Measuring the Impact of Antimicrobial Stewardship Programs: Integrating Health Economics and Outcomes Research

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10 x ‘20 Progress: Status Update From the IDSA in 2013

- Infections caused by “ESKAPE” pathogens continue to increase
- Only two new antibacterials have been approved since 2009
- Seven antibacterials are under clinical development for treatment of resistant Gram-negative pathogens

Increase in Last Resort Antimicrobial Use

http://www.plosone.org/article/info:doi/10.1371/journal.pone.0036649

2008 and 2011 Hospital Drug Expenses

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>2008¹ Expenditures ($ Thousands)</th>
<th>% Change From 2007</th>
<th>2011² Expenditures ($ Thousands)</th>
<th>% Change From 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antineoplastics</td>
<td>3,344,742</td>
<td>5.0</td>
<td>2,994,336</td>
<td>5.7</td>
</tr>
<tr>
<td>Hemostatic modifiers</td>
<td>3,459,980</td>
<td>6.6</td>
<td>2,702,472</td>
<td>–3.9</td>
</tr>
<tr>
<td><strong>Antinfectives,</strong></td>
<td><strong>3,188,596</strong></td>
<td><strong>7.3</strong></td>
<td><strong>2,152,871</strong></td>
<td><strong>–8.0</strong></td>
</tr>
<tr>
<td><strong>systemic</strong></td>
<td><strong>Blood growth factors</strong></td>
<td><strong>1.6</strong></td>
<td><strong>1,492,320</strong></td>
<td><strong>–3.4</strong></td>
</tr>
<tr>
<td><strong>Hospital solutions</strong></td>
<td><strong>1,697,024</strong></td>
<td><strong>17.5</strong></td>
<td><strong>1,339,415</strong></td>
<td><strong>–5.0</strong></td>
</tr>
</tbody>
</table>

Antimicrobial Stewardship

- **Antimicrobial stewardship** is a rational, systematic approach to the use of antimicrobial agents to achieve optimal outcomes\(^1,2\).
- The primary goal should be to improve patient care and public health\(^1,2\)
  - Financial goals are *secondary*

  | Correct agent | Cure or prevent infection |
  | Correct dose  | Minimize toxicity |
  | Appropriate duration | Prevent resistance |


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Cost Silos Within Hospitals

- Cost evaluations often include many individual target components
  - For example, pharmacy costs, patient outcomes, hospital resource utilization
  - Evaluation of any single component does not capture the *total* cost of care
- Consideration of all aspects of care differentiates the most profitable hospitals from other hospitals\(^1\)
- Minimization of *total* resource utilization to manage infection is an appropriate target "cost" for evaluation\(^2\)
- However, the hospital perspective cannot capture societal benefits of success (e.g., return to work)

Outcome Measures

Patient outcomes

- Patient morbidity (e.g., admission to ICU, LOS in hospital or ICU)
- Patient mortality

Collateral damage

- Selection of pathogenic organisms (e.g., CDI)
- Resistance
- Toxicity

Drug consumption/costs

- Defined daily doses, days of therapy, length of therapy
- Predefined costs, prices, or charges

Process measures

- Appropriateness of therapy
- For prevention of resistance
- Adherence to guidelines
- Time to appropriate therapy

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Patient Outcomes

Guidelines

![Graph showing initial and after patient outcomes](image)

- Initially Appropriate Therapy
- Duration of Treatment

Benefits of ASPs

- A 2005 Cochrane review found that 77% (51/66) of included studies observed significant improvements in inpatient prescribing, resistance, and/or CDI\(^1\)
  - The authors concluded that ASPs are successful and can reduce resistance or HAIs
- Costs may be avoided by introduction of ASPs\(^2\)
  - However, captured costs vary between studies
  - Also, the costs of the ASP itself may not be included\(^1,2\)

SHEA, IDSA, PIDS Policy Statement on Antimicrobial Stewardship

**Recommendations**

- ASPs should be required through regulatory mechanisms
- Minimum requirements for ASPs
  - Multidisciplinary team
  - Formulary limited to nonduplicative antibiotics with demonstrated clinical need
  - Institutional guidelines for the management of common infection syndromes
  - Additional interventions to detect/eliminate multidrug regimens, antibiotic therapy for nonbacterial syndromes, excessively broad-spectrum empiric regimens
  - Internal benchmarking (institutional level)
  - Antiobigram indicating antibiotic susceptibility rates to key pathogens


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**ASP Elements**

*An Overview*

<table>
<thead>
<tr>
<th>Passive measures</th>
<th>Active interventions</th>
<th>Restrictive measures</th>
<th>Supportive/supplemental measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Guidelines and clinical pathways</td>
<td>• Prospective audit with intervention and feedback</td>
<td>• Antibiotic order form</td>
<td>• IV-oral conversion</td>
</tr>
<tr>
<td>• Educational sessions/workshops</td>
<td>• Streamlining and de-escalation of therapy</td>
<td>• Formulary restriction and authorization</td>
<td>• Dose optimization</td>
</tr>
</tbody>
</table>

Antimicrobial Stewardship Strategies and Health Care Information Technology

Core Antimicrobial Stewardship Strategies
- Prospective audit with intervention and feedback
- Formulary restriction and preauthorization

Supplemental Antimicrobial Stewardship Strategies
- Education
- Guidelines & clinical pathways
- Antimicrobial order forms
- De-escalation of therapy
- Dose optimization
- Parenteral-to-oral conversion

CDS System, CPOE, EHR

Improved antimicrobial utilization


EHR/CDS Systems
Build or Buy?

Advantages and Disadvantages of In-House Development Versus Purchase of EHR/CDS Systems

<table>
<thead>
<tr>
<th></th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-house development</td>
<td>• Can tailor to specific needs</td>
<td>• Expensive(^1)</td>
</tr>
<tr>
<td></td>
<td>• Can make changes rapidly and as needed</td>
<td>• Contingent on resources and in-house expertise</td>
</tr>
<tr>
<td></td>
<td>• Can update as needed to reflect new evidence and practice</td>
<td>• Starting from scratch</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Time and effort intensive(^1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Burdens ongoing functions of the institution(^2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Existing EHR system may not support advanced CDS system(^1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Requires ongoing commitment to maintenance and updates</td>
</tr>
<tr>
<td>Commercial EHR/CDS products</td>
<td>• Lower cost</td>
<td>• Additional work required for validation and local customization(^1)</td>
</tr>
<tr>
<td></td>
<td>• Rapidly available</td>
<td>• Adaptation may take time</td>
</tr>
<tr>
<td></td>
<td>• Best practice already established from networking with other customers</td>
<td>• Sources of knowledge may not be robust and updates may not keep pace with new information(^2)</td>
</tr>
<tr>
<td></td>
<td>• Drawbacks and limitations have been addressed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• EHR certified for Meaningful Use</td>
<td></td>
</tr>
</tbody>
</table>

Third-Party Antimicrobial Stewardship CDS System Vendors

<table>
<thead>
<tr>
<th>CDS System</th>
<th>Vendor</th>
<th>Market Presence</th>
</tr>
</thead>
<tbody>
<tr>
<td>SafetySurveillor®¹</td>
<td>Premier Inc., Charlotte, NC</td>
<td>Unknown</td>
</tr>
<tr>
<td>TheraDoc Antibiotic Assistant²,³</td>
<td>Hospira Inc., Lake Forest, IL</td>
<td>600 facilities in 41 states</td>
</tr>
<tr>
<td>QC Pathfinder®⁴</td>
<td>Vecna, Cambridge, MA</td>
<td>Clients include the Department of Veterans Affairs and US Department of Defense</td>
</tr>
<tr>
<td>MedMined® Surveillance Advisor⁵</td>
<td>CareFusion, San Diego, CA</td>
<td>Unknown</td>
</tr>
<tr>
<td>Sentri7®⁶</td>
<td>Pharmacy OneSource Inc., Bellevue, WA</td>
<td>400 hospital contracts in 45 states</td>
</tr>
<tr>
<td>Vigilanz Dynamic Infection Control Monitor®⁷</td>
<td>Vigilanz Corporation, Minneapolis, MN</td>
<td>Unknown</td>
</tr>
</tbody>
</table>


A Randomized Controlled Trial to Evaluate Use of a CDS System to Optimize Antimicrobial Use

**Problem:** Previous system for managing antimicrobial use was labor- and time-intensive

**Objective:** To compare effectiveness and cost-effectiveness of manually generated (control) versus CDS system–generated alerts for use of restricted antimicrobials

**Results:**

<table>
<thead>
<tr>
<th>Interventions (%)</th>
<th>Antimicrobial Expenditures</th>
<th>Daily Time (person-hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>8%</td>
<td>$200 000</td>
</tr>
<tr>
<td>CDS System</td>
<td>16%</td>
<td>$400 000</td>
</tr>
<tr>
<td>Control</td>
<td>$370 006</td>
<td></td>
</tr>
<tr>
<td>CDS System</td>
<td>$285 812</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusions:** Use of CDS system increased interventions for inadequate antimicrobial therapy, with substantial time and cost savings for the hospital

Nebraska Medical Center CDS System

Responsible Parties for Handling Alerts

ASP Personnel
- Drug-bug mismatches
- Antimicrobial use for potentially inappropriate indications
- Targeted drugs (as needed)
- Targeted organisms (as needed)
- Targeted institution-specific issues

Floor Pharmacists
- Missing height/weight data
- Pneumococcal/influenza vaccine
- Polyanitbacterials
- Positive culture results
- Renal function changes
- Lack of positive cultures with continued antimicrobial therapy
- Intravenous-to-oral switching
- New drug levels

Implementation Plan

Low Hanging Fruit

- Low hanging fruit = most obtainable targets
  - IV-to-oral conversions, batching of IV antimicrobials, therapeutic substitutions, and formulary management
- Obtainable targets require fewer resources and less effort
- Applicable in various healthcare settings
  - Includes limited resource hospitals
- Associated with cost savings
  - ASP using interventions focused on obvious need saved > $800,000

De-escalation of Therapy

• Decrease number of agents and/or spectrum of activity as appropriate in response to culture results and clinical outcomes
• Optimizing initial therapy may work against steps to limit use of broad-spectrum agents
  – De-escalation recognizes both aspects

Organism Identification and the Initiation of Targeted Antimicrobial Therapy*

<table>
<thead>
<tr>
<th>Standard identification and testing methods</th>
<th>Rapid molecular identification methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood drawn</td>
<td>Blood drawn</td>
</tr>
<tr>
<td>Positive blood culture</td>
<td>Positive blood culture</td>
</tr>
<tr>
<td>Gram stain</td>
<td>Gram stain</td>
</tr>
<tr>
<td>Empiric and broad-spectrum antimicrobial therapy</td>
<td>Rapid molecular identification</td>
</tr>
<tr>
<td>Standard organism identification and susceptibility</td>
<td>Standard organism identification and susceptibility</td>
</tr>
</tbody>
</table>

Day 0  Day 1  Day 2  Day 3  Day 4

Targeted antimicrobial therapy

*This is meant to be an illustration of differences between the two methods, but these timelines are hypothetical and may not occur in clinical practice.
Rapid Determination of S. aureus and Drug Susceptibility From Blood Cultures
Earlier Initiation of Appropriate Therapy


<table>
<thead>
<tr>
<th></th>
<th>MSSA</th>
<th>MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed notification pulse</td>
<td>49.8</td>
<td>5.2</td>
</tr>
<tr>
<td>Early notification pulse</td>
<td>5.8</td>
<td>1.1</td>
</tr>
<tr>
<td>(n=48)</td>
<td>(n=12)</td>
<td>(n=50)</td>
</tr>
</tbody>
</table>

*Physicians were notified of positive culture results after Gram staining was completed, followed 48 to 72 hours later by results of speciation and susceptibility. 
*Physicians were notified of a positive blood culture result after use of a real-time PCR system.


Effect of PNA FISH Implementation for Patients With Blood Cultures Positive for *Candida* Species

<table>
<thead>
<tr>
<th></th>
<th>Time to Species Identification</th>
<th>Time to Targeted Therapy</th>
<th>Time to Culture Clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Time to Species Identification</td>
<td>0.2</td>
<td>2.5</td>
<td>4</td>
</tr>
<tr>
<td>(n=61)</td>
<td>(n=21)</td>
<td>(n=61)</td>
<td>(n=21)</td>
</tr>
<tr>
<td>Median (IQR) Time to Culture Clearance</td>
<td>0.2</td>
<td>4.3</td>
<td>5</td>
</tr>
<tr>
<td>(n=61)</td>
<td>(n=21)</td>
<td>(n=61)</td>
<td>(n=21)</td>
</tr>
</tbody>
</table>

meca Gene Testing and ID Clinical Pharmacist Intervention in Patients With S. aureus Bacteremia

Earlier Initiation of Optimal Therapy

Prospective, Single-center Study

Time to Optimal Antimicrobial Therapy, mean, hours

Without Clinical Pharmacist Intervention (n=30)

With Clinical Pharmacist Intervention (n=16)


Antifungal Use and Cost After Identification of C. albicans by PNA FISH


Cost per Patient, a,b,c

C. albicans

$169,290

$107,942

Non-C. albicans

$260,107

$191,224

• Caspofungin use in patients with candidemia due to C. albicans decreased from 8.7 DDD/patient to 3.2 DDD/patient after PNA FISH implementation (p<0.05)

**Rapid *S. aureus* Identification and Targeted Antimicrobial Therapy in Patients With *S. aureus* Bacteremia**

**Total Hospital Cost**

**Single-center, Nonequivalent, Comparative Study (2008, 2009)**

- PCR results were communicated to an ID pharmacist who recommended effective, targeted antimicrobial therapy and an ID consult.


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**Characteristics of the Ideal Biomarker of Infection**

- Easy to use and interpret
- Easily and rapidly available
- Inexpensive
- Reproducible
- Good sensitivity and specificity
- Dynamic (rapid increases and decreases)
- Level not dependent on underlying disease
- Level not modified by treatment or intervention for any ancillary conditions
- Continuous (not a discrete variable)
- Correlation with clinical severity and mortality

C-Reactive Protein as a Biomarker for Infection

- Prognostic marker in determining severity of CAP and need for hospitalization\(^1\)
- Has been shown to distinguish bacterial from fungal infection\(^2\)
  - Levels more than 100 mg/L indicative of bacterial infection
  - Elevated levels less than 100 mg/L indicative of fungal infection
- Widely used to test for bacterial infection in children\(^3\)
  - A recent report determined that current evidence for CRP diagnostic accuracy in children and neonates with suspected sepsis or suspected infection is poor and rarely drove clinical decision making


Procalcitonin as a Biomarker for Infection

- PCT is a useful, accurate biomarker for infection\(^1\)
  - More useful than other common inflammatory markers
- Significantly elevated levels in sepsis\(^1\)
  - Good indicator of response to treatment, severity, and mortality
- Higher levels of PCT in bacterial infection than in fungal infection\(^1\)
- Potential as a diagnostic marker for pneumonia, abdominal infection, urinary tract infection, lower respiratory tract infection, and myocardial infarction, and to guide antibiotic therapy in CAP\(^1\)
- Predicts real-time PCR results in blood samples from patients with possible sepsis\(^2\)

**Studies Evaluating PCT**

*Respiratory Tract Infection*

**Results**

- Patients for whom PCT was used to guide antibiotic therapy had lower antibiotic exposure
  - Mainly because of lower antibiotic prescription rates for COPD exacerbations and bronchitis

![Antibiotic Courses](chart.png)


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**Example: Case Study ASP Models**

*From the Community Setting*

<table>
<thead>
<tr>
<th>Case study</th>
<th>Small rural hospital (150-bed)</th>
<th>Small suburban hospital (80-bed, part of larger hospital network)</th>
<th>Large university-affiliated community hospital (220-bed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Challenges</td>
<td>No specialized staff</td>
<td>No ID specialist</td>
<td>No ID-trained pharmacist May need separate ASP from affiliated university hospital</td>
</tr>
<tr>
<td>Staffing solution</td>
<td>With institutional support: Establish stewardship (with ID specialist) and P&amp;T committees</td>
<td>In absence of local champion: 1. Collaborate with other hospitals within network and central P&amp;T committee 2. Liaise with remote physician to provide support and expertise</td>
<td>Option 1: Integrate stewardship activities with existing academic committee by involving a physician and pharmacist</td>
</tr>
<tr>
<td>Without institutional support: Appoint an ASP champion and ID specialist</td>
<td>If physician champion is available: 1. Stewardship activities through the P&amp;T committee</td>
<td>Option 2: Recruit independent ASP team</td>
<td></td>
</tr>
</tbody>
</table>

Summary

• The primary reasons for an ASP are improved patient care and reduced resistance
  – Financial concerns, particularly drug acquisition costs, are secondary
  – Overall institutional value must be maximized
• HEOR methodologies can be used to measure relevant outcomes
  – Outcomes should be defined a priori and measured at predefined times
• ASPs optimize antimicrobial utilization to:
  – Cure or prevent infections
  – Prevent toxicity of or emergence (or spread) of resistance to agents used

Summary

• Core and supplemental strategies have been recommended for ASPs
• ASPs must be tailored to your hospital
  – Key personnel should be involved with development and implementation
  – All parts of an ASP should be well thought out before making a formal proposal
• ASPs have been shown to improve a variety of outcomes
  – Clinical
  – Collateral damage
  – Antimicrobial consumption and costs
Back Up Slides

GAIN Act

**Incentives**

• Data exclusivity
  – 5 additional years of data exclusivity beyond existing Hatch/Waxman data exclusivity

• Accelerated review

• Fast track review
  – Early, frequent communication with FDA

• Updated guidance
  – Timetable for FDA to develop/issue draft/final guidance; opportunity for written recommendations

• Pathogen-focused drug development
  – FDA to clarify trials and endpoints for approval