The Pharmacist’s Role in Antimicrobial Stewardship

Ruth Lynfield, MD
State Epidemiologist and Medical Director Minnesota Department of Health

Era of Antibiotics: Great Moments in Pharmacy, Artist George Bender

1928 – Alexander Fleming discovered a mold with bacteria-killing properties

Introduction of Antibiotics

“For most of the infectious diseases on the wards of Boston City Hospital in 1937, there was nothing to be done beyond bed rest and good nursing care.”

Photo credit, LIFE

Lewis Thomas. The Youngest Scientist
**Introduction of Antibiotics (cont.)**

"I remember the astonishment when the first cases of pneumococcal and streptococcal septicemia were treated in Boston in 1937. The phenomenon was almost beyond belief. Here were moribund patients, who would surely have died without treatment, improving in their appearance within a matter of hours of being given the medicine and feeling entirely well within the next day or so...we became convinced, overnight, that nothing lay beyond reach for the future. Medicine was off and running."

Lewis Thomas. *The Youngest Science*

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**The Power of Effective Antibiotics**

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<table>
<thead>
<tr>
<th>Disease</th>
<th>Pre-Antibiotic Death Rate</th>
<th>Death with Antibiotics</th>
<th>Change in Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community Pneumonia¹</td>
<td>≤35%</td>
<td>≤10%</td>
<td>≤25%</td>
</tr>
<tr>
<td>Hospital Pneumonia²</td>
<td>≤60%</td>
<td>≤30%</td>
<td>≤30%</td>
</tr>
<tr>
<td>Heart Infection³</td>
<td>≤100%</td>
<td>≤25%</td>
<td>≤75%</td>
</tr>
<tr>
<td>Brain Infection⁴</td>
<td>&gt;80%</td>
<td>&lt;20%</td>
<td>&lt;60%</td>
</tr>
<tr>
<td>Skin Infection⁵</td>
<td>11%</td>
<td>&lt;0.9%</td>
<td>&lt;10%</td>
</tr>
</tbody>
</table>

*By comparison...treatment of heart attacks with aspirin or clot busting drugs*⁶

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B. Spellberg

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Emergence of Antimicrobial Resistance

- When bacteria are exposed to an antibiotic, susceptible cells die.
- Those that are resistant (or acquire resistance through mutation, genetic rearrangement or acquisition of genes) survive.
- With reduced competition from susceptible bacteria, resistant bacteria thrive and outcompete others.
- Antibiotics also impact “normal flora” which otherwise could limit the expansion of pathogens.
  - Non-pathogenic but resistant bacteria can impact the microbial niche by increasing the reservoir of resistance genes.

Selective Pressure

- MRSA
- XDR TB
- Quinolone resistant gonorrhea
- MRSA
- C. difficile
- Candida glabrata
- Multi-drug resistant S. pneumoniae
- XDR TB
- CARBAPENEM RESISTANT ENTEROBACTERIACEAE
- MRSA
- C. difficile
- Candida glabrata
- Multi-drug resistant S. pneumoniae
- XDR TB
- CARBAPENEM RESISTANT ENTEROBACTERIACEAE
Annual U.S. Estimates of MRSA

**Severe / Invasive Infections**
- 94,000 new infections
- 19,000 deaths

**Mild-moderate infections**
- 250,000 hospital discharges
- 6-8 million outpatient/ER visits

(JAMA, Klevens 2007; CID 2007 [2004 NIS data]; EID 2006, McCaig [NAMCS])

The new generation of resistant infections is almost impossible to treat

- Jerome Groopman, August 11, 2008

In August, 2000, Dr. Roger Wetherbee, an infectious-disease expert at New York University's Tisch Hospital, received a disturbing call from the hospital's microbiology laboratory. At the time, Wetherbee was in charge of handling outbreaks of dangerous microbes in the hospital, and the laboratory had isolated a bacterium called *Klebsiella pneumoniae* from a patient in an intensive-care unit. "It was literally resistant to every meaningful antibiotic that we had."

Susceptibility Profile of *Klebsiella pneumoniae* carbapenamase (KPC) Producing *K. pneumoniae*

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Interpretation</th>
<th>Antimicrobial</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>I</td>
<td>Chloramphenicol</td>
<td>R</td>
</tr>
<tr>
<td>Amoxiclav</td>
<td>R</td>
<td>Ciprofloxacin</td>
<td>R</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>R</td>
<td>Ertapenem</td>
<td>R</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>R</td>
<td>Gentamicin</td>
<td>R</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>R</td>
<td>Imipenem</td>
<td>R</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>R</td>
<td>Meropenem</td>
<td>R</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>R</td>
<td>Pipercillin/Tazo</td>
<td>R</td>
</tr>
<tr>
<td>Cefotetan</td>
<td>R</td>
<td>Tobramycin</td>
<td>R</td>
</tr>
<tr>
<td>Ceftazolin</td>
<td>R</td>
<td>Trimeth/ Sulfa</td>
<td>R</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>R</td>
<td>Polymyxin B</td>
<td>MIC &gt;4µg/ml</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>R</td>
<td>Colistin</td>
<td>MIC &gt;4µg/ml</td>
</tr>
<tr>
<td>Cefepime</td>
<td>R</td>
<td>Tigecycline</td>
<td>S</td>
</tr>
</tbody>
</table>
Mortality: Carbapenem Resistant vs. Susceptible *Klebsiella pneumoniae*

<table>
<thead>
<tr>
<th></th>
<th>CRKP</th>
<th>CSKP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Mortality</td>
<td>48%</td>
<td>20%</td>
</tr>
<tr>
<td>Attributable Mortality</td>
<td>38%</td>
<td>12%</td>
</tr>
</tbody>
</table>

OR 3.71 (1.97-7.01)

OR 4.5 (2.16-9.35)

A. Srinivasan, J. Patel – DHQP CDC

Geographical Distribution of Highly Resistant *Klebsiella* and Related Bacteria

CDC, Unpublished Data, Nov. 2006

CDC, Unpublished Data, Mar. 2011
Highly Resistant Enterobacteriaceae, Minnesota

- February 2009: KPC+ K. pneumoniae confirmed at MDH
- 2010: 14 KPC+ isolates
  - K. pneumoniae (8)
  - E. cloacae (6)
- 2011: 21 KPC+ isolates
  - K. pneumoniae (10)
  - E. cloacae (7)
  - K. oxytoca (4)
  - NDM: 1 K. pneumonia and 1 E. coli of same patient
- 2012: 29 KPC+ isolates
  - K. pneumoniae (17)
  - E. cloacae (10)
  - K. oxytoca (2)
  - E. coli (1)

Clostridium difficile Infection

Antibiotic exposure is the most important risk factor for the development of Clostridium difficile associated disease

Estimated Burden of Healthcare-Associated C. difficile in U.S.

- Hospital-acquired, hospital-onset: 156,500 cases, $1.3 billion in excess costs, and 9,000 deaths annually
- Hospital-acquired, post-discharge (up to 4 weeks): 30,000 cases, $0.3 billion in excess costs, and 3,000 deaths annually
- Nursing home-onset: 263,000 cases, $2.2 billion in excess costs, and 16,500 deaths annually
New Antibiotics

On average it takes 10 years and $800 million dollars per new antibiotic that comes on the market

Antibiotic Approvals, U.S.

Table 1: Antibiotic Approvals (1985-Present)

Source: IDSA’s 2004 Bed Bugs: No Drugs Report (modified)

www.idsociety.org

Antibiotic Use in Inpatients in US

- One in three inpatients receive 2 or more antibiotics
- Of inpatients receiving antibiotics, 3 of 4 receive unnecessary/redundant therapy
- U.S. antibiotic resistant infections are responsible for:
  - $20 billion in excess healthcare costs
  - $35 billion in societal costs
  - 8 million additional hospital days

CDC, 2010
Adverse Effects

142,000 visits to emergency departments for adverse events attributed to antibiotics in 2008


We Need to Improve Antibiotic Use!

- Antibiotics are misused
- Antibiotic misuse adversely impacts the individual patient and other patients in the community
- Improving antibiotic use improves patient outcomes and saves money

What Can Be Done?
Combating Antimicrobial Resistance

- Antimicrobial Stewardship
- Immunizations
- Infection Control
- Novel antibiotics

Antimicrobial Stewardship Program (ASP)

- Promotes the selection of the optimal antimicrobial drug regimen, dose, duration of therapy and route of administration
- Antimicrobial stewardship should occur across the continuum of healthcare (including acute care, long-term care, and ambulatory care)
Objectives of ASP
- Limit the selective pressure on bacterial populations that would select for antimicrobial resistant strains
- Achieve optimal clinical outcomes related to antimicrobial use
- Minimize toxicity and other adverse events
- Reduce costs attributable to suboptimal antimicrobial use

Institutional ASP
- Multidisciplinary interprofessional ASP Team: pharmacist, physician, clinical microbiologist, infection preventionist
- Restricting antimicrobial formulary to most clinically and epidemiologically effective and cost efficient antimicrobial agents
- Institutional guidelines for management of common infection syndromes
- Interventions to improve antimicrobial use
- Processes to measure and monitor antimicrobial use
- Facility-specific antibiogram

ASP Survey, Minnesota
- Sent to infection preventionists at 132 acute care hospitals in Minnesota, December 2011
  - Critical Access Hospitals: 37/79 (47%) responded
    - 10/37 (27%) have ASP
  - Other: 28/53 (53%) responded
    - 18/28 (64%) have ASP
**Does Your ASP Team Include?**

- Pharmacist
- Physician
- Infection Preventionist
- Clinical Microbiologist
- Administration
- Other members
- Information Technologist

*IPPS (n=18)  CAH (n=10)*

**Why doesn’t your hospital have an ASP in place?**

- Not necessary
- Not interested
- Never heard of/considered it
- Lack of resources
- Lack of administration support
- Lack of clinician support
- Other

*CAH (n=27)  IPPS (n=10)*

**Other responses:**
- CAH: In process of starting an ASP, informal ASP concepts in place
- IPPS: In process of starting an ASP, high turn over in IP department

**What would be helpful for starting an ASP at your hospital?**

1. Access to “getting started” ASP materials: Protocols
2. Access to “getting started” ASP materials: Order sets
3. Educational materials for physicians
4. Educational materials for pharmacists
5. Educational materials for nursing
6. Educational materials for patients
7. Support from administration
8. Support from clinicians
9. Educational/promotional materials to present to administration
10. Educational/promotional materials to present to clinicians
11. No response
MN ASP Survey Findings

• Interest in ASP across hospitals
• Need to increase awareness of ASP among CAH
• Goals of existing ASP are aligned with SHEA/IDSA
• Electronic medication administration is widely used
• Antibiograms are available
• Targeting important antibiotics and pathogens; some algorithms have been developed
• ASP membership appears to vary widely; IT staff not engaged

MDH Antimicrobial Stewardship Steering Group: Objectives

• Apply published guidelines and experience and expertise of Steering Group to identify best practices and key ASP components
• Acknowledge and address unique resource limitations and challenges of various types of healthcare facilities
• Use evidence-based measures to identify recommendations

MDH Antimicrobial Stewardship Steering Group: Objectives (cont.)

• Incorporate use of electronic order-entry and decision-support systems as tools to promote implementation of ASP where feasible
• Develop ASP Guide that incorporates published guidelines, best practices, and considerations of resources and other limitations
• Make ASP Guide available to promote development and implementation of an effective ASP in every Minnesota healthcare facility
Minnesota Guide to a Comprehensive Antimicrobial Stewardship Program

www.health.state.mn.us/divs/idepc/dtopics/antibioticresistance/index.html

Getting Started on an ASP

First steps:
- Get the ear of senior leadership
- Review key ASP literature
- Look for clues of existing ASP elements such as pharmacy and therapeutics committee, patient safety committees
- Acquire access to antimicrobial use and microbiology data for baseline data (e.g., antimicrobial budget, antimicrobial utilization, antimicrobial resistance patterns)
- Identify a physician or pharmacist to champion the ASP

At a minimum, an ASP includes a pharmacist and a physician motivated to develop expertise in stewardship and become familiar with local prescribing and resistance trends.

ASP Infrastructure

- Establish an interdisciplinary ASP Team
  - Evaluate ASP Team membership on a regular basis
- Conduct baseline assessments to determine ASP goals/objectives
- Develop, define, and document
  - Facility expectations
  - ASP Team member roles and responsibilities
- Communicate ASP goals, objectives, and facility expectations
- Develop a process for the ASP Team to communicate with Infection Prevention & Control
ASP Strategies

- Identify strategies that are most appropriate to your patient populations and/or units to maximize the impact of the ASP on patient outcomes and costs
- ASP strategies are presented a tiered approach:
  - Core: baseline approaches that should always be in place as part of a comprehensive ASP
  - Expanded: strategies that can be implemented as possible and as are relevant to the facility/unit

ASP Strategies (cont.)

1. Review formulary, pharmaceutical contacts, and identify restricted antimicrobials
2. Review use of an antimicrobial or antimicrobial class within the facility (e.g. drug utilization evaluation)
3. Utilize an antibiogram
4. Optimize antimicrobial prescribing
5. Review clinical syndromes
   Is treatment indication documented? Does it follow evidence-based practice guidelines?
6. Review and analyze patient outcome data (e.g. C. difficile)
7. Evaluate the ASP

Additional Information Found in Appendices of the Guide

- Guidelines, position papers, peer-reviewed literature, drug use evaluation resources
- Antimicrobial prescribing and utilization assessment
- Antimicrobial stewardship perception survey
- Antimicrobial use prevalence survey
Additional “Pearls”

• Reimbursing time of pharmacist and physician enables the program to be sustainable
• Regional alliances may be helpful, especially for small/critical access hospitals
• Preceptorships of pharmacist within area institution(s) may be useful to gain expertise
• Engage hospitalists and ED physicians
• Encourage representation from private practices and ID practices on ASP/antibiotic committee

Drug Use Evaluation

• Identifies how a medication or class is being used
• Emphasizes improved utilization
• Pharmacy and Therapeutics Committee may be able to support effort
  – Target high use medication- overutilization
  – Target high cost medication- less expensive equivalent alternative (on formulary)
  – Target redundant therapy- “medication error”

Drug Use Evaluation (cont.)

– Pick a limited number of criteria:
  • Indication (clinical/based on susceptibilities)
  • Dosing (dose, route, frequency, duration, timing of dose with other medications that may interfere)
  • Adverse drug effects
  • Data collection tool
  • Randomly select group of patients
  • Can be retrospective look (generally 6-12 months)
  • Generate report and recommendations
  • Discuss findings with healthcare providers, administration, other stakeholders
  • Determine whether/what interventions and when to re-assess
Role of the Pharmacist

• Be a champion for antimicrobial stewardship
• Educate, listen, hand hold
  – Understand the challenges in your facility
  – Work with other interested persons to overcome the challenges
• Provide consultations
• Start ASP with “low hanging fruit”
  – DUE for using drug on formulary vs. not (for example use of particular carbapenems)
  – Move from IV to oral therapy
• Expand ASP per institutional needs

Antimicrobial Stewardship

“...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.”

- Sir Alexander Fleming, June 1945

The New York Times

Antibiotics Research Subsidies Weighed by U.S.

By Andrew Pollack Published: November 5, 2010

Margaret A. Hamburg, commissioner of the Food and Drug Administration, said at a news conference last month. The world’s weakening arsenal against “superbugs” has prompted scientists to warn that everyday infections could again become a major cause of death just as they were before the advent of penicillin around 1940.

“For these infections, we’re back to dancing around a bubbling cauldron while rubbing two chicken bones together,” said Dr. Brad Spellberg, an infectious disease specialist at Harbor-U.C.L.A. Medical Center in Torrance.
Post-Antibiotic Era

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Questions?