Antibiotic Stewardship is Here to Stay: Are You Ready?

DSHS Healthcare Safety Conference 2018
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Learning Objectives

• Describe factors that are driving antibiotic stewardship efforts
• Discuss best practices that can be implemented to improve antibiotic use
• Discuss how antibiotic stewardship can improve patient safety
Disclosures

• I am an employee of Vizient which is a healthcare company
Why Do We Need Antibiotic Stewardship?

• Up to 50% of antimicrobial use is inappropriate
• Antibiotics are unlike any other drug, in that the use of the agent in one patient can compromise its efficacy in another.
• Antibiotic overuse has negative consequences
• The antibiotic pipeline has improved but may not be sustained and is limited for highly resistant organisms.

Source: Centers for Disease Control
Figure 1. The evolution of β-lactamases. ESBL = extended-spectrum β-lactamase; KPC = Klebsiella pneumoniae carbapenemase; MBL = metallo-β-lactamase; TEM-1, TEM-2, SHV-1, TEM, SHV, CTX-M = types of β-lactamases.

Wild-Type

Penicillins

β-lactamase (TEM-1, TEM-2, SHV-1)

β-lactam/β-lactamase inhibitors; Cephalosporins

AmpC; ESBL (TEM, SHV, CTX-M)

Carbapenems

Carbapenemase (KPC, MBL)

NDM-1

mcr-1
Superbugs Don’t Respect Borders
How NDM-1 spread around the world

Source: Pew Charitable Trust
Some Reasons Why We Have a Global Antibiotic Resistance Problem
# Antibiotic Exposure Increases the Risks of Resistance

## Pathogen and Antibiotic Exposure

<table>
<thead>
<tr>
<th>Pathogen and Antibiotic Exposure</th>
<th>Increased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbapenem Resistant Enterobacteriaceae and Carbapenems</td>
<td>15 fold</td>
</tr>
<tr>
<td>ESBL producing organisms and cephalosporins</td>
<td>6- 29 fold</td>
</tr>
</tbody>
</table>


2. Slide credit A. Srinivasan, MD (CDC)
THE MODERN ERA OF ANTIBIOTIC STEWARDSHIP
Estimated minimum number of illnesses and deaths caused annually by antibiotic resistance*:

At least $2,049,442$ illnesses, $23,000$ deaths

*bacteria and fungus included in this report

CDC Report 2013
Antimicrobial stewardship is a coordinated program that promotes the appropriate use of antimicrobials (including antibiotics), improves patient outcomes, reduces microbial resistance, and decreases the spread of infections caused by multidrug-resistant organisms.

**7 Core Elements of a Successful Antibiotic Stewardship Program**

- **Leadership**
- **Commitment**
- **Accountability**
- **Drug Expertise**
- **Action**
- **Tracking**
- **Education**

**Source:** CDC Core Elements for Antibiotic Stewardship
Antimicrobial Stewardship Partners

- Other Clinicians & Residents
- Clinical Pharmacy
- Quality and Safety
- Administration
- Infection Prevention
- Nursing
- Microbiology Lab
- Information Technology
- Pharmacy and Therapeutics Committee
- Physicians & Fellows

Antibiotic utilization reduction goals

• By 2020, the United States will
  • Reduce inappropriate antibiotic use for monitored conditions/agents by 20% from 2014 levels
  • Reduce inappropriate outpatient antibiotic use for monitored conditions/agents by 50% from 2010 levels
  • Eliminate the use of medically important antibiotics for growth promotion in animals
White House Antimicrobial Summit – June 2015

• Convened 150 key stakeholders across human and animal health sectors to discuss the increasing problem of antibiotic resistance

Human Health
Session 1: Improving Inpatient Prescribing; Focus on Patients
Session 2: Improving Outpatient Prescribing; Focus on Families
Session 3: Improving Long-term Care Prescribing; Focus on Aging Population
Post 2015 Work

• Harmonizing antibiotic susceptibility testing between FDA approved breakpoints and other agencies (21st Century Cures Act)
• Developing incentives to encourage drug companies to develop antibiotics
  • Patent protection (5 additional years for Qualified Infectious Diseases Products)
  • Accelerated drug approval – less clinical trials required
• Veterinary Feed Directive Act
• FDA considering a “licensing fee” for antibiotics
• Presidential Advisory Council on Combating Antibiotic Resistant Bacteria (PAC CARB)
  • National benchmark for antibiotic utilization known as the standardized antibiotic administration ratio (SAAR)
  • Reporting through NHSN

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm610503.htm
Stewardship Seats At the Table

- Agency for Healthcare Research and Quality
- American Hospital Association
- American Society of Health Systems Pharmacists (ASHP)
- American Society of Consultant Pharmacists
- Association of State and Territorial Health Officials (ASTHO)
- Center for Disease Control and Prevention
- Center for Medicare and Medicaid Services (CMS)
- Federal Office of Rural Health Policy
- IDSA – Infectious Diseases Society of America
- The Joint Commission
- Leapfrog Group

- NQF – National Quality Forum
- QIO/QINs
- Pediatric Infectious Diseases Society (PIDS)
- PEW Charitable Trusts
- Society of Hospital Medicine (SHM)
- Society of Infectious Diseases Pharmacists
- Society for Healthcare Epidemiology of America (SHEA)
- The Joint Commission
- The White House
- U.S. News & World Report – Best Children’s Hospital Honor Roll

*Since 2014
1. Leaders establish antimicrobial stewardship as an organizational priority.

2. Educate staff and licensed independent practitioners involved in antimicrobial ordering, dispensing, administration, and monitoring about antimicrobial resistance and antimicrobial stewardship practices. Education occurs upon hire and annually thereafter.

3. Educate patients, and their families as needed, regarding the appropriate use of antimicrobial medications, including antibiotics. 

   **REMOVED FOR CAH and ACUTE CARE – 10/1/17**

   [Link](https://www.jointcommission.org/issues/article.aspx?Article=YorQ4E0NZh1SOmOxW2H%2FtFFcVyCrphOFImQsZM%2BIvPc%3D)

4. The organization has an antimicrobial stewardship multidisciplinary team that includes the following members, when available in the setting: Pharmacist(s), infection disease physician, infection preventionists (part time/consultant staff acceptable)
The organization’s antimicrobial stewardship program includes the following core elements:
- Leadership commitment
- Accountability
- Tracking
- Education
- Action
- Drug expertise
- Reporting

The organization’s antimicrobial stewardship program uses organization-approved multidisciplinary protocols.

The organization collects and analyzes data on its antimicrobial stewardship program, including antimicrobial prescribing and resistance patterns.

The organization takes action on improvement opportunities identified in its antimicrobial stewardship program.
Stewardship in Critical Access Hospitals

- Medicare Beneficiary Quality Improvement Project (MBQIP)
  - Listed under patient safety/inpatient core improvement initiative
  - Required to fully implement an antibiotic stewardship program
    - Follow the CDC Core Elements by August 31, 2022 (4 year lead time)
    - Necessary to receive Flex grant funding
- Encourages to collaborate with health departments and QIO-QINs
- 2018 expectations
  - Enroll in National Healthcare Safety Network (NHSN)
  - Submit NHSN Annual Facility Survey
  - Become familiar with the CDC’s 7 Core Elements

https://www.ruralcenter.org/resource-library/mbqip-measures
Critical Access Hospitals Use Antibiotics About As Much As Larger Hospitals

Mean Rates of Total Antibiotic Use

<table>
<thead>
<tr>
<th>Number of Beds</th>
<th>Mean Rate (DOT/1,000 days present)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤25 beds</td>
<td>627.6</td>
</tr>
<tr>
<td>26-50 beds</td>
<td>713.6</td>
</tr>
<tr>
<td>&gt;50 beds</td>
<td>595.4</td>
</tr>
</tbody>
</table>

Slide Credit: Centers for Disease Control
ANTIBIOTIC SAFETY
Antibiotics and the Patient Safety Impact

- What if something bad happens without an antibiotic? What is the **number needed to treat**?
  - Complications to common respiratory infections are very rare
  - Over 4400 patients with colds need to be treated to prevent 1 case of pneumonia

- What if something bad happens with an antibiotic? What is the **number needed to harm**?
  - Antibiotic adverse events can be severe
    - Life-threatening allergic reactions (e.g., anaphylaxis)
    - Antibiotic-associated diarrhea (e.g., *C. difficile* infection)
    - 1 in 1000 antibiotic prescriptions leads to an ER visit for an adverse event (~200,000 estimated ER visits/year in U.S.)
  - Antibiotic adverse events have long-term consequences for chronic disease: disruption of microbiota and microbiome linked to chronic disease


Slide source: CDC
Adverse Events

- 1488 hospitalized patients were given antibiotics
- 20% experienced at least 1 antibiotic-associated adverse event
- 20% of non-indicated antibiotic regimens were associated with an adverse event, including 7 cases of *C. difficile*
- There was a 3% increased risk of an adverse event for every 10 days of antibiotics
- The most common (first 30 days)

<table>
<thead>
<tr>
<th>Description</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI (diarrhea, vomiting, nausea)</td>
<td>42</td>
</tr>
<tr>
<td>Renal (&gt; 1.5 times rise in creatinine)</td>
<td>24</td>
</tr>
<tr>
<td>Hematologic (anemia, leukopenia, thrombocytopenia)</td>
<td>15</td>
</tr>
</tbody>
</table>

FDA News Release

FDA updates warnings for fluoroquinolone antibiotics on risks of mental health and low blood sugar adverse reactions

July 10, 2018

The U.S. Food and Drug Administration today is requiring safety labeling changes for a class of antibiotics called fluoroquinolones to strengthen the warnings about the risks of mental health side effects and serious blood sugar disturbances, and make these warnings more consistent across the labeling for all fluoroquinolones taken by mouth or given by injection.
“Easy Wins” for Antibiotic Stewardship

• Avoiding overtreatment of asymptomatic bacteriuria
• Limiting duration of therapy
• Assessment of antibiotic use at transition of care
• Appropriate testing and treatment of *C. difficile*
• Avoiding duplicate anaerobic therapy
The 5 D’s of Antibiotic Stewardship

• Goal: Ensure the 5 D’s of optimal antimicrobial therapy

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Does the condition require antibiotic therapy?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Is the bacteria susceptible?</td>
</tr>
<tr>
<td>Dose</td>
<td>What is the recommended dose?</td>
</tr>
<tr>
<td>Duration</td>
<td>What is the recommended duration?</td>
</tr>
<tr>
<td>De-escalation</td>
<td>Can the antibiotic be switched from IV to oral?</td>
</tr>
</tbody>
</table>

## Asymptomatic Bacteriuria is Common

<table>
<thead>
<tr>
<th>Population</th>
<th>% ASB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy pre-menopausal women</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Women 65-90 years old</td>
<td>6-16%</td>
</tr>
<tr>
<td>Women ≥90 years old</td>
<td>22-43%</td>
</tr>
<tr>
<td>Female long-term care residents</td>
<td>25-50%</td>
</tr>
<tr>
<td>Men &gt;65 years old</td>
<td>5-21%</td>
</tr>
<tr>
<td>Male long-term care residents</td>
<td>15-35%</td>
</tr>
<tr>
<td>Indwelling urinary catheters</td>
<td>100%</td>
</tr>
</tbody>
</table>


Slide courtesy of P. Tamma, MD
Urine culture on admission increases antibiotic use and length of stay

- Retrospective cohort study of a national dataset from 2009 to 2014 (230 hospitals)
- Total of 88,841 patients included
  - No urine culture (n=47,411) vs urine culture (n=41,070) on admission
- Evaluated admissions based on MS-DRG. Patients were case matched by facility, age, gender, and 3 measures of disease severity
- Obtaining a urine culture on admission led to an increase in days of inpatient antibiotic use (incidence rate ratio, 1.26, p<0.001) and resulted in an additional 36,607 days of inpatient antibiotic treatment
- 2.1% increase in LOS (p=0.004) equaling 6,071 additional bed days

Does the patient have any UTI symptoms?

- Flank Pain
- Acute Hematuria
- *Delirium
- *Rigors
- *Fever
- Pelvic Discomfort
- Urgency
- Frequency
- Dysuria
- Suprapubic Pain

*Interpret with caution

Does a non-UTI diagnosis likely account for the symptoms?

- No
  - Do not send urine culture
- Yes
  - Work-up other cause

Send urine culture

Consider empiric antibiotics for UTI

Review urine culture results

Continue on other side

Kicking UTI
The No Knee-Jerk Antibiotics Campaign
Symptomatic UTI versus Asymptomatic Bacteriuria

**PYURIA, cloudy urine, foul smell or positive urinalysis are not symptoms of UTI and are not indications for antibiotics**

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**What is missing?**
- Cloudy urine
- Foul-smelling urine

doi:10.1016/j.idc.2013.09.005
Were there more than 10,000 organisms/ml? 

- **NO**
  - Was patient on antibiotics when urine culture sent? 
    - **NO**
      - Re-evaluate case
    - **YES**
      - Base decision on symptoms prior to urine culture

- **YES**
  - Is patient currently on antibiotics for UTI?
    - **NO**
      - Are symptoms still present?
        - **NO**
          - Do not start antibiotics
        - **YES**
          - Add antibiotics to treat the organism(s) isolated
    - **YES**
      - Are symptoms still present?
        - **NO**
          - Do antibiotics cover the organism isolated?
            - **NO**
              - Stop antibiotics given for UTI
            - **YES**
              - Continue antibiotics
      - **YES**
        - Change to appropriate antibiotics
        - **NO**
          - Re-evaluate with attention to upper urinary tract or obstruction

Original symptoms improving? 

- **YES**
  - Continue antibiotics
- **NO**
  - Review urine culture results

**Duration of antibiotic use**

- **No catheter**
  - Cystitis in female: treat for 3-5 days
  - Cystitis in male: treat for 7 days
  - Pyelonephritis: treat for 7-14 days
- **Has urinary catheter**
  - Improving rapidly: treat for 7-10 days
  - Slow improvement: treat for 10-14 days

Mental status changes & UTIs

• Bacteriuria and delirium are both independently common in the elderly

• Although patients with symptomatic UTIs may present with delirium, no evidence that delirium, falls, or confusion are symptoms of a UTI in the absence of urinary symptoms
  – 72 elderly residents without traditional UTI symptoms with and without bacteriuria were evaluated: no differences in insomnia, malaise, fatigue, anorexia between the two groups

• If a patient has signs of systemic infection and delirium, empiric antibiotic therapy may be warranted


Slide courtesy of B. Trautner, MD
Summary: Asymptomatic bacteriuria

- Treatment of asymptomatic bacteriuria is common
- Educate both nurses and prescribers
  - Foul-smelling urine, cloudy urine, pyuria, or mental status changes alone ≠ urinary tract infection
- Keep algorithms simple and available at point of care
- If education not enough, consider discontinuing reflex urine culture results reporting

Example from a large health system (2018)

Current:
Greater or equal to 5 WBC, any nitrites, any leukocyte esterase

Changing to:
Greater or equal to 10WBC with symptoms of a UTI
- Nitrites and leukocyte esterase not used
Antibiotic Stewardship and Duration

• The right drug at the right dose for the right duration

• Objectives:
  – Optimize patient safety –
    • Right **duration** maximizes cure and minimizes antibiotic exposure thus reducing adverse drug events such as CDI and other toxicities
    • Facilitates earlier removal of invasive devices
    • Improves drug compliance
  – Reduce resistance – shortest **duration** needed for cure reduces selection of resistance
  – Decrease costs – optimizing **duration** can save money

Slide courtesy of K. Trivedi, MD
Historical Perspective on Duration

• Staphylococcal sepsis treated in 1941 with PCN over 4 days with clinical improvement but when drug ran out, succumbed to infection – prolonged treatment need to avoid failure?

• Meads et al. administered PCN for PNA until definite clinical improvement and Temp < 100ºF x 12 hours, then another 2-3 days of treatment
  – Need to treat beyond resolution of symptoms driven by desire to prevent relapse; however in further case series analysis, not relapses but reinfections with distinct bacterial serotypes

• Unclear how desire to prevent reinfection transformed into dogma that antibiotic resistance can be prevented by continuing therapy beyond resolution of sx

Prolonged Antibiotic Course Increases Resistance

- Prospective, randomized double-blind clinical trial in 51 French ICUs of adults with VAP (n=401)
  - Randomized to 8 days vs. 15 days of therapy
  - No difference in mortality or recurrent infections
    - More recurrences in 8-day arm for NLFGN
  - MDROs emerged less frequently in patients receiving 8 days

Table. Infections for Which Short-Course Therapy Has Been Shown to Be Equivalent in Efficacy to Longer Therapy

<table>
<thead>
<tr>
<th>Disease</th>
<th>Treatment, Days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Short</td>
</tr>
<tr>
<td>Community-acquired pneumonia&lt;sup&gt;1-3&lt;/sup&gt;</td>
<td>3-5</td>
</tr>
<tr>
<td>Nosocomial pneumonia&lt;sup&gt;6,7&lt;/sup&gt;</td>
<td>≤8</td>
</tr>
<tr>
<td>Pyelonephritis&lt;sup&gt;10&lt;/sup&gt;</td>
<td>5-7</td>
</tr>
<tr>
<td>Intraabdominal infection&lt;sup&gt;11&lt;/sup&gt;</td>
<td>4</td>
</tr>
<tr>
<td>Acute exacerbation of chronic bronchitis and COPD&lt;sup&gt;12&lt;/sup&gt;</td>
<td>≤5</td>
</tr>
<tr>
<td>Acute bacterial sinusitis&lt;sup&gt;13&lt;/sup&gt;</td>
<td>5</td>
</tr>
<tr>
<td>Cellulitis&lt;sup&gt;14&lt;/sup&gt;</td>
<td>5-6</td>
</tr>
<tr>
<td>Chronic osteomyelitis&lt;sup&gt;15&lt;/sup&gt;</td>
<td>42</td>
</tr>
</tbody>
</table>

Abbreviation: COPD, chronic obstructive pulmonary disease.

Transitions of Care – Denver Health

• 53% of discharge antibiotic prescriptions were inappropriate
  – UTI, CAP, SSTI accounted for 67% of inappropriate prescriptions
• Excessive duration of therapy 33%
• Suboptimal antibiotic selection 17%
Transitions of Care – Hospital of University of Pennsylvania

- 70% of discharge antibiotic prescriptions were inappropriate
- 76% of those inappropriate were due to absence of an acceptable indication and inappropriate duration

CLOSTRIDIUM DIFFICILE
ASSOCIATED DISEASE
Antibiotics and Risk For C. difficile

<table>
<thead>
<tr>
<th>Very Commonly Related to CDI</th>
<th>Less Commonly Related to CDI</th>
<th>Uncommonly Related to CDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>Other penicillins</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Sulfonamides</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Trimethoprim</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Cephalosporins (3\textsuperscript{rd} and 4\textsuperscript{th} generation higher risk)</td>
<td>Trimethoprim-Sulfamethoxazole</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Macrolides</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td></td>
<td>Carbapenems</td>
<td>Daptomycin</td>
</tr>
</tbody>
</table>

References:

Diagnostic testing stewardship

1. Only test symptomatic patients (3 or more unformed stools within the last 24 hrs)
2. Evaluate the consistency of the stool. Only test diarrheal stools
3. Do not test stools of patients who have been on laxatives
4. Do not retest for at least 7 days during the same episode of diarrhea
5. Cancel order if > 24 hours old
6. Do not test stool from asymptomatic patients
7. Empower nursing to obtain order
8. Empower laboratory to discontinue order

<table>
<thead>
<tr>
<th>Bristol Stool Chart</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
</tr>
<tr>
<td>• Separate hard lumps, like nuts (hard to pass)</td>
</tr>
<tr>
<td>Type 2</td>
</tr>
<tr>
<td>• Sausage-shaped but lumpy</td>
</tr>
<tr>
<td>Type 3</td>
</tr>
<tr>
<td>• Like a sausage but with cracks on its surface</td>
</tr>
<tr>
<td>Type 4</td>
</tr>
<tr>
<td>• Like a sausage or snake, smooth and soft</td>
</tr>
<tr>
<td>Type 5</td>
</tr>
<tr>
<td>• Soft blobs with clear-cut edges (passed easily)</td>
</tr>
<tr>
<td>Type 6</td>
</tr>
<tr>
<td>• Fluffy pieces with ragged edges, a mushy stool</td>
</tr>
<tr>
<td>Type 7</td>
</tr>
<tr>
<td>• Watery, no solid pieces. Entirely Liquid</td>
</tr>
</tbody>
</table>
Duplicate Anaerobe Therapy

• Anaerobes are normal flora of the intestinal tract
  – Most intestinal anaerobes are gram-negative organisms (e.g., Bacteroides spp., Prevotella spp., etc.)

• Routine double coverage of βL-βLI or carbapenems with metronidazole is not recommended given the excellent anaerobic activity of these agents
Exceptions for Duplicate Coverage

- **C. difficile** infections
  - Addition of metronidazole to clindamycin, βL-βLI, or carbapenems in patients who cannot receive oral vancomycin or fidaxomicin based on 2017 guidelines

- Necrotizing fasciitis
  - Addition of clindamycin to βL-βLI

- Parasitic infections
  - Addition of metronidazole for *Trichomonas, Giardia, Entamoeba histolytica* to clindamycin, βL-βLI, or carbapenems
What’s The Harm?

• Resistance is rare and not a major clinical concern
• Metronidazole is relatively inexpensive (<10 USD/day)
• Can have side effects: Generally not serious but still cause discomfort
  – Peripheral neuropathy when administered in high doses and over prolonged periods of time
  – Headache (18%)
  – Metallic taste (9%)
  – Nausea (10%)
  – Disulfiram-reaction
    • Abdominal cramps, nausea, emesis, headaches, flushing

How Can You Change This Practice?

• Likely a knowledge gap
  – Educate clinicians that use of multiple drugs active against anaerobes is not necessary and puts patients at risk for additional drug toxicities

• When conducting post-prescription review on piperacillin-tazobactam or carbapenems, look out for metronidazole!

• Consider educating nurses on surgical wards

• Engage staff pharmacists and clinical pharmacists
QUESTIONS