Antimicrobial Stewardship:

Michael J. Rybak, Pharm.D., M.P.H
Professor of Pharmacy and Adjunct Professor of Medicine
Director, Anti-Infective Research Laboratory
Eugene Applebaum College of Pharmacy & Health Sciences
Wayne State University
Disclosures

➢ Provided lectures and or consulted for, and or received research support from:
  – Astellas
  – Cubist
  – Forest
  – Pfizer
  – Rib-X
  – Triax
  – NIH
  – MDCH
Learning Objectives

- Describe the burden of antimicrobial resistance
- Understand the basic principles of antimicrobial stewardship
- Describe the components of a successful antimicrobial stewardship program (ASP)
- Give examples of ASP interventions, the relationship to patient outcomes and control of antimicrobial resistance
Outline

- Antimicrobial Stewardship Overview
- Applications to CAP
- Skin and Skin Structure Infections
- Future Directions
Drug Resistance Rising

1 = *Staphylococcus aureus* resistant to methicillin
2 = *Enterococci* resistant to vancomycin
3 = *Pseudomonas aeruginosa* resistant to imipenem
4 = *Acinetobacter* spp resistant to imipenem
5 = *Candida* spp resistant to fluconazole

Bad Bugs, No Drugs: A Public Health Crisis

- IDSA 2004 policy report, with periodic updates\(^1,2\)
- Growing resistance in Gram-positive and Gram-negative pathogens, limited treatment options\(^1\)
- Key organisms: “ESKAPE”\(^1\)
  - *Enterococcus faecium*
  - *Staphylococcus aureus*
  - *Klebsiella pneumoniae*
  - *Acinetobacter baumanii*
  - *Pseudomonas aeruginosa*
  - *Enterobacter species*

Impact of Drug-resistant Pathogens (methicillin-resistant *S aureus*)

- Inappropriate therapy, fewer alternatives\(^1,2\)
- Poor outcomes
  - Higher mortality\(^1,2\)
  - Prolonged hospitalization\(^3\)
  - Increased difficulty with placement of an extended care facility
  - Need of isolation precautions (may negatively impact on quality of patient care)
  - Increased costs\(^3\)

The Burden of Antimicrobial Resistance

Impacts both clinical and economic outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Methicillin-susceptible S. aureus&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Methicillin-resistant S. aureus&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Imipenem-susceptible P. aeruginosa&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Imipenem-resistant P. aeruginosa&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>6.7%</td>
<td>20.7%&lt;sup&gt;b&lt;/sup&gt;</td>
<td>16.7%</td>
<td>31.1%&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Hospital charges</td>
<td>$73,165</td>
<td>$118,414&lt;sup&gt;c&lt;/sup&gt;</td>
<td>$48,381</td>
<td>$81,330&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
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<sup>a</sup> Relative risk: 1.86; 95% CI, 1.38-2.51.
<sup>b</sup> $P = .003.$
<sup>c</sup> $P = .03.$
<sup>d</sup> $P < .001.$

The Cost of Resistance

- Clinical outcomes associated with antimicrobial-resistant infections (ARI)
  - 6.5% attributable mortality
  - Twice as likely to die vs. uninfected
  - LOS increase of 11 days

- Economic outcomes associated with ARI\(^1\)
  - Attributable cost: $18,588 – $29,069
  - Combined hospital and societal cost for 188 patients = $13.35 – $18.75 million

- Extrapolated nationwide: $16.6 – $26 billion annually

LOS, length of stay.
Resistance Is Multifactorial
Stewardship Is Only Part of the Solution

Transfer of patient with resistant organism

Antimicrobial Resistance in Hospitals

Transfer of resistant genes between organisms

In vivo selection by antimicrobial use

Patient-to-patient transfer via poor hand hygiene or environmental contamination

Patient-to-patient transfer facilitated by antimicrobial use

Integrated Healthcare Systems

Resistance

Acute Care Facility

Home Care

Outpatient/Ambulatory Facility

Long Term Care Facility

Resistance
Pathogenesis of HAI

- Usually bacterial infection
- Colonization usually precedes infection
  - Both colonized and infected patients are contagious
- Bugs are spread from patient to patient by healthcare workers
  - Hands, equipment (e.g., stethoscope)
  - Transient colonization most common
- Role of environment
- Major risks: indwelling devices, debilitated state
  - More frequent contact with HCW, higher risk
- Prevention: hand hygiene, contact precautions, patient isolation, cohorting
- Example, methicillin-resistant *Staphylococcus aureus* (MRSA)
Direct effect of antimicrobials on acquisition

- Enterobacter spp. and 3rd generation cephalosporins
- Avoid Cephalosporin use: emergence of resistance in 20-25% of instances.
- In the setting of 3rd generation cephalosporins, AmpC hyperproducing Enterobacter rapidly emerge
- Direct antimicrobial pressure causes resistance: initial isolate cephalosporin-susceptible; second isolate resistant

Kaye et al, Antimicrob Agents Chemother. 2001 Sep;45(9):2628-30
Projected Cost Savings if Antimicrobial Resistance Rates Reduced from 13.5% to 10%

Declining Development of New Antimicrobials

Misconceptions about Antibiotics

- Fallacies that promote “spiraling empiricism”
  - Broader is better
  - Failure to respond is failure to cover
  - When in doubt, change drugs, or add another
  - More disease(s), more drugs
  - Sickness requires immediate treatment
  - Response implies diagnosis
  - Bigger disease, bigger drugs
  - Bigger disease, newer drugs
  - Antibiotics are nontoxic

Antibiotic Stewardship Fundamentals

Definition
- “An ongoing effort…to optimize antimicrobial use in order to improve patient outcomes, ensure cost-effective therapy, and reduce adverse sequelae of antimicrobial use (including antimicrobial resistance)”

Axioms/Assumptions
- Antibiotic prescribing behaviors can be changed
- Antibiotic use drives antibiotic resistance
- Reduced antibiotic use decreases resistance or slows its increase
- Appropriate antibiotic use improves patient outcomes and reduces costs

The Antibiotic Use Thought Process = Antimicrobial Stewardship

1. Assess patient
2. Make diagnosis
3. Select treatment plan

- Are antibiotics needed? What are my options? Formulary restrictions? Will it work?
- Risk stratification (severity, risk factors for MDROs)
- Guidelines (local or national)
- Spectrum of activity and local antibiogram
- Nonscientific inputs: peer opinion, marketing

4. Implement plan
5. Reassess patient
6. Modify plan

- Are antibiotics still needed? Can I streamline therapy? Specific microbiology Convenience and cost
Guidelines Can Assist in the Development of Antimicrobial Stewardship

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

Timothy H. Dellit,1 Robert C. Owens,2 John E. McGowan, Jr.,2 Dale N. Gerding,4 Robert A. Weinstein,5 John P. Burke,6 W. Charles Huskins,7 David L. Paterson,9 Neil O. Fishman,9 Christopher F. Carpenter,10 P. J. Brennan,9 Marianne Billeter,11 and Thomas M. Hooton12

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

The Rationale and Methods for Stewardship Programs Have Been Well Described

- IDSA/SHEA Guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis.* 2007;44:159-177.
Goals of Antimicrobial Stewardship

- Optimize clinical outcomes while minimizing\(^1,2\) unintended consequences of antimicrobial use
  - Optimize antimicrobial therapy in each patient and in the population (PK/PD considerations)
- Unintended consequences include the following\(^1,2\)
  - Toxicity
  - Selection of pathogenic organisms (eg, *C. difficile*)
  - Emergence of resistant pathogens

Other Important Aspects of Antimicrobial Stewardship

- The appropriate use of antimicrobials is an essential part of patient safety
- Comprehensive infection control is essential to reduce spread of resistant organisms
- Stewardship should also reduce healthcare costs without adversely impacting clinical outcomes

Reasons for Uncertainty

- Variable implementation
  - Restrictions common in academic centers, not community hospitals
  - Role of pharmacist, physician, ID fellow unclear and varies
  - Limited use of local guidelines
  - Limited use of CPOE and CDSS
  - Program funding inconsistent
  - Administrative support and data analysis inconsistent

CPOE, computerized provider order entry; CDSS, clinical decision support system.
Two Proactive Core Strategies

- **Prospective audit with intervention and feedback**
  - Can increase appropriate use of antimicrobials
  - Incorporates streamlining/de-escalation
    - Culture- and susceptibility-based
    - Eliminates redundant therapy

- **Formulary restriction and preauthorization**
  - Can lead to immediate and significant reductions in antimicrobial use and cost
  - As a means of controlling antimicrobial resistance is less clear (and) may simply shift to an alternative agent with resulting increased resistance

**Advantages:**
- Can be customized to the facility
- Preserves the prescribers autonomy
- Can be facilitated through computer surveillance
- Circumvents potential for delays in initiating therapy

**Disadvantages:**
- Recommendations are optional
- Potential for inappropriate exposure

**Advantages:**
- Initial orders funneled through experts
- Immediate educational opportunities
- Control of antimicrobial use

**Disadvantages:**
- Delay in therapy for critically ill patients
- Labor intensive
- Loss of prescriber autonomy

“Back-End Approach”

Prospective audit with intervention and feedback

Formulary restriction and preauthorization requirements

“Front-End Approach”

**Education**
- Most frequently employed intervention
- Essential element of any antimicrobial stewardship program (ASP)

**Guidelines**
- ASP should facilitate development of evidenced-based guidelines
- Must be tailored to local practice and epidemiology

**Computer Surveillance**
- Opportunity for screening information as it becomes available
- Can develop alerts, reports, and decision support pathways

**Outcomes Measurement**
- Determines the impact of new policies
- Opportunities for research and publication

Stewardship Strategies: Restrictive Formularies

- There is no totally "open" or "closed" formulary, just varying degrees of restriction
- May help control costs
- Unknown if restriction may increase selective pressure (and therefore increase resistance)
- Puts pharmacy in a "police" role, drains ID Staff
- Need mechanism to avoid delay in therapy
- Generally a "front end" approach, therefore limited impact on duration of therapy

Stewardship Strategies: Criteria Monitored Drug Program

- Target drugs prescribed for specific patient indications
  - Prescribing outside criteria requires ID approval
- Criteria determined by ID physicians and pharmacy
- Literature support for recommendations
- Pharmacist and/or ID physicians may be monitoring service

Stewardship Strategies: Therapeutic Guidelines and Pathways

- Disease-based treatment guidelines to target:
  - Selection: initial empiric therapy and alternatives
  - Dosing: pharmacodynamic/Pharmacokinetic optimization
  - Route: IV/PO conversions
  - De-escalation of therapy
  - Duration of therapy, facilitate discharge from hospital

- Must have multidisciplinary involvement and input from all stakeholders (eg, surgery, pulmonary, nurse managers…)

- Should account for local resistance patterns

Antibiogram Example – Miracle University Hospital

| GRAM-NEGATIVE AEROBES | Cefazolin | Cefotetan | Cefotaxime | Ceftriaxone | Ceftazidine | Ceftazolin | Cefepime | Amikacin | Gentamicin | Tobramycin | Aztreonam | Imipenem | Meropenem | Ciprofloxacin | Levofoxacin | Ampicillin | pipemidic acid | Pipemidic acid | Pipemidic acid | Pipemidic acid |
|-----------------------|-----------|-----------|------------|-------------|-------------|------------|-----------|----------|-----------|------------|-----------|----------|----------|-----------|-------------|-------------|-----------|--------------|--------------|--------------|--------------|---------------|
| MIC breakpoint (ug/ml) | 8          | 8         | 8          | 8           | 8           | 8          | 8         | 8        |<8         |<8          |<8        |<8       |<8       |<8        |<8           |<8           |<8        |<8            |<8            |<8            |<8            |<8/38         |
Antimicrobial Stewardship and the Treatment of CABP

- Guidelines and Pathways are an effective tool for applying antimicrobial stewardship principles
- Guideline-recommended antimicrobial therapy for established by IDSA and ATS
  - Addresses three populations of patients
    - Outpatients
    - Non-ICU inpatients
    - ICU patients

ATS, American Thoracic Society; IDSA, Infectious Diseases Society of America.
2007 IDSA/ATS Treatment Guidelines for Inpatient Management of CAP

CAP Inpatient Therapy

Medical Ward
- Respiratory Fluoroquinolone alone
  - or β-lactam + Advanced Macrolide

ICU
- No Pseudomonas Risk
  - No β-lactam Allergy
    - β-lactam + Advanced Macrolide or Respiratory Fluoroquinolone
  - β-lactam Allergy
    - Respiratory Fluoroquinolone + Aztreonam

- Pseudomonas Risk
  - No β-lactam Allergy
    - Antipseudomonal β-lactam + Ciprofloxacin or 750-mg Levofloxacin or Aminoglycoside + Advanced Macrolide or Aminoglycoside + Antipneumococcal Fluoroquinolone
  - β-lactam Allergy
    - Aztreonam + Aminoglycoside + Antipneumococcal Fluoroquinolone

Guidelines and Pathways: Support for Antibiotic Stewardship in CABP

- Evaluation of a critical pathway in EDs of 19 hospitals
  - Multicenter, randomized controlled trial
  - Clinical prediction rule to guide
    - Hospital admission
    - Practice guidelines
    - Use of levofloxacin

- Results
  - 1743 CABP patients studied
  - Compared with conventional therapy, implementation of pathway led to
    - 1.7-day reduction in median LOS (4.4 vs. 6.1; \( P = .04 \))
    - 1.7-mean day reduction of IV therapy (4.6 vs. 6.3; \( P = .01 \))
    - More likely to receive monotherapy (64% vs. 27%; \( P < .001 \))

Critical Pathway Versus Conventional Management and Quality of Life

Critical Pathway Versus Conventional Management and Clinical Outcomes

Use of Evidence-Based Guidelines and Pathways: Support for ASP in CABP

- Retrospective cohort study: 22,196 CABP patients
- 31 Adventist Health System institutions
- Patients enrolled in the clinical pathway:
  - ~50% more likely to receive blood cultures and appropriate therapy
  - 80% reduction in the likelihood of respiratory failure requiring mechanical ventilation (OR, 0.20; 95% CI, 0.12-0.33)
  - Significantly lower mortality rate (OR, 0.37; 95% CI, 0.2-0.7)

Mortality by Pathway Status and Pneumonia Severity Level

Outcomes on CABP Pathway Versus Non-pathway

Impact of Compliance with CABP Guidelines

- Prospective evaluation of adherence to 1998 IDSA guidelines for treatment of inpatients with CABP
- Conducted in 46 Veterans Health Administration Hospitals
- Results
  - Compliance with antibiotic selection:
    - 85.3% (592/694) for patients admitted to general ward
    - Only 40% (26/65) patients admitted to ICU
  - Modification of antibiotic regimen was 83.8%
    - 69.5% of changes were IV to PO conversions
  - Authors concluded that greater use of treatment guidelines increase use of early switch from IV to PO therapy

Initial Antibiotic Selection

Reasons for Antibiotic Change

Antimicrobial Stewardship and Skin and Soft Tissue Infections (SSTIs)

SSTI Hospitalization by Type of Infection (2004; 869,777)

- Cellulitis and abscess
- Infection due to vascular device
- Other deeper or health care-associated infections
- Ulcer
- Post-op wound infection
- Gangrene/necrotizing fasciitis

Note: All included in definition of complicated SSSI (cSSSI) except other superficial infections and gangrene/necrotizing fasciitis.

Antibiotic Resistance and Treatment Outcomes

CA-MRSA leads to significantly greater rates of hospitalization, failure of initial therapy and infection recurrence in patients with cSSSI vs. those with CA-MRSA.

CA-MRSA, community-acquired methicillin resistant S. aureus; CA-MSSA, community-acquired methicillin-sensitive S. aureus.
**S. aureus Infections in US Veterans, Maryland, 1999-2008**

- Collected all *S. aureus* positive blood and clinical culture data from 1999-2008 from 3 VA Medical Centers
  - Defined unique culture as 1\textsuperscript{st} culture within 6-month period
  - Classified on
    - Methicillin susceptibility
    - Community or hospital onset

- Classified cultures from sterile or non-sterile body site according to CDC defined criteria

- Collected all ICD-9-CM codes associated with culture

- Defined invasive or non-invasive *S. aureus* infection on basis of isolation from specific body site:
  - Invasive: sterile body site (ie, blood, pleural fluid, CSF, etc.)
  - Noninvasive: nonsterile site within concurrent culture from as sterile site

**S. aureus Infections in US Veterans, Maryland, 1999-2008**

Conclusions

– Overall incidence of *S. aureus* infections increased from 1999-2008

– Driven by a rapid increase in community-onset MRSA skin and soft tissue infections

– Increase was striking after 2003, and coincides with the time that USA300 became a major contributor to noninvasive *S. aureus* infections

– Data suggested a shift in the distribution of *S. aureus* infections to noninvasive community-onset MRSA

MRSA: A Common Cause of ABSSSI

- The Infectious Disease Society of America guidelines for treating hospitalized patients with complicated skin and skin structure infection*
  - “Empirical therapy for MRSA should be considered” pending culture results

* cSSSI defined as deeper soft-tissue infections, surgical/traumatic wound infection, major abscesses, cellulitis, infected ulcers and burns

Vancomycin is used as initial therapy in 55% of ABSSSI.

Study period January 1, 2000 to June 30, 2009.
SSTIs Requiring Hospitalization at an Academic Medical Center: Opportunities for Antimicrobial Stewardship

- Evaluated cohort of consecutive adults hospitalized for SSSI during 1-year period (2007)
  - 477-bed academic medical center in Denver
- Classified as cellulitis, cutaneous abscess, or SSTI with additional complicating factors
- Results: 322 patients evaluated
  - 66 (20%): cellulitis
  - 103 (32%): abscess (incision and drainage in 98%)
  - 153 (48%): complicating factors
    - IV drug use, diabetes mellitus, alcohol use

SSTIs Requiring Hospitalization at an Academic Medical Center: Opportunities for Antimicrobial Stewardship

- 150 patients had positive cultures from deep tissue, blood, or abscess
  - *S. aureus* or Streptococci identified in 145 (97%)

- Use of antibiotics
  - Broad aerobic gram-negative activity in 61%-80% of patients
  - Anaerobic coverage 73%-83% of patients

- Median duration of therapy, days
  - Cellulitis: 13 (IQR 10-14)
  - Cutaneous abscess: 13 (IQR 10-16)
  - SSSI with complications: 14 (IQR 11-17)

- Treatment failure, recurrence, rehospitalization within 30 days
  - Cellulitis: 12.1%
  - Cutaneous abscess: 4.9%
  - SSTI with complications: 9.2%

IQR, interquartile range.
SSTIs Requiring Hospitalization at an Academic Medical Center: Opportunities for Antimicrobial Stewardship

- ESR and CRP determined in nearly 70% of patients
- Blood cultures 47% to 58% of the time
- Imaging studies in 94% of patients
  - SSTI with complicating factors: 86%
  - Significant association with use of plain film and cellulitis ($P < .04$)
  - Advanced imaging (CT, MRI) in 20% of all cases
  - Yield of imaging studies: 14 (4%)
    - 4 (1%): plain film; ultrasound: 1 (0.3%); CT: 7 (2%); MRI: 3 (1%)

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; CT, computed tomography.
SSTIs Requiring Hospitalization at an Academic Medical Center: Opportunities for Antimicrobial Stewardship

➢ Additional therapy results
  – 85% of cellulitis patients received MRSA coverage
    ● Of these, approximately 50% discharged on TMP/SMX
    ● Highest rate of failure was cellulitis
      – Of interest, 5/8 (63%) cases of cellulitis failure discharged on TMP/SMX

➢ Conclusions
  – Substantial health care resources used to treat SSTI
  – Some diagnostic testing is poorly defined, expensive, and unnecessary
  – Many patients received broad antibiotic coverage including gram-negative and anaerobic coverage
  – Duration of hospitalization for treatment appeared excessive and many patient could have received part of their therapy at home

Summary: Antimicrobial Stewardship Programs

- Driven by increasing antibiotic resistance
  - Limited pipeline
- Needs leaders and training programs
- Requires administration support
- Some components may be forced based on:
  - Future JCAHO and CMS requirements
- Requires evaluation of ASP impact
  - To improve and develop
  - Maintain services and resources