

- >189,000 Nurse practitioners (NPs) in the United States
- 23% of outpatient antibiotic prescriptions (and increasing)

Perceptions about antimicrobial stewardship

- Single-center survey of 58 NPs
  - Unfamiliar with antimicrobial stewardship program
  - Aware and concerned about antibiotic overuse and consequences
  - Would like more education and feedback on antibiotic prescribing

Call to Action: APPs in ASP

- Key role for APPs
  - Majority with prescriptive authority
  - Frequent prescribing of antibiotics
  - Experience with patient care

NP ASP Action Items

- Advance your knowledge
- Optimize your antibiotic prescribing performance and practice
- Advocate for adoption of at least one ASP recommended action in your practice setting
- Reach out and connect with APPs in your local region


EDITORIAL
The urgent need for nurse practitioners to lead antimicrobial stewardship in ambulatory health care
Education and Antibiotic Prescribing

- Education for NPs in urgent cares
  - Antibiotic use in common pediatric infections
  - Decrease in inappropriate antibiotic prescribing for session attendees (9% to 6%; p <0.01)

4 Moments of Antibiotic Prescribing

- Agency for Healthcare Research and Quality Safety Program for Improving Antibiotic Use
- Opportunities for optimization

**Moment 1**
- Does this patient have an infection that requires antibiotics?

**Moment 2**
- Have I ordered appropriate cultures before antibiotics? What empirical antibiotic therapy should I initiate?

**Moment 3**
- A day or more has passed. Can I stop antibiotics? Can I narrow therapy? Can I change from IV to PO?

**Moment 4**
- What duration of antibiotic therapy is needed?

Tamma PD, Miller MA, Cosgrove SE. *JAMA*. 2019;321(2):139-140.
1. Does this patient have an infection that requires antibiotics?

- Initiation of antibiotics for a variety of reasons:
  - Isolated symptom (e.g. fever) vs. constellation of symptoms
  - Provider discomfort
  - Lack of knowledge or understanding
  - Parental/patient request or expectation

What other processes are going on with this patient?

Does this patient meet diagnostic criteria?

Could this be non-infectious or non-bacterial?

Tamma PD, Miller MA, Cosgrove SE. JAMA. 2019;321(2):139-140.
1. Does this patient have an infection that requires antibiotics?

- **Acute otitis media (AOM)**
  - >50% resolve without antibiotics
  
  - Consider “watchful waiting” for patients with mild symptoms:
    - ≥ 6 months with unilateral AOM without otorrhea
    - ≥ 2 years with bilateral AOM without otorrhea
  
  - “Safety net antibiotic prescription” if no improvement in 48-72 hours

- Cost-effective and 65% reduction in antibiotic use

Tamma PD, Miller MA, Cosgrove SE. *JAMA.* 2019;321(2):139-140.

1. Does this patient have an infection that requires antibiotics?

- **Aspiration pneumonia**
  - Consider non-infectious diagnoses and waiting to initiate treatment

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Aspiration Pneumonia</th>
<th>Aspiration Pneumonitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Subacute to chronic</td>
<td>Acute</td>
</tr>
<tr>
<td>Signs/symptoms</td>
<td>Cough, tachypnea, respiratory distress, fever</td>
<td>Cough, tachypnea, respiratory distress, fever</td>
</tr>
<tr>
<td>Imaging</td>
<td>Infiltrate</td>
<td>Infiltrate</td>
</tr>
</tbody>
</table>

- **Asymptomatic bacteriuria**
  - No benefit observed with treatment
  - No harm observed with avoiding treatment

Tamma PD, Miller MA, Cosgrove SE. JAMA. 2019;321(2):139-140.
1. Does this patient have an infection that requires antibiotics?

- **Group A Streptococcus (GAS) Pharyngitis**
  - 70% outpatients with sore throat receive antibiotics
    - 20-30% actually have GAS pharyngitis
    - Significantly lower < 3 years ‡ testing is not routinely indicated
  - Rapid testing cannot distinguish between colonization and carriage
    - 25% of healthy children are colonized
    - Consider colonization vs. actual infection
  - 0% resistance for GAS for amoxicillin

Speaking with Families

• Inaccurate prescriber perception that parents demand antibiotics

• 109 parent interviews demonstrated:
  • None planned to ask for antibiotics
  • **Seeking reassurance and guidance** regarding child’s condition
  • Wary about using antibiotics, concerned about adverse effects

• Opportunities for tailoring communication
  • Explain why antibiotics are not needed
  • Positive treatment recommendations
  • Contingency plan

2. What empirical antibiotic therapy should I initiate?

- What are the most common pathogens for this infection and this patient?
  - Clinical practice guidelines or tertiary resources
  - Consideration of patient factors (e.g., MRSA history, immunocompromised)
  - Utilization of antibiogram (if available)

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### Table: 2019 Gram Positive Antibiogram (% Susceptible)

<table>
<thead>
<tr>
<th>Organism</th>
<th># of isolates tested</th>
<th>Ampicillin</th>
<th>Cefazolin</th>
<th>Cefdinir</th>
<th>Erythromycin</th>
<th>Gentamicin</th>
<th>Lincomycin</th>
<th>Meropenem</th>
<th>Nitrofurantoin</th>
<th>Oxacillin</th>
<th>Penicillin</th>
<th>Penicillin (G)</th>
<th>Rifampin</th>
<th>Tobramycin</th>
<th>Tetracycline</th>
<th>Trimethoprim</th>
<th>Vancomycin</th>
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<tr>
<td><em>Staphylococcus aureus</em></td>
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<td><strong>MSSA</strong></td>
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<td>Streptococcus pneumoniae</td>
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<td>Nonlymph meningitis</td>
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</tr>
</tbody>
</table>

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Tamma PD, Miller MA, Cosgrove SE. *JAMA*. 2019;321(2):139-140.
2. What empirical antibiotic therapy should I initiate?

- What resistance mechanisms does this bacteria carry?
  - Pathogen-specific

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Streptococcus pneumoniae</th>
<th>Haemophilus influenza</th>
<th>Moraxella catarrhalis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance Mechanism</td>
<td>Decreased affinity for penicillin binding proteins</td>
<td>Beta-lactamase (30%)</td>
<td>Beta-lactamase (100%)</td>
</tr>
<tr>
<td>Treatment</td>
<td>High-dose ampicillin or amoxicillin</td>
<td>Ampicillin/sulbactam Amoxicillin/clavulanate</td>
<td>Ampicillin/sulbactam Amoxicillin/clavulanate</td>
</tr>
</tbody>
</table>

Tamma PD, Miller MA, Cosgrove SE. *JAMA.* 2019;321(2):139-140.
2. What empirical antibiotic therapy should I initiate?

- Will the antibiotic reach the site of infection?
  - Difficult to penetrate = central nervous system, bone/joint, lung, abscess or vegetation

- Utilize Lexi-Comp or Micromedex or clinical practice guidelines

- Urinary tract infections
  - Cefdinir: 12-18% excreted in urine
  - Cephalexin: >90% excreted in urine
  - Cefixime: 50% excreted in urine

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Tamma PD, Miller MA, Cosgrove SE. *JAMA*. 2019;321(2):139-140.
2. What empirical antibiotic therapy should I initiate?

• What allergies does this patient have?
  • 10% report penicillin allergies; 1% truly allergic
  • 26% increased *C. difficile* risk and 69% increased MRSA risk
  • True allergy = Hives, immediate reactions (within 1 hour), swelling, wheezing
  • Consider challenging low-risk patients in controlled setting or allergy referral
  • Low risk of cross-reactivity between penicillins and cephalosporins
    • Similar side chains = higher likelihood of reaction

**Beta-lactam Cross Reactivity**

| Amoxicillin | Ampicillin | Cephalaxin | Cefadroxil | Cefaclor | Cefazolin | Cefotaxim | Ceftriaxone | Cefepime | Ceftazidime | Ceftobiprole | Cefotetan | Cefoxitin | Ceftazidime | Cefepime | Cefuroxime | Cefepime | Ceftaroxone | Ceftazidime | Ceftobiprole | Cefepime | Cefuroxime | Cefepime | Ceftaroxone | Ceftazidime | Ceftobiprole | Cefepime | Cefuroxime | Cefepime | Ceftaroxone | Ceftazidime | Ceftobiprole | Cefepime | Cefuroxime | Cefepime | Ceftaroxone | Ceftazidime | Ceftobiprole | Cefepime | Cefuroxime | Cefepi | Ceftaroxone | Ceftazidime | Ceftobiprole | Cefepi | Cefuroxime | Cefepi | Ceftaroxone | Ceftazidime | Ceftobiprole | Cefepi | Cefuroxime | Cefepi | Ceftaroxone | Ceftazidime | Ceftobiprole | Cefepi | Cefuroxime | Cefepi | Ceftaroxone | Ceftazidime | Ceftobiprole | Cefepi | Cefuroxime | Cefepi | Ceftaroxone |
|-------------|------------|------------|------------|----------|----------|----------|------------|----------|------------|------------|----------|----------|------------|----------|------------|----------|------------|------------|------------|----------|------------|----------|------------|------------|------------|----------|------------|----------|------------|------------|------------|----------|------------|----------|------------|------------|------------|----------|------------|----------|------------|------------|------------|----------|------------|----------|------------|------------|------------|
| 6/7 | 6 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 | 6/7 |

**Similar Side Chain Tables**


**TABLE 6.** Chemical Structures of 7-Position Side Chains of Penicillins and Cephalosporins

<table>
<thead>
<tr>
<th>Related</th>
<th>Related</th>
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<tbody>
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<td>Penicillin G</td>
<td>Cephalaxin</td>
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</table>

**TABLE 7.** Chemical Structures of 3-Position Side Chains of Penicillins and Cephalosporins

<table>
<thead>
<tr>
<th>Related</th>
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<tbody>
<tr>
<td>Cephalaxin</td>
<td>Cefadroxil</td>
<td>Cefaclor</td>
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<td>Ceftriaxone</td>
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<td>Cefepime</td>
<td>Ceftaroxone</td>
<td>Cefuroxime</td>
</tr>
<tr>
<td>Not Related</td>
<td>Not Related</td>
<td>Not Related</td>
<td>Not Related</td>
<td>Not Related</td>
</tr>
</tbody>
</table>

3. Can I narrow antibiotics?

- Opportunity to decrease broad-spectrum antibiotic use
- How to utilize susceptibility results?
  - Minimum inhibitory concentration (MIC) and interpretation
  - **Common misconceptions**
    - MICs can be compared
    - Lowest is best
  - Specific for each antibiotic and bacteria combination
  - Consider what’s susceptible + infection and patient factors

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC Interp</th>
<th>MIC Dilution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefuroxime</td>
<td>R</td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td>R</td>
<td>&gt;=8</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>S</td>
<td>&lt;=0.5</td>
</tr>
<tr>
<td>Inducible Clindamycin</td>
<td>Pos</td>
<td>Pos</td>
</tr>
<tr>
<td>Linezolid</td>
<td>S</td>
<td>2</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>S</td>
<td>0.5</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>R</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>Quinupristin/Dalfopristin</td>
<td>S</td>
<td>0.5</td>
</tr>
<tr>
<td>Rifampin</td>
<td>S</td>
<td>&lt;=0.5</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>S</td>
<td>&lt;=1</td>
</tr>
<tr>
<td>Trimethoprim/Sulfamethoxazole</td>
<td>S</td>
<td>&lt;=10</td>
</tr>
</tbody>
</table>

Tamma PD, Miller MA, Cosgrove SE. JAMA. 2019;321(2):139-140.
Image Source: KhanAcademy.
3. Can I switch from IV to PO?

- Which antibiotic is my patient receiving?
  - Certain antibiotics: IV = PO (e.g., ciprofloxacin, SMX/TMP, metronidazole)

- What is the indication?
  - Prolonged IV course required for certain infections (e.g., endocarditis, central line infections, meningitis)
  - IV to PO for infant UTI, gram negative bacteremia

- Is my patient improving?
  - Minimize line entries, potentially reduce cost and length of stay
  - IV to PO transition policy

Tamma PD, Miller MA, Cosgrove SE. JAMA. 2019;321(2):139-140.
4. What duration of antibiotic therapy is needed?

- Variability in prescribed antibiotic durations
  - Late-career physicians more likely to prescribe >8-day durations
  - Mean durations = 7-8 days
- New practice trend = shorter is better

![Table 1. Diseases for Which Short-course Antibiotic Therapy Has Been Found to Be Equally Effective to Longer Traditional Courses of Therapy (With References)](image)
4. What duration of antibiotic therapy is needed?

- Uncomplicated, late-onset group B Streptococcal (GBS) bacteremia
  - ≤ 8 vs. > 8 days IV antibiotics
  - No difference in GBS reoccurrence
- Gram-negative bacteremia
  - 7 vs. 14 days - noninferior
- Surgical prophylaxis
  - No post-operative antibiotics for clean and clean-contaminated procedures
  - Limit to < 24 hours

Summary

• Consequences of inappropriate antibiotic use include resistance, adverse effects, and cost.

• APPs have a role in antimicrobial stewardship as they are frequent prescribers of antibiotics.

• Opportunities for optimization of antibiotic prescribing exist within each step of antibiotic decision-making.
Questions?

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Clostridium difficile

Staphylococcus