Strategies for Optimizing Anti-Infective Therapy in the Home Infusion Setting

Thursday, April 7
7:00-8:45 a.m.
Hilton Orlando—Florida Ballroom 4

Supported by an unrestricted educational grant from Cubist Pharmaceuticals

A Symposium Held in Conjunction with the 2011 NHIA Annual Conference & Exposition

NHIA 20th Annual Conference & Exposition
Shaping Our Horizon
Strategies for Optimizing Anti-Infective Therapy in the Home Infusion Setting

Thursday, April 7, 7:00 to 8:45 a.m.

06-S. Strategies for Optimizing Anti-infective Therapy in the Home Infusion Setting
Supported by an educational grant from Cubist Pharmaceuticals
Hilton Orlando – Florida Ballroom 4
Pharmacist, Pharmacy Technician and Nurse Continuing Education Contact Hours: 1.5
ACPE Pharmacist and Pharmacy Technician Program #: 207-999-11-232-L01-P&T
Knowledge-Based Learning Activity

Education Overview:
Antimicrobial drug resistance and emerging “super bugs” remain a global crisis as we face a future with few new drugs in the antimicrobial pipeline. Clinicians are increasingly being called upon to identify and implement strategies that will prolong the efficacy of our current arsenal. Education is an essential component in ensuring that clinicians have the knowledge base needed to fully comprehend the alarming trends in microbial resistance, and to understand the steps that must be taken today in order to sustain our current level of control over these microorganisms. With clinicians at the patient’s bedside playing a pivotal role in antimicrobial treatment success or failure, educational programming that addresses these concepts and provides guidance for future clinical best practice is foundational to their success.

With antimicrobial stewardship and optimization as the cornerstones, this program will educate clinicians regarding their crucial role in appropriate selection and delivery of available treatment regimens that are based on the individual patient’s medical condition, self-care abilities, and level of caregiver support. Novel delivery approaches will be examined, including prolonged and continuous antimicrobial administration, in concert with strategies to improve patient compliance through education and clinical monitoring. Clinicians will leave this program armed with the critical knowledge they need to be effective antimicrobial stewards in the home infusion setting.

Faculty: David J. Feola, Pharm.D., Ph.D., BCPS, Assistant Professor, Pharmacy Practice and Science, University of Kentucky College of Pharmacy, Lexington, KY

Dr. Feola is an Assistant Professor at the University of Kentucky College of Pharmacy in the Department of Pharmacy Practice and Science, and holds a Joint Appointment in the Division of Infectious Diseases, Department of Internal Medicine at the UK College of Medicine. He received a Doctor of Pharmacy degree in 1997, a Doctor of Philosophy degree in Clinical and Experimental Therapeutics in 2005, and completed residency training in both Pharmacy Practice and Infectious Diseases Therapeutics. His research program focuses on mechanistic and translational investigations to define the role of alternative macrophage activation in the pathophysiology of pulmonary fibrosis. This is accomplished through the use of a mouse model of Pseudomonas aeruginosa infection and through clinical studies in patients with cystic fibrosis. The goal of this research is to identify potential therapeutic targets to slow the progression of chronic inflammation and tissue remodeling as the immune system interfaces with bacterial pathogens in the lungs. He also coordinates the infectious diseases module in the Advanced Therapeutics course for the Doctor of Pharmacy Program, and provides clinical service to the Infectious Diseases inpatient consult team at the UK Chandler Medical Center.

Pharmacist and Nurse Education Objectives:
1. Describe factors influencing trends in resistance of organisms.
2. Discuss the current status of antimicrobial resistance rates and patterns among common pathogens.
4. List strategies to achieve optimum outcomes when administering antimicrobial agents in the alternate-site setting.

Pharmacy Technician Education Objectives:
1. Describe factors influencing trends in resistance of organisms.
2. Discuss the current status of antimicrobial resistance rates and patterns among common pathogens.
4. List strategies to achieve optimum outcomes when administering antimicrobial agents in the alternate-site setting.
Learning Assessment Questions:

1. You are treating a patient with outpatient parenteral antimicrobial therapy (OPAT) for a severe skin infection with community-acquired MRSA. It is important to understand that compared to hospital-acquired MRSA strains, in general community-acquired MRSA strains have:
   a. More virulence, more resistance
   b. More virulence, less resistance
   c. Less virulence, more resistance
   d. Less virulence, less resistance

2. In the monitoring of home antimicrobial therapy, beta-lactamase production by the infecting organism can lead to:
   a. Treatment failure
   b. Change in antimicrobial agent
   c. Need for combination therapy
   d. All of the above

3. You sit on your organization’s OPAT team, charged with making policy decisions based on formulary inclusion and use of antimicrobials. Which of the following drug classes has the highest rate of collateral damage associated with its use?
   a. 3rd generation cephalosporins
   b. 1st generation cephalosporins
   c. Aminopenicillins
   d. Fluoroquinolones
   e. Tetracyclines

4. Which of the following statements is true regarding antimicrobial stewardship?
   a. Always make sure that you cover all infectious possibilities with empiric therapy
   b. Err on the side of caution with empiric treatment of infectious diseases because as long as we redirect therapy when we get culture results, outcomes aren’t affected by inadequate initial therapy
   c. We must balance adequate empiric therapy with judicious antimicrobial use
   d. All of the above are true

5. Which of the following statements concerning antimicrobial use and resistance is false?
   a. Resistance is higher in healthcare-associated infections compared to infections from the community
   b. Receipt of previous antimicrobial therapy is a risk factor for resistance
   c. Care settings with highest antimicrobial use are associated with highest resistance rates
   d. Increased duration of therapy decreases the likelihood of colonization with resistant organisms
   e. All of the above are true

Answers can be found on the last page of this booklet.
Strategies for Optimizing Anti-Infective Therapy in the Home Infusion Setting

David J. Feola, Pharm.D., Ph.D.
Assistant Professor
University of Kentucky College of Pharmacy

Top 5 Things to Know for CE:

- Make sure your BADGE IS SCANNED each time you enter a session, to record your attendance.
- Carry the Evaluation Packet you received on registration with you to EVERY session. If you're not applying for CE, we still want to hear from you! Your opinions about our conferences are very valuable.
- Pharmacists, Pharmacy Technicians, and Nurses need to track their hours on the Statement of Continuing Education Certificate form as they go.
- FOR CE: At your last session, total the hours and sign both pages of your Statement of Continuing Education Certificate form.
  - Keep the PINK copies for your records.
  - Place the YELLOW and WHITE copies in your Evaluation packet.
  - Make sure an evaluation form from each session you attended is completed and in your Evaluation packet. (Forgot to pick up an evaluation form at a session? Extras are available in an accordion file near the registration desk.)
  - Put your name and unique member ID number (six digit number on the bottom of your badge) on the outside of the packet, seal it, and drop it in the drop boxes in the NHIA registration area at the convention center.

Disclosures

David Feola declares no conflicts of interest or financial interest in any service or product mentioned in this program.

Clinical trials and off-label uses will not be discussed during this presentation.
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Hospital Acquired Infections

- Pennsylvania 2009
- Health Care Cost Containment Counsel

<table>
<thead>
<tr>
<th></th>
<th>Without Infection</th>
<th>With HAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>1.8%</td>
<td>9.4%</td>
</tr>
<tr>
<td>Length of Stay</td>
<td>4.9 days</td>
<td>21.6 days</td>
</tr>
<tr>
<td>Average Charge</td>
<td>$37,635</td>
<td>$306,943</td>
</tr>
<tr>
<td>Readmission Rate</td>
<td>16.3%</td>
<td>40.7%</td>
</tr>
</tbody>
</table>

"Patients/consumers can use this report as an aid in making decisions about where to seek treatment..."

PA Health Care Cost Containment Council, February 2011

Educational Objectives

1. Describe factors influencing trends in resistance of microorganisms.
2. Discuss the current status of antimicrobial resistance rates and patterns among common pathogens.
4. List strategies to achieve optimum outcomes when administering antimicrobial agents in the alternate-site setting.
Presentation Overview

- Why antimicrobial management is essential
- What is antimicrobial stewardship
  - IDSA Guidelines: Definition
  - Application to OPAT
- How to implement/role of practitioners
  - Recommendations
  - Novel delivery approaches
  - Strategies in the alternate-site setting

Why Stewardship is Needed

- Antimicrobial resistance results in
  - Increased morbidity/mortality
  - Increased healthcare costs
- Practices in antimicrobial use often inadequate, not routinely implemented
  - Up to 50% antimicrobial prescribing inappropriate
  - Causal relationship between antimicrobial use and emergence of resistance

A Disturbing Trend

- Sulfa, HC, AG, Chloramphenicol
- TCN, MAC, Vanc, Rif, Tmp
  - No new classes, Modification of existing agents
- LZD, DAP, Tig
- CPT, DAL, New Entities
- Limited PCN-resistant S. aureus
- MRSA
- VRE
- VISA in 7 states
- VRSA
- LZD-R S. aureus
- MDR
- Pseudomonas and Acinetobacter metallo-beta-lactamases, carbapenemases
- Over half of companies END antimicrobial research and development

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The Critical Balance

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 needed;
Resistance has a negative impact on outcomes

“Collateral damage”

Appropriate Initial Therapy

"Difference in mortality not significant. LOS significantly increased"

Antimicrobial Use and Resistance

- Changes in use parallel changes in resistance
- Resistance higher in healthcare-associated infections
- Patients with resistant infections more likely to have received prior antimicrobials
- Hospital areas of highest resistance associated with highest antimicrobial use
- Increased duration of therapy increase likeliness of colonization with resistant organisms

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Resistance and OPAT

- Most common resistant organisms in OPAT
  - Methicillin-resistant Staph aureus (MRSA)
  - Vancomycin-resistant Enterococci (VRE)
  - Multidrug-resistant Gram-negatives
    - P. aeruginosa
    - K. pneumoniae
    - E. coli
    - Penicillin-resistant Streptococcus pneumoniae

CDC. Multidrug-Resistant Organisms in Non-Hospital Healthcare Settings. www.cdc.gov/ncidod/dhqp/ar_multidrugFAQ.html

MRSA and 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 and McKinnon P. Diag Microbiol Inf Dis 2005;52

VRE and Outcomes

- VRE bacteremia
  - Decreased survival:
    - 24% vs. 59%
  - Length of Stay:
    - 34.8 vs. 16.7 days
  - Attributable cost: $27,190
  - VRE bloodstream meta-analysis
    - Mortality increase: 30%

Salgado CD et al. Inf Cont HOSP Epid 2003;24:690-8
ESBL Production and Outcomes

- Non-urinary tract isolates of Klebsiella, E. coli
- Length of stay
  - 21 days vs. 11 days (P=0.006)
- Clinical success
  - 48% vs. 86% (P=0.027)

Lee, et al. Inf Cont Hosp Epi 2006;27:1226-32

Emergence of Resistance

- Susceptible Bacteria
- Mutations
- Resistance Gene Transfer
- New Resistant Bacteria

Selection for Resistant Strains

- Antimicrobial Exposure
- Resistant Strains Rare
- Resistant Strains Dominant
Collateral Damage

- Fluroquinolones—selection of resistant isolates when appropriate pharmacodynamic parameters are not met (AUC/MIC)
  - *Pseudomonas aeruginosa*
  - Methicillin-susceptible Staph aureus
  - *Streptococcus pneumoniae*

Jacobi GA. Clin Infecc Dis 2005;41:S720-6

Collateral Damage

- 3rd generation cephalosporins
- Cause/associated with several different problems (oximinocephalosporins)
  - Extended-spectrum beta-lactamases
  - Selection of stably derepressed isolates Gram-negatives
  - Selection of vancomycin-resistant enterococcus
  - Contribution to MRSA emergence
  - Increased cases of *Clostridium difficile* associated diarrhea/colitis

Dancer SJ. J Antimicrobial Chemotherapy 2001; 48: 463-478

Pseudomonas aeruginosa
Correlation Between Imipenem Use and Resistance

### Mechanism Classes

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Affected Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug modification/degradation</td>
<td>β-lactams, FQ, AGL, TCN, macrolides, linezolid, clindamycin</td>
</tr>
<tr>
<td>Decreased bacterial permeability</td>
<td>Sulfos, AGL, TCN, doxycyclin, carbapenems</td>
</tr>
<tr>
<td>Alteration of target site</td>
<td>β-lactams, FQ, TCN, vancomycin, linezolid, clindamycin, macrolides</td>
</tr>
<tr>
<td>Efflux pumps</td>
<td>FQ, AGL, TCN, macrolides, carbapenems</td>
</tr>
</tbody>
</table>

### β-Lactamases

- More than 340 different types have been described
  - More than 120 ESBLs
  - New ESBLs identified monthly
- Classified by:
  - Plasmid vs. chromosomally mediated
  - Genes located on plasmids can spread
  - Constitutive vs. inducible production
  - Expression relates to β-lactam exposure

### TEM and SHV β-Lactamases

- Extended spectrum beta-lactamases (ESBL)
  - Mutants of classical enzymes
  - Hydrolyze most extended-spectrum cephalosporins and aztreonam
  - Carbapenems are spared
  - Inhibited by clavulanic acid
- Organisms that produce ESBLs
  - *Klebsiella, E. coli*, other Enterobacteriaceae and non-fermenting Gram-negative bacteria
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Molecular Basis of ESBLs

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Ceftazidime MIC (µg/mL)</th>
<th>Amino acid position</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEM-1</td>
<td>&lt;0.12</td>
<td>Glu Arg Glu</td>
</tr>
<tr>
<td>TEM-12</td>
<td>4-32</td>
<td>Glu Ser Glu</td>
</tr>
<tr>
<td>TEM-10</td>
<td>64</td>
<td>Glu Ser Lys</td>
</tr>
<tr>
<td>TEM-26</td>
<td>&gt;256</td>
<td>Lys Ser Glu</td>
</tr>
</tbody>
</table>

Treatment of ESBL Producers

- Carbapenems: current drugs of choice
- Cefepime: more stability but reports of treatment failures
- Little reported experience with trimethoprim/sulfamethoxazole, aminoglycosides and fluoroquinolones
- Tigecycline may be an option

Inducible Beta-lactamases

- Produced by the SPACE Bacteria
  - Serratia marcescens
  - Pseudomonas aeruginosa
  - Acinetobacter species
  - Citrobacter species
  - Enterobacter species
- β-lactamase under the control of the ampC gene (turn on) and repressor gene (turn off)
  - Mutation is loss of the repressor gene – terminology is the isolate becomes "stably de-repressed"
  - Drugs of choice: carbapenems, cefepime

Stable Derepression

- Selection of stable derepressed mutants: susceptible when tested, then resistance 3 days later

Carbapenems: Emerging Resistance

- Meropenem and P. aeruginosa
  - Up-regulation of efflux pumps
  - Loss of the OprD protein (porin channel)

- Both mutations needed for resistance development
  - MIC 0.12–0.5 µg/ml (before mutation)
  - MIC 2–4 µg/ml (with one mutation)
  - MIC >8 µg/ml (with both mutations)

- Emergence of carbapenemases

Livermore D. JAC 2001; 47: 247-250

Perilous Cycle: KPC Example

- Resistant Pathogen
  - ESBL-producing E. coli, K. pneumonia, SPACE, KPC

- Infection
  - Unknown pathogen
  - ESBL-producing bacteria
  - KPC-producing infection

- Antimicrobial Resistance
  - ESBL production
  - Carbapenemase development

- Antimicrobial Use
  - Oximinocephalosporins
  - Carbapenems

PCN Binding Proteins

- MRSA – loss of the target site – PBP2 which is replaced by PBP2a
  - meca gene, associated with other resistance genes in the Staphylococcal chromosome cassette (SCCmec)
  - PBP2a confers resistance to all beta-lactams
- Streptococcus pneumoniae
  - PCN resistance when mutations in 4 PBPs
  - If PCN resistant, increased macrolide resistance, FQ resistance still low

CA-MRSA Prescribing Trends

- KY Medicaid Database

MRSA Treatment Options

- FDA-approved
  - Vancomycin, linezolid, daptomycin, tigecycline, telavancin
- Not FDA-approved, often used
  - SMX-TMP, clindamycin, doxycycline
CA-MRSA vs. HA-MRSA

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CA-MRSA</th>
<th>HA-MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptibility</td>
<td>Chloramphenicol</td>
<td>Usually susceptible</td>
</tr>
<tr>
<td></td>
<td>Clindamycin</td>
<td>Usually susceptible</td>
</tr>
<tr>
<td></td>
<td>Erythromycin</td>
<td>Usually resistant</td>
</tr>
<tr>
<td></td>
<td>TMP/SMZ</td>
<td>Usually susceptible</td>
</tr>
<tr>
<td>SCC mec type</td>
<td>IV</td>
<td>II</td>
</tr>
<tr>
<td>Lineage</td>
<td>USA 300</td>
<td>USA 100, USA 200</td>
</tr>
<tr>
<td>Toxins</td>
<td>More</td>
<td>Fewer</td>
</tr>
<tr>
<td>PVL</td>
<td>Common</td>
<td>Rare</td>
</tr>
</tbody>
</table>

Weber JT. CID 2005;41 Suppl 4:S269-72

CA-MRSA Importance of I&D

- 166 patients randomized to receive cephalexin or placebo after incision and drainage
- 87.8% of positive cultures were MRSA

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of Isolates</th>
<th>MRSA</th>
<th>PVL-positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalexin (82)</td>
<td>Cure</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Failure</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Placebo (84)</td>
<td>Cure</td>
<td>76</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Failure</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>


Vancomycin

- Glycopeptide antimicrobial that inhibits transpeptidation reaction
  - D-ala–D-ala
- Mechanisms of resistance: change in bacterial target
  - D-ala–D–loc (VanA, B, D)
  - D-ala–D–ser (VanC, E, I)
  - Enterococcus sp.
    - E. faecium incidence of resistance higher that E. faecalis
    - VanA gene is on a plasmid

Am J Health Syst Pharm 2000;57:S4-9
Clin Infect Dis 2006; 2006; 42:S35–9
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Vancomycin Resistance

- MRSA increasing MICs to vancomycin (1-2 mcg/ml)
  - Still susceptible, but increase in treatment failures
  - VISA mechanism: increased cell wall structural material
- VRSA mechanism: MRSA acquires the VanA gene
  - Rare in the US

Vancomycin MIC and Outcomes

- Clinical success rates decrease with increasing MICs, even in the susceptible range

<table>
<thead>
<tr>
<th>Vancomycin MIC (μg/ml)</th>
<th>Percent Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.5</td>
<td>96</td>
</tr>
<tr>
<td>0.5-1.0</td>
<td>28</td>
</tr>
<tr>
<td>1.0-2.0</td>
<td>10</td>
</tr>
<tr>
<td>2.0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source</th>
</tr>
</thead>
</table>

MRSA Treatment Options

- Vancomycin still the standard
  - What are the local MICs for MRSA (i.e., 0.5 vs. 2 μg/ml)
  - Need for higher doses
- Alternatives to Vancomycin
  - Hospitalized SSSI – Daptomycin, linezolid, tigecycline
  - Hospital-acquired pneumonia – linezolid, tigecycline, telavancin
  - Bacteremia – Daptomycin monotherapy
  - Endocarditis – Daptomycin monotherapy
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Resistance and OPAT

- Risk factors for infection with resistant organisms
  - Severity of illness
  - Previous exposure to antimicrobial agents
  - Underlying disease conditions
    - Chronic renal disease, DM, PVD, skin lesions
  - Invasive procedures
    - Dialysis, invasive devices, urinary catheterization
  - Repeated contact with healthcare system
  - Previous colonization with drug-resistant organisms
  - Advanced age

CDC. Multidrug-Resistant Organisms in Non-Hospital Healthcare Settings. www.cdc.gov/ncidod/dhqp/ar_multidrugFAQ.html

Economic Impact of Resistance

- S. aureus bacteremia
  - Methicillin resistance: 100% greater cost of therapy

- Klebsiella and E. coli infections
  - ESBL production: 66% greater cost of therapy

- Pseudomonas aeruginosa infections
  - Imipenem resistance: 68% greater cost of therapy

Lodise T and McKinnon P. Diag Microbiol Inf Dis 2005;52
Lee, et al. Inf Cont Hosp Epi 2006;27:1226-32

Antimicrobial Stewardship

- Infection control plus antimicrobial management
- Appropriate antimicrobial selection, dosing, route, and duration
- System selection of antimicrobials that cause the least collateral damage
  - MRSA
  - ESBLs
  - Clostridium difficile
  - Stable derepression
  - Metallo-beta-lactamases and other carbapenemases
  - VRE
Guideline Resources

- IDSA and SHEA
  - Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship
  - Dellit TH et al. CID 2007;44:159-77

- IDSA
  - Practice Guidelines for Outpatient Parenteral Antimicrobial Therapy
  - Tice AD et al. CID 2004;38:1651-72

- ASM and SHEA
  - Antimicrobial Resistance Prevention Initiative

Role of Infection Control

- Infection control trumps everything else
  - Hand hygiene – must have hand washing police
  - Barrier precautions
  - Devotion to all aspects of strict infection control
    - Nursing staff
    - Medical staff
    - Medical staff leadership

Infection Control – is it cost effective?

<table>
<thead>
<tr>
<th>Infection</th>
<th>Cost Savings</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAP</td>
<td>$25,072</td>
</tr>
<tr>
<td>Bacteremia</td>
<td>$23,242</td>
</tr>
<tr>
<td>Surgical Site Infection</td>
<td>$10,443</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>$758</td>
</tr>
</tbody>
</table>

Strategies for Optimizing Anti-Infective Therapy in the Home Infusion Setting

**Resistance and OPAT**

- **Home precautions**
  - Wash hands with soap and water after physical contact with infected person, and before leaving the home
  - Wash towels after each use
  - Wear disposable gloves for contact of body fluids, and wash hands after glove removal
  - Change linens on a routine basis
  - Clean patient environment regularly
  - Notify all who provide care that the patient is colonized/infected with a multidrug-resistant pathogen

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**Hand Hygiene**

- **Bacterial contamination of mobile phones**
  - 110 nurses carrying mobile phones
    - 79.1% of phones had visible bacteria
    - 68.6% had S. aureus
  - Flora on mobile phones at a teaching hospital
    - S. aureus 33%
    - P. aeruginosa 2%
    - Acinetobacter spp. 9.1%

- **Behavioral changes necessary**
  - Single-most effective measure to prevent spread of resistant organisms
  - Multifaceted educational programs, persistence

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**Goals of Stewardship**

- **Primary goal**
  - Optimize clinical outcome/minimize unintended consequences of antimicrobial use
  - Unintended consequences:
    - Toxicity
    - Selection of pathogenic organisms
    - Emergence of resistant pathogens

- **Secondary goal**
  - Reduce healthcare costs without adversely impacting quality of care
**Active Core Strategies**

- Prospective audit with intervention and feedback to reduce inappropriate antimicrobial use
- Formulary restriction and pre-authorization leading to reductions in antimicrobial use and cost

*NOTE – neither of these strategies are mutually exclusive*

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**Assessments**

- Antimicrobial consumption
  - Defined daily dose
  - Cost
  - Days of treatment
- Antimicrobial adverse events
- Resistance patterns/development
- Clinical outcomes measurements


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**Elements for Consideration**

- Parenteral to oral conversion
  - OPAT allows for IV treatment to continue, while minimizing cost
- Streamlining/de-escalating therapy
  - Often requires changes in home care/monitoring
- Dose optimization
  - Based on PK/PD parameters
- Educational programs
  - Prescribers, clinicians, patients, caregivers
- Guidelines/clinical pathways development
  - Incorporate local antimicrobial resistance data
Strategies for Optimizing Anti-Infective Therapy in the Home Infusion Setting

Formulary Restriction: Example

- After initiation of formulary restriction
- Third-generation cephalosporins use decreased
- Cefepime use remained stable
- Rates of ceftazidime-resistant K. pneumoniae decreased

PK/PD relationships using MIC

- Concentration-dependent killing
  - Higher the concentration, the greater the rate & extent of bactericidal activity
  - CpK/MIC ratio or AUC/MIC correlate with activity
  - Aminoglycosides, fluoroquinolones, metronidazole

PK/PD relationships using MIC

- Time-dependent killing
  - Saturation of the killing rate occurs at low multiples of the MIC
  - Killing dependent upon time above the MIC
  - Beta-lactams, vancomycin, clindamycin, macrolides

Strategies for Optimizing Anti-Infective Therapy in the Home Infusion Setting

Continuous Infusion

- Vancomycin
  - Continuous infusion unlikely to substantially improve patient outcomes
- Beta-lactams
  - Meta-analysis of 9 RCT
  - Clinical failure rate lower, statistically significant in studies of patients receiving same total daily dose
  - No differences in mortality


Continuous Infusion

- Piperacillin/tazobactam
  - Hartford Hospital utilizing CI since 1999
  - Results dependent upon MIC
  - Use for P. aeruginosa

Success Rates

<table>
<thead>
<tr>
<th></th>
<th>Clinical</th>
<th>Microbiologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous</td>
<td>94%</td>
<td>89%</td>
</tr>
<tr>
<td>Intermittent</td>
<td>82%</td>
<td>73%</td>
</tr>
</tbody>
</table>


PK/PD Challenges in OPAT

- Must balance optimum dosing and convenience
- Continuous infusion of beta-lactams increasingly studied
- Intricate communication required for therapeutic drug monitoring and dosage adjustment in home
- Adequate dosing must minimize collateral damage
- Treatment duration with antimicrobials an issue on the horizon

Tice AD et al. CID 2004;38:1651-72.
Treatment Duration

- Adequate duration essential
  - However, increases in duration equate with increases in resistance development
- Experts call for study of treatment duration to attempt to minimize
- Will require individualized patient case decisions and coordination
  - OPAT uniquely positioned to impact this issue

Example: CAP Guidelines
- 2007: "Patients with CAP should be treated for a minimum of 5 days, should be afibrile for 48-72h, and should have no more than 1 sign of CAP-associated clinical instability before discontinuation of therapy."


Research Priorities

- Antimicrobial duration of therapy
- Validation of mathematical models of resistance
- Long-term impact of formulary restrictions
- Focusing interventions on “collateral damage issues”
- Development of more rapid susceptibility tests
- Bad bugs/no drugs – stimulate research


Mandel LA et al. CID 2007;44(Suppl 2):S27-72
Critical Success Factors

- Collegial and educational relationship
- Review of antimicrobial orders by a consistent accountable team
- Support of hospital/medical leadership
- FTE's dedicated to stewardship
- Development of criteria and guidelines for anti-infective use
- Formulary restriction
- Education of prescribers to insure compliance

Summary and Conclusions

- Antimicrobial Stewardship programs show great promise and offer new opportunities for patient care and cost impact
- Recommendation by both IDSA/ASHP and the CDC offer firm foundations to obtain support and funding for antimicrobial stewardship programs
- Huge opportunity for advancement of clinical pharmacy practice, role of OPAT
Strategies for Optimizing Anti-Infective Therapy in the Home Infusion Setting

Answers:
B
D
A
C
D
SHAPING OUR HORIZON

Maximizing 20 Years of Achievement to Craft a Future of Possibilities