Building Stewardship: A Team Approach

Enhancing Antibiotic Stewardship in Acute Care Hospitals

September 7, 2011 1:00-2:30pm
Importance and Impact of Antimicrobial Stewardship
Hosp Pharm 2010;45(11 Suppl 1):S1-S5
Antimicrobial Therapy

A Balancing Act

Appropriate initial antibiotic while improving patient outcomes and heathcare

Unnecessary antibiotics and adverse patient outcomes and increased cost
Antimicrobial Prescribing

Empiric
- Initial administration of a broad-spectrum antibiotic regimen that attempts to improve outcomes and minimize resistance.

Defined or Targeted
- Modification of antimicrobial therapy once the cause of infection is identified. Therapy may also be discontinued if the diagnosis of infection becomes unlikely. ¹
- Focus on de-escalation of antibiotic therapy with the goal of minimizing resistance and toxicity, and improving cost-effectiveness. ², ³

Bad Bugs: No ESKAPE

- *Enterococcus*
- *S. aureus*
- *Klebsiella* spp.
- *Acinetobacter*
- *P. aeruginosa*
- *Enterobacter* spp.

Antimicrobial stewardship involves the *optimal selection, dose and duration* of an antibiotic resulting in the cure or prevention of infection with *minimal unintended consequences* to the patient including emergence of resistance, adverse drug events, and cost.

Ultimate goal is improved patient care and healthcare outcomes

Dellit TH, et al. CID 2007;44:159-77,  
Containment and Antimicrobial Resistance Surveillance

Human/animal infections
- Disease burden
- Diagnostics
- Prescriber behaviour
- Consumer expectations and adherence
- Consumer health education

Antimicrobial drugs
- Effective drug regulations
- Essential drug lists
- Drug approval systems
- Drug delivery systems
- Drug quality
- Management of drug supply

Rational drug use

AMR containment

Monitoring drug use and selection

Monitoring drug resistance

Monitoring drug supplies

ASHP Statement on the Pharmacist’s Role in Antimicrobial Stewardship and Infection Prevention and Control

Promoting optimal antimicrobial use
Reducing the transmission of infections
What Every Health Care Executive Should Know: The Cost of Antimicrobial Resistance

- Antimicrobial Resistance: Patients and hospitals in Peril
- The Clinical Consequences of Antimicrobial Resistance
- Transmission Control to Prevent the Spread of MDROs in Health Care Facilities
- Antimicrobial Stewardship
Building The Team

Antimicrobial Control

Infectious Diseases Specialists

Administration

Clinical Pharmacists

OR Personnel

Surgical Infection Experts/Surgeons

Infection Control

Microbiology

Pulmonary/Intensivist

Nursing
Antimicrobial Stewardship Strategies

- Prospective audit with intervention and feedback
- Formulary restriction and preauthorization

Supplemental Strategies
- Education, guidelines, clinical pathways
- Dose optimization via PK-PD
- De-escalation/Streamlining
- Antimicrobial order forms/order sets if CPOE
- IV-PO switch
- Computerized decision support
- Others

Dellit TH, et al. CID 2007;44:159-77
Antimicrobial Stewardship Care Bundle

- Prospective audit system
  - Stewardship program
  - Outcomes
    - Reason for treatment, cultures, empirical, and de-escalation
    - LOS, mortality, and % interventions accepted

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Control Phase</th>
<th>Intervention Phase</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documented indication for antibiotic therapy</td>
<td>76/80 (95)</td>
<td>80/80 (100)</td>
<td>0.12</td>
</tr>
<tr>
<td>Appropriate cultures collected</td>
<td>70/80 (87)</td>
<td>76/80 (95)</td>
<td>0.09</td>
</tr>
<tr>
<td>Appropriate empirical therapy</td>
<td>55/80 (69)</td>
<td>65/80 (81)</td>
<td>0.06</td>
</tr>
<tr>
<td>Appropriate deescalation(^3)</td>
<td>41/57 (72)</td>
<td>52/58 (90)</td>
<td>0.01</td>
</tr>
<tr>
<td>All indicators concurrently</td>
<td>13/80 (16)</td>
<td>43/80 (54)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**IV to Oral interchange**

Computer Surveillance and Decision Support in Antimicrobial Stewardship

- Sentri7
- SafetySurveillor
- TheraDoc
- Computerized physician order entry
- Benchmarking and local antimicrobials point prevalence surveys (state may consider doing this)

Antimicrobial Management Team Question of the Week

Doron, Shira
To: Tufts MC Antimicrobial Management Team
Cc:

Q: Three days ago, I admitted a 72 year old patient from a long-term acute care facility to the MICU with ventilator associated pneumonia (VAP). The patient had recently been treated with a cephalosporin for a complicated UTI and I was concerned about infection due to an Extended Spectrum Beta-lactamase (ESBL) producing organism, so I prescribed meropenem, as well as cipro and vancomycin. The sputum culture on admission to the MICU did indeed grow an ESBL Klebsiella pneumoniae. The isolate was susceptible to ertapenem (MIC<0.5), meropenem (MIC<1), and amikacin (MIC<2). Since the antibiotics prescribed using the VAP order form are about to expire I want to renew the patient’s antibiotics to finish an 8 day course. Should I continue meropenem? Is there a difference in the clinical efficacy between ertapenem and meropenem for the treatment of pneumonia?

A: Ertapenem has excellent penetration into the lung tissue and the epithelial lining fluid and is a good choice for treatment of pneumonia caused by Gram positive or Gram negative pathogens. In this case, there would be no reason to continue treatment with meropenem. At Tufts, one of the most common causes of late-onset VAP is Pseudomonas aeruginosa, against which ertapenem does not provide sufficient in vitro activity, making it a poor choice for empiric therapy (before you know the culture results). However, in this case, since you know the organism is Klebsiella, ertapenem would be the most appropriate. We always recommend de-escalating antibiotics; since the spectrum of ertapenem is narrower than meropenem, we would recommend switching to ertapenem for the remainder of the treatment course. In addition, once the organism is identified there is no need for double coverage with cipro, and the vancomycin can be safely discontinued as well.

The recommendations in this e-mail are based on published guidelines and the clinical expertise of our staff and may not apply to every patient. Please use clinical judgment when applying these concepts. The Antimicrobial Management Team serves adult patients at Tufts Medical Center. Some of the concepts presented here may not be appropriate for pediatric patients. Please do not hit "reply all" when responding to this message. To view previous AMT questions of the week, please see http://intranet.nemc.org/nmPharm2/Guidelines__Forms-ID.htm.

The Antimicrobial Management Team
Shira Doron, MD Kenneth Lawrence, PharmD Lisa Davidson, MD
Antimicrobial Order Forms

<table>
<thead>
<tr>
<th>DATE:</th>
<th>TIME:</th>
<th>(24-hour clock)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Patient Allergies:**

<table>
<thead>
<tr>
<th>Weight (lbs):</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Physicians Orders (Excludes Medication Orders):**

<table>
<thead>
<tr>
<th>TABLE 1: Risk Factors for Multi-drug Resistant Organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Interstitial for more than 3 days in the preceding 30 days</td>
</tr>
<tr>
<td>• Residence in a nursing home or extended care facility</td>
</tr>
<tr>
<td>• Recipient of home infusion therapy</td>
</tr>
<tr>
<td>• Chronic dialysis within the preceding 30 days</td>
</tr>
<tr>
<td>• Recipient of home wound care</td>
</tr>
<tr>
<td>• Family member with multi-drug-resistant pathogen</td>
</tr>
<tr>
<td>• Antimicrobial therapy in the preceding 90 days</td>
</tr>
<tr>
<td>• Immune-suppressed disease or therapy</td>
</tr>
</tbody>
</table>

**Patient in the hospital 5 days or longer or who has risk factors for:**

**Multi-drug resistant organisms (see Table 1 at right): should receive the following **1 drug regimen** (no A&M approval required for 72 hours):**

**Drug 1:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg)</th>
<th>Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI</td>
<td>6.5 IV Gtt h x 72 hours OR</td>
<td></td>
</tr>
<tr>
<td>PPI</td>
<td>0 mg IV Gtt h x 72 hours OR</td>
<td></td>
</tr>
</tbody>
</table>

**Drug 2:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg)</th>
<th>Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobramycin</td>
<td>0 mg IV Gtt h x 72 hours OR</td>
<td></td>
</tr>
<tr>
<td>Tobramycin</td>
<td>0 mg IV Gtt h x 72 hours OR</td>
<td></td>
</tr>
</tbody>
</table>

**Drug 3:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg)</th>
<th>Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>0 mg IV Gtt h x 72 hours OR</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**

a. Adjust dose for renal dysfunction. See Table-MEMC Dosage Adjustment for Renal Failure pamphlet or the Antibiotic Guidelines.
b. See Antibiotic Guidebook for tobramycin dosing.
c. Evidence suggests that intracavitary use provides higher lung concentrations than vancomycin and may be clinically superior in patients with known MRSA pneumonia.
d. Vancomycin dosing for pneumonia:

<table>
<thead>
<tr>
<th>Dose</th>
<th>1st Dose</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 75 kg</td>
<td>15 mg/kg</td>
<td>24 h</td>
</tr>
<tr>
<td>50-74 kg</td>
<td>15 mg/kg</td>
<td>24 h</td>
</tr>
<tr>
<td>&lt; 50 kg</td>
<td>15 mg/kg</td>
<td>24 h</td>
</tr>
</tbody>
</table>

**Vancomycin PK:**

<table>
<thead>
<tr>
<th>Dose</th>
<th>1st Dose</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 75 kg</td>
<td>15 mg/kg</td>
<td>24 h</td>
</tr>
<tr>
<td>50-74 kg</td>
<td>15 mg/kg</td>
<td>24 h</td>
</tr>
<tr>
<td>&lt; 50 kg</td>
<td>15 mg/kg</td>
<td>24 h</td>
</tr>
</tbody>
</table>

*Normax:72

Promax:12

Peak serum:200 pg/mL

Mean trough:75 pg/mL
Benefits of a HAP Protocol at Tufts Medical Center

Antimicrobial therapy of established infection should be limited to 4–7 days, unless it is difficult to achieve adequate source control.

Bowel injuries due to penetrating, blunt, or iatrogenic trauma repaired within 12 h and any other intraoperative contamination of the operative field by enteric contents should be treated with antibiotics for ≤24 hours.

Lack of evidence of infections includes, being afebrile, have normal WBC, and tolerating an oral diet.
Diagnostic and Pathogen Identification Techniques

- Biomarkers
  - Procalcitonin
  - CRP
- PNA FISH
- PCR
- E-test of patient samples

Bouza E, et al CID 2007;44:382-7
Measuring the Effectiveness of an Antimicrobial Stewardship Program

- Antimicrobial usage
  - Days of therapy
  - Appropriateness of treatment
- Antimicrobial cost
- Bacterial susceptibilities
- Patient outcomes
- Antimicrobial adverse events
- Acceptance of recommendations
- Prescribers surveys
The Public is Aware of Antimicrobial Resistance
Infectious Disease Society of America’s

Bad Bugs Need Drugs

10x '20

Ten new ANTIBIOTICS by 2020
How to Make Antimicrobial Stewardship Work: Practical Considerations for Hospitals of All Sizes
Hosp Pharm 2010;45(11 Suppl1):S10-S18
Provide advice on some of the practical aspects of starting a new stewardship program or expanding an existing program, with special commentary regarding the unique challenges facing community and teaching institutions.
The members of the team have to fit the personal available
  - Staff physician with ID interest
  - P&T chair or committee member
  - Hospitalist with interest in ID
  - Non–ID-trained clinical pharmacist
  - Staff pharmacists (with certification in stewardship)
Performing selected stewardship activities should be considered successful

- Helping patients is the goal, not struggling to follow guidelines at the expensive to a successful program for your institution

- Lines of authority and reporting are key
  - Quality and Safety
  - P&T for assistance with P&P and protocol approval
Process Metrics (Measuring Success)

- **Outcome Metrics**
  - CMS outcomes (CABP and SCIP)
  - Percentage of appropriate IV to PO
  - Point prevalence of antimicrobial use
  - Percent of appropriate antimicrobial regimens
  - Percent of patients with VAP or ABSSTI treat according to protocol (antimicrobial and non-antimicrobial metrics)
  - Antibiogram changes over time

- **Process Metrics**
  - Percent of recommendations accepted (numbers and type)
  - CMS outcomes
Consideration for Community Hospitals

- Challenges faced by Community Hospitals
  - Lack of sufficient resources
    - Private ID or NO ID physicians (or those that do not want to be involved)
    - ID pharmacist
    - No extra staff (especially pharmacy)
    - On site laboratory for C&S data
    - Antibiograms which include non-formulary agents
    - No IT systems for data gathering or analysis
    - Dealing with non-compliant prescribers
    - Embrace use of non-traditional stewardship personnel
Putting Stewardship into Practice

- One the program is approved the following should be determined
  - What activities will be performed?
  - By which person?
  - How frequently?
  - With what authority?
  - What is the time line for reporting the data?

- Advertise, market and educate direct care providers about the programs (think grass roots politics)
- Notify clinicians about changes that impact the program
- Report program successes and failures
- Share data with individual prescribers /departments when possible
Pharmacokinetics and Pharmacodynamics of Antimicrobials: It’s Not Just for Mice Anymore
Clinical Infectious Diseases 2007; 45:S89-95
Pharmacokinetic/Pharmacodynamic Parameters

- Provide descriptors of antimicrobial activity profiles
- Provide surrogate markers to predict drug activity
- Integrate “bug” and “drug” data
Different Drugs Impact Bugs Differently

- **β-lactams**
  - “not much happens until an adequate proportion of PBP are occupied”
  - Smaller doses, more frequently
  - Prolonged or continuous infusion
  - Time>MIC

- **Aminoglycosides/Fluoroquinolones**
  - AUC:MIC
  - Cmax/MIC

- **Dose AND MIC matter**
Defining Targets

- **β-lactams (stasis and near maximal killing)**
  - Cephalosporins: 35% and 65%
  - Carbapenems: 20% and 40%
  - Penicillins: 30% and 50%

- **Fluoroquinolones (stasis and near maximal killing)**
  - AUC/MIC: 20-25 and 250-300
  - Ambrose et al in CABP: 30 needed for clinical cure
  - HAP/VAP: AUC/MIC for levofloxacin 87 need for micro cure
Relationship between different measures of drug exposure and the microbiological effect a mouse model of pneumonia
Concentration vs. Time-dependence
Time-dependent Killing

- Best represented by Time > MIC
- Optimal Time > MIC varies
  - Usually at least 40% of dosing interval
  - >50% in neutropenia
Best represented by Cmax:MIC ratio
- Cmax:MIC ratio >8-12 associated with clinical success
- Optimal ratio varies with drug and organism
Dose-fractionation experiment with lomefloxacin in an animal model
Same total dose given as different regimens

AUC/MIC Ratio – MIC component

- Varies by particular isolate of organism
  - “Same drug, different bug”
  - Ex. Ciprofloxacin vs. *Pseudomonas*

![Graph showing AUC/MIC ratio for Cipro-sensitive and Cipro-resistant organisms.](image)
AUC/MIC Ratio – AUC component

- Traditional pharmacokinetic parameter
- Calculated based on total serum concentrations of drug
  - Obtained by sampling at multiple time points and integrating under curve
AUC/MIC Ratio – AUC component

- Surrogate for AUC of unbound drug at site of infection...at receptor site
- Does not account for susceptibility of organism
- Difficult to measure in clinical practice

Diagram:
- Assayed
- Protein Binding
- Entry into infected site
- Access to bacterial target
- Effective
Monte Carlo simulation: applied to PK/PD models

Random pharmacokinetics and MIC values from dataset

Calculate pharmacodynamic parameter

Plot results in a probability chart

AUC

MIC

AUC:MIC

Determining probability of target attainment in the patient population

- Monte Carlo simulation
  - determine distribution of antimicrobial potency (e.g., MIC distribution)
  - determine distribution of antimicrobial exposures (e.g., AUCs)
  - computer program randomly selects parameters from each of the distributions (500, 5000... iterations = patients) and the probability distribution of achieving the preset level (pharmacodynamic target attainment = specific AUC:MIC or T>MIC) is computed
May be a better surrogate marker of activity than drug exposure (AUC) or MIC alone

Studies have shown AUC/MIC to be predictive of antimicrobial activity

Probability of developing resistance during treatment for nosocomial pneumonia

**Clostridium difficile (CD)**

- Gram-positive anaerobic bacteria
- Exotoxin producing
- Fecal-oral transmission
  - *C. difficile* infection (CDI) onset median 2-3 days
- Most common cause of infectious diarrhea
  - 20-30% of antibiotic-associated diarrhea

2. Centers for Disease Control and Prevention
Background: Pathogenesis of CDI

1. Ingestion of spores transmitted from other patients via the hands of healthcare personnel and environment.

2. Germination into growing (vegetative) form.

3. Altered lower intestine flora (due to antimicrobial use) allows proliferation of *C. difficile* in colon.

4. Toxin A & B Production leads to colon damage +/- pseudomembrane.

CDI Risk Factors

- Age
- Hospital duration
- Antibiotic usage
- Chemotherapy
- Gastrointestinal disruption

CDI Diagnosis

- **Diarrhea**
  - 3 or more unformed stools

- **Positive stool test**
  - Enzyme immunoassay vs. polymerase chain reaction

- **Pseudomembranous colitis**
  - Colonoscopic or histopathologic findings

## CDI Classification

<table>
<thead>
<tr>
<th>Clinical definition</th>
<th>Supportive clinical data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild or moderate</td>
<td>WBC less than 15,000 <strong>AND</strong> SCr less than 1.5 times premorbid level</td>
</tr>
<tr>
<td>Severe</td>
<td>WBC greater than 15,000 <strong>OR</strong> SCr greater than 1.5 times premorbid level</td>
</tr>
<tr>
<td>Severe, complicated</td>
<td>Hypotension, shock, ileus, megacolon</td>
</tr>
</tbody>
</table>

CDI Treatment

- Discontinue any potential causative agent
- Immediately initiate empirical treatment
  - Severe or complicated
- Data of probiotic usage is inconclusive
  - Not recommended for primary prophylaxis

# Treatment of Initial Episodes

<table>
<thead>
<tr>
<th>Initial Episodes</th>
<th>Recommended Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild or moderate</td>
<td>Metronidazole 500 mg PO TID for 10-14 days</td>
</tr>
<tr>
<td>Severe</td>
<td>Vancomycin 125 mg PO QID for 10-14 days</td>
</tr>
<tr>
<td>Severe, complicated</td>
<td>Vancomycin 500 mg PO QID plus metronidazole 500 mg IV Q8H</td>
</tr>
</tbody>
</table>

# Recurrent Treatment

<table>
<thead>
<tr>
<th>Recurrent Infection</th>
<th>Recommended Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>First recurrence</td>
<td>Same as initial episode</td>
</tr>
<tr>
<td>Second recurrence</td>
<td>Vancomycin tapered and/or pulsed</td>
</tr>
</tbody>
</table>

Vancomycin vs. Metronidazole

- Prospective, randomized, double-blind, placebo-controlled trial
  - 150 patients completed study
  - Stratified patients: mild or severe

- Compared metronidazole 250 mg PO QID to vancomycin 125 mg PO QID for 10 days

Vancomycin vs. Metronidazole

Table 2. Rate of cure of *Clostridium difficile*-associated diarrhea by disease severity and treatment.

<table>
<thead>
<tr>
<th>Disease severity</th>
<th>No. of patients cured/no. of patients treated (%)</th>
<th>P&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Mtz group 37/41 (90) Vm group 39/40 (98) Total 76/81 (94)</td>
<td>.36</td>
</tr>
<tr>
<td>Severe</td>
<td>Mtz group 29/38 (76) Vm group 30/31 (97) Total 59/69 (86)</td>
<td>.02</td>
</tr>
<tr>
<td>All</td>
<td>Mtz group 66/79 (84) Vm group 69/71 (97) Total 135/150 (90)</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** Mtz, metronidazole; Vm, vancomycin.

<sup>a</sup> P values were calculated using Fisher’s exact test.
Why are New Therapies for CDI are Needed?

- Treatment failures with both metronidazole and vancomycin
- Increasing rates of recurrence with both vancomycin and metronidazole
- Risk of VRE colonization with both agents
- ADRs with current treatments especially, metronidazole
Fidaxomicin

- Macrocycles, a new class of antibacterials for oral administration
- Bactericidal against *C. difficile*, with a PAE of 6-10 hrs
- Inhibits RNA synthesis by RNA polymerases
- Fecal concentration are 5000 times the MIC90 of *C difficile* isolates
- Preservation of the microbiota of the GI tract compared with vancomycin
- Minimal systemic absorption measured in the ng/ml range
- Food does increase systemic absorption but increased serum concentration is NOT clinically significant
- Clinical resistance has been observed in the lab and in one treated patient (MIC from 0.06 to 6 mcg/ml)

Product Label  Dificid 2011
Fidaxomicin versus Vancomycin for Clostridium difficile Infection

NEJM 2011; 364: 422-61
Population

- Adult patients (> 16 y.o.) with a diagnosis of *C. difficile* infection
  - Presence of diarrhea: a change in bowel habits, > 3 unformed bowel movements in the 24-hour period before randomization
  - *C. difficile* Toxin A, B, or both in a stool specimen obtained 48 hours before randomization

- Exclusion Criteria:
  - Received: oral bacitracin, fusidic acid, or rifaximin
  - Life-threatening of fulminant *C. difficile* infection, toxic megacolon, previous exposure to fidaxomicin, a history of ulcerative colitis or Crohn’s disease, or > 1 occurrence of *C. difficile* infection within 3 months before the start of the study were excluded
Outcomes

- **Clinical Cure**: resolution of diarrhea with maintenance of resolution for duration of therapy and no further Rx
- **Clinical failure**: persistence of diarrhea, need for additional Rx, or both
- **Global cure**: resolution of diarrhea without recurrence
- **Clinical recurrence**: If subjects remained in study and had a follow up assessment at day 36-40, after randomization they were evaluated for recurrence. Defined as reappearance of diarrhea within 4 weeks after stopping study medication, + toxin assay, and need for treatment
### Demographics and Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Modified Intention-to-Treat Population</th>
<th>Per-Protocol Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fidaxomycin (N=287)</td>
<td>Vancomycin (N=309)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>60.3±16.9</td>
<td>62.9±16.9</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>57.1</td>
<td>54.7</td>
</tr>
<tr>
<td>Unformed stools per day (no.)</td>
<td>8.1±4.2</td>
<td>8.3±5.4</td>
</tr>
<tr>
<td>Inpatient (%)</td>
<td>58.2</td>
<td>60.5</td>
</tr>
<tr>
<td>Lack of response to metronidazole (%)</td>
<td>4.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Treatment for <em>C. difficile</em> infection in previous 24 hr (%)</td>
<td>38.3</td>
<td>39.8</td>
</tr>
<tr>
<td>Previous episode of <em>C. difficile</em> infection (%)</td>
<td>16.7</td>
<td>17.5</td>
</tr>
<tr>
<td>BI/NAP1/027 strain (%)†</td>
<td>37.5</td>
<td>38.6</td>
</tr>
</tbody>
</table>
Rates of Primary and Secondary End Points

- **Clinical Cure**
  - mITT: 88.2%, 85.8%
  - PP: 92.1%, 89.8%

- **Recurrence**
  - mITT: 15.4%, 25.3%
  - PP: 13.3%, 24.0%

- **Global Cure**
  - mITT: 74.6%, 64.1%
  - PP: 77.7%, 67.1%

P-values:
- Clinical Cure: P=0.006
- Recurrence: P=0.005
- Global Cure: P=0.004
Clinical Cure Rates at the EOT, According to Subgroups in the MITT and Per-Protocol Populations

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>MITT Fidax</th>
<th>MITT Vanco</th>
<th>PP Fidax</th>
<th>PP Vanco</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 65 years</td>
<td>103/122 (84.4)</td>
<td>131/152 (86.2)</td>
<td>99/113 (87.6)</td>
<td>122/138 (88.4)</td>
</tr>
<tr>
<td>Inpatient</td>
<td>136/167 (81.4)</td>
<td>146/187 (78.1)</td>
<td>128/146 (87.7)</td>
<td>136/162 (84)</td>
</tr>
<tr>
<td>No Previous episode of CDI</td>
<td>211/239 (88.3)</td>
<td>217/255 (85.1)</td>
<td>203/222 (91.4)</td>
<td>209/235 (88.9)</td>
</tr>
<tr>
<td>NAP1/BI/027</td>
<td>59/75 (78.7)</td>
<td>7/83 (80.7)</td>
<td>56/65 (86.2)</td>
<td>61/72 (84.7)</td>
</tr>
<tr>
<td>Non NAP1/BI/027</td>
<td>117/125 (93.6)</td>
<td>121/132 (91.7)</td>
<td>115/119 (96.6)</td>
<td>119/126 (94.4)</td>
</tr>
<tr>
<td>Concurrent Systemic ABX</td>
<td>67/83 (80.7)</td>
<td>72/94 (76.6)</td>
<td>63/71 (88.7)</td>
<td>67/80 (83.8)</td>
</tr>
<tr>
<td>Moderate CDI</td>
<td>102/111 (91.9)</td>
<td>88/106 (83)</td>
<td>99/105 (94.3)</td>
<td>84/97 (86.6)</td>
</tr>
<tr>
<td>Severe CDI</td>
<td>92/112 (82.1)</td>
<td>109/123 (88.6)</td>
<td>89/101 (88.1)</td>
<td>107/115 (93)</td>
</tr>
</tbody>
</table>

No differences between the groups were significant
Number/total number (percent)
### Recurrence Rates at the EOT, According to Subgroups in the MITT and Per-Protocol Populations

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>MITT Fidax</th>
<th>MITT Vanco</th>
<th>P value</th>
<th>PP Fidax</th>
<th>PP Vanco</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 65 years</td>
<td>20/103 (19)</td>
<td>40/131 (30.5)</td>
<td>0.05</td>
<td>16/85 (19)</td>
<td>31/103 (30)</td>
<td>0.08</td>
</tr>
<tr>
<td>Inpatient</td>
<td>24/136 (18)</td>
<td>40/146 (27)</td>
<td>0.05</td>
<td>19/106 (18)</td>
<td>29/111 (26)</td>
<td>0.15</td>
</tr>
<tr>
<td>No Previous episode of CDI</td>
<td>30/211 (14)</td>
<td>52/217 (24)</td>
<td>0.01</td>
<td>22/175 (13)</td>
<td>41/183 (22)</td>
<td>0.02</td>
</tr>
<tr>
<td>NAP1/BI/027</td>
<td>16/59 (27)</td>
<td>14/67 (21)</td>
<td>0.42</td>
<td>11/45 (24)</td>
<td>13/55 (24)</td>
<td>0.93</td>
</tr>
<tr>
<td>Non NAP1/BI/027</td>
<td>12/117 (10)</td>
<td>34/121 (28)</td>
<td>&lt;0.001</td>
<td>8/103 (8)</td>
<td>27/106 (25.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Concurrent Systemic ABX</td>
<td>14/81 (17)</td>
<td>5/90 (28)</td>
<td>0.10</td>
<td>8/56 (14)</td>
<td>20/65 (31)</td>
<td>0.03</td>
</tr>
<tr>
<td>Mild CDI</td>
<td>7/59 (12)</td>
<td>20/68 (29)</td>
<td>0.02</td>
<td>4/44 (9)</td>
<td>13/55 (24)</td>
<td>0.06</td>
</tr>
<tr>
<td>Severe CDI</td>
<td>12/92(13)</td>
<td>29/109 (27)</td>
<td>0.02</td>
<td>9/77 (12)</td>
<td>22/95 (23)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Number/total number (percent)
Xpert C. difficile/Epi

Commercially available test in the world to detect and differentiate the epidemic strain of *C. difficile* (027/NAP1/BI).

- With rapid and accurate identification of epidemic strain, Infection Control professional can stay ahead of potential outbreak situation.

Innovative multiplex design enables detection of *C. difficile* Infection (CDI) and 027/NAP1/BI strain call-out in a single cartridge

- Cepheid’s Xpert *C. difficile*/Epi is a real time PCR test that runs on the GeneXpert system

- GeneXpert system is the first to fully automate and integrate all the steps required for PCR-based DNA testing: sample preparation, DNA amplification and detection
Vancomycin PO capsules 125 mg Q6h x 10 days
- Red book AWP $31.82 per capsule
- $1275 per course
- Inpatient, a vancomycin slurry is made by pharmacy for treatment of CDI
- Outpatient, capsules are dispensed and covered by payors
- Patient assistance program for PO Vancomycin

Metronidazole 500 mg PO Q8h x 10 days
- Red book AWP $1.38
- $41.40 per course

Fidaxomicin 200 mg PO Q12h x 10 days
- Reported cost of $2800
# Antibiogram: Gram-negative bacteria, 2008

<table>
<thead>
<tr>
<th>Gram Negative Organisms</th>
<th>Percent Susceptible</th>
<th>Inpatient, All Sources</th>
<th>Penicillins &amp; Related Antibiotics</th>
<th>1\textsuperscript{st}</th>
<th>2\textsuperscript{nd}</th>
<th>3\textsuperscript{rd}</th>
<th>4\textsuperscript{th}</th>
<th>Aminoglycosides</th>
<th>Quinolone</th>
<th>UTI Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter baumannii (39)</td>
<td></td>
<td></td>
<td></td>
<td>90</td>
<td>71</td>
<td>89</td>
<td>89</td>
<td>0</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>Enterobacter cloacae (102)</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>qns</td>
<td>0</td>
<td>50</td>
<td>100</td>
<td>0</td>
<td>55</td>
</tr>
<tr>
<td>E. coli (465)</td>
<td></td>
<td></td>
<td></td>
<td>56</td>
<td>77</td>
<td>54</td>
<td>91</td>
<td>99</td>
<td>80</td>
<td>99</td>
</tr>
<tr>
<td>Klebsiella oxytoca (36)</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>qns</td>
<td>qns</td>
<td>86</td>
<td>100</td>
<td>55</td>
<td>100</td>
</tr>
<tr>
<td>Klebsiella pneumoniae (309)</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>55</td>
<td>44</td>
<td>63</td>
<td>100</td>
<td>59</td>
<td>97</td>
</tr>
<tr>
<td>Proteus mirabilis (77)</td>
<td></td>
<td></td>
<td></td>
<td>72</td>
<td>97</td>
<td>94</td>
<td>98</td>
<td>100</td>
<td>81</td>
<td>100</td>
</tr>
<tr>
<td>Pseudom aeruginosa (353) (CF sputum: KirbyBauer) (22)</td>
<td></td>
<td></td>
<td></td>
<td>86</td>
<td>(77)</td>
<td>(36)</td>
<td>(40)</td>
<td>(61)</td>
<td>75</td>
<td>(72)</td>
</tr>
<tr>
<td>Serratia marcescens (85)</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>83</td>
<td>96</td>
<td>0</td>
<td>94</td>
</tr>
<tr>
<td>Stenotroph. maltophilia (31)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# New CLSI Breakpoints for Enterobacteriaceae

<table>
<thead>
<tr>
<th>Agent</th>
<th>Susc</th>
<th>Interm</th>
<th>Resis</th>
<th>Susc</th>
<th>Interm</th>
<th>Resis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin</td>
<td>≤ 8</td>
<td>16</td>
<td>≥32</td>
<td>≤ 1</td>
<td>2</td>
<td>≥4</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>≤ 8</td>
<td>16-32</td>
<td>≥64</td>
<td>≤ 1</td>
<td>2</td>
<td>≥4</td>
</tr>
<tr>
<td>Ceftizoxime</td>
<td>≤ 8</td>
<td>16-32</td>
<td>≥64</td>
<td>≤ 1</td>
<td>2</td>
<td>≥4</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>≤ 8</td>
<td>16-32</td>
<td>≥64</td>
<td>≤ 1</td>
<td>2</td>
<td>≥4</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>≤ 8</td>
<td>16</td>
<td>≥32</td>
<td>≤ 1</td>
<td>8</td>
<td>≥16</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>≤ 8</td>
<td>16</td>
<td>≥32</td>
<td>≤ 1</td>
<td>8</td>
<td>≥16</td>
</tr>
</tbody>
</table>


CLSI M100-S20, 2010
New CLSI Breakpoints for Enterobacteriaceae 2011

- Why the changes?
  - Better PKPD data and knowledge about resistance mechanism especially ESBLs ± AmpC
- What were they based upon?
  - Mostly PD, expert opinion and a few case series.
- How does the change impact treatment?
  - May use any agent based on the observed MIC result and pts factors, carbapenem are not always needed
- How does it impact reporting of ESBL?
  - Susceptibility of cephalosporins should NOT be changed if identified as an ESBLs
Impact of Revised Breakpoints

Cumulative Ceftriaxone MIC Distribution for Isolates w/ ESBL, Plasmid-mediated(p) AmpC, ESBL + pAmpC
Impact of Revised (New) and Old Breakpoints

*Klebsiella spp.* and *E. coli* (n=264)

**FIG. 2.** Cumulative ceftriaxone MIC distribution.

Some ESBL producing isolates are susceptible in-vitro

Poor outcomes in patients with infections due to ESBLs cephls

Bacteria often have ESBLs and AmpC-like enzymes

No need for ESBL testing or confirmatory test with new breakpoints.

Hospitals using FDA-approved AST devices can utilize existing FDA interpretive breakpoints

Either FDA or CLSI susceptibility interpretive breakpoints are acceptable to accrediting bodies.
# New Carbapenem Breakpoints for Enterobacteriaceae

<table>
<thead>
<tr>
<th>Drug</th>
<th>Susceptible</th>
<th>Interm</th>
<th>Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doripenem</td>
<td>≤ 1</td>
<td>2</td>
<td>≥4</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>≤ 0.25</td>
<td>0.5</td>
<td>≥1</td>
</tr>
<tr>
<td>Imipenem</td>
<td>≤ 1</td>
<td>2</td>
<td>≥4</td>
</tr>
<tr>
<td>Meropenem</td>
<td>≤ 1</td>
<td>2</td>
<td>≥4</td>
</tr>
</tbody>
</table>
## New Carbapenem Breakpoints

Putting it Together: MIC Cutoffs and % Target Attainment by PK-PD Monte Carlo Simulation ($t \geq MIC = 35\%$) for Susceptibility Breakpoints and Capture of KPCs) **USING PK-PD BP FOR ERTAPENEM**

<table>
<thead>
<tr>
<th>Drug</th>
<th>S</th>
<th>I</th>
<th>R</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Meropenem</strong></td>
<td></td>
<td></td>
<td></td>
<td>Current: $\leq 4 / 8 / \geq 16$</td>
</tr>
<tr>
<td></td>
<td>$\leq 1$</td>
<td>2</td>
<td>$\geq 4$</td>
<td>(from Jones)</td>
</tr>
<tr>
<td>KPC capture</td>
<td>1.2%</td>
<td>15%</td>
<td>84%</td>
<td></td>
</tr>
<tr>
<td>PK-PD TA</td>
<td>93%</td>
<td>81%</td>
<td>54%</td>
<td>1 g Q8h</td>
</tr>
<tr>
<td><strong>Imipenem</strong></td>
<td></td>
<td></td>
<td></td>
<td>Current: $\leq 4 / 8 / \geq 16$</td>
</tr>
<tr>
<td></td>
<td>$\leq 1$</td>
<td>2</td>
<td>$\geq 4$</td>
<td>(from Jones)</td>
</tr>
<tr>
<td>KPC capture</td>
<td>0%</td>
<td>14%</td>
<td>86%</td>
<td></td>
</tr>
<tr>
<td>PK-PD TA</td>
<td>95 / 95</td>
<td>84 / 91</td>
<td>50 / 76</td>
<td>500 q 6h / 1 g q 8h</td>
</tr>
<tr>
<td><strong>Ertapenem</strong></td>
<td></td>
<td></td>
<td></td>
<td>Current: $\leq 2 / 4 / \geq 8$</td>
</tr>
<tr>
<td></td>
<td>$\leq 0.25$</td>
<td>0.5</td>
<td>$\geq 1$</td>
<td>(from Jones)</td>
</tr>
<tr>
<td>KPC capture</td>
<td>0%</td>
<td>0.3%</td>
<td>99.7%</td>
<td></td>
</tr>
<tr>
<td>PK-PD TA</td>
<td>91%</td>
<td>80%</td>
<td>55%</td>
<td>1 g q 24 h</td>
</tr>
<tr>
<td><strong>Doripenem</strong></td>
<td></td>
<td></td>
<td></td>
<td>Approved 6-28-09</td>
</tr>
<tr>
<td></td>
<td>$\leq 1$</td>
<td>2</td>
<td>$\geq 4$</td>
<td>(from Fig 4, Dori doc)</td>
</tr>
<tr>
<td>KPC capture</td>
<td>0%</td>
<td>2.3%</td>
<td>97.7%</td>
<td></td>
</tr>
<tr>
<td>PK-PD TA</td>
<td>95%</td>
<td>75%</td>
<td>40%</td>
<td>From J&amp;J analysis, NHV</td>
</tr>
</tbody>
</table>