Understanding *C. difficile* Infections and Gram-Negative Infections: Are We There Yet?

Erik R. Dubberke, MD, MSPH, FSHEA
Associate Professor of Medicine
Director, Section of Transplant ID
Washington University School of Medicine
St. Louis, MO

Antimicrobial-Resistant Bacteria are a Global Threat

**GREAT PRIORITY LIST OF ANTIBIOTIC-RESISTANT BACTERIA TO GUIDE RESEARCH, DISCOVERY, AND DEVELOPMENT OF NEW ANTIBIOTICS**

**ANTIBIOTIC RESISTANCE THREATS in the United States, 2013**

**Faces of**

**ANTIMICROBIAL RESISTANCE**

**Greatest Threats**

**CDC**
- Urgent
  - *Clostridium difficile*
  - Carbapenem-resistant *Enterobacteriaceae*
  - Neisseria gonorrhoeae
- Serious
  - Multidrug-resistant (MDR) *Acinetobacter*
  - Drug-resistant *Campylobacter*
  - Fluoroquinolone-resistant *Escherichia coli*
  - *VRE*
  - *MDR Pseudomonas*
  - Drug-resistant *Salmonella*
  - Drug-resistant *Shigella*
  - Methicillin-resistant *S. aureus* (MRSA)
  - Drug-resistant *Pneumococcus*
  - Drug-resistant *tuberculosis*
- Concerning
  - Vancomycin-resistant *S. aureus*
  - Erythromycin-resistant Group A *Strep*
  - Clindamycin-resistant Group B *Strep*

**WHO**
- Critical
  - Carbapenem-resistant *Acinetobacter*
  - Carbapenem-resistant *Pseudomonas*
  - Carbapenem-resistant *Enterobacteriaceae*
- High
  - *VRE*
  - Vancomycin-intermediate MRSA
  - Ceftazidime-resistant *K. pneumoniae*
  - Fluoroquinolone-resistant *Campylobacter*
  - Fluoroquinolone-resistant *Salmonella*
  - Neisseria gonorrhoeae
- Medium
  - Penicillin non-susceptible *Pneumococcus*
  - Ampicillin-resistant *H. influenzae*
  - Fluoroquinolone-resistant *Shigella*

10,000,000 Deaths Annually by 2050

**Annual deaths attributable to antimicrobial resistance by 2050**

**Treatment and Prevention of Infections Due to Resistant Bacteria is an Ongoing Challenge**

- Population vs. patient
  - Antimicrobial stewardship: prevent development/promotion of resistant bacteria
  - Need effective antibiotics if resistant bacteria causing infection

- Need not be mutually exclusive
Current Therapeutic Options for Antimicrobial-Resistant Gram-Negative Infections

Kerry L. LaPlante, Pharm, FCCP
Professor of Pharmacy
University of Rhode Island, College of Pharmacy

Adjunct Professor of Medicine
The Warren Alpert Medical School of Brown University
Senior Director of the Rhode Island Infectious Diseases Research (RID) Program
Co-Director of Antimicrobial Stewardship Program and Infectious Diseases Pharmacotherapy Specialist
Providence Veterans Medical Center
Providence, RI

Which of the following songs sums up your entire professional career to date?

a. “I Will Survive”
b. “Chariots of Fire”
c. “Friends in Low Places”
d. “Mo Money”
e. “Flight of the Bumblebee”

Antimicrobial Resistance Threats: CDC


WHO Establishes Priority Level for Resistant Gram-Negative Bacteria (2017)

Priority 1: CRITICAL

- Acinetobacter baumannii, carbapenem-resistant
- Pseudomonas aeruginosa, carbapenem-resistant
- Enterobacteriaceae*, carbapenem-resistant
- Enterobacteriaceae*, 3rd-generation cephalosporin-resistant


Mechanisms of Antibiotic Resistance in Gram-Negative Bacteria


### Classes of β-Lactamases in Gram-Negative Bacteria

<table>
<thead>
<tr>
<th>Ambler Classification</th>
<th>Description or Characteristics</th>
<th>Examples of Enzymes</th>
<th>Bacterial Strains</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class A (serine β-lactamase)</td>
<td>Cephalosporinases (ESBLs) Usually clavulanic acid susceptible, except for KPC TEM, SHV, CTX-M, KPC VEB</td>
<td>Enterobacteriaceae, Pseudomonas spp.</td>
<td></td>
</tr>
<tr>
<td>Class B (metallo-β-lactamase or MBL)</td>
<td>Contain metal ion (Zn) Carbapenemases Not inhibited by clavulanic acid Inhibited by antitaxin</td>
<td>Ampicillin, Acinetobacter spp., Pseudomonas spp.</td>
<td></td>
</tr>
<tr>
<td>Class C (AmpC β-lactamase – serine β-lactamase)</td>
<td>Resistant to clavulanic acid Intrinsic in certain species of Gram-negative CMY, DHA</td>
<td>Enterobacteriaceae, Pseudomonas spp.</td>
<td></td>
</tr>
<tr>
<td>Class D (serine β-lactamase)</td>
<td>Susceptible to clavulanic acid Carbapenemase OXA</td>
<td>Enterobacteriaceae, OXA-48 like, Acinetobacter spp.</td>
<td></td>
</tr>
</tbody>
</table>

Note: Enzymes underlined are carbapenemases.

### Antimicrobial-Resistant P. aeruginosa, All HAIs 2011–2014

<table>
<thead>
<tr>
<th>Resistance type</th>
<th>Overall</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbenepen (N=22,593)</td>
<td>19.3%</td>
<td>20.0%</td>
<td>17.8%</td>
<td>20.4%</td>
<td>19.2%</td>
</tr>
<tr>
<td>Cephalosporins (N=26,772)</td>
<td>10.3%</td>
<td>11.7%</td>
<td>9.9%</td>
<td>10.8%</td>
<td>9.5%</td>
</tr>
<tr>
<td>Fluoroquinolone (N=26,897)</td>
<td>21.6%</td>
<td>23.5%</td>
<td>20.8%</td>
<td>22.3%</td>
<td>20.7%</td>
</tr>
<tr>
<td>Aminoglycoside (N=27,197)</td>
<td>9.7%</td>
<td>10.6%</td>
<td>9.1%</td>
<td>9.8%</td>
<td>9.6%</td>
</tr>
<tr>
<td>Piperacillin/tazobactam (N=23,662)</td>
<td>10.0%</td>
<td>12.8%</td>
<td>10.0%</td>
<td>10.1%</td>
<td>9.0%</td>
</tr>
<tr>
<td>Multidrug-Resistant (N=27,289)</td>
<td>14.2%</td>
<td>15.7%</td>
<td>13.3%</td>
<td>14.8%</td>
<td>13.5%</td>
</tr>
</tbody>
</table>


### MDR Pseudomonas – Impact

![Graph showing impact of MDR Pseudomonas](image)


### Patient Case

![Patient case image](image)

**Patient Case: Mr. Z**

**CC:** 76-year-old man residing in LTCF with a history of complicated UTIs presents to the ED complaining of painful urination and slight hematuria

**HPI:** April 10th hospitalization for UTI. No indwelling urinary catheter present, patient performs self-catheterization

**PMHx:** Diabetes, PVD, prostate CA

**ROS:** Fever 38.9°C (102.2°F); WBC 18K

**PE:** Acute costovertebral angle pain

---

**Patient Case: Mr. Z (cont’d)**

- **Management plan:**
  - Patient is empirically given imipenem 500 mg IV q6h

- **New information:**
  - AMS Team reviews records from his last admission (~30 days prior); urine culture grew *P. aeruginosa*, previously treated with IV then PO levofloxacin 750 mg × 10 days (4/10 to 4/20/2017)
  - Blood and urine culture from current admission shows Gram-negative rods

---

**Audience Question**

Before recommending a change in therapy, what would you consider?

- Imipenem may be overly broad, recommend narrowing therapy
- Recommend to empirically cover for MDR *P. aeruginosa*
- Recommend to empirically cover for KPCs
- Recommend nothing, stay the course and await C&S
- Make a phone call to the primary team to discuss further

---

**Assessing Patient Risk for MDR Infection to Guide Empiric Therapy**

- **Identify patients** who have received substantial previous broad-spectrum antimicrobial therapy, had prolonged hospitalizations, undergone multiple invasive interventions, or known to have been colonized or infected with a resistant Gram-negative organism, or at risk for infection from a resistant Gram-negative pathogen.
- **Consult local epidemiologic data and antibiograms** for assistance in selecting empiric antimicrobial therapy in patients considered at risk for infection with resistant Gram-negative pathogens.

---

**Risk Factors for Infection with MDR Gram-Negative Pathogens**

- **Previous hospitalization**
- **Previous antibiotic exposure**
- **Previous stay in ICU**
- **Residence in LTC facilities**
- **Infection or colonization with Gram-negative pathogens in the previous year**
- **Comorbidities**
- **Immunocompromised states**
- **Older age (>65)**
- **Previous invasive procedures and/or presence of devices**
- **Mechanical ventilation**

---

**Over Half of *P. aeruginosa* Isolates Non-susceptible to Pip-Tazo Also Non-susceptible to a Carbapenem**

<table>
<thead>
<tr>
<th>Region</th>
<th>Pip-Tazo (PTZ-NS)</th>
<th>Meropenem (MER-NS)</th>
<th>MDR (PTZ-NS also MER-NS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New England</td>
<td>19</td>
<td>17</td>
<td>44</td>
</tr>
<tr>
<td>Mid-Atlantic</td>
<td>27</td>
<td>20</td>
<td>52</td>
</tr>
<tr>
<td>East North Central</td>
<td>21</td>
<td>18</td>
<td>51</td>
</tr>
<tr>
<td>West North Central</td>
<td>14</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>South Atlantic</td>
<td>25</td>
<td>20</td>
<td>49</td>
</tr>
<tr>
<td>East South Central</td>
<td>22</td>
<td>18</td>
<td>57</td>
</tr>
<tr>
<td>West South Central</td>
<td>26</td>
<td>25</td>
<td>68</td>
</tr>
<tr>
<td>Mountain</td>
<td>22</td>
<td>25</td>
<td>64</td>
</tr>
<tr>
<td>Pacific</td>
<td>20</td>
<td>12</td>
<td>40</td>
</tr>
</tbody>
</table>

PTZ, piperacillin/tazobactam; MER, meropenem; MDR = % of PTZ-NS isolates that were also MER-NS.

2012 INFORM Surveillance data, *Pseudomonas aeruginosa* resistance, Forest Laboratories, LLC.
NEWER ANTIMICROBIAL AGENTS IN THE MANAGEMENT OF INFECTIONS CAUSED BY MULTIDRUG-RESISTANT GRAM-NEGATIVE BACTERIA

**Ceftolozane-Tazobactam (ZERBAXA®)**

- **Class/MOA**: Novel cephalosporin/β-lactamase inhibitor combination
- **Approval**:
  - Complicated urinary tract infections (cUTIs), including pyelonephritis
  - Complicated intra-abdominal infections (cIAIs)
- **Investigational**:
  - Ventilator-associated bacterial pneumonia (VABP) and ventilated hospital-acquired bacterial pneumonia (HABP) with dose of 3 g q8h (2000 mg ceftolozane and 1000 mg tazobactam)
  - cUTIs dose: 1.5 g q8h (1000 mg ceftolozane and 500 mg tazobactam) plus meropenem 500 mg q8h
- **Spectrum**:
  - Activity against multidrug-resistant Gram-negative bacilli.
  - Tazobactam extends the activity to include most ESBLs & anaerobic species
  - Polent activity versus Pseudomonas aeruginosa, including drug-resistant phenotypes such as carbapenem, piperacillin/tazobactam, and ceftazidime-resistant isolates, as well as MDR strains
- **Dose not covered**:
  - MSSA, SRSA, enterococcus

*Label includes a warning about decreased efficacy seen in patients with renal impairment


**Ceftolozane-Tazobactam: Activity Against P. aeruginosa**

- **Demonstrated in vitro activity against P. aeruginosa isolates tested that had**:  
  - Chromosomal AmpC
  - Loss of outer membrane (Op/D) or
  - Up-regulation of efflux pumps (MexXY, MexAB)
- **Not active against bacteria producing metallo-β-lactamases**

**Current FDA susceptibility interpretive criteria:**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Minimum Inhibitory Concentrations (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>54 / 4*</td>
</tr>
</tbody>
</table>

*Ceftolozane-tazobactam susceptibility testing performed with a fixed 4 µg/ml concentration of tazobactam


**Ceftolozane-Tazobactam: In Vitro Activity**

- Ceftolozane-tazobactam activity tested against P. aeruginosa isolates from patients hospitalized with pneumonia (USA - 2012)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Cumulative (%) inhibited at MIC (µg/mL)</th>
<th>MIC80 / MIC84 (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomonas aeruginosa (n=1018)</td>
<td>92.8 / 94.1 / 94.6</td>
<td>0.5 / 4</td>
</tr>
<tr>
<td>Ceftazidime-non-S (n=268)</td>
<td>73.1 / 77.7 / 78.8</td>
<td>4 / &gt;32</td>
</tr>
<tr>
<td>Cefepime-non-S (n=239)</td>
<td>70.7 / 77.0 / 79.1</td>
<td>4 / &gt;32</td>
</tr>
<tr>
<td>Meropenem-S (n=290)</td>
<td>75.7 / 78.0 / 79.2</td>
<td>2 / &gt;32</td>
</tr>
<tr>
<td>Piperacillin-tazobactam-non-S (n=31)</td>
<td>78.5 / 81.4 / 83.0</td>
<td>2 / &gt;32</td>
</tr>
<tr>
<td>CAZ &amp; MEM &amp; P/T-ESBL-S (n=158)</td>
<td>60.1 / 63.9 / 67.1</td>
<td>6 / &gt;32</td>
</tr>
<tr>
<td>Levofloxacin-non-S (n=307)</td>
<td>81.4 / 82.7 / 84.4</td>
<td>2 / &gt;32</td>
</tr>
<tr>
<td>Gentamicin-non-S (n=197)</td>
<td>73.6 / 79.1 / 79.3</td>
<td>2 / &gt;32</td>
</tr>
<tr>
<td>Multidrug-resistant (MDR) (n=246)</td>
<td>72.4 / 75.5 / 77.0</td>
<td>2 / &gt;32</td>
</tr>
<tr>
<td>Extensively drug-resistant (XDR) (n=174)</td>
<td>63.2 / 66.1 / 69.0</td>
<td>4 / &gt;32</td>
</tr>
</tbody>
</table>


**Phase 3 Clinical Trials: Ceftolozane-Tazobactam for cUTIs**

- **Primary endpoint**: composite of microbiological eradication and clinical cure rate (composite cure rate) at 5–9 days after end of therapy—TOC visit.
- **Of 1083 patients enrolled, 800 (73.9%) of whom 656 (82.0%) had pyelonephritis were included in the microbiological MITT population.

<table>
<thead>
<tr>
<th>cUTI treatment</th>
<th>Ceftolozane-tazobactam 1.5g q8h</th>
<th>Levofloxacin 750mg QD-q2d</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>microbiological modified intent-to-treat patients</td>
<td>76.9%</td>
<td>68.4%</td>
<td>8.5%; 95% CI, 2.3–14.6*</td>
</tr>
<tr>
<td>microbiologically evaluable patients</td>
<td>83.3%</td>
<td>75.4%</td>
<td>8%; 95% CI, 2.14*</td>
</tr>
</tbody>
</table>

*“as the lower bound of the two-sided 95% CI around the treatment difference was positive and greater than zero, superiority was indicated”


**Newer Agents for Antibiotic-Resistant Gram-Negative Bacteria**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Mechanism of action</th>
<th>Status</th>
<th>Spectrum of Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftolozane-tazobactam</td>
<td>Anti-pseudomonal cephalosporin/BLI combination</td>
<td>Approved: cUTI, including pyelonephritis</td>
<td>Gram-negatives, including MDR P. aeruginosa and ESBL-producing strains</td>
</tr>
<tr>
<td>Ceftazidime-avibactam</td>
<td>Anti-pseudomonal cephalosporin/BLI combination</td>
<td>Approved: cUTI, including pyelonephritis</td>
<td>Gram-negatives, including MDR P. aeruginosa, ESBL-producing strains, KPCs</td>
</tr>
</tbody>
</table>

BLI β-lactamase inhibitor; cUTI, complicated urinary tract infection; cUTI, complicated intra-abdominal infection; ESBL, extended spectrum β-lactamase; HAP, hospital-acquired pneumonia; MDR, multi-drug resistant; KPC, K. pneumoniae carbapenemase.

Ceftazidime-Avibactam: Activity Against *P. aeruginosa*

- Demonstrated in vitro activity against *P. aeruginosa* in the presence of:
  - some AmpC beta-lactamases
  - certain strains lacking outer membrane porin (OprD)
- Not active against bacteria producing metallo-P-lactamases and may not have activity against Gram-negative bacteria that overexpress efflux pumps or have porin mutations

Current FDA susceptibility interpretive criteria:

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Susceptible (S)</th>
<th>Resistant (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>≤8 / 4*</td>
<td>≥16 / 4*</td>
</tr>
</tbody>
</table>

* Ceftazidime-avibactam susceptibility testing performed with a fixed 4 µg/mL concentration of avibactam.

Ceftazidime-Avibactam: In Vitro Activity

<table>
<thead>
<tr>
<th>Class/MAO</th>
<th>Established cephalosporin/novel non-beta-lactam beta-lactamase inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval</td>
<td>Based upon two Phase 2 trials</td>
</tr>
<tr>
<td>Investigational</td>
<td>Neosomial pneumonia, including those with ventilator-associated pneumonia with dose of 2.5 g qid (2000 mg ceftazidime and 500 mg avibactam)</td>
</tr>
<tr>
<td>Spectrum</td>
<td>Gram-negative infections, including extended-spectrum beta-lactamases (ESBLs: Ambler class A, B, C, and D) and Klebsiella pneumoniae carbapenemases (KPCs), including CTX-M types</td>
</tr>
<tr>
<td>Dose &amp; Adjustments*</td>
<td>≤8 / 4*</td>
</tr>
<tr>
<td>Safety</td>
<td>The most common adverse reactions (incidence &gt;10% in either indication) were vomiting, nausea, constipation, and anxiety</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Monitor CrCl at least daily in patients with changing renal function and adjust dose accordingly.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Susceptible (S)</th>
<th>Resistant (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>≤8 / 4*</td>
<td>≥16 / 4*</td>
</tr>
</tbody>
</table>

*Label includes a warning about decreased efficacy seen in patients with renal impairment.

**Avibactam: In Vitro Activity**

Ceftazidime-avibactam isolates from patients hospitalized in USA (2012–2013)

<table>
<thead>
<tr>
<th>Minimum Inhibitory Concentrations (µg/mL)</th>
<th>Susceptible (S)</th>
<th>Resistant (R)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5–4 µg/mL</td>
<td>67.6</td>
<td>99.0</td>
</tr>
<tr>
<td>50 µg/mL</td>
<td>97.5</td>
<td>99.0</td>
</tr>
<tr>
<td>500 µg/mL</td>
<td>95.6</td>
<td>99.0</td>
</tr>
<tr>
<td>5000 µg/mL</td>
<td>97.3</td>
<td>100.0</td>
</tr>
<tr>
<td>50,000 µg/mL</td>
<td>80.7</td>
<td>93.4</td>
</tr>
<tr>
<td>500,000 µg/mL</td>
<td>87.0</td>
<td>95.3</td>
</tr>
<tr>
<td>5,000,000 µg/mL</td>
<td>80.7</td>
<td>93.1</td>
</tr>
<tr>
<td>Extensively drug-resistant (DRD) (n=247)</td>
<td>74.5</td>
<td>88.1</td>
</tr>
</tbody>
</table>


**Microbiological Response for cUTIs**

*Response seen in 97 (90.7%) with ceftazidime-resistant pathogens.


**Current Availability of Ceftazidime-Tazobactam Susceptibility Tests**

- **Disks**
  - MAST Disk – Distributed by Hardy Diagnostics, commercially available FDA approved diameters for:
    - Enterobacteriaceae: ≥21mm (S), 18–20mm (I), and <17mm (R)
    - *P. aeruginosa*: ≥21mm (S), 17–20mm (I), and <16mm (R)

- **Gradient Strips**

- **Panels**
  - Vitrek 2 (Biomérieux) card approved and will undergo beta-lactamase testing: anticipate commercial availability in May/June 2017, software updates started in March 2017
  - Microscan (Beckman Coulter) expect commercial availability in late 2017/2018
  - Phoenix (BD) expect commercial availability late 2017/2018
  - Trek Panel (ThermoFisher Scientific) commercially available since Q1 2016

Status and availability on April 10, 2017.
Current Availability of Ceftazidime-Avibactam Susceptibility Tests

**Approved Tests**
- KB Disks from Hardy Diagnostic and BD
- Custom Sensititre (ThermoFisher)

**Tests in Development**
- Etest – RUO only available at [www.avycazeval.com](http://www.avycazeval.com), expected approval Q3 2017
- Phoenix – FDA approved, but not available yet

**Automated Tests**
- Vitek 2 – Software validation Q1 2017, expected approval Q2 2018
- Phoenix – FDA approved, but not available yet
- MicroScan – Expected to be available mid 2018

Patient Case: Mr. Z (cont’d)

- **Management plan:**
  - Patient remains on imipenem 500 mg IV q6h
- **New information:**
  - After 2 days, patient remains febrile with positive urine and blood cultures
  - C&S reveals *P. aeruginosa* with resistance to ceftazidime, pip/tazo, ciprofloxacin, and imipenem; susceptible to tobramycin and colistin

TJC Standard:

**CDC’s Core Elements of ASP**

1. **Leadership Commitment is critical to success of ASPs**
   - Dedicate necessary personnel, financial, and information technology resources

2. **Accountability**
   - Appoint single leader responsible for program outcomes
   - Physician involvement demonstrated to be highly effective

3. **Drug Expertise**
   - Appointing a single pharmacist leader responsible for working to improve antibiotic use

4. **Education**
   - Educating healthcare providers about resistance and encouraging optimal prescribing patterns

5. **Action**
   - Implement policies and interventions to improve antibiotic use

6. **Tracking**
   - Mentoring the antimicrobial stewardship program, which may include information on antibiotic prescribing and resistance patterns

7. **Reporting**
   - Regularly report findings to healthcare providers and other relevant staff

The Joint Commission recommends that organizations use this document when designing their antimicrobial stewardship program.

The Effect of Molecular Rapid Diagnostic Testing on Clinical Outcomes in Bloodstream Infections

**Meta-analysis**

Thirty-one studies (n=5920 patients)
- Mortality significantly lower with mRDT than conventional micro (OR, 0.66; 95% CI, 0.54-0.80).
- Mortality risk mRDT in studies with AMS (OR, 0.64; 95% CI, 0.51-0.79).
- Non-ASP studies failed to demonstrate a significant decrease in mortality risk (0.72; 0.46-1.12).
- Significant decreases in mortality risk were observed with:
  - Gram-positive (OR, 0.73; 95% CI, 0.55-0.97)
  - Gram-negative organisms (0.51; 0.33-0.78)
  - Yeast (0.90; 0.49-1.67)
  - Time to effective therapy decreased (weighted mean difference) of 5.03 hours (95% CI, -8.60 to -1.45 hours)
  - Length of stay decreased by 2.48 days (-3.90 to -1.06 days)

mRDT, molecular rapid diagnostic testing

Infection Control and Antimicrobial Stewards Working Together to Prevent HAIs, including *C. difficile*

**MUST HAVE** Leadership support, protected workload & resources

**Summary**
- Antibiotic resistance is extremely high and is receiving global (WHO) and national (CDC) priority levels
- Newer antimicrobial agents are part of the armamentarium in the management of infections caused by MDR Gram-negative bacteria
- Antimicrobial stewardship strategies minimize the burden of serious bacterial infections and MDROs in healthcare institutions

**Mystery Product Profile**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Treatment of <em>C. difficile</em> infection (CDI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product description / Mechanism of action</td>
<td>It inhibits nucleic acid synthesis by binding to and disrupting the DNA of microbial cells; activity against anaerobic bacteria</td>
</tr>
<tr>
<td>Pharmacokinetics / dynamics</td>
<td>Oral, 100% absorbed, re-excreted into colon when inflamed. MIC&lt;sub&gt;50&lt;/sub&gt; = 0.5 mcg/mL, MIC&lt;sub&gt;90&lt;/sub&gt; = 2.0 mcg/mL. Stool concentration: 1.9–77.3 mcg/gm, 40% &lt;10 mcg/gm, 30% &lt;5 mcg/gm</td>
</tr>
<tr>
<td>Efficacy (double-blind RCTs only)</td>
<td>Initial cure (vs. vancomycin): 72% (81%)* to 84% (97%)* Recurrence (vs. vancomycin): 23% (21%) to 14% (7%)*</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic metabolites cleared in urine; inhibits CYP2C9 and CYP3A4, may interfere with medications metabolized by these enzymes (e.g. warfarin, tacrolimus)</td>
</tr>
<tr>
<td>Common adverse reactions</td>
<td>Nausea (12%) sometimes accompanied by headache, anorexia, and occasionally vomiting; diarrhea; epigastric distress; and abdominal cramping</td>
</tr>
<tr>
<td>Warnings</td>
<td>Convulsive seizures and peripheral neuropathy; contraindicated in first trimester of pregnancy</td>
</tr>
</tbody>
</table>

*RCT = randomized controlled trial
*p<0.05

**Applying the Latest Approaches in the Management of *C. difficile* Infection and Recurrence**

Erik R. Dubberke, MD, MSPH, FSHEA
Associate Professor of Medicine
Director, Section of Transplant ID
Washington University School of Medicine
St. Louis, MO

**Audience Question**

Would you prescribe this product?
- a. Yes
- b. No

- 42% Yes
- 58% No

**C. difficile** is an “Urgent Threat”
- Over 450,000 cases per year
  - Over 29,000 associated deaths
- Most common cause of healthcare-associated infections in US

### CDI in the Community

![CDI in the Community Diagram]

- Community onset-healthcare associated
- Nursing home onset
- Hospital onset


### Current Pathogenesis Model for CDI

1. **C. difficile exposure**
2. **Antimicrobial(s)**
3. **Asymptomatic C. difficile colonization**
4. Acquisition of a toxigenic strain of C. difficile and failure to mount an anamnestic antibody response results in CDI.


### Current Pathogenesis Model for CDI

- **C. difficile exposure**
- **Antimicrobial(s)**
- **Asymptomatic C. difficile colonization**
- Acquisition of a toxigenic strain of C. difficile and failure to mount an anamnestic antibody response results in CDI.


### CDI: The Host

- **Risk Factors**
  - Age ≥65: 3.93 (.009) vs. 3.76 (.024)
  - Female: 1.02 (.971)
  - Horn index >1: 4.20 (.077) vs. 2.06 (.086)
  - Concomitant antibiotics: 2.20 (.095) vs. 2.06 (.19)
  - Gastric acid suppression: 0.92 (.870)
  - Prior CDI: 2.70 (.041) vs. 2.58 (.09)
  - Anti-toxin A: 0.40 (.401)
  - Anti-toxin B: 0.12 (.045) vs. 0.11 (.05)


### Antibiotics and CDI Risk

- **Very Commonly Related**
  - Clindamycin
  - Ampicillin
  - Amoxicillin
  - Cephalosporins
  - Fluoroquinolones

- **Less Commonly Related**
  - Beta-lactam inhibitors
  - Macrolides
  - Carbapenems
  - Tigecycline

- **Uncommonly Related**
  - Aminoglycosides
  - Metronidazole
  - Rifampin
  - Tetracyclines
  - Daptomycin
  - Sulfonamides
  - Trimethoprim


### Microbiota Disruption, Antibiotics, and C. difficile Exposure Timing

- **Firmicutes and Bacteroidetes**
  - Likely combination of metabolic pathways more important than individual organisms
  - ? Bile salt metabolism

CDI Risk: *C. difficile* Strain

- Current epidemic strain: BI / NAP1 / ST1 / 027
  - Higher attack rate
  - NAP1: 55%
  - Non-NAP1: 29%
  - More severe disease
  - 50% higher recurrence rate
- Natural history of CDI
  - Predominant/more virulent strains emerge


Toxin B is Key

- *Toxin B is Key*
- Virulence no different between wild-type and toxin B only strains
- Virulence significantly reduced for toxin A only strains


Patient Case

- 86-year-old female with hypertension
  - Recently completed a course of ciprofloxacin for a UTI
  - 2 days of abdominal cramping, 5–7 diarrheal bowel movements per day
  - BP 96/52 mm Hg, but responded to IV fluids
  - Her creatinine was at its baseline; WBC was 14,700/mm³, and stool was positive for *C. difficile* toxins by EIA.

Audience Question

**How would you treat her CDI?**

- a. Metronidazole 500 mg PO every 8 hours*
- b. Vancomycin 125 mg PO every 6 hours*
- c. Fidaxomicin 200 mg PO every 12 hours*

*all regimens are for 10 days

CDI Treatment Stratified by Severity: First CDI Episode (2010 Guidelines)*

<table>
<thead>
<tr>
<th>Clinical scenario</th>
<th>Supportive clinical data</th>
<th>Recommended treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to moderate</td>
<td>Leukocytosis (WBC &lt;15,000 cells/mL) or SCr level ≥1.5 x premorbid level</td>
<td>Metronidazole 500 mg 3 times per day PO for 10-14 days</td>
</tr>
<tr>
<td>Severe</td>
<td>Leukocytosis (WBC 215,000 cells/mL) or SCr level ≥21.5 x premorbid level</td>
<td>Vancomycin 125 mg 4 times per day PO for 10-14 days</td>
</tr>
<tr>
<td>Severe, complicated</td>
<td>Hypotension or shock, ileus, megacolon</td>
<td>Vancomycin 500 mg 4 times per day PO or by nasogastric tube plus metronidazole 500 mg Q 8 hrs</td>
</tr>
</tbody>
</table>

*Updated IDSA/SHEA *C. difficile* guidelines expected in Summer 2017.

Metronidazole Also Inferior For Non-Severe CDI

- Vancomycin superior to metronidazole on multivariable analysis, including controlling for clinical severity (p<0.013)
**Fidaxomicin for CDI**

- Novel antimicrobial: macrocyclic
- Narrow spectrum: No activity against Gram-negatives
  - Sparing of Bacteroides spp., bifidobacterium, clostridial clusters IV and XIV
- Decrease in recurrences
  - Studies included patients with first and second CDI episodes
  - Role of dysbiosis?

**Impact on Microbiome: Fidaxomicin vs. Vancomycin**

![Graph showing impact on microbiome](image)


**Mystery Product Profile**

**METRONIDIZOLE**

- Poor / inconsistent penetration to site of infection
- More side effects
- Inferior efficacy compared to vancomycin in double-blinded randomized controlled trials


**Should Treatment of Initial CDI Focus on Recurrence Risk?**

- If metronidazole is inferior for mild/moderate CDI, no need to select treatment based on CDI severity
- Major differentiators in currently available treatments
  - Impact of concomitant antibiotics
  - Recurrence

**Impact of Concomitant Antibiotics on Response to CDI Treatment**

![Graph showing impact of concomitant antibiotics](image)


**Back to the Case**

- The patient responded appropriately to a 10-day course of vancomycin. One month later, she complained of foul smell to her urine
  - She was prescribed another course of ciprofloxacin for a “UTI”
  - Three days later, she developed clinically significant diarrhea, and she tested positive for *C. difficile* toxins again
Audience Question

How would you treat this patient?

- Vancomycin 125 mg PO QID for 10 days
- Fidaxomicin 200 mg PO BID for 10 days
- Vancomycin 125 mg PO QID for 10 days, followed by fecal microbiota transplantation
- Vancomycin 125 mg PO QID for 10 days, followed by bezlotoxumab 10 mg/kg IV x 1

Recurrent CDI

- Recurrence risk after first episode 10% to 30%
  - Risk increases with additional recurrences
- Associated with worse outcomes
  - Readmissions (RR=2.5; 95% CI, 2.2–2.9)
  - Costs ($11,631; 95% CI, $8,937–$14,588)
  - Mortality (HR=1.3; 95% CI, 1.1–1.6)

Ten Days of Fidaxomicin May Not Be Enough for Recurrent CDI: Potential Role for Chaser or Taper

- Ten Days of Fidaxomicin May Not Be Enough for Recurrent CDI: Potential Role for Chaser or Taper

Recurrent CDI: 2010 IDSA/SHEA Guidelines*

- Clinical scenario
  - First recurrence: Treat as first episode according to disease severity
  - Second recurrence: Treat with oral vancomycin taper and/or pulse dosing
  - Third recurrence: FMT is recommended

Risk Factors Associated with CDI Recurrence

- Findings from Selected Key Publications

Abrupt Stop vs. Taper or Pulse of Vancomycin

- Abrupt Stop vs. Taper or Pulse of Vancomycin

**FMT Prospective Trials:**

**Single Dose FMT Efficacy 60%−70%**

<table>
<thead>
<tr>
<th>Study</th>
<th>Single dose</th>
<th>Second dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Youngster (n=20)</td>
<td>70%</td>
<td>90%</td>
</tr>
<tr>
<td>Hirsch (n=19)</td>
<td>68%</td>
<td>89%</td>
</tr>
<tr>
<td>Orenstein (n=34)</td>
<td>52%</td>
<td>79%</td>
</tr>
<tr>
<td>Youngster (n=14)</td>
<td>70%</td>
<td>90%</td>
</tr>
<tr>
<td>Van Nood (n=16)</td>
<td>81%</td>
<td>94%</td>
</tr>
<tr>
<td>Lee (PP n=178, mITT n=219)</td>
<td>62% / 51%</td>
<td>84% / 73%</td>
</tr>
<tr>
<td>Khanna (n=30)*</td>
<td>87%</td>
<td>97%</td>
</tr>
<tr>
<td>Press release (n=59)*</td>
<td>56%</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Same product*

**When the Cardiologists Start to Demand Bezlotoxumab…**

- No difference in resolution of CDI
  - 80% bezlotoxumab vs. 80% placebo
- Caution with congestive heart failure
  - Serious adverse events
    - 15/118 (13%) bezlotoxumab vs. 5/104 (5%) placebo
  - Death
    - 23/118 (20%) bezlotoxumab vs. 13/104 (13%) placebo

**Bezlotoxumab: 30-day Readmission**

| Data compiled from MODIFY I and MODIFY II comparing bezlotoxumab (BZO) or placebo, both with standard of care antibiotics. |

**Conclusions**

- Risk of CDI and recurrent CDI related to:
  - Host (immune response)
  - Microbiome (antimicrobial exposures)
  - *C. difficile* strain
- Metronidazole IS no longer first-line treatment
  - Treatment selection based on recurrence risk, not severity
- Current approach to prevent recurrence is with microbiome preservation / restoration
- Immune restoration approach now available