Antimicrobial Stewardship for All: What You Need to Know

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Mercy Health Saint Mary’s
Grand Rapids, Michigan
Disclosure

• Marc Scheetz:
  • Merck: Grant/Research Support
  • Premier: Speaker's Bureau
Objectives

• Discuss emerging issues in antimicrobial resistance among pathogens commonly causing infectious diseases and the implications for antimicrobial drug use in healthcare facilities.

• Describe and develop methods for surveillance of antimicrobial resistance in healthcare facilities.

• Explain the components of an effective antimicrobial stewardship program.

• Apply appropriate metrics for evaluating antimicrobial consumption in healthcare facilities.

• Develop methods for monitoring trends and identifying opportunities for improvement in antimicrobial use within a healthcare facility.
Antimicrobial Stewardship for All – What You Need to Know

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Emerging Issues in Antimicrobial Resistance
“...It is **not difficult to make microbes resistant** to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body. The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant... “

—Sir Alexander Fleming

Nobel Prize Lecture, 1945
“...The microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out....In such a case the thoughtless person playing with penicillin treatment is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organisms. I hope this evil can be averted.”

—Sir Alexander Fleming

New York Times

June 26, 1945
“A good gulp of whiskey at bedtime – it’s not very scientific, but it helps.”

—Sir Alexander Fleming, when questioned about the common cold
EXTRA! EXTRA!
“New” Superbug Isolated in U.S. Patient!

Alert to U.S. Healthcare Facilities: First mcr-1 Gene in E. coli Bacteria found in a Human in the United States

Researchers find second 'super' gene in US patient

U.S. Officials Confirm Superbug Resistant to All Antibiotics

http://emergency.cdc.gov/han/han00390.asp
mcr-1 “Superbugs”

• Plasmid-mediated colistin resistance (mcr-1) found in ≈1% of hospitalized patients in China

• Historical isolates with mcr-1 gene from the 1980s in Enterobacteriaceae

• mcr-1 gene has been identified in humans, food animals, and environmental samples in 20 countries

CDC Health Alert Network. http://emergency.cdc.gov/han/han00390.asp
Multidrug-Resistant Bacteria

• Multidrug-resistant bacteria no longer only a “hospital” problem

• Case in point: extended-spectrum beta-lactamase (ESBL)-producing Escherichia coli
  – 18% community-acquired
  – 53% healthcare-associated
  – 29% hospital-acquired

Origin of Infection due to ESBL-Producing Bacteria

Time for a Poll
How to vote via the web or text messaging

From any browser

From a text message
How to vote via text message

How's my presentation so far?

- Respond at PollEv.com/ashp
- Text a **KEYWORD** to 22333

<table>
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<th>Response</th>
<th>Votes</th>
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<td>It's aw-right.</td>
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From a text message
How to vote via the web

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- It's amazing. 152964
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From any browser

Respond at PollEv.com/ashp
Text a KEYWORD to 22333
Question #1: Which one of the following currently represents the largest threat related to antimicrobial resistance, according to the Centers for Disease Control and Prevention?

A. *Neisseria gonorrhoeae*
B. *Staphylococcus aureus*
C. *Escherichia coli*
D. *Streptococcus pneumoniae*
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Emerging Antimicrobial Resistance: Pathogens of Concern

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<thead>
<tr>
<th>Concerning Threats</th>
<th>Serious Threats*</th>
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<tr>
<td>• Vancomycin-Resistant <em>Staphylococcus aureus</em></td>
<td>• Multidrug-Resistant <em>Acinetobacter</em></td>
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<td>• Fluconazole-Resistant <em>Candida</em></td>
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<td>• ESBL-producing <em>Enterobacteriaceae</em></td>
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<td>• Erythromycin-Resistant Group A <em>Streptococcus</em></td>
<td>• Methicillin-Resistant <em>Staphylococcus aureus</em></td>
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<td>• Drug-Resistant <em>Streptococcus pneumoniae</em></td>
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ESBL = extended spectrum beta-lactamase
* = List not all inclusive

http://www.cdc.gov/drugresistance/biggest_threats.html
Emerging Antimicrobial Resistance: Pathogens of Concern

Urgent Threats

- *Clostridium difficile*
- Carbapenem-resistant *Enterobacteriaceae*
- *Neisseria gonorrhoeae*

## World Health Organization Antimicrobial-Resistant Pathogens of Concern

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<thead>
<tr>
<th>Pathogen</th>
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<td><em>Escherichia coli</em></td>
<td>cephalosporins, fluoroquinolones</td>
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<td><em>Klebsiella pneumoniae</em></td>
<td>cephalosporins, carbapenems</td>
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<td><em>Streptococcus pneumoniae</em></td>
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<td>Non-typhoidal <em>Salmonella</em></td>
<td>fluoroquinolones</td>
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<td><em>Shigella</em> species</td>
<td>fluoroquinolones</td>
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<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td>↓ susceptibility to cephalosporins</td>
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</table>

http://apps.who.int/iris/bitstream/10665/112647/1/WHO_HSE_PED_AIP_2014.2_eng.pdf?ua=1
Mechanisms of Resistance

“Strong and ubiquitous selection pressure has seemingly been accompanied by a shift from ‘natural’ resistance, such as inducible chromosomal enzymes, membrane impermeability, and drug efflux, to the modern paradigm of mobile gene pools that largely determine the epidemiology of modern antibiotic resistance.”

Question #1: Which one of the following currently represents the largest threat related to antimicrobial resistance, according to the Centers for Disease Control and Prevention?

A. *Neisseria gonorrhoeae*
B. *Staphylococcus aureus*
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Mechanisms of Resistance

• Target modification or mimicry
  – Porin modification
  – Seen in fluoroquinolone and β-lactam resistance

• Altered drug entry or expulsion/efflux

• Drug modification (destruction or modification)
  – β-lactamases
  – Methylases (e.g., aminoglycosides)

Mechanisms of Resistance

• Resistance can transfer from one genus of bacteria to another
  – Via mobile gene pools
  – e.g., β-lactamases between *Escherichia coli* and *Klebsiella pneumoniae*
  – Vancomycin resistance *vanA* gene cluster from *Enterococcus* (VRE) to *Staphylococcus aureus* (VRSA)

• Resistance can transfer from the environment to humans

Mechanisms of Resistance

• Horizontal transfer may vary depending on location and the environment of bacteria
  – Environmental: transduction by bacteriophages
  – Gastrointestinal tract: transformation or conjugation plasmids
“...there is an urgent, immediate need for new agents with activity against these panresistant organisms. There is no evidence that this need will be met in the foreseeable future.”

Question #2: A decrease in which one of the following outcomes is associated with antimicrobial resistance?

A. Healthcare costs
B. Hospital length of stay
C. Mortality
D. Clinical cure rate
Question #2

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The Toll of Drug Resistance

• Increased rate of treatment failure
• Extended length of hospital stay
• Increased need for isolation precautions
• Increased mortality
• Increased costs both during hospitalization and after discharge

Implications for Healthcare

• Patient placement and discharge planning may require home infusion and/or long-term care stays

• Judicious use of antibiotics, particularly broad-spectrum agents, is needed

• Efforts must be targeted to decrease resistance
Implications for Healthcare

• Will minimum inhibitory concentration (MIC) reporting be “enough”?

• Increasing need for rapid diagnostic tests
  – Penicillin-Binding Protein 2 (PBP2) for *Staphylococcus aureus*

• More sophisticated diagnostic tools will be needed
  – Matrix-Assisted Laser Desorption/Ionization Time-of-Flight mass spectrometry (MALDI-TOF)

Iredell J et al. *BMJ* 2016;352:h6420
Question #2: A decrease in which one of the following outcomes is associated with antimicrobial resistance?

- Healthcare costs
- Hospital length of stay
- Mortality
- Clinical cure rate
Surveillance of Antimicrobial Resistance
Question #3: The most effective surveillance efforts focus on antimicrobial resistance trends in which of the following?

A. The ICU of an individual institution
B. All patient care areas in an individual institution
C. All inpatient floors in a multi-hospital health system
D. All emergency departments within the State of Nevada
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Surveillance of Antimicrobial Resistance

• Surveillance efforts will [ideally] encompass local, regional, national, and international populations

• Local surveillance
  – Broken down by location – i.e., ICU vs. hospital vs. emergency department
  – Collectively as a “community”

• Surveillance should [ideally] include both clinical and microbiological information as well as antimicrobial use patterns

Surveillance of Antimicrobial Resistance

- Findings should be used to guide treatment decisions

- Findings should be used to track effectiveness of interventions over time

Question #3: The most effective surveillance efforts focus on antimicrobial resistance trends in which of the following?

A. The ICU of an individual institution
B. All patient care areas in an individual institution
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Goals for Surveillance Efforts

- **Specific**: well-defined questions, produces generalizable results
- **Measurable**: validated tests, standardized methodology
- **Assessable**: outcomes can be identified and evaluated
- **Realistic**: timetable sensible, achievable
- **Targeted**: address relevant issue, clearly defined outcomes
Application and Outcomes of Surveillance Efforts

• Improve empiric antimicrobial prescribing

• Guide antimicrobial policies and utilization

• Education

• Monitor the use of antimicrobial drugs and susceptibility of pathogens

Application and Outcomes of Surveillance Efforts

- Direct infection control efforts
- Reduce the spread of resistant organisms
- Identify resistance patterns as they emerge
- Monitor changes in resistance patterns

Question #4: Which one of the following culture reports would be most appropriate to request for constructing an antibiogram?

A. Without stratification by location
B. Stratified by ICU and non-ICU locations
C. Stratified by ICU, inpatient, and community locations
D. Stratified by inpatient care areas (e.g., floors)
Your poll will show here

1
Install the app from pollev.com/app

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Make sure you are in Slide Show mode

Still not working? Get help at pollev.com/app/help
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Open poll in your web browser
**Oldie But Goodie: The Antibiogram**

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1) 49% sensitive for meningitis  
2) 74% sensitive for meningitis  
3) 48 non-urine isolates *E. faecium* (83% were VRE)  
4) 36 non-urine isolates *E. faecalis* (11% were VRE)  
5) 750 mg or MosiRoPacin 400 mg  
6) Tigecycline 76%  
7) Erythromycin tested  
8) This organism is known to harbor inducible AmpC beta lactamas and may develop resistance during prolonged therapy with third generation cephalosporins such as ceftriaxone and cefotaxime.
# Antibiogram: Application to Practice

## Mercy Health Saint Mary’s
### INPATIENT ANTIBIOMGRAM
**January – December 2015**

Produced by Inpatient Pharmacy and Microbiology Departments

| Staphylococcus aureus | Vancomycin | Oxacillin | Tetracycline | Azithromycin | Ampicillin | Amoxicillin | Cefazolin | Ceftriaxone | Ceftazidime | Tobramycin | Aztreonam | Meropenem | Ciprofloxacin | Levofloxacin | Pipercillin-tazobactam | # Isolates |
|----------------------|------------|-----------|--------------|--------------|------------|-------------|-----------|------------|------------|------------|-----------|----------|-----------|----------------|----------------|--------------------------|-----------|
|                      | 60         | 100       | 82           | 95           | 100        | 100         | 100       | 96         | 98         | 86         | 99        | 45       | 179       |                  |                  |                          | 136       |

1) 49% sensitive for 5) 750 mg or Moxifloxacin
2) Only 2 S. pneumoniae isolates from ER (inpatient isolates added to total)
3) 76% sensitive for meningitis
4) C. freundii and C. koseri
5) E. aerogenes and E. cloacae
6) Levofloxacin 750 mg or Moxifloxacin 400 mg
7) This organism is known to harbor inducible AmpC beta lactamases and may develop resistance during prolonged therapy with third generation cephalosporins

## Mercy Health Saint Mary’s
### H2CC - ICU ANTIBIOMGRAM
**January – December 2015**

Produced by Inpatient Pharmacy and Microbiology Departments

| Staphylococcus aureus | Vancomycin | Oxacillin | Tetracycline | Azithromycin | Ampicillin | Amoxicillin | Cefazolin | Ceftriaxone | Ceftazidime | Tobramycin | Aztreonam | Meropenem | Ciprofloxacin | Levofloxacin | Pipercillin-tazobactam | # Isolates |
|----------------------|------------|-----------|--------------|--------------|------------|-------------|-----------|------------|------------|------------|-----------|----------|-----------|----------------|----------------|--------------------------|-----------|
|                      | 60         | 100       | 82           | 95           | 100        | 100         | 100       | 96         | 98         | 86         | 99        | 45       | 179       |                  |                  |                          | 136       |

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2) Only 2 S. pneumoniae isolates from ER (inpatient isolates added to total)
3) 76% sensitive for meningitis
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5) E. aerogenes and E. cloacae
6) Levofloxacin 750 mg or Moxifloxacin 400 mg
7) This organism is known to harbor inducible AmpC beta lactamases and may develop resistance during prolonged therapy with third generation cephalosporins

## Mercy Health Saint Mary’s
### Emergency Department ANTIBIOMGRAM
**January – December 2015**

Produced by Inpatient Pharmacy and Microbiology Departments

| Staphylococcus aureus | Vancomycin | Oxacillin | Tetracycline | Azithromycin | Ampicillin | Amoxicillin | Cefazolin | Ceftriaxone | Ceftazidime | Tobramycin | Aztreonam | Meropenem | Ciprofloxacin | Levofloxacin | Pipercillin-tazobactam | # Isolates |
|----------------------|------------|-----------|--------------|--------------|------------|-------------|-----------|------------|------------|------------|-----------|----------|-----------|----------------|----------------|--------------------------|-----------|
|                      | 60         | 100       | 82           | 95           | 100        | 100         | 100       | 96         | 98         | 86         | 99        | 45       | 179       |                  |                  |                          | 136       |

1) 49% sensitive for 5) 750 mg or Moxifloxacin
2) Only 2 S. pneumoniae isolates from ER (inpatient isolates added to total)
3) 76% sensitive for meningitis
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5) E. aerogenes and E. cloacae
6) Levofloxacin 750 mg or Moxifloxacin 400 mg
7) This organism is known to harbor inducible AmpC beta lactamases and may develop resistance during prolonged therapy with third generation cephalosporins

**Note – Only**

1) Less than 30 isolates tested
2) Only 2 S. pneumoniae isolates from ER (inpatient isolates added to total)
3) 76% sensitive for meningitis
4) C. freundii and C. koseri
5) E. aerogenes and E. cloacae
6) Levofloxacin 750 mg or Moxifloxacin 400 mg
7) This organism is known to harbor inducible AmpC beta lactamases and may develop resistance during prolonged therapy with third generation cephalosporins
Antibiogram: Application to Practice

<table>
<thead>
<tr>
<th>Organism</th>
<th>Penicillin</th>
<th>Oxacillin</th>
<th>Vancomycin</th>
<th>Clindamycin</th>
<th>Tetracycline</th>
<th>Azithromycin</th>
<th>Ampicillin</th>
<th>Amoxicillin - Sulbactam</th>
<th>Cefazolin</th>
<th>Cefotaxine</th>
<th>Cefepine</th>
<th>Gentamicin</th>
<th>Tobramycin</th>
<th>Amikacin</th>
<th>Aztreonam</th>
<th>Sulfamethoxazole Trimethoprim</th>
<th>Meropenem</th>
<th>Imipenem</th>
<th>Cloxacillin</th>
<th>Ciprofloxacin</th>
<th>Levofloxacin</th>
<th>Piperacillin - Tazobactam</th>
<th># Isolates</th>
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<tbody>
<tr>
<td>Staphylococcus aureus</td>
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<td>Staphylococcus epidermidis</td>
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<td>Enterococcus species Other</td>
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<td>Streptococcus pneumonia</td>
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<td>Acinetobacter baumannii²</td>
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<td>Citrobacter koseri</td>
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<td>Enterobacter aerogenes</td>
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<td>Enterobacter cloacae</td>
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<td>Klebsiella pneumoniae</td>
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<td>Klebsiella oxytoca</td>
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<td>Proteus mirabilis</td>
<td>79</td>
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</tr>
</tbody>
</table>

1) 49% sensitive for meningitis  2) 74% sensitive for meningitis  3) 48 non-urine isolates E. faecium (83% were VRE)  4) 36 non-urine isolates E. faecalis (11% were VRE)
5) 750 mg or Moxifloxacin 400 mg  6) Tigecycline: 76%  7) Erythromycin tested
8) This organism is known to harbor inducible AmpC beta lactamases and may develop resistance during prolonged therapy with third generation cephalosporins such as ceftriaxone and cefotaxime.
Antibiogram Trends: 
Application to Practice

<table>
<thead>
<tr>
<th>Inpatient—Fluoroquinolones</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Escherichia coli</strong></td>
<td>80%</td>
<td>79%</td>
</tr>
<tr>
<td></td>
<td>↑(4%)</td>
<td>↔</td>
</tr>
<tr>
<td><strong>Proteus mirabilis</strong></td>
<td>66%</td>
<td>61%</td>
</tr>
<tr>
<td></td>
<td>↑(12%)</td>
<td>↔</td>
</tr>
<tr>
<td><strong>Pseudomonas</strong></td>
<td>84%</td>
<td>78%</td>
</tr>
<tr>
<td></td>
<td>↑(17%)</td>
<td>↓(6%)</td>
</tr>
<tr>
<td><strong>Streptococcus pneumoniae</strong></td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>↑*</td>
<td>↔</td>
</tr>
</tbody>
</table>

*100% susceptibility for the first time in 5 years*
### Critical Care Unit—Fluoroquinolones

<table>
<thead>
<tr>
<th>Organism</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Escherichia coli</strong></td>
<td>83%</td>
<td>79%</td>
</tr>
<tr>
<td></td>
<td>↑(15%)</td>
<td>↔</td>
</tr>
<tr>
<td><strong>Proteus mirabilis</strong></td>
<td>61%</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>↑(26%)</td>
<td>↓(11%)</td>
</tr>
<tr>
<td><strong>Klebsiella pneumoniae</strong></td>
<td>98%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>↑(8%)</td>
<td>↔</td>
</tr>
<tr>
<td><strong>Pseudomonas</strong></td>
<td>90%</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>↑(33%)</td>
<td>↓(15%)</td>
</tr>
<tr>
<td><strong>Streptococcus pneumoniae</strong></td>
<td>100%</td>
<td>95%+</td>
</tr>
<tr>
<td></td>
<td>↑*</td>
<td></td>
</tr>
</tbody>
</table>

*100% susceptibility for the first time in 5 years  †1 resistant isolate
Question #4: Which one of the following culture reports would be most appropriate to request for constructing an antibiogram?

A. Without stratification by location
B. Stratified by ICU and non-ICU locations
C. Stratified by ICU, inpatient, and community locations
D. Stratified by inpatient care areas (e.g., floors)
Targeted Surveillance for High Risk Populations or Procedures

• Hospital setting: surgical prophylaxis/site infections, healthcare-associated infections

• Community setting: respiratory and urinary tract infections

• Everyone: *Clostridium difficile* infections

Targeted Surveillance for High Risk Antimicrobial Therapies

• Hospital setting: e.g., carbapenems

• Community setting: e.g., 3rd-generation cephalosporins

• Everyone: fluoroquinolones

Rapid Pathogen Identification: Immediate Surveillance

- Polymerase chain reaction (PCR)-based detection technology
- Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry
- Microarrays
- Microfluidics
- Cell lysis-based approach
- Whole-genome sequencing

Role of Clinical Decision Support Software in Surveillance

- Surveillance may be possible with integrated, advanced clinical decision support software

- May allow for decision making at the patient level and more rapid identification of worrisome trends on a real-time basis

Components of an Effective Antimicrobial Stewardship Program
Antimicrobial Stewardship Programs (ASPs)

- What we know about ASPs: improved clinical outcomes

- We “want” to have an impact on antimicrobial prescribing....but now we are going to “have to”

- Components defined by guidelines and now regulatory bodies
“The primary goal of antimicrobial stewardship is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms (such as Clostridium difficile), and the emergence of resistance.”

Who Cares About ASPs?

• The White House

• Centers for Disease Control and Prevention (CDC)

• Centers for Medicare & Medicaid Services (CMS)

• The Joint Commission

• U.S. Food and Drug Administration (FDA)
White House National Action Plan for Combating Antibiotic-Resistant Bacteria

- In March 2015, the White House released a National Action Plan for Combating Antibiotic-Resistant Bacteria
- Several objectives were outlined, including the need for antimicrobial stewardship programs in all healthcare settings
- A reduction in inappropriate antibiotic use by 50% in outpatient settings and 20% in inpatient settings is expected

CMS Proposed Standards for Infection Prevention and Control and Antibiotic Stewardship Programs (§482.42)

• Proposed requirements would stipulate that the following goals are met:

1. Coordinate among all components of the hospital responsible for antibiotic use and factors that lead to antimicrobial resistance

2. Document the evidence-based use of antibiotics

3. Demonstrate improvements in proper antibiotic use, such as reductions in *Clostridium difficile* infections and antibiotic resistance

The Joint Commission Antimicrobial Stewardship Standard for Hospitals

• Standard goes into effect on January 1, 2017

• Recommends core elements as described in the CDC Core Elements of Hospital Antibiotic Stewardship Programs
U.S. Food and Drug Administration

• FDA advises restricting use of fluoroquinolones for uncomplicated infections

• FDA Guidance for Industry (GFI) #213
  – Initially recommended phasing out “medically important” antibiotics in feed animals
  – December 2016: will be illegal to use “medically important” antibiotics in food or water for production purposes in feed animals


Outcomes Associated with ASPs

• Decreased antimicrobial use (particularly broad-spectrum agents)

• Decreased inappropriate prescribing

• Improved adherence to treatment guidelines

• Improved patient outcomes
  – Decreased treatment failure
  – Increased clinical cure rates

Outcomes Associated with ASPs

• Decreased *Clostridium difficile* infection

• Decreased hospital length of stay

• Decreased costs

• Decreased antimicrobial resistance...?
CDC Core Elements of Hospital Antibiotic Stewardship Programs

• **Leadership Commitment**: allow for dedicated time, resources, and participation

• **Accountability**: assign a stewardship program leader responsible for program outcomes

• **Drug Expertise**: identify a pharmacist leader

• **Action**: implement at least one recommended action/intervention

CDC Core Elements of Hospital Antibiotic Stewardship Programs

• **Tracking:** monitor prescribing and resistance patterns

• **Reporting:** regular reporting on antibiotic use, resistance, and outcome measures

• **Education:** educate clinicians about resistance and optimal prescribing
Checklist for Core Elements of Hospital Antibiotic Stewardship Programs

The following checklist is a companion to Core Elements of Hospital Antibiotic Stewardship Programs. This checklist should be used to systematically assess key elements and actions to ensure optimal antibiotic prescribing and limit overuse and misuse of antibiotics in hospitals. CDC recommends that all hospitals implement an Antibiotic Stewardship Program.

Facilities using this checklist should involve one or more knowledgeable staff to determine if the following principles and actions to improve antibiotic use are in place. The elements in this checklist have been shown in previous studies to be helpful in improving antibiotic use though not all of the elements might be feasible in all hospitals.

<table>
<thead>
<tr>
<th>LEADERSHIP SUPPORT</th>
<th>ESTABILISHED AT FACILITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Does your facility have a formal, written statement of support from leadership that supports efforts to improve antibiotic use (antibiotic stewardship)?</td>
<td>Yes</td>
</tr>
<tr>
<td>B. Does your facility receive any budgeted financial support for antibiotic stewardship activities (e.g., support for salary, training, or IT support)?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACCOUNTABILITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Is there a physician leader responsible for program outcomes of stewardship activities at your facility?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DRUG EXPERTISE</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Is there a pharmacist leader responsible for working to improve antibiotic use at your facility?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>KEY SUPPORT FOR THE ANTIBiotic STEWARDSHIP PROGRAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does any of the staff below work with the stewardship leaders to improve antibiotic use?</td>
</tr>
</tbody>
</table>

| B. Clinicians                                      | Yes | No |
| C. Infection Prevention and Healthcare Epidemiology | Yes | No |
| D. Quality Improvement                             | Yes | No |
| E. Microbiology (Laboratory)                       | Yes | No |
| F. Information Technology (IT)                     | Yes | No |
| G. Nursing                                         | Yes | No |
IDSA/SHEA* Guidelines for...Antimicrobial Stewardship: Team Members

- **Essential:** Infectious diseases physician, pharmacist, hospital administration, medical staff leadership, local providers

- **Optimal:** clinical microbiologist, infection control specialist, information system specialist, hospital epidemiologist

---

* IDSA/SHEA = Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America
Question #5: Which one of the following is considered a core strategy for an antimicrobial stewardship program?

A. Formulary restriction and preauthorization
B. Education
C. Guidelines and clinical pathways
D. Antimicrobial cycling
Your poll will show here

1. Install the app from pollev.com/app
2. Make sure you are in Slide Show mode

Still not working? Get help at pollev.com/app/help
.or
Open poll in your web browser
IDSA/SHEA* Guidelines for...Antimicrobial Stewardship: Core Strategies

- Prospective audit with intervention and feedback
- Formulary restriction and preauthorization

* IDSA/SHEA = Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America
IDSA/SHEA Guidelines for...Antimicrobial Stewardship: Supplemental Strategies

• Education

• Guidelines and clinical pathways

• Antimicrobial order forms
IDSA/SHEA Guidelines for...Antimicrobial Stewardship: Supplemental Strategies

- Streamlining or de-escalation of therapy

- Dose optimization

- Parenteral-to-oral conversion

- Computer surveillance and clinical decision support

IDSA/SHEA Guidelines for...Antimicrobial Stewardship: Supplemental Strategies

• Antimicrobial cycling—NOT RECOMMENDED

• Combination therapy—NOT RECOMMENDED
Question #5: Which one of the following is considered a core strategy for an antimicrobial stewardship program?

A. Formulary restriction and preauthorization
B. Education
C. Guidelines and clinical pathways
D. Antimicrobial cycling
Antimicrobial Consumption Metrics in the Hospital Setting.

Marc H. Scheetz, Pharm.D., MSc
Associate Professor of Pharmacy Practice
Midwestern University Chicago College of Pharmacy
Downers Grove, Illinois
Infectious Diseases Pharmacist
Northwestern Memorial Hospital, Chicago, Illinois
Antimicrobial Stewardship Manuscripts

Manuscripts identified in PubMed using key words “antimicrobial stewardship”, search completed 5/9/16 (Scheetz)

*2016 data projected based on rate of manuscript publication through 5/9/16
What is Antimicrobial Stewardship?

• “...antimicrobial-use regulation employing sophisticated epidemiologic methods, molecular biological organism typing, and precise resistance mechanism analysis will be required to determine the best methods to prevent and control this problem and ensure our optimal antimicrobial-use "stewardship." Consideration of the long-term effects of antimicrobial selection, dosage, and duration of treatment on resistance development should be a part of every antimicrobial treatment decision.”

Policy Statement of SHEA, IDSA, and PIDS

1. Antimicrobial stewardship programs should be required through regulatory mechanisms.
2. Antimicrobial stewardship should be MONITORED in ambulatory healthcare settings.
3. Education about antimicrobial resistance and antimicrobial stewardship must be accomplished.
4. Antimicrobial use DATA should be collected and readily available for both inpatient and outpatient settings.
5. Research on antimicrobial stewardship is needed.

Slightly less prominent...

“Team members should include... a pharmacist”

“Antimicrobial stewardship is a patient safety issue and a public health issue....”

In addition to members of IDSA and the SHEA, representatives from diverse geographic areas, pediatric and adult practitioners, and a wide breadth of specialties representing major medical societies were included among the panel’s membership (American College of Emergency Physicians [ACEP], American Society of Health-System Pharmacists [ASHP], American Society for Microbiology [ASM], PIDS, Society for Academic Emergency Medicine [SAEM], Society of Infectious Diseases Pharmacists [SIDP], and the Surgical Infection Society [SIS]).
“This guideline does not specifically address the structure of an ASP, which has been well outlined in a previous guideline [8] and in the CDC’s Core Elements of Hospital Antibiotic Stewardship Programs and Core Elements of Antibiotic Stewardship for Nursing Homes [7, 9]. These documents emphasize the importance of physician and pharmacist leadership for an ASP, the need for infectious diseases expertise, and the role of measurement and feedback as critical components of ASPs.”

What Should Stewardship Programs be Measuring?

• Resistance >> yes, complex.

• Outcomes >> yes, complex.

• Cost >> until we are “under the auspices of quality...” and probably even then.

• ATB Use >> the driver of the above outcomes!!!
Question #6: What is the best measure of antimicrobial consumption according to the 2016 IDSA/SHEA guideline?

A. Defined Daily Doses (DDDs)
B. Purchased Grams of Antibiotics (PGA)
C. Days of Therapy (DOTs)
D. Renally-adjusted Days of Therapy (raDOTs)
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Question #6: What is the best measure of antimicrobial consumption according to the 2016 IDSA/SHEA guideline?

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D. Renally-adjusted Days of Therapy (raDOT)
... straight from the horse’s mouth.

Measurement.

XX. Which Overall Measures Best Reflect the Impact of ASPs and their Interventions?

Recommendation

21. We suggest monitoring antibiotic use as measured by days of therapy (DOTs) in preference to defined daily dose (DDD) (weak recommendation, low quality evidence).

XXI. What is the Best Measure of Expenditure on Antibiotics to Assess the Impact of ASPs and Interventions?

Recommendation

22. We recommend measuring antibiotic costs based on prescriptions or administrations instead of purchasing data (good practice recommendation).

Tracking and Analyzing: Antibiotic Consumption
Antibiotic Use, by the Numbers/Numerators

• Antibiotic use should be quantified to compare with:
  – Self
  – Others

• Defined Daily Doses (DDDs)
  – http://www.whocc.no/atcddd/
  – Can be calculated from purchasing data

• Days of Therapy (DOTs)
  – More accurate... barcoding¹

• NHSN-AUR (National Healthcare Safety Network-Antibiotic Use and Resistance Module) (Antibiotic Days)


Step 1. Comparing to self

• You are often your own best control!

• A denominator is probably helpful for temporal changes (census shifts, new programs, etc)
  – Standardize to patient day(s)

• Stratifications can be useful
  – Use in intensive care vs. general floors, etc.

• NOTE: Refrain from analyzing trends in variables that you cannot impact!!!!
Step 1. Comparing to Self

• A denominator is necessary.
  — DDDs per 1000 patient days
  — Duration of therapy (DOTs) per 1000 patient days
  — Cost per patient day

• Internal validity first: control for changes in hospital/program size across time

• External validity: control for variables likely to affect use/cost (e.g., patient severity of illness, patient disease state)
NHSN AUR Module

• Aggregated monthly, with summaries
  – Inpatient units singly & combined (FacWideIN)
• Numerator: Antimicrobial days (Days of Therapy Administered)
  – 89 antimicrobials (antibacterial, antifungal, and anti-influenza agents)
  – Stratification by route of administration:
    – IV/IM/Oral/Respiratory
• Denominators:
  – Days Present: number of days spent in specific unit or facility
  – Admissions: number of patients admitted to the facility

So What is the Difference between all of these Antibiotic-Use Metrics?
Question #7: True or False: Days of Therapy (DOTs) can be predicted from Defined Daily Doses (DDDs)

A True
B False
Your poll will show here

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or
Open poll in your web browser
Question #7: True or False: Days of Therapy (DOTs) can be predicted from Defined Daily Doses (DDDs)

A True

B False
DDDs do not always equal DOTs

DDDs do not always equal DOTs

• ... but agreement between DDD and DOT is generally good (i.e., $r^2$ is high).\(^1\)
  – Pick one method and stick with it.

• Likely reasons that DDD > DOT\(^2\)
  – WHO classification is high compared to practice.\(^1\)
    – e.g. ceftriaxone WHO DDD = 2 g per day; many give 1 g per day
  – Not all “ordered” doses are given.

• Likely reasons that DDD < DOT\(^1\)
  – Renal function adjustments not captured
    – e.g. Vancomycin DDD = 2 g per day; patients with renal failure may receive 2 g per week.
  – WHO classification is low compared to practice.
    – e.g. Ampicillin/Sulbactam DDD = 2 g per day; many are giving much more than this

National Healthcare Safety Network (NHSN)

Surveillance for Antimicrobial Use and Antimicrobial Resistance Options

Resources for NHSN Users Already Enrolled

- **Introduction to the NHSN Antimicrobial Use and Resistance (AUR) Module (updated January 2016)** [PDF - 571 KB]
- **New! Antibiotic Stewardship - March 2016 [Video - 36 min]**
  - YouTube link - Antibiotic Stewardship
  - CDC Streaming Video - Antibiotic Stewardship
  - Slide set - Antibiotic Stewardship [PDF - 1 MB]
- **New! Analysis of Antibiotic Resistance Data - March 2016 [Video - 48 min]**
  - YouTube link - Analysis of Antibiotic Resistance Data
  - CDC Streaming Video - Analysis of Antibiotic Resistance Data
  - Slide set - Analysis of Antibiotic Resistance Data [PDF - 1 MB]
- **New! Antimicrobial Use and Resistance Module Protocol - March 2016 [Video - 36 min]**
  - YouTube link - Antimicrobial Use and Resistance Module Protocol
  - CDC Streaming Video - Antimicrobial Use and Resistance Module Protocol
  - Slide set - Antimicrobial Use & Resistance Module Protocol [PDF - 780 KB]
- **New! Standardized Antibiotic Administration Ratio - March 2016 [Video - 24 min]**
  - YouTube link - Standardized Antibiotic Administration Ratio
  - CDC Streaming Video - Standardized Antibiotic Administration Ratio
  - Slide set - Standardized Antimicrobial Administration Ratio [PDF - 956 KB]

What are the Differences with ADs and DOTs

• NHSN ADs are based on eMAR and/or BCMA administrations
  – If a patient is scheduled to receive vancomycin thrice weekly because of renal dysfunction, there will be 3 ADs for a week of therapy.
  – The same patient can be counted as 7 DOTs based on calendar days of antibiotic therapy.

• Does the floor shift below you? I.e. what about denominators?
  – It depends... NHSN uses Days Present.
  – “days present is calculated as the number of patients who were present for any portion of each day of a calendar month for a patient care location”

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NHSN Methods vs. DOT methods

**Piperacillin-Tazobactam**
\[ y = 0.5088x \]
\[ R^2 = 0.8077 \]

**Cefepime**
\[ y = 0.5515x \]
\[ R^2 = 0.8543 \]

**Imipenem and Meropenem**
\[ y = 0.5279x \]
\[ R^2 = 0.5485 \]

**Ertapenem**
\[ y = 0.5517x \]
\[ R^2 = 0.7207 \]

NHSN Methods vs. DOT methods

$y = 1.92x$

$R^2 = 0.99$

It matters less where you start with metrics... but more *that* you start tracking.
Internal tracking

• You are often your own best control!

• A denominator is necessary to standardize and control for census shifts, new programs, etc.
  – Standardize to patient days (e.g., 1,000 patient days).

• Stratifications can be useful
  – Use in MICU vs. general floors, etc.

• NOTE: Refrain from reporting trends in variables that you cannot impact!!!!
Trend your Data.

• A picture is worth a thousand words/statistics.

• At least 3 time points before/after (assuming for homogenous data) are necessary to determine the secular trend (i.e., non-periodic trend).¹

Amikacin Use
I lied. These are stock data.
Predicting the Future is Hard.
Forecasting

Facility Wide Vancomycin Use

Scheetz et al. Unpublished because the reviewers didn’t like it.
Simple Regressive Methods

Whole Hospital, Vancomycin Use

Vancomycin, Whole Hospital

It gets more complex.
Question 8: Which statement about seasonality in hospital antibiotic use is correct?

A. There usually is not seasonal variation.
B. There is seasonal variation, but it is not predictable.
C. There is seasonal variation, and it is predictable.
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Question 8: Which statement about seasonality in hospital antibiotic use is correct?

A. There usually is not seasonal variation.
B. There is seasonal variation, but it is not predictable.
C. There is seasonal variation, and it is predictable.
Seasonal Variation in Antibiotic Consumption in British Columbia (top) and Denmark (bottom), 1997–2000.

Monthly Variability in Vancomycin

FACWIDE IV VANCOMYCIN C_SUM DOTs/1000 DP

Slide courtesy of Dr. Jim Rhodes.
Linking consumption to resistance... even more difficult
Visual Interpretation can be Adequate.

![Graph showing the relationship between C. CRE isolates per 1000 Patient Days and Meropenem DOT per 1000 Patient Days. The graph includes a Sigmoid-4 Parameter Model described by:

\[ f = y_0 + \frac{a}{1 + \exp\left(-\frac{x-x_0}{b}\right)} \]

And the coefficient of determination, \( r^2 = 0.64 \).]

Co-trending Consumption and Resistance
Meropenem DOT/1000 Patient Days and CRE Isolates

MIC= minimum inhibitory concentration in mg/L
CRE= carbapenem resistant Enterobacteriaceae

Two Comparisons:
1. Effect of antibiotic in February 2013 → on CDI in February 2013
2. Effect of antibiotic in February 2013 → on CDI in March 2013
Two Comparisons:
1. Effect of antibiotic in February 2013 → on CDI in February 2013
2. Effect of antibiotic in February 2013 → on CDI in March 2013

Ho CDI per 100,000DP

Carbapenem ADs per 1000 DP

Time

One Month

Slide courtesy Dr. Page Crew.
Cancer Ward: One-Month Lag, Correlation between Carbapenem ADs and HO CDI Incidence, January 2013 - September 2014

y = 0.602x + 7.6805
p = 0.041
r = 0.46
R² = 0.21197

Slide courtesy Dr. Page Crew.
Comparing to Others.
External Benchmarking

• Again, a denominator is necessary.
  - DDDs per 1000 patient days
  - DOTs per 1000 patient days
  - Cost per patient day

• Internal validity first: control for changes in hospital/program size across time

• External validity: control for variables likely to affect use/cost (e.g., patient severity of illness, patient disease state)

• Be aware that it is very difficult to compare yourself with other hospitals at this time.
  - A study by Pakyz et al. demonstrated that the only variable that predicted broad-spectrum antimicrobial use in a multi-hospital study was total duration of antibiotic use.¹

Standardized Antimicrobial Administration Ratio (SAAR)

SAAR is an Observed-to-Expected (O-to-E) ratio

- **Observed antibacterial use** – Days of therapy reported by a healthcare facility for a specified category of antimicrobial agents in a specified patient care location or group of locations

- **Predicted/Expected antibacterial use** – Days of therapy predicted on the basis of nationally aggregated AU data for a healthcare facility’s use of a specified category of antimicrobial agents in a specified patient care location or group of locations

The SAAR metric is constructed by using an indirect standardization method for comparing observed to expected days of therapy. Detailed information on the SAAR can be found in the NHSN AUR Module Protocol: [http://www.cdc.gov/nhsn/pdfs/pscmanual/11pscaurcurrent.pdf](http://www.cdc.gov/nhsn/pdfs/pscmanual/11pscaurcurrent.pdf).
Interpreting SAAR values

The SAAR is a ratio. The calculated SAAR value is always greater than 0, and a value of 1.0 suggests equivalency between observed and predicted antimicrobial use.

- A high SAAR (above 1.0) that achieves statistical significance (i.e., different from 1.0) may indicate excessive antimicrobial use.
- A SAAR that is not statistically different from 1.0 indicates antimicrobial use is equivalent to the referent population’s antimicrobial use.
- A low SAAR (below 1.0) that achieves statistical significance (i.e., different from 1.0) may indicate antimicrobial under use.

Note: A SAAR alone is not a definitive measure of the appropriateness or judiciousness of antimicrobial use, and any SAAR may warrant further investigation. For example, a SAAR above 1.0 that does not achieve statistical significance may be associated with meaningful excess of antimicrobial use and further investigation may be needed. Also, a SAAR that is statistically different from 1.0 does not mean that further investigation will be productive.
SAAR Calculations Cover 5 Antibiotic Agent Categories

High value targets for antimicrobial stewardship programs:

1. Broad spectrum agents predominantly used for hospital-onset/multi-drug resistant bacteria – aminoglycosides, some cephalosporins, penicillin B-lactam/b-lactamase inhibitor combinations, and other agents

2. Broad spectrum agents predominantly used for community-acquired infection – ertapenem, some cephalosporins, and some fluroquinolones

3. Anti-MRSA agents – ceftaroline, dalbavancin, daptomycin, linezolid, oritavancin, quinupristin/dalfopristin, tedizolid, telavancin, and vancomycin

4. Agents predominantly used for surgical site infection prophylaxis – cefazolin, cefotetan, cefoxitin, cefuroxime

High level indicators for antimicrobial stewardship programs:

5. All antibiotic agents – All agents included in NHSN AUR protocol
Other Manifestations of Consumption

Tracking and Analyzing Costs... because you probably “have to”
Question 9: A dollar bill, today, is worth:

A. More today than it will be in 1 year
B. Less today than it will be in 1 year
C. The same today as it will be in 1 year
D. At least 4 pulls on the quarter slot machines
Your poll will show here

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Question 9: A dollar bill, today, is worth:

A. More today than it will be in 1 year
B. Less today than it will be in 1 year
C. The same today as it will be in 1 year
D. At least 4 pulls on the quarter slot machines
You CANNOT escape COST!

What can you do?

• Due to compounding of market price increases, yearly drug cost increases can often be logarithmic.

• This must be understood by administration.

• Failing to account for increasing drug costs will doom your ASP in short order.

• An example
  – Assume a fixed rate of 11% per year increase in drug costs.
  – Predict what a reasonable reduction in Antibiotic Costs would be from your ASP.
If you must look at cost, adjust!

- Antimicrobial Expenditures (Increasing 11% per Year)
- Reasonable Use (60% of Pre-AST Use)
- What Administrators Sometimes Think? (10% per Year Savings)

Key Takeaways

• Who to compare with:
  – Self? Absolutely!
  – Others? Yes, but realize that this is more difficult.

• What to measure
  – Antibiotic use/consumption? (yes!!)
  – Antibiotic cost? (yes, but carefully)
A call to action

“There is perhaps never been a more critical juncture for antimicrobial stewardship. There is growing interest from key stakeholders—clinicians, healthcare administrators, and policy makers—and a growing body of evidence demonstrating the benefits of stewardship. We now need to harness the interest and the science to move forward toward making stewardship programs and integral part of healthcare facilities.”

Key Takeaways

• Key Takeaway #1: Antimicrobial drug resistance is reaching a critical level. It results in increased hospitalizations, treatment failures, mortality, and costs. Efforts to curb antimicrobial resistance are greatly needed.

• Key Takeaway #2: The pharmacist is a key member of the antimicrobial stewardship team and should pursue a leadership role in stewardship efforts.

• Key Takeaway #3: The CDC and IDSA/SHEA guidelines provide guidance and recommendations for establishing an antimicrobial stewardship program, including program components and strategies.
Questions?
References


References


References


References


References


References


References


References


References


Recommended Resources


Recommended Resources

• The White House National Action Plan for Combating Antibiotic-Resistant Bacteria:
  https://www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibiotic-resistant_bacteria.pdf

• The Joint Commission Antimicrobial Stewardship Standard:
  https://www.jointcommission.org/assets/1/6/New_Antimicrobial_Stewardship_Standard.pdf

• CMS Proposed Rule on Infection Control and Antibiotic Stewardship Programs:
Recommended Resources

• ASHP Resource Center: http://www.ashp.org/menu/PracticePolicy/ResourceCenters/Inpatient-Care-Practitioners/Antimicrobial-Stewardship

• CDC Get Smart for Healthcare: http://www.cdc.gov/gets smart/healthcare/index.html

• CDC Antimicrobial Stewardship Resources: http://www.cdc.gov/gets smart/healthcare/
Recommended Resources

• IDSA Promoting Antimicrobial Stewardship in Human Medicine: http://www.idsociety.org/Stewardship_Policy/

• American Hospital Association’s Antimicrobial Stewardship User Guide: http://www.ahaphysicianforum.org/resources/appropriate-use/antimicrobial/
Recommended Resources
