Past, Present, and Future of Antimicrobial Stewardship

Haley J Morrill, Pharm.D.
Antimicrobial Stewardship Fellow
Director: Kerry L. LaPlante, Pharm.D.

Rhode Island Infectious Diseases (RIID) Research Program of the Providence Veterans Affairs Medical Center and University of Rhode Island College of Pharmacy
Disclaimer

- The information disseminated in this lecture is given in my personal capacity and not in my capacity as a VA employee nor does it necessarily reflect the views of the United States Department of Veterans Affairs
OBJECTIVES

PAST
1. Demonstrate the need for antimicrobial stewardship to preserve current antimicrobial treatment

PRESENT
2. Identify the goals of antimicrobial stewardship
3. Discuss and apply antimicrobial stewardship interventions
4. Discuss commonly used metrics for evaluating an antimicrobial stewardship program

FUTURE
5. Describe the future needs for antimicrobial stewardship
Limited New Antibacterial Classes

Recent Approvals (Last 10 years)

**GRAM POSITIVES**
- **Daptomycin** *(MRSA)*
  - 2003
  - Lipopeptide
- **Tigecycline** *(MRSA)*
  - 2005
  - Glycylcycline
- **Telavancin** *(MRSA)*
  - 2009
  - Lipoglycopeptide
- **Ceftaroline** *(MRSA)*
  - 2010
  - 5th generation CS
- **Fidaxomycin** *(C. diff)*
  - 2011
  - Macroycles
- **Fusidic acid?** *(MRSA)*

**GRAM NEGATIVES**
- **Tigecycline** *(no P. aug, Proteus spp or Providencia, some A. baumannii)*
- **Ceftaroline** *(no P. aug, or A. baumannii)*
History of Resistance

• Antimicrobial resistance is not a new phenomenon
• Sulfonamides, penicillin, and streptomycin available for use in the 1930s-1940s
  – Recognized early that bacteria exposed to antimicrobial agents evolved strategies to survive them

Sir Alexander Fleming on June 26, 1945:

“The microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out....In such cases the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope this evil can be averted.”
Cause of Antibiotic Resistance

- Humans did NOT invent antibiotics
  - Bacteria “invented” antibiotics billions of years ago and “invented” antibiotic resistance at the same time
  - Bacteria have learned to target virtually every targetable biochemical pathway with antibiotics, and have learned to create defense mechanisms to defeat virtually all such antibiotics
- Resistance already exists to drugs we have not yet invented
  - Bacteria found in caves that have been isolated from the surface of the planet for 4 million years.
  - Resistance found to synthetic antibiotics that did not exist until the 20th century
- Bacteria cause resistance, not humans
  - Humans apply natural selection – select for pre-existing resistance
  - We don’t create resistance, but do increase its rate of spread!

Widespread Resistance

- National surveillance data and independent studies show that drug resistant, disease-causing bacteria have multiplied and spread at alarming rates in recent decades.

IDSA Report

“BAD BUGS, NO DRUGS: As Antibiotic Discovery Stagnates ... A Public Health Crisis Brews”

<table>
<thead>
<tr>
<th>ESKAPE Pathogens</th>
<th>Class</th>
<th>“Superbugs”</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E</strong> Enterococcus faecium</td>
<td>Gm+</td>
<td>Vancomycin-resistant <em>E. faecium</em> (VRE)</td>
</tr>
<tr>
<td><strong>S</strong> Staphylococcus aureus</td>
<td>Gm+</td>
<td>Methicillin-resistant <em>S. aureus</em> (MRSA)</td>
</tr>
</tbody>
</table>
| **K** *Klebsiella pneumoniae*  
*Or C = Clostridium difficile (C. Diff) – Gm+ | Gm- | Extended-spectrum beta-lactamases (ESBLs), *Klebsiella pneumoniae* carbapenemase (KPCs) |
| **A** Acinetobacter baumanii | Gm- | ESBLs, carbapenemases |
| **P** Pseudomonas aeruginosa | Gm- | ESBLs, carbapenemases |
| **E** *Enterobacter* species  
(le *E. coli*, *proteus spp*, *serratia spp..*) | Gm- | ESBLs, Carbapenem-resistant *Enterobacteriaceae* (CRE) |
Resistance is Everywhere

Centers for Disease Control and Prevention. Get Smart for Healthcare. Available at: http://www.cdc.gov/getsmart/healthcare/
Public Health Threat

• Threat of infections without treatment is impending
  – Already have been reports of pan-resistant (resistant to all available antibiotics) pathogens

• If the current rate of resistance continues, some experts believe we may enter a postantibiotic era

• Must preserve the limited effective antibiotics that are currently available

INAPPROPRIATE ANTIBIOTIC USE
The Bitter Truth

- Estimated that 50% of antimicrobial use in hospitals is inappropriate

Centers for Disease Control and Prevention. Get Smart for Healthcare. Available at: http://www.cdc.gov/getsmart/healthcare/
Inappropriate Use

- Given when they are not needed
- Continued when they are no longer necessary
- Given at the wrong dose (under-dosed)
- Broad spectrum agents are used to treat very susceptible bacteria
- The wrong antibiotic is given to treat an infection
Inappropriate Antimicrobial Use

• Overuse and misuse leads to the emergence and spread of resistant bacteria
  – Getting an antibiotic increases a patient’s chance of becoming colonized or infected with a resistant organism

Antibiotics Are a Shared Resource

• How we use antibiotics in one patient today directly how effective the drug will be in another patient tomorrow
  – Resistant bacteria have the potential to spread to others, promoting resistant infections

Centers for Disease Control and Prevention. Get Smart for Healthcare. Available at: http://www.cdc.gov/getsmart/healthcare/
Selection for Antimicrobial-Resistant Strains

Resistant Strains Rare

Antimicrobial Exposure

Resistant Strains Dominant
Consequences of Resistance

- Increased morbidity
- Increased mortality
- Increased healthcare costs

Healthcare Associated Infections (HAIs) and Resistant Bacteria

- 16% of HAIs are associated with multidrug-resistant pathogens, including:
  - Methicillin-resistant *S. aureus* (MRSA)
  - Vancomycin-resistant *enterococcus faecium* (VRE)
  - *Pseudomonas aeruginosa* (*P. aeruginosa*)
  - *Klebsiella pneumoniae* (*K. pneumoniae*)


**Clostridium difficile (C. Diff)**

- Antibiotic exposure is the single most important risk factor for the development of *Clostridium difficile* associated disease (CDAD)

- Up to 85% of patients with CDAD have antibiotic exposure in the 28 days before infection

Bacteria Are Killing!

- HAIs are the 6th leading cause of death in the United States
  - 1.7 million HAIs annually
  - 34.4 million annual discharges
  - 99,000 resultant deaths
  - $28-33 billion excess healthcare costs

In Rhode Island...

- Every day, 17 people develop a HAI (6,266/365)
- Every day, someone dies from a HAI (365/365)
- Every day, 3 people develop a drug-resistant HAI (1,003/365)
- Once a week, someone dies from a drug-resistant HAI (59/52)

Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship


1Harborview Medical Center and the University of Washington, Seattle; 2Maine Medical Center, Portland; 3Emory University, Atlanta, Georgia; 4Hines Veterans Affairs Hospital and Loyola University Stritch School of Medicine, Hines, and 5Stroger (Cook County) Hospital and Rush University Medical Center, Chicago, Illinois; 6University of Utah, Salt Lake City; 7Mayo Clinic College of Medicine, Rochester, Minnesota; 8University of Pittsburgh Medical Center, Pittsburgh, and 9University of Pennsylvania, Philadelphia, Pennsylvania; 10William Beaumont Hospital, Royal Oak, Michigan; 11Ochsner Health System, New Orleans, Louisiana; and 12University of Miami, Miami, Florida
Antimicrobial Stewardship: Definition

• Any activity that promotes appropriate antimicrobial:
  1. Drug
  2. Dosing
  3. Duration
  4. Route

Goals of Antimicrobial Stewardship

- Limit inappropriate use
  - Improve patient care and health outcomes
  - Minimize unintended consequences
  - Reduce healthcare costs

Multi-disciplinary team

CORE MEMBERS:
- ID physician
- ID pharmacist

Optimal Patient Care

Healthcare Epidemiologists
Clinical Pharmacists
Clinical Microbiologists
Information System Specialists
Infection Control Professionals
Hospital Administration
P&T Committee

Strategies

CORE
• Prospective audit with intervention and feedback
• Formulary restriction and preauthorization

SUPPLEMENTAL
• Education
• Guidelines and clinical pathways
• Antimicrobial order forms
• Streamlining or de-escalation of therapy
• Dose optimization
• IV to PO conversion

Prospective Audit and Feedback

- Antimicrobial use reviewed and recommendations made to optimize use
- **Back-end** program - Antimicrobial use is reviewed AFTER antimicrobial therapy has been initiated
- “Unsolicited” feedback – unlike an ID consult
- Recommendations are voluntary

PVAMC Audit With Feedback

• Print out a list of all patients on IV and PO antimicrobials
• Fill out patient templates (next slide)
• Identify potential interventions
• Discuss potential interventions with ID team
• Relay interventions to prescriber
• Document interventions in excel
# Antimicrobial Stewardship Workup Template

<table>
<thead>
<tr>
<th>Basic Info</th>
<th>DATE</th>
<th>LAST NAME</th>
<th>Age/Race</th>
<th>HT</th>
<th>WT</th>
<th>Loc/Att</th>
<th>Abx All</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug (route, dose, freq)</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
<th>D5</th>
<th>D6</th>
<th>D7</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Days of Therapy</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Admission Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>From where</td>
</tr>
<tr>
<td>On what day</td>
</tr>
<tr>
<td>DX</td>
</tr>
<tr>
<td>1st Intervention</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Documentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date/Time</td>
</tr>
<tr>
<td>ID</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Res/Int</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl:</td>
</tr>
<tr>
<td>DATE</td>
</tr>
<tr>
<td>WBC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Limitations to communication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Cr:</td>
</tr>
<tr>
<td>SCr/ BUN</td>
</tr>
<tr>
<td>Tmax</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRSA nares</td>
</tr>
<tr>
<td>Date</td>
</tr>
<tr>
<td>Date</td>
</tr>
<tr>
<td>Date</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vanc Dose/Mon</td>
</tr>
<tr>
<td>Asx UTI</td>
</tr>
<tr>
<td>Surg</td>
</tr>
<tr>
<td>IV to PO</td>
</tr>
<tr>
<td>Drug optimization</td>
</tr>
<tr>
<td>De-escalation</td>
</tr>
<tr>
<td>Stop Abx</td>
</tr>
<tr>
<td>Daily time (minutes):</td>
</tr>
<tr>
<td>D1</td>
</tr>
</tbody>
</table>

| Further Details |

<table>
<thead>
<tr>
<th>IV to PO Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low WBC</td>
</tr>
<tr>
<td>Afebrile</td>
</tr>
<tr>
<td>Pt Improving</td>
</tr>
<tr>
<td>On PO medication</td>
</tr>
<tr>
<td>No GI problems</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>UTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteriuria</td>
</tr>
<tr>
<td>Pyuria</td>
</tr>
<tr>
<td>Symptoms</td>
</tr>
<tr>
<td>MSSA</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Accepted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Why?</td>
</tr>
<tr>
<td>Unable to contact</td>
</tr>
<tr>
<td>Loss to follow-up</td>
</tr>
<tr>
<td>Clinical picture changed</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>
Impact of a Stewardship Program

• Process measures:
  – How did the intervention result in the desired change in antimicrobial use?
  – Accomplished a task?
  – Ex- Level of acceptance?
    • Types of recs
    • # recs made
    • % recs implemented

• Outcome measures:
  – Did the process implemented reduce any unintended consequences of antimicrobial use?
  – Eg- Think of stewardship goals (next slide)

Outcomes Metrics Examples

- **Goal 1 - Improve Pt Outcomes**
  - Clinical success
  - Microbiologic success

- **Goal 2 - Improved Pt Safety**
  - Antibiotic adverse effects
  - *C. Difficile* infections
  - Nosocomial infection rates
  - Mortality

- **Goal 3 - Reduced Resistance**
  - Changes in antimicrobial susceptibility among specific organisms
    - Antibiogram

- **Goal 4 - Reduced Cost**
  - Antimicrobial Use
  - Length of Stay
  - Re-admissions

Measuring Antimicrobial Use

**Defined Daily Dose (DDD):**
- Developed by the WHO
  - Grams used / WHO DDD
- **Advantages**
  - Easier data collection
- **Disadvantages**
  - Actual doses often differ from WHO-approved DDD (ie levofloxacin DDD= 500mg)
    - Pt 1- 750mg x 10 days = 7500mg/500mg = 15 DDD
    - Pt 2- 500mg x 10 days= 5000mg/500mg = 10 DDD

**Days of Therapy (DOT):**
- Calendar day on which a pt received the drug in question
- **Advantages**
  - May be more accurate when hospitals use doses that differ from the WHO specified doses (ie impaired renal function, pediatric patients)
- **Disadvantages**
  - More difficult to measure
  - Number of doses per day not measured

PVAMC Stewardship Program

• Prospectively audit all antimicrobial use (IV and PO) daily (Mondays-Fridays)
• Reviewed 420 patients since September 2012
  – 272 reviewed by PharmD fellow
  – 103 reviewed by pharmacy student
  – 45 reviewed by PharmD resident
• Mean time spent per patient = 18.8 minutes (+/- 14.7)
<table>
<thead>
<tr>
<th>Antibiotics with Usage</th>
<th>GRAMS PER YEAR</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin/tazobactam</td>
<td>19,336</td>
<td>28,125</td>
<td>33,281</td>
<td>35,260</td>
<td></td>
</tr>
<tr>
<td>Vancomycin (IV only)</td>
<td>2,081</td>
<td>4,898</td>
<td>5,796</td>
<td>9,303</td>
<td></td>
</tr>
<tr>
<td>Metronidazole (IV only)</td>
<td>1,539</td>
<td>1,843</td>
<td>4,823</td>
<td>1,185</td>
<td></td>
</tr>
</tbody>
</table>
# Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (mean ± SD)</td>
<td>70.8 (+/-14.3)</td>
</tr>
<tr>
<td>Male gender</td>
<td>404 (96.2)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>388 (92.4)</td>
</tr>
<tr>
<td><strong>Service Admitted</strong></td>
<td></td>
</tr>
<tr>
<td>General Medicine</td>
<td>310 (73.8)</td>
</tr>
<tr>
<td>ICU</td>
<td>43 (10.2)</td>
</tr>
<tr>
<td>Surgery</td>
<td>58 (13.8)</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>9 (2.1)</td>
</tr>
<tr>
<td>Length of stay in days (mean ± SD)</td>
<td>6.5(+/-8.4)</td>
</tr>
</tbody>
</table>

*N = 420
# Most Frequently Involved Antibiotics

<table>
<thead>
<tr>
<th>Rank</th>
<th>Antibiotic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vancomycin IV</td>
<td>141 (33.6 %)</td>
</tr>
<tr>
<td>2</td>
<td>Piperacillin/ Tazobactam</td>
<td>139 (30.7%)</td>
</tr>
<tr>
<td>3</td>
<td>Azithromycin</td>
<td>86 (20.5%)</td>
</tr>
<tr>
<td>4</td>
<td>Ceftriaxone</td>
<td>69 (16.4%)</td>
</tr>
<tr>
<td>5</td>
<td>Oseltamivir</td>
<td>41 (9.8%)</td>
</tr>
<tr>
<td>6</td>
<td>Metronidazole</td>
<td>40 (9.5%)</td>
</tr>
</tbody>
</table>

*N = 420*
Antimicrobial Indication

- Bloodstream: 26%
- Urinary Tract Infection: 19%
- Skin/Soft Structure: 17%
- Pneumonia: 5%
- Surgical Prophylaxis: 7%
- C. Diff: 7%
- COPD exacerbation: 6%
- Intra-abdominal: 5%
- Influenza: 2%
- Bone and Joint: 1%
- Other: 1%

*N = 420
Intervention Description

- In 133 patients (31.7%) an intervention was made
- Total number of interventions made = 198
- Total number of interventions accepted = 145
- Acceptance Rate = 73.2%
- Avg. # Interventions per week = 9
Types of Interventions

- Vancomycin: 38
- IV to PO: 42
- De-escalation: 18
- Optimization: 42
- Discontinuation: 35

*N = 198
FUTURE ANTIMICROBIAL STEWARDSHIP NEEDS

ASPs Should Be Required

• No national or coordinated legislative or regulatory policies mandating antimicrobial stewardship at this time

• Pending legislation - Strategies to Address Antimicrobial Resistance (STARR) Act
  – Creates an antimicrobial task force and advisory board
  • Gather data on emergence of AMR, recommend prevention strategies, develop a public health action plan to combat spread of antimicrobial resistance
  – Requires a pharmacist to serve on the advisory board

IDSA’s Efforts to Promote Antimicrobial Stewardship. Available at: http://www.idsociety.org/Stewardship_Policy/.
Stewardship Policy

• DHHS and the Healthcare Infection Control Practices Advisory Committee - **Top 5 Campaign Messages**
  – Since 2010, antimicrobial stewardship has been one of the top five messages for a healthcare worker and consumer awareness campaign

• The Joint Commissions - **National Patient Safety Goal 07.03.01**
  – Implement evidence-based practices to prevent health-care associated infections due to multidrug-resistant organisms
  – Prevention and control strategies should be tailored to the specific needs of each hospital
  – Includes: Periodic risk assessments, education, surveillance program, process/outcomes measures, implement policies and procedures to reduce transmission of MDROs, alerts

http://www.hhs.gov/ash/initiatives/hai/actionplan/hhs_hai_action_plan_final_06222009.pdf
http://jointcommission-lms.org/1900_00_HAI_NPSG_7/player.html
Stewardship Education

• “Significant knowledge deficits in the areas of antimicrobial stewardship and antimicrobial resistance among healthcare providers in the US”
  – Shortage of trained personnel for ASPs
  – All prescribing clinicians

• ASP certificate programs

• ASP education should be a required curriculum component for medical and pharmacy students, and postgraduate residents and fellows

Antimicrobial Use Data

• Antimicrobial use data to track and benchmark is lacking
  – Both inpatient and outpatient settings

• Need a reliable and accurate national system for collecting data on antimicrobial use

Antimicrobial Stewardship Research

• Knowledge gaps exist in understanding:
  – Antimicrobial resistance
  – Interventions to limit emergence and transmission of resistance
  – Our ability to measure associated impacts and clinical outcomes

Past, Present, and Future of Antimicrobial Stewardship

Haley J Morrill, Pharm.D.
Antimicrobial Stewardship Fellow
Director: Kerry L. LaPlante, Pharm.D.

Rhode Island Infectious Diseases (RIID) Research Program of the Providence Veterans Affairs Medical Center and University of Rhode Island College of Pharmacy