Understanding Antimicrobial Stewardship

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Objectives

- Describe the role of resistance
- Analyzed the scope of the problem with resistance
- Discuss the elements and activities of antimicrobial stewardship program (ASP)
- Understanding the rationale for ASP
- Evaluate components lead to a successful ASP
How Antibiotic Resistance Happen?

1. Lots of germs. A few are drug resistant.

2. Antibiotics kill bacteria causing the illness, as well as good bacteria protecting the body from infection.

3. The drug-resistant bacteria are now allowed to grow and take over.

4. Some bacteria give their drug-resistance to other bacteria, causing more problems.

http://www.cdc.gov/drugresistance/threat-report-2013/
Selection for Antimicrobial-Resistant Strains

Resistant Strains Rare

Antimicrobial Exposure

Resistant Strains Dominant

Examples of How Antibiotic Resistance Spreads

Animals get antibiotics and develop resistant bacteria in their guts.

Drug-resistant bacteria can remain on meat from animals. When not handled or cooked properly, the bacteria can spread to humans.

Fertilizer or water containing animal feces and drug-resistant bacteria is used on food crops.

Drug-resistant bacteria in the animal feces can remain on crops and be eaten. These bacteria can remain in the human gut.

Simple using antibiotics creates resistance. These drugs should only be used to treat infections.

http://www.cdc.gov/drugresistance/threat-report-2013/
Emergence of Antimicrobial Resistance

Susceptible Bacteria

Resistant Bacteria

Resistance Gene Transfer

Mutations

New Resistant Bacteria

Antibiotic Use Drives Resistance

Penicillin 1942

Methicillin 1961

Vancomycin 1958 (increased use in 1980s)

vanA genetic transfer 2002

S. aureus → PRSA → MRSA

VRE → vanA genetic transfer 2002 → VRSA
Gram-Positive Resistance

**METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA)**
- **80,461** severe MRSA infections per year
- **11,285** deaths from MRSA per year
- Staph bacteria are a leading cause of healthcare-associated infections

**VANCOMYCIN-RESISTANT STAPHYLOCOCCUS AUREUS**
- **13 cases** in 4 states since 2002
- Some Staphylococcus strains are resistant to Vancomycin leaving few or no treatment options

**THREAT LEVEL**
- **SERIOUS**
  - This bacteria is a serious concern and requires prompt and sustained action to ensure the problem does not grow.

- **CONCERNING**
  - This bacteria is concerning, and careful monitoring and prevention action are needed.
Antibiotic Use Drives Resistance

Enteric GNRs

Ampicillin 1961

GNRs (TEM+)

3rd gen cephs 1980s

GNRs (ESBL+, AmpC+)

Carbapenems 1985 (increased use in 1990s)

Polymyxins 1958, increased use in 2000s

CRE

GNRs resistant to polymyxins
Gram-Negative Resistance

MULTIDRUG-RESISTANT ACINETOBACTER

- 7,300 multidrug-resistant Acinetobacter infections
- 500 deaths from multidrug-resistant infections
- 12,000 Acinetobacter infections per year
- At least three different classes of antibiotics
- No longer cure resistant Acinetobacter infections
- 1,900 resistant Klebsiella spp.
- 1,400 resistant E. coli
- CRE have become resistant to all or nearly all available antibiotics

EXTENDED SPECTRUM β-LACTAMASE (ESBL) PRODUCING ENTEROBACTERIACEAE

- 26,000 drug-resistant infections
- 1,700 deaths
- 140,000 enterobacteriaceae infections per year
- $40,000 in excess medical costs per year for each infection
- 51,000 Pseudomonas infections per year

THREAT LEVEL

- SERIOUS

This bacteria is a serious concern and requires prompt and sustained action to ensure the problem does not grow.

This bacteria is an immediate public health threat that requires urgent and aggressive action.
WHO Report Reveals Global Antimicrobial Resistance Warning

United States *population 300m*
>23,000 deaths, >2.0m illnesses
Overall societal costs Up to $20 billion direct
Up to $35 billion indirect

European Union *population 500m*
25,000 deaths per year, 2.5m extra hospital days
Overall societal costs (€ 900 million, hosp. days)
Approx. €1.5 billion per year

Thailand *population 70m*
>38,000 deaths, >3.2m hospital days
Overall societal costs US$ 84.6–202.8 mill. direct
>US$1.3 billion indirect
Casual Association between Antimicrobial Use & the Emergence of Antimicrobial Resistance

- Changes in antimicrobial use are paralleled by changes in the prevalence of resistance

- Antimicrobial resistance is more prevalent in healthcare-associated bacterial infections, compared with those from community-acquired infections.

- Patients with healthcare-associated infections caused by resistant strains are more likely than control patients to have received prior antimicrobials.

- Areas within hospitals that have the highest rates of antimicrobial resistance also have the highest rates of antimicrobial use.

- Increasing duration of patient exposure to antimicrobials ↑ the likelihood of colonization with resistant organisms.

Antimicrobial Resistance
Key Prevention Strategies

- Prevent Transmission
- Prevent Infection
- Effective Diagnosis & Treatment
- Optimize Use

Susceptible Pathogen → Antimicrobial Use → Infection → Effective Diagnosis & Treatment

Antimicrobial Resistance

Inappropriate Antimicrobial Therapy Impact Mortality


Relative Risk = 2.37
(95% C.I. 1.83-3.08; p < .001)

42.0% mortality
17.7% mortality

No. Infected Patients

# Survivors

# Deaths

Antibiotic Prescriptions per 1000 Persons
All Ages According to State, 2010

The frequency with which doctors prescribe antibiotics varies greatly from state to state. The reasons for this variation are being studied and might suggest areas where improvements in antibiotic prescribing (fewer unnecessary prescriptions) would be most helpful.

http://www.cdc.gov/drugresistance/threat-report-2013/
Tomorrow’s Antibiotics: The Drug Pipeline

The number of new antibiotics developed and approved has steadily decreased in the past three decades, leaving fewer options to treat resistant bacteria.

Number of Antibacterial New Drug Application (NDA) Approvals vs. Year Intervals*

*Intervals from 1980–2009 are 5-year intervals; 2010–2012 is a 3-year interval. Drugs are limited to systemic agents. Data courtesy of FDA’s Center for Drug Evaluation and Research (CDER).
Antimicrobial Approval Timeline

1998
- Rifapentine
- Linezolid

1999
- Quinupristin/Dalfopristin
- Moxifloxacin
- Gatifloxacin

2000
- Cefditoren
- Ertapenem

2001
- Gemifloxacin
- Daptomycin

2002

2003
- Tigecycline

2004
- Telithromycin

2005
- Doripenem

2006
- Ceftazidime/avibactam

2008

2009
- Telavancin

2010
- Ceftaroline

2011
- Fidaxomicin

2014
- Tedizolid
- Dalbavancin
- Oritavancin
- Ceftolazane/tazobactam
- Ceftazidime/avibactam

In development: ceftobiprole, eravacycline, Imipenem-MLK 7655, plazomicin, brilacidin & more...

Antimicrobial Stewardship?

- Working relationship between infection control & antimicrobial management

- Selection of antimicrobials from each class of drugs that does the least collateral damage

- Collateral damage issues include
  - Methicillin-resistant *Staphylococcus aureus* (MRSA)
  - Extended spectrum β-lactamase (ESBL)
  - *Clostridium difficile* (*C. difficile*)
  - Vancomycin-resistant enterococci (VRE)
  - Metalloenzymes & other carbapenemases

- Appropriate de-escalation when culture results are available

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

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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 per IDSA

• Antimicrobial stewardship is an activity that promotes

  ▫ Appropriate selection of antimicrobials
  
  ▫ Appropriate dosing of antimicrobials
  
  ▫ Appropriate route & duration of antimicrobial therapy

Stewardship Guidelines

- Recommendation from the Infectious Diseases Society of America (IDSA) & the Society for Healthcare Epidemiology of America (SHEA)

- Endorsed by the following organizations:
  - American Society of Health-System Pharmacists (ASHP)
  - American Academy of Pediatrics
  - Infectious Diseases Society for Obstetrics and Gynecology
  - Pediatric Infectious Diseases Society (PIDS)
  - Society for Hospital Medicine
  - Society of Infectious Disease Pharmacists (SIDP)

Goal of Antimicrobial Stewardship

• **Primary Goal**
  - Optimize clinical outcomes while minimizing *unintended consequences* of antimicrobial use
    - *Unintended consequences* include the following
      - Toxicity
      - Selection of pathogenic organisms such as *C. difficile*
      - Emergence of resistant pathogens

• **Secondary Goal**
  - Reduce healthcare costs without adversely impacting the quality of care

Additional Aspects of Antimicrobial Stewardship

- Appropriate use of antimicrobials is an essential part of patient safety

- Frequency of inappropriate antimicrobial use is often used as a surrogate marker for the avoidance impact on antimicrobial resistance

- Combination of antimicrobial stewardship & comprehensive infection control has been shown to limit the emergence & transmission of antimicrobial resistant bacteria

Core Team Members

- **Physician (infectious diseases)**
  - Critical as their role will interact with medical staff
  - Mediate disagreements
  - Set goals for program
  - Diplomatic and collegial
  - Have an interest in antibiotic utilization and patient safety

- **Clinical pharmacist (infectious diseases trained)**
  - Liaison for pharmacy and members
  - Intervene
  - Set goals for program
  - Confidence advising physician and other providers

Other Members to Build The Team

Antimicrobial Stewardship Program

- Infectious Diseases Specialists
- Infection Control
- Microbiology
- Clinicians
- Nursing
- Information Systems
- Patient Safety & Quality
- Pharmacy
- Hospital Administration
Potential Proactive Core Strategies

• Prospective audit with intervention & feedback (A-I)

• Formulary restriction & pre-authorization (A-II)
  ▫ Can lead to significant & immediate reductions in antimicrobial use & cost

Antimicrobial Prescribing Process & Antimicrobial Stewardship Strategies

- Patient evaluation
  - Education/guideline strategies
  - Antibiotic cycling strategies
  - Formulary/restriction strategies
  - Computer-assisted strategies
- Choice of antimicrobial to prescribe
- Prescription ordering
  - Review and feedback strategies
- Dispensing of antimicrobial
Restriction or Formulary Policies

Impact of Quinolone Restriction on Resistance Patterns of Escherichia coli Isolated from Urine by Culture in a Community Setting

Hospital and Societal Costs of Antimicrobial-Resistant Infections in a Chicago Teaching Hospital: Implications for Antibiotic Stewardship

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Clin Infect Disease. 2009; 49: 869-75; 1175-84
Prospective Audit with Intervention and Feedback

- Report on a regular basis the results of audits & interventions to the P & T Committee & other hospital groups as appropriate
  - Provide targeted feedback to physicians individually or to physician services based on the results of prospective audits

- Plan additional prospective audits & seek help from others when antimicrobials are not used appropriately

- Report on the financial impact of interventions & feedback

Formulary Restriction & Pre-authorization

- Report rates of resistance designed to show the effects of formulary restriction & pre-authorization
  - ESBL rates in key bacteria (i.e. *K. pneumoniae*)
  - CDAD hospital rates compared to previous rates
  - MRSA rates compared to previous rates
  - SPACE bacteria rates of resistance to key antimicrobials (*Acinetobacter* spp. & *P. aeruginosa* resistance rates to cefepime, imipenem/meropenem, fluoroquinolones)
  - Monitor for transferable resistance in gram-negative bacteria (i.e. MBLs & KPC 1-3)

Elements for Consideration & Prioritization

1. Educational programs – but with active intervention (AIII, B-II)

2. Guidelines & clinical pathways – seek multidisciplinary involvement & approval (A-I)
   - Incorporate local antimicrobial resistance patterns (A-I)
   - Provide education & feedback to practitioners (A-III)

Elements for Consideration & Prioritization

3. Antimicrobial cycling – is not recommended due to insufficient data

4. Antimicrobial order forms (B-II)
   ▫ Shown to be effective component of the program & can facilitate implementation of practice guidelines

5. Combination therapy
   ▫ Insufficient data for routine use (C-II)
   ▫ Has a role to ↑ coverage in empiric therapy in patients at risk for multidrug-resistant pathogens

Elements for Consideration & Prioritization

6. Streamlining or de-escalation therapy (A-II)
   ▫ Based on culture results & eliminate of redundant therapy can ↓ antimicrobial exposure & ↓ cost

7. Dose optimization (A-II)
   ▫ Based on PK/PD parameters & includes patient characteristics, causative organisms, site of infection, in addition to PK/PD characteristics of the drug
Intravenous (IV) to Oral (PO) Therapy

CRITERIA FOR CONVERSION FROM PARENTERAL TO ORALENTERAL MEDICATIONS
Conversion from parenteral to oralenteral medications is considered only when 1 of the following clinical conditions exist:
1. the patient can tolerate at least a full liquid diet for a minimum of 24 h;
2. the patient has a feeding tube in place; and
3. the patient is taking other oral or enteral medications.

Figure 1. Total and intravenous (iv) antibiotic costs, in US dollars. NPI, no pharmacy intervention; PI, sequential, iv moxifloxacin with pharmacist-initiated automatic conversion to oral moxifloxacin; PI switch, iv β-lactam plus a macrolide with pharmacy intervention to switch therapy to an oral quinolone. *P < .0001, vs. comparators.
Dose Optimization

• Bactericidal activity of β-lactams correlates with amount of time > MIC for the bacteria

• Fluoroquinolones & aminoglycosides are concentration dependent agents
  ▫ $C_{\text{max}}$:MIC (extended interval aminoglycosides)
  ▫ AUC:MIC for fluoroquinolones – high dose, short course therapy for CAP
Elements for Consideration & Prioritization

8. Parenteral to oral conversion (A-I)

- When the patient’s condition allows
  - ↓ length of stay
  - ↓ healthcare costs

- Development of clinical criteria & guidelines allowing conversion to use of oral agents can facilitate implementation at the institutional level (A-III)

Rationale for Optimization of Antimicrobial Utilization

- Resistance
  - Inherent
  - Exposure

- Patient safety
  - Adverse events
  - Possibly death

- Cost
  - Broad coverage
  - Inappropriate use
  - Discontinued IV and switch to PO
# Antibiotic Resistance: Who Will Pay the Bills?

**Theoklis E. Zaoutis**

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<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>Patients with ARI</th>
<th>Patients without ARI</th>
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<tbody>
<tr>
<td>n (%)</td>
<td>1391</td>
<td>188 (13.5)</td>
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<td>APACHE II score</td>
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<td>54.8*</td>
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<td>LOS (days)</td>
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<td>HAI (n)</td>
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<td>135*</td>
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<tr>
<td>Cost per day ($)</td>
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<td>2098*</td>
<td>1581*</td>
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<tr>
<td>Total cost ($)</td>
<td>19,267</td>
<td>58,029*</td>
<td>13,210*</td>
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<td>Death [n (%)]</td>
<td>70</td>
<td>34 (18.1)*</td>
<td>36 (3.0)*</td>
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* $p<0.001$
Cost to the Patient and the Public


George Sakoulas, MD,¹ Gary P. Wormser, MD,¹ Paul Visintainer, PhD,² Wilbert S. Aronow, MD,³⁎ and Robert B. Nadelman, MD¹
Implementation Strategy

• Phase I
  ▫ Perform a Gap Analysis
  ▫ Aware of regulatory requirements
    • CMS Core Measures for Antibiotic Use
    • Other measures: CLABSI, 30-day mortality for CAP, and post-operative sepsis
  ▫ Patient Safety
  ▫ Top antibiotics used
    • Where is it being use and why
  ▫ Other factors – plan for ASP? Incentive?
Implementation Strategy

• Phase II: Collaborate

• Phase III: Local Champions

• Phase IV: How can I simplified the process?

• Phase V: Do I have the data to show what I implemented worked or have a good outcome?
Research Priorities & Future Directions

- Antimicrobial cycling
- Clinical validation of mathematical models regarding antimicrobial resistance
- Long-term impact of formulary restrictions
- Focusing interventions on “collateral damage issues”
- Development of > rapid susceptibility tests
- Bad bugs/no bugs – stimulate research
- Influence of pharmaceutical industry marketing on antimicrobial prescribing & strategies to counteract inappropriate detailing
California Senate Bill 1311

- Law was signed on September 29, 2014
  - Requires all general acute care hospitals to adopt & implement ASP by July 1, 2015
  - Minimum 1 MD or PharmD who is knowledgeable about ASP
  - “Under existing law, a violation of the provisions governing health facilities constitutes a misdemeanor punishable by a fine not to exceed $1,000, by imprisonment in a county jail, or by both that fine and imprisonment.”
Summary

• Antimicrobial resistance is at a critical threaten

• Optimize antimicrobial therapy with a goal to improve patient safety

• Collaboration is the key to a successful program

• Identify and measure where improvement is needed to be implemented

• Implementation and intervention is vital in the overall success of the program in addition to patient outcome and stepwise implementation
  
  ▫ Data, collection is the key to measuring sucess