Measuring the Impact of Antimicrobial Stewardship Interventions on Antimicrobial Resistance

Michael Postelnick, RPh BCPS AQ Infectious Diseases
Senior Infectious Diseases Pharmacist
Northwestern Memorial Hospital
Chicago, IL
Call to 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.”

- Sir Alexander Fleming, June 26, 1945

Do Antimicrobial Stewardship Interventions Effect Resistance?

Davey P et al. Cochrane Database of Systematic Reviews
2013, Issue 4. Art. No.: CD003543
Evolution of Antimicrobial Stewardship
NMH 1987-2015

- 1987-1990: Implement Antimicrobial Formulary and Pharmacokinetic Dosing Service
- 1991-2002: Prospective audit and feedback
- 2002-2003: Initiate “Formal” Stewardship Program
- 2003: Implement Clinical Decision Support
- 2013: CDC-AU participation
What Have We Accomplished

• Continued control of antimicrobial costs
  • 2014 cost savings = $120,000
• Empiric Antimicrobial Use Guidelines and Incorporation into Order Sets
• Optimized Dosing of Antimicrobials
  • Comprehensive dosing protocols
  • Prolonged infusion protocols for beta-lactams
• Leveraging Clinical Decision Support for Bug-drug Mismatches and Restricted Antimicrobials
• Expansion of Training Programs for Infectious Diseases Pharmacists
Where Have We Struggled

• Measurement of Impact on Utilization and Resistance
  • Systematic metrics
  • Benchmarking

• Antimicrobial Stewardship Outcomes Research
Presentation Overview

- Measuring Antimicrobial Use
- Measuring Antimicrobial Resistance
- Designing Studies that Measure Relationships Between Interventions and Outcomes
- Representative Use-Resistance Studies
- Some Thoughts on New Stewardship Tools
Measuring Antimicrobial Use

It is widely believed that you cannot manage what you cannot measure. It is also true that you cannot measure what you cannot define.

# Measuring Antimicrobial Use

<table>
<thead>
<tr>
<th>Measure</th>
<th>Calculation</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Use?</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOT/1000 PD</td>
<td>DOT/(PD/1000)</td>
<td>More accurate than DDD</td>
<td>Requires pt. level data</td>
<td>Becoming standard metric</td>
</tr>
<tr>
<td>DOT/1000 admissions</td>
<td>DOT/(admissions/1000)</td>
<td>Not a function of LOS</td>
<td>Requires risk adjustment (RA)</td>
<td>Secondary measure</td>
</tr>
<tr>
<td>DDD/1000 PD</td>
<td><a href="http://www.whocc.no/ddd/definition_and_general_considera/">Link</a></td>
<td>Easily calculated, does not require pt level data</td>
<td>Less accurate and consistent</td>
<td>Comparison across countries</td>
</tr>
<tr>
<td>LOT/discharge</td>
<td>Total LOT/discharge</td>
<td>Provides average duration of tx</td>
<td>Not normalized for LOS, needs RA</td>
<td>Identify excessive tx durations</td>
</tr>
<tr>
<td>DOT/LOT ratio</td>
<td>DOT/LOT</td>
<td>Measures aggregate combo tx</td>
<td>Pt level data needed</td>
<td>Identify unnecessary combo</td>
</tr>
<tr>
<td>Proportion receiving abx</td>
<td>Treated pts/admissions</td>
<td></td>
<td>Needs risk adjustment</td>
<td>Identify unnecessary tx</td>
</tr>
</tbody>
</table>
Interpreting Antimicrobial Use Data

• Benchmarking
  • Use data must be risk adjusted
    • Internal – ICU vs general care floor
    • External – Academic medical center vs small rural hospital

• Identify Outliers
  • Perform DUE to determine intervention strategies (if needed)
    • Unnecessary therapy
    • Prolonged durations
    • Unusual resistance patterns
Benchmarking by Unit

Risk-adjusted Benchmarking

Measuring Antimicrobial Resistance
The Hospital Antibiogram

• Most widely available measure of resistant organisms
• Measures proportion of susceptible organisms over time
• Designed for:
  • Assisting empiric antimicrobial selection
  • Guidance on formulary choices
• CLSI sets guidance for construction

Schulz LT et al. Pharmacotherapy 2012;32(8):668–676
Antibiograms to Assess Stewardship Interventions

Schulz LT et al. Pharmacotherapy 2012;32(8):668–676
What Factors Effect the Ability to Demonstrate Interventional Impact on Resistance?

• Magnitude of Change
  • Time-series analysis to forecast resistance changes related to antibiotic use
  • Ceftazidime/gram negative bacilli and imipenem/Pseudomonas examined
  • Complex mathematical model designed for analysis
    • Lag-time accounted for
  • Impact of changes in antimicrobial use significant but small
    • 6% of variation in Pseudomonas susceptibility predicted by imipenem use variation

What Factors Effect the Ability to Demonstrate Interventional Impact on Resistance?

• **Dynamics of Resistance are Complex**
  - Bacterial resistance mechanisms effect multiple antibiotics
  - Stewardship interventions local-resistance is global
  - Unintended consequences (“squeezing the balloon”)
  - Multiple simultaneous interventions
    - Stewardship
    - Infection Control
  - Regression to the mean
Designing Studies to Measure Impact of Stewardship Interventions
Non-experimental Study Design-Before and After Study

https://www.urbanreproductivehealth.org/toolkits/measuring-success/types-evaluation-designs
Example Before and After Study

• Program of restriction and prior authorization requirements implemented in 575 bed teaching hospital

• Consecutive 6 month periods before and after interventions analyzed for antimicrobial expenditures

• 12 month periods before and after prior authorization implementation examined for susceptibilities

• Patient outcomes for bacteremia also assessed

• Results
  • Annualized antimicrobial expenditure savings = $864,000
  • Improvement in susceptibilities-particularly the ICUs
  • No change in patient outcomes in bacteremia

Example Before and After Study

Example Before and After Study

1. Stewardship interventions are remarkably successful in decreasing cost and resistance.

2. Study methodology compromise interpretation of results

Advantages and Disadvantages of Non-Experimental Design

Advantages:
1. Relatively easy to perform
2. Requires fewer resources and data collection
3. Results relatively rapidly available

Disadvantages:
1. Weak Internal validity
2. Easily confounded by random events
3. No way to clearly ascertain causality as there is no comparison group
Advantages

- Able to observe trends over time
- Easier to control for confounders, regression to the mean
- Statistically more robust

https://www.urbanreproductivehealth.org/toolkits/measuring-success/types-evaluation-designs
Quasi-Experimental Study Design

A1, B1 - Pre-intervention MRSA rates
A2, B2 – Post-intervention MRSA rates

Intervention - mupirocin decolonization in group A1

https://www.urbanreproductivehealth.org/toolkits/measuring-success/types-evaluation-designs
Strengths and Weaknesses of Quasi-Experimental Design

**Strengths**

1. Control group
2. More likely possible to control for random events
3. Easier to control for seasonality
4. More likely to reflect true impact of intervention

**Weaknesses**

1. More time-consuming
2. More resource-intensive
3. Still subject to some confounding
Representative Studies Examining Antimicrobial Use and Resistance
Aminoglycoside Use and Resistance - 1991

• Single center study

• 1980-1990 – aminoglycosides mainstays of Gram-negative treatment

• Primary aminoglycoside varied (gentamicin vs amikacin)

• No standard measure of use

• Resistance proportion but not rate calculated

• Move to new hospital potential late confounder

Aminoglycoside Use and Resistance - 1991

Aminoglycoside Use and Resistance - 2012

• Multi-center (29 academic medical centers)

• Data measured 2002-2009

• Use patterns differed between institutions

• Use defined at DOTs/1000 patient days

• Resistance proportion and rate calculated

• Aminoglycoside use significantly declined
  • Gentamicin – 45% decline
  • Tobramycin – 38% decline
  • Amikacin – no change
  • Total – 41% decline

Aminoglycoside Use and Resistance - 2012

# Trends in Gentamicin Resistance

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>E. Coli</td>
<td>1.1</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>15.8</td>
<td>29</td>
<td>20</td>
</tr>
</tbody>
</table>

Observations

• Overall aminoglycoside use has significantly declined

• Decline in use has variable effect on organism susceptibility
  • E. coli – progressive decline in gentamicin activity
  • Pseudomonas – apparent improvement in gentamicin activity

• Effect of choice of agent
  • Single center – potentially some impact
  • Globally – minimal impact
Use-Resistance Relationship is Complex

- 531 bed academic medical center
- Multi-modal stewardship program implemented
  - Prospective audit with intervention and feedback
  - Formulary restriction and preauthorization
  - Education
  - VAP antibiotic cycling program
  - Streamlining/de-escalation
- Implemented in fall 2004
- Antibiotic data (DDD/1000 pt days) collected 2003-2008
- Antibiogram data utilized as available

Slain D et al. Critical Care Research and Practice, Volume 2011, Article ID 416426
Use-Resistance Relationship is Complex

Slain D et al. Critical Care Research and Practice, Volume 2011, Article ID 416426
Some Thoughts on Stewardship Tools
Leveraging the EMR and Clinical Decision Support (CDS) Tools

• EMR and CDS tools for stewardship have been recently evaluated\textsuperscript{1-3}.
• EMR vendors offer some stewardship tools
  • Vary by vendor
  • Many require local IT support and resources
  • No comprehensive tool yet available
• Add-on CDS tools add many capabilities/expense
  • Enhance program scope
  • Enhance productivity
  • Add expense
  • No point of order capabilities

Rapid Diagnostic Aids and Tools

• Diagnostic uncertainty drives a significant amount of antimicrobial use

• Clinical symptoms may mimic infections

• Lack of early organism ID significantly delays de-escalation

• Routine microbiologic tests have evolved little over the past 100+ years
Diagnostic Aids – Is it an infection? Has the infection been treated adequately?

Procalcitonin in respiratory infections

Review: Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections
Comparison: 1 Procalcitonin algorithm versus no procalcitonin algorithm stratified by clinical setting
Outcome: 1 Mortality at 30 days

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>PCT Algorithm n/N</th>
<th>No PCT Algorithm n/N</th>
<th>Odds Ratio M-H, Random 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>507</strong></td>
<td><strong>501</strong></td>
<td><strong>0.32 [0.01, 7.98]</strong></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>507</strong></td>
<td><strong>501</strong></td>
<td><strong>0.32 [0.01, 7.98]</strong></td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>0 (PCT Algorithm), 1 (No PCT Algorithm)</td>
<td>1</td>
<td><strong>Test for overall effect Z = 0.69 (P = 0.49)</strong></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td>Tau² = 0.0, Chi² = 0.0, df = 0 (P = 1.00); I² = 0.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**2 Emergency department trials**
- Christ-Crain 2004: 4/124 vs 3/119; OR = 1.29 (0.28, 5.80)
- Christ-Crain 2006: 16/151 vs 20/151; OR = 0.89 (0.45, 1.75)
- Stolz 2007: 3/102 vs 2/106; OR = 1.58 (0.26, 9.53)
- Schuetz 2009: 34/671 vs 33/588; OR = 1.06 (0.65, 1.73)
- Kristoffersen 2009: 2/103 vs 1/107; OR = 2.10 (0.19, 23.31)
- Long 2009: 0/63 vs 0/64; OR = 0.0 (0.0, 0.0)
- Long 2011: 0/77 vs 0/79; OR = 0.0 (0.0, 0.0)

**Subtotal (95% CI)**
- **1201** vs **1314**; OR = 1.05 (0.72, 1.52)

**3 Intensive care unit trials**
- Nobre 2008: 5/25 vs 8/27; OR = 0.59 (0.16, 2.14)
- Hochreiter 2009: 7/24 vs 5/19; OR = 1.15 (0.30, 4.44)
- Schroeder 2009: 0/4 vs 0/4; OR = 0.0 (10.0, 0.0)
- Stolz 2009: 8/51 vs 12/50; OR = 0.59 (0.22, 1.59)
- Bouadma 2010: 37/183 vs 49/211; OR = 0.84 (0.52, 1.36)

**Subtotal (95% CI)**
- **287** vs **311**; OR = 0.79 (0.53, 1.17)

**Total (95% CI)**
- **2085** vs **2126**; OR = 0.91 (0.70, 1.19)

**Test for subgroup differences:** Chi² = 1.48, df = 2 (P = 0.48); P = 0.0%
Table 5. Antibiotic treatment overall and stratified by setting and ARI diagnosis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Procalcitonin group</th>
<th>Control group</th>
<th>Adjusted OR or difference (95% CI)</th>
<th>P of the regression model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>n = 2085</td>
<td>n = 2126</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiation of antibiotics, n (%)</td>
<td>1341 (64%)</td>
<td>1778 (84%)</td>
<td>0.24 (0.20 to 0.29)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Duration of antibiotics (days), median (IQR)</td>
<td>7 (4 to 10)</td>
<td>10 (7 to 13)</td>
<td>-2.75 (-3.12 to -2.39)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total exposure of antibiotics (days), median (IQR)</td>
<td>4 (0 to 8)</td>
<td>8 (5 to 12)</td>
<td>-3.47 (-3.78 to -3.17)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Rapid Diagnostics Tests

• Polymerase Chain Reaction
• Multiplex PCR
• Nanoparticle Probe Technology
• Peptide Nucleic Acid Fluorescent In Situ Hybridization (PNA-FISH)
• Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS)
Rapid Diagnostic Tests + Stewardship = Improved Outcomes (MALDI-TOF MS)

<table>
<thead>
<tr>
<th>Study</th>
<th>Organisms</th>
<th>Patients</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perez et al.</td>
<td>Gram-negative</td>
<td>201 patients with bacteremia</td>
<td>46hr ↓ time to ab optimized time to active treatment, LOS, and hospital costs</td>
</tr>
<tr>
<td>Huang et al.</td>
<td>Aerobic gram-positive, gram-negative and yeast</td>
<td>501 patients with bacteremia or fungemia</td>
<td>↓ time to organism ID, effective and optimal therapy, decreased LOS and mortality</td>
</tr>
<tr>
<td>Wenzler et al.</td>
<td>Acinetobacter baumannii</td>
<td>109 patients with pneumonia or bacteremia</td>
<td>↓ time to effective therapy increased cure rate</td>
</tr>
<tr>
<td>Perez</td>
<td>Gram-negative</td>
<td>265 patients with drug resistant bacteremia</td>
<td>Decreased time to optimal antibiotic therapy and decreased mortality</td>
</tr>
</tbody>
</table>

Making Antibiograms More Clinically Relevant

Limitations of Traditional Antibiograms

• Do not provide disease-specific advice

• Do not help identify organism distribution associated with a specific infection

• Unhelpful for polymicrobial infections

• Focused microbiologically, not clinically
Making Antibiograms More Clinically Relevant

Combination Antibiograms

• Provide data on what drug combinations cover a specific pathogen
• Help determine probability of activity of a combination regimen against a pathogen

Weighted Incidence Syndromic Combination Antibiogram (WISCA)

• Clinical syndrome focused
• Assesses coverage against pathogens isolated from patients with specific syndromes
• Provides guidance for a clinician facing a specific clinical syndrome

Making Antibiograms More Clinically Relevant

Hebert C et al. *Infect Control Hosp Epidemiol* 2012;33(4):381-388
Summary and Conclusions

- Although robust data are lacking, traditional stewardship interventions appear to have at least a transient effect on antimicrobial resistance.
- Benchmarking methods are improving and can help identify potential problem antimicrobial use areas.
- Antibiograms are not a good measure of stewardship impact.
- Study design is important to accurately measure intervention impact.
- Rapid diagnostics hold promise.
- Challenge: Re-invent antimicrobial stewardship for the 21st century.