Optimizing Infectious Diseases Outcomes in Antimicrobial Stewardship Programs

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Disclosures

- Dr. Bachmeier has NO financial disclosures
Objectives

- Discuss the impact of antimicrobial therapy and resistance on clinical outcomes
- Review components of antimicrobial stewardship programs and opportunities to improve patient care
- Recognize dosing strategies to optimize antimicrobial pharmacodynamics
- Describe the development of evidence-based guidelines to implement clinical pathways
- Outline novel concepts of antibiotic heterogeneity to address gram negative resistance

Novel Drug Mechanism Targets are Lacking

Critical Balance of Antibiotic Use

- **Importance of appropriate empiric therapy**
  - Mortality increases when initial therapy is inappropriate

- **Effect of broad-spectrum therapy on resistance**
  - Resistance increases when broad-spectrum agents are overused
  - Resistance has a negative impact on outcomes

Inadequate Treatment Leads to Poor Outcomes

- **Impact of Empiric Antibiotic Treatment on Mortality**

  - Bacteremia
  - Community-acquired Bacteremia
  - S. aureus Bacteremia
  - Ventilator-acquired Pneumonia

  - Appropriate Initial Treatment
  - Inappropriate Initial Treatment

  - p < 0.001
  - p < 0.05
  - p < 0.02
  - p < 0.04

Antibacterial Resistance is Increasing

Antimicrobial Resistance Among Staphylococcus aureus, enterococi and Pseudomonas aeruginosa in the United States

Antibiotic Resistance Leads to Poor Outcomes

- Non-urinary tract isolates of ESBL Klebsiella and E. coli vs non-ESBL infections
- Length of stay
  - 21 days vs. 11 days (p=0.006)
- Clinical success
  - 48% vs. 86% (p=0.027)

ESBL = extended spectrum beta-lactamase

Lee, et al. Inf Cont Hosp Epi 2006;27:1226-32
Antibiotic Resistance Leads to Poor Outcomes

- **MRSA vs. MSSA bacteremia**
  - Clinical Failure
    - 59.6% vs. 33% ($P<0.001$)
  - Length of Stay (infection-related)
    - 20.1 vs. 13.7 days ($P<0.001$)
  - Mortality (infection-related)
    - 30.6% vs. 15.3% ($P=0.001$)

Lodise T. Diag Microbiol Inf Dis 2005;52.

Guiding Antimicrobial Principles

- **For severe infections, start broad**
  - If you get it wrong, you’re in trouble
- **Get it in the patient quickly**
- **De-escalation of therapy is a necessity$^1,2$**
  - The right drug is always the narrowest spectrum agent that produces a successful response and causes the fewest significant adverse effects and the least collateral damage
- **Treat for the most appropriate length of time, then stop**
- **Each of these can be addressed through collaborative efforts**

Goals of Stewardship

- **Primary goals**
  - Improve clinical outcomes
  - Prevent adverse drug events
  - Limit the selection of pathogenic organisms
  - Reduce the incidence of antimicrobial resistance

- **Secondary goals**
  - Reduce healthcare related costs without adversely affecting outcomes


Targeted Outcomes in Stewardship Programs

- **Patient specific**
  - Improved survival
  - Decrease length of hospital (and/or ICU) stay

- **Pharmacodynamic**
  - Target dose attainment

- **Microbiologic**
  - Increased drug/class susceptibility
  - Decreased *clostridium difficile* infections
Antimicrobial Stewardship Team Members

- Hospital Epidemiology & Infection Control
- Medical Information Systems
- Microbiology Laboratory
- Hospital Administration
- Infectious Diseases Dept.
- Antimicrobial Stewardship Program Directors
  - ID Pharm.D
  - ID Physician
- Physicians; Hospitalists Critical Care
- Chair, P&T Committee
- Clinical Pharmacists

Comprehensive Antimicrobial Stewardship is Multifaceted

- **Active core strategies**
  - Prospective audit with intervention and feedback
  - Formulary restriction and preauthorization

- **Supplemental strategies**
  - Education
  - Guidelines and clinical pathways
  - Antimicrobial order forms
  - Antibiotic cycling
  - Dose optimization
  - De-escalating/streamlining therapy
  - Conversion from parenteral to oral therapy

Pharmacist Role in Improving Antimicrobial Outcomes

Clinical outcomes in a randomized controlled trial comparing the antimicrobial stewardship program to usual practice

- **RR 2.8 (2.1-3.8)**
- **RR 1.7 (1.3-2.1)**
- **RR 0.2 (0.1-0.4)**

**Therapy**


The University of Kentucky Experience

- Multidisciplinary antimicrobial control program implemented in 1998
- Initial focus on formulary management and restriction
  - Cephalosporins
  - Vancomycin

**Antimicrobial drug expenditures, $**

- **Projected**
- **Actual**

Martin CA et al. AJHP 2005;62(7):732-738
Impact of Antimicrobial Stewardship on C. difficile Episodes


Improving Outcomes Through Thoughtful Dosing and Administration

- Maximizing the benefit of a drug requires optimizing the pharmacodynamic properties of the drug
  - Most benefit is in the sickest patients or those with risk factors for MDR organisms w/higher MIC values
- Crucial considering our limited armamentarium
- With the lack of new drugs for MDR organisms, being strategic with dosing and administration is more important than ever
Optimal Pharmacodynamic Parameters Differ Among Antibiotics

Extended Infusions Optimize Beta-Lactam Pharmacodynamics

Comparison of time above the MIC among various piperacillin doses

Probability of piperacillin-tazobactam target attainment of 50% $T_{\geq}\text{MIC}$

Extended Infusion Dosing Strategies

- Unnecessary to exceed MIC for a 24-hour interval in most cases

- Target $\%ft > MIC$ for $\beta$-Lactam antibiotics
  - Penicillins – 50% $ft > MC$
  - Cephalosporins – 60-70% $ft > MC$
  - Carbapenems – 40% $ft > MC$

- Results of PK/PD experiments support extended-infusion dosing regimens for $\beta$-lactam antibiotics


Improved Survival Associated with Extended Infusion PTZ

The use of Clinical Guidelines to Improve Outcomes

- **IDSA Stewardship Guidelines Statements**
  - Multidisciplinary development of evidence-based practice guidelines incorporating local microbiology and resistance patterns can improve antimicrobial utilization (AI).
  - Guideline implementation can be facilitated through provider education and feedback on antimicrobial use and patient outcomes (AIII).
- **Incorporate national guidelines when possible**
- **An additional crucial step is to tailor the pathway based on microbiology, hospital formulary, etc.**
- **Antimicrobial selection is only one component (diagnostics, etc.)**

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Get With the Guidelines

- **Multidisciplinary development of evidence-based practice guidelines incorporating local resistance patterns**
- **Provides practitioners education and feedback**

<table>
<thead>
<tr>
<th></th>
<th>Pre-VAP Clinical Guideline</th>
<th>Post-VAP Clinical Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate initial therapy</td>
<td>48%</td>
<td>94%</td>
</tr>
<tr>
<td>Duration of therapy</td>
<td>14.8 days</td>
<td>8.6 days</td>
</tr>
<tr>
<td>VAP recurrence</td>
<td>24%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Ibrahim EH et al. *Crit Care Med* 2001 29;1109-15  
VAP = ventilator associated pneumonia
Additional Examples for Guideline Development

- **Community-acquired pneumonia**
  - 20 hospitals randomized
  - Decreased LOS of 1.7 days
    - 4.4 vs 6.1 days; \( p = 0.04 \)
  - Fewer IV therapy days
    - 4.6 vs 6.3 days; \( p = 0.01 \)
  - No increase in complications or readmission

- **General ICU infections**
  - 77% reduction in antimicrobial use
  - 30% reduction in overall cost of care
  - Decreased mortality
    - 20% vs 5.6%; \( p = 0.02 \)

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Moving From “Restriction” to “Facilitation”

- **Martin CA, Armitstead JA, Mynatt RP, and Hoven AD** *AJHP* 2011; 68:109-10
  - Programs with a heavy-handed restriction approach may inadvertently be doing a disservice to patients
  - We should be focusing more on getting the right drug to the patient rather than merely restricting drugs
  - The only dose of a drug proven to save lives is THE FIRST ONE
Timeliness of Antibiotics Affects Survival in Sepsis

- Delays in effective antimicrobial therapy increases mortality with each passing hour

<table>
<thead>
<tr>
<th>Time from Hypotension Onset, (hrs)</th>
<th>Survival fraction</th>
<th>Mortality Risk and Time to Effective Antimicrobial Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.0</td>
<td>Odds ratio of death (95% confidence interval)</td>
</tr>
<tr>
<td>within 1 hour</td>
<td>0.8</td>
<td>10</td>
</tr>
<tr>
<td>within 6th hour</td>
<td>0.4</td>
<td>1</td>
</tr>
<tr>
<td>0.02</td>
<td>0.2</td>
<td>1</td>
</tr>
<tr>
<td>0.04</td>
<td>0.4</td>
<td>1</td>
</tr>
<tr>
<td>0.06</td>
<td>0.6</td>
<td>1</td>
</tr>
<tr>
<td>0.08</td>
<td>0.8</td>
<td>1</td>
</tr>
<tr>
<td>0.10</td>
<td>1.0</td>
<td>1</td>
</tr>
</tbody>
</table>


Electronic Sepsis Bundle

- **Electronic order set**
  - Can be initiated by any healthcare provider that recognizes sepsis/septic shock

- **Automated notification to key personnel**
  - Rapid response team
  - Hospital Operations Administrator
    - (for bed transfer, nursing ratio, etc.)
  - Materials management
  - Clinical Pharmacist (PharmD on-call)

- **Septic Shock Carts**
  - Deployed to key areas
  - Contains all supplies necessary for initial resuscitation
Initial Impact of Electronic Sepsis Bundle on Antimicrobial Timing

![Graph showing the impact of electronic sepsis bundle on antimicrobial timing.]

Pharmacist Bedside Response in Initial Sepsis

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>PharmD Sepsis Response (n=49)</th>
<th>Control (n=59)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics administered within 1 hour, n (%)</td>
<td>41 (77.5)</td>
<td>11 (23.7)</td>
<td>22.4 (7.5-69)</td>
</tr>
<tr>
<td><strong>Secondary Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP ≥ 65 mmHg within 6 h</td>
<td>43 (87.7)</td>
<td>45 (76.3)</td>
<td>2.2 (0.7-7.7)</td>
</tr>
<tr>
<td>CVP ≥ 8 mmHg within 6 h</td>
<td>26 (53.1)</td>
<td>19 (32.2)</td>
<td>2.4 (1.0-5.6)</td>
</tr>
<tr>
<td>Death</td>
<td>24 (48.9)</td>
<td>32 (54.2)</td>
<td>0.5 (0.2-1.2)</td>
</tr>
</tbody>
</table>

Delayed Antifungal Therapy Leads to Increased Mortality

Timing of antifungal therapy and mortality in patients with candidemia


The Candida Score: A Risk Stratification Tool

- Simple point-based bedside scoring tool
- Points
  - Multifocal Candida colonization (1)
  - Surgery on ICU admission (1)
  - TPN 1)
  - Severe sepsis (2)
- Scores >2.5 have 7x higher likelihood of invasive Candidiasis

Candida Isolates in UKMC ICU Patients

<table>
<thead>
<tr>
<th>Organism</th>
<th>ICU</th>
<th>CT</th>
<th>1MED</th>
<th>1THC</th>
<th>2BUR</th>
<th>2NS</th>
<th>2PIC</th>
<th>25IC</th>
<th>3BMC</th>
<th>4NIC</th>
<th>4NCU</th>
<th>4PIC</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida albicans</td>
<td>24</td>
<td>35</td>
<td>26</td>
<td>26</td>
<td>7</td>
<td>33</td>
<td>7</td>
<td>21</td>
<td>6</td>
<td>9</td>
<td>4</td>
<td>13</td>
<td>211</td>
</tr>
<tr>
<td>Candida guilliermondii</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Candida krusei</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Candida lipolytica</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Candida lusitania</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Candida parapsilosis</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Candida tropicalis</td>
<td>4</td>
<td>2</td>
<td>12</td>
<td>2</td>
<td>5</td>
<td>9</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>39</td>
</tr>
<tr>
<td>Candida glabrata</td>
<td>19</td>
<td>10</td>
<td>19</td>
<td>13</td>
<td>4</td>
<td>12</td>
<td>3</td>
<td>7</td>
<td>9</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Grand Total</td>
<td>52</td>
<td>52</td>
<td>63</td>
<td>47</td>
<td>17</td>
<td>60</td>
<td>12</td>
<td>34</td>
<td>19</td>
<td>12</td>
<td>5</td>
<td>23</td>
<td>394</td>
</tr>
</tbody>
</table>

Projected fluconazole susceptibility:
- C. albicans: 175/175 (98%)
- C. glabrata: 87/60 (69%)

Susceptibility based on surveillance data: Pfaller, et al. JCM 07

Candida Score

Yes (Start micafungin)

No (No antifungal therapy)

<table>
<thead>
<tr>
<th>Cx (-), pt improves (cont. micafungin)</th>
</tr>
</thead>
</table>

C x (-), no improvement (DC micafungin)

C x (+), Flu-S species (change to flu)

C x (+), Flu-R species (cont. micafungin)

Continue to evaluate

Cx = culture
Pt = patient
DC = discontinue
Flu = fluconazole
S = susceptible
R = resistant
Antimicrobial Cycling

- Scheduled removal and substitution of a specific antimicrobial for a given time period to prevent or reverse the development of resistance
- Aimed to minimize selective pressures
- Difficult to fully implement due to concerns regarding allergies, adverse effects, guideline recommendations
- Insufficient data to support routine use
  - Leads to resistance patterns cycling


Promoting Antibiotic Heterogeneity Throughout Healthcare Systems

- Novel concept of antibiotic mixing throughout a cohort to limit antimicrobial selective pressures
  - Measured by antibiotic heterogeneity index (AHI)
  - Goal of >0.85 (complete heterogeneity = 1)
- Prospectively favor or restrict antibiotic classes based on recent use and changes in resistance

STRATEGIC ANTIBiotic HETEROGENEITY REDUCES Gram NEGATIVE RESISTANCE

<table>
<thead>
<tr>
<th></th>
<th>Pre-establishment period</th>
<th>PAMS</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistant <em>P. aeruginosa</em></td>
<td>8.9%</td>
<td>3.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multidrug-resistant <em>P. aeruginosa</em> and <em>A. baumannii</em></td>
<td>1.7%</td>
<td>0.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Metallo-B-lactamase organisms</td>
<td>1.2%</td>
<td>0.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ESBL organisms</td>
<td>2.2%</td>
<td>2.4%</td>
<td>NS</td>
</tr>
</tbody>
</table>


 AN HONEST ASSESSMENT OF WHERE ANTIMICROBIAL STEWARDSHIP STANDS

- Does a good job of promoting the idea that antimicrobial use matters to society (at least the inpatient society)
  - *Nobel causes*
- Does a poor job of talking about community antibiotic use
  - *Not to mention the use in agriculture*
- Beginning to address use at the level of individual patients (timing, selection, etc.)
- We need to be thinking about ways to win wars, not individual battles
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