Antimicrobial Stewardship Strategies to Reduce Hospital-Acquired Clostridium Difficile Infections
Disclosure

Lucas Schulz
Merck Health Solutions: Consultant; Theravance: Speaker’s Bureau

Tristan Timbrook
Biofire Diagnostics, LLC: Consultant, Speaker’s Bureau; GenMark Diagnostics, Inc.: Advisory Board, Consultant

All other planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.
Antimicrobial Stewardship Is A Team Sport

Erin K. McCreary, Pharm.D., BCPS
Education & Development Coordinator
Infectious Diseases Clinical Pharmacist
UW Health
Madison, WI
@erinmccreary
Learning Objective

• Design team-based antimicrobial stewardship initiatives to reduce Clostridium difficile infection (CDI) rates in an acute care setting.
Antimicrobial Stewardship Team

- Physicians
  - AMS physicians
  - ID fellows
  - MD representative from speciality areas
- Microbiology lab
  - Director
  - Fellows
  - Technicians
- Infection control team
- Epidemiologist
- Hospital leadership
- Environmental services
- Pharmacists
  - AMS pharmacists
  - Decentralized pharmacists
  - Drug policy program
  - Medication safety coordinator
  - Informatics
  - Residents
  - APPE and IPPE Students
- Nurses
- Patients and families
Antimicrobial stewardship programs (ASPs) positively impact patient care, but metrics to assess ASP impact are poorly defined. We used a modified Delphi approach to select relevant metrics for assessing patient-level interventions in acute-care settings for the purposes of internal program decision making. An expert panel rated 90 candidate metrics on a 9-point Likert scale for association with 4 criteria: improved antimicrobial prescribing, improved patient care, utility in targeting stewardship efforts, and feasibility in hospitals with electronic health records. Experts further refined, added, or removed metrics during structured teleconferences and re-rated the retained metrics.

Six metrics were rated >6 in all criteria: 2 measures of *Clostridium difficile* incidence, incidence of drug-resistant pathogens, days of therapy over admissions, days of therapy over patient days, and redundant therapy events. Fourteen metrics rated >6 in all criteria except feasibility were identified as targets for future development.

**Keywords.** antimicrobial stewardship; patient safety; process measure; outcome measure; quality metrics.
CDI at UW Health

<table>
<thead>
<tr>
<th>UNIVERSITY OF WI HOSPITALS &amp; CLINICS AUTHORITY</th>
<th>No. of Infections Reported (A)</th>
<th>Number of Patient Days</th>
<th>Predicted No. Infections (B)</th>
<th>Standardized Infection Ratio (SIR) (A/B)</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>217</td>
<td>162344</td>
<td>156.006</td>
<td>1.391</td>
<td>Worse than the National Benchmark</td>
</tr>
</tbody>
</table>
# CDI at UW Health

<table>
<thead>
<tr>
<th>No. of Infections Reported (A)</th>
<th>Number of Patient Days</th>
<th>Predicted No. Infections (B)</th>
<th>Standardized Infection Ratio (SIR) (A/B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNIVERSITY OF WI HOSPITALS &amp; CLINICS AUTHORITY</td>
<td>217</td>
<td>162344</td>
<td>156.006</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.391</td>
</tr>
</tbody>
</table>

**Evaluation**

Worse than the National Benchmark
## CDI at UW Health: Comparison

<table>
<thead>
<tr>
<th>Peer Institutions</th>
<th>Reported Infections</th>
<th>Predicted Infections</th>
<th>SIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regional #1 (small community)</td>
<td>27</td>
<td>65</td>
<td>0.453</td>
</tr>
<tr>
<td>Regional #2 (large community)</td>
<td>23</td>
<td>47</td>
<td>0.48</td>
</tr>
<tr>
<td>Regional #3 (large academic)</td>
<td>210</td>
<td>151</td>
<td>1.391</td>
</tr>
<tr>
<td>Regional #4 (large academic)</td>
<td>172</td>
<td>174</td>
<td>0.99</td>
</tr>
<tr>
<td>Regional #5 (large academic)</td>
<td>199</td>
<td>166</td>
<td>1.19</td>
</tr>
<tr>
<td>National #1 (large academic)</td>
<td>95</td>
<td>118</td>
<td>0.80</td>
</tr>
<tr>
<td>National #2 (large academic)</td>
<td>78</td>
<td>119</td>
<td>0.66</td>
</tr>
</tbody>
</table>
CDI at UW Health: Comparison

<table>
<thead>
<tr>
<th>Peer Institutions</th>
<th>Reported Infections</th>
<th>Predicted Infections</th>
<th>SIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regional #1 (small community)</td>
<td>27</td>
<td>65</td>
<td>0.453</td>
</tr>
<tr>
<td>Regional #2 (large community)</td>
<td>23</td>
<td>47</td>
<td>0.48</td>
</tr>
<tr>
<td>Regional #3 (large academic)</td>
<td>210</td>
<td>151</td>
<td>1.391</td>
</tr>
<tr>
<td>Regional #4 (large academic)</td>
<td>172</td>
<td>174</td>
<td>0.99</td>
</tr>
<tr>
<td>Regional #5 (large academic)</td>
<td>199</td>
<td>166</td>
<td>1.19</td>
</tr>
<tr>
<td>National #1 (large academic)</td>
<td>95</td>
<td>118</td>
<td>0.80</td>
</tr>
<tr>
<td>National #2 (large academic)</td>
<td>78</td>
<td>119</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Only 38 hospitals in the US have more hospital-onset cases of CDI than UW
## CDI at UW Health: Comparison

<table>
<thead>
<tr>
<th>Peer Institutions</th>
<th>Reported Infections</th>
<th>Predicted Infections</th>
<th>SIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regional #1 (small community)</td>
<td>27</td>
<td>65</td>
<td>0.453</td>
</tr>
<tr>
<td>Regional #2 (large community)</td>
<td>23</td>
<td>47</td>
<td>0.48</td>
</tr>
<tr>
<td>Regional #3 (large academic)</td>
<td>210</td>
<td>151</td>
<td>1.391</td>
</tr>
<tr>
<td>Regional #4 (large academic)</td>
<td>172</td>
<td>174</td>
<td>0.99</td>
</tr>
<tr>
<td>Regional #5 (large academic)</td>
<td>199</td>
<td>166</td>
<td>1.19</td>
</tr>
<tr>
<td>National #1 (large academic)</td>
<td>95</td>
<td>118</td>
<td>0.80</td>
</tr>
<tr>
<td>National #2 (large academic)</td>
<td>78</td>
<td>119</td>
<td>0.66</td>
</tr>
</tbody>
</table>

94% of hospitals in the US have a **better SIR** than UW
CDI Reduction Efforts

- Testing algorithm redesign
- Admission screening in high-risk populations
- Nursing documentation of stool consistency
- Enhanced PPE requirements and education
- Enhanced hand-washing education and auditing
- Environmental services initiatives
- Post-prescription review and feedback
- Oral vancomycin prophylaxis
- Probiotics
- Proton pump inhibitor de-prescribing
**CDI Reduction Efforts**

- Testing algorithm redesign – all patients
- Admission screening in high-risk populations – oncology and transplant
- Nursing documentation of stool consistency – all patients
- Enhanced PPE requirements and education – all patients
- Enhanced hand-washing education and auditing – all patients
- Environmental services initiatives – all patients
- Post-prescription review and feedback – all patients on antibiotics
- Oral vancomycin prophylaxis – oncology and transplant
- Probiotics – medicine units
- Proton pump inhibitor de-prescribing – all patients
Antibiotic Exposure and CDI Risk

- Clindamycin
- Cephalosporins
- Carbapenems
- Fluoroquinolones
- ß-lactam/ß-lactamase inhibitor combinations
Effects of control interventions on *Clostridium difficile* infection in England: an observational study

Kate E Dingle, Xavier Didelot, T Phuong Quan, David W Eyre, Nicole Stoesser, Tanya Golubchik, Rosalind M Harding, Daniel J Wilson, David Griffiths, Alison Vaughan, John M Finney, David H Wyllie, Sarah J Oakley, Warren N Fawley, Jane Freeman, Kirsti Morris, Jessica Martin, Philip Howard, Sherwood Gorbach, Ellie J C Goldstein, Diane M Citron, Susan Hopkins, Russell Hope, Alan P Johnson, Mark H Wilcox, Timothy E A Peto, A Sarah Walker, Derrick W Crook, the Modernising Medical Microbiology Informatics Group*

FDA Drug Safety Communication: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects

Safety Announcement

[07-26-2016] The U.S. Food and Drug Administration (FDA) approved changes to the labels of fluoroquinolone antibacterial drugs for systemic use (i.e., taken by mouth or by injection). These medicines are associated with disabling and potentially permanent side effects of the tendons, muscles, joints, nerves, and central nervous system that can occur together in the same patient. As a result, we revised the Boxed Warning, FDA’s strongest warning, to address these serious safety issues. We also added a new warning and updated other parts of the drug label, including the patient Medication Guide.

We have determined that fluoroquinolones should be reserved for use in patients who have no other treatment options for acute bacterial sinusitis (ABS), acute bacterial exacerbation of chronic bronchitis (ABECB), and uncomplicated urinary tract infections (UTI) because the risk of these serious side effects generally outweighs the benefits in these patients. For some serious bacterial infections the benefits of fluoroquinolones outweigh the risks, and it is appropriate for them to remain available as a therapeutic option.
Pilot: Who, What, When

- Transplant unit and MICU/SICU
  - Highest incidence of CDI
- FQs commonly prescribed for:
  - Lower respiratory tract infections
  - Abdominal infections
  - Urinary tract infections
  - Bloodstream infections
- July 2016
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Historical Empiric Therapy</th>
<th>Proposed New Empiric Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic Shock – unknown origin empiric coverage of Pseudomonas</td>
<td>Vancomycin PLUS Piperacillin/tazobactam AND Ciprofloxacin</td>
<td>- Vancomycin(^A) PLUS piperacillin/tazobactam PLUS tobramycin OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Vancomycin(^A) PLUS cefepime PLUS tobramycin OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Vancomycin(^A) PLUS meropenem PLUS tobramycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For patients with IgE-mediated or severe reaction to (\beta)-lactam: vancomycin(^A) PLUS aztreonam PLUS tobramycin PLUS metronidazole</td>
</tr>
<tr>
<td>Community-acquired Pneumonia</td>
<td>Moxifloxacin</td>
<td>No risk factors for MDRO: ceftriaxone OR ampicillin/sulbactam</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If concern for atypical bacteria or Legionnaires' disease: ADD azithromycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For patients with IgE-mediated or severe reaction to (\beta)-lactam: vancomycin(^A) AND aztreonam</td>
</tr>
<tr>
<td>Healthcare-associated Pneumonia</td>
<td>Vancomycin PLUS Piperacillin/tazobactam AND Ciprofloxacin</td>
<td>With risk factors for MDRO: vancomycin(^A) PLUS piperacillin/tazobactam OR cefepime</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If patient in septic shock: ADD tobramycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If concern for atypical bacteria or Legionnaires' disease: ADD azithromycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For patients with IgE-mediated or severe reaction to (\beta)-lactam: vancomycin(^A) PLUS aztreonam</td>
</tr>
<tr>
<td>Sepsis (without septic shock) of urinary origin/pyelonephritis</td>
<td>Vancomycin AND/OR ciprofloxacin</td>
<td>No risk factors for MDRO: ceftriaxone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>With risk factors for MDRO: vancomycin(^A) PLUS cefepime</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For patients with IgE-mediated or severe reaction to (\beta)-lactam: vancomycin(^A) PLUS tobramycin</td>
</tr>
<tr>
<td>Intraabdominal infection – with or without septic shock(^B)</td>
<td>Ciprofloxacin AND metronidazole</td>
<td>No risk factors for MDRO:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- ceftriaxone AND metronidazole OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- cefoxitin OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- piperacillin/tazobactam</td>
</tr>
<tr>
<td></td>
<td></td>
<td>With risk factors for MDRO: vancomycin(^A) PLUS piperacillin/tazobactam PLUS tobramycin OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- vancomycin(^A) PLUS cefepime PLUS tobramycin PLUS metronidazole OR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- vancomycin(^A) PLUS meropenem with or without tobramycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>For patients with IgE-mediated or severe reaction to (\beta)-lactam: vancomycin(^A) PLUS aztreonam PLUS tobramycin PLUS metronidazole</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Historical Empiric Therapy</td>
<td>Proposed New Empiric Therapy</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>---------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Cystitis or Uncomplicated Urinary Tract Infection (non-renal transplant)</td>
<td>Ciprofloxacin OR Levofloxacin</td>
<td>Nitrofurantoin Fosfomycin Cefpodoxime</td>
</tr>
<tr>
<td>Positive urine culture in the deceased renal transplant donor</td>
<td>Ciprofloxacin</td>
<td>No risk factors for MDRO: ceftriaxone</td>
</tr>
<tr>
<td>ADD Vancomycin IF concern for Gram-positive organisms</td>
<td></td>
<td>Concern for extended spectrum Gram-negative rods: cefepime or piperacillin/tazobactam</td>
</tr>
<tr>
<td>For patients with IgE-mediated or severe reaction to β-lactam:</td>
<td></td>
<td>tobramycin or aztreonam</td>
</tr>
<tr>
<td>Cystitis in renal transplant patient</td>
<td>Ciprofloxacin</td>
<td>No antibiotic. Await final culture results to start therapy. If treatment started, provide 5-7 day therapy course</td>
</tr>
<tr>
<td>ASYMPTOMATIC &lt;3 months post renal transplant</td>
<td></td>
<td>No treatment, unless associated rise in creatinine</td>
</tr>
<tr>
<td>ASYMPTOMATIC &gt;3 months post renal transplant</td>
<td></td>
<td>Nonsystemic therapies • nitrofurantoin if CRCL &gt;40 mL/min</td>
</tr>
<tr>
<td>SYMPTOMS present</td>
<td></td>
<td>fosfomycin if CRCL &lt;40 mL/min or concern for drug resistant isolates</td>
</tr>
<tr>
<td>Pyelonephritis in renal transplant patient</td>
<td>Ciprofloxacin</td>
<td>No risk factors for MDRO: ceftriaxone</td>
</tr>
<tr>
<td>ADD Vancomycin IF concern for Gram-positive organisms</td>
<td></td>
<td>Concern for extended spectrum Gram-negative rods: cefepime or piperacillin/tazobactam</td>
</tr>
<tr>
<td>For patients with IgE-mediated or severe reaction to β-lactam:</td>
<td></td>
<td>tobramycin (while awaiting pathogen identification) OR aztreonam²</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Historical Empiric Therapy</td>
<td>Proposed New Empiric Therapy</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Cholangitis in the historical liver transplant recipient                 | Ciprofloxacin PLUS amoxicillin OR moxifloxacin            | • Piperacillin/tazobactam PLUS metronidazole OR  
• Cefepime PLUS metronidazole  
For patients with IgE-mediated or severe reaction to β-lactam:  
• vancomycin (trough goal 10-20 mcg/mL) PLUS tobramycin OR  
• vancomycin (trough goal 10-20 mcg/mL) PLUS aztreonam | Cefpodoxime OR cefuroxime PLUS amoxicillin (Enterococcus coverage)  
If no oral options, page 3333 for fluoroquinolone approval                                                                                                                                              |
| Intra-abdominal infection – Other community or healthcare associated       | Ciprofloxacin AND metronidazole                           | No risk factors for MDRO:  
• ceftiraxone AND metronidazole | Base on final culture results, some examples of potential oral options:  
• cefpodoxime OR cefuroxime PLUS metronidazole  
• amoxicillin/clavulanic acid  
If final culture results require fluoroquinolone step down (e.g. Pseudomonas) single oral dose prior to discharge is acceptable                                                                                                                                 |
| Community-acquired Pneumonia^{B}                                         | Vancomycin PLUS Piperacillin/tazobactam AND Ciprofloxacin | With risk factors for MDRO:  
• vancomycin^{C} PLUS piperacillin/tazobactam OR  
• vancomycin^{C} PLUS meropenem  
With risk factors for MDRO and IgE-mediated or severe reaction to β-lactam:  
• vancomycin^{C} PLUS aztreonam PLUS metronidazole | Potential oral options:  
• cefpodoxime OR cefuroxime PLUS azithromycin OR doxycycline  
If no oral options, page 3333 for fluoroquinolone approval                                                                                                                                 |
| Healthcare-associated Pneumonia^{B}                                     | Moxifloxacin OR Levofloxacin                              | No risk factors for MDRO:  
• ceftiraxone PLUS doxycycline OR  
• ceftiraxone PLUS azithromycin  
For patients with IgE-mediated or severe reaction to β-lactam:  
• vancomycin^{C} PLUS aztreonam^{B} | Double coverage for Pseudomonas is not required in clinically stable, general care patient  
If no oral options, page 3333 for fluoroquinolone approval                                                                                                                                 |

\[^A\] Additional comments or considerations for each condition.
Pilot: How

- Aminoglycoside safety
- Cross-table antibiogram
- Physician support
- Pharmacist education
- Nursing and resident education
- Electronic decision support
**DRUG WARNING:** Use of fluoroquinolones is restricted at University Hospital. Use requires approval via ID consult or 3333 pager per P&T restriction.

Use weblinks at right for guidance in selecting alternatives to fluoroquinolones.

Follow weblink at right for guidance on managing patients with a reported beta-lactam allergy/intolerance.

You may also discuss alternatives with the unit pharmacist.

<table>
<thead>
<tr>
<th>Alternative</th>
<th>Details</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>cefpodoxime (VANTIN) tab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>fosfomycin (MONUROL) oral packet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nitrofurantoin monohydrate (MACROBID) cap</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ampicillin/subactam (UNASYN) intraVENSUS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>aztreonam (AZACTAM) intraVENSUS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>azithromycin (ZITHROMAX) intraVENSUS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cefotaxime (ROCEPHIN) intraVENSIX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cefepime (MAXIPIME) intraVENSUS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>gentamicin (GARAMYCIN) intraVENSUS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>piperacillin/tazobactam (ZOSYN) intraVENSUS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sulfamethoxazole-trimethoprim (BACTRIM DS) 800-160 MG per ...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tobramycin (NEBCYN) intraVENSUS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefepime and metRONI Dazole</td>
<td><em><strong>PANEL</strong></em></td>
<td></td>
</tr>
<tr>
<td>Cefpodoxime and metRONI Dazole</td>
<td><em><strong>PANEL</strong></em></td>
<td></td>
</tr>
<tr>
<td>Cefepime - Tobramycin</td>
<td><em><strong>PANEL</strong></em></td>
<td></td>
</tr>
<tr>
<td>Vancomycin and Tobramycin</td>
<td><em><strong>PANEL</strong></em></td>
<td></td>
</tr>
</tbody>
</table>
### ciprofloxacin (CIPRO) bag

#### Suspected Indication (Select all that apply)
- Pneumonia
- Septicemia
- Abdominal Infection
- Gynecological/Pelvic
- Clostridium difficile
- Cellulitis, Skin and Soft Tissue
- Diabetic Foot Infection
- Osteomyelitis/Septic Arthritis
- Urinary Tract Infection
- Endocarditis
- Meningitis
- Sinusitis/Other ENT
- Neutropenic Fever
- Sexually Transmitted Infection
- Burn Wound
- Surgical Wound Infection
- Prosthetic Device Infection
- Line Infection
- Transplant Donor Infection
- Site Not Specified
- Non-Infectious
- Surgical Prophylaxis

#### Dosing of this medication varies based on severity of illness. Does this patient have sepsis or concern for sepsis (probable or documented infection plus systemic manifestations of infection)?
- Yes
- No

#### Approved Fluoroquinolone Use

#### Dose:
- 400 mg
- 600 mg

#### Route:
- Intravenous
- Intravenous

#### Frequency:
- Once
- Q 24 Hrs
- Q 12 Hrs
- Q 8 Hrs
- On Call
Current inpatient consult recommendation

- Approval via 3333 (restricted drug) pager
- One time dose after hours - use between 2300 and 0700 only
- Aztreonam - per fluoroquinolone restriction procedure
- Posaconazole - per approved oncology treatment protocol
- Rehab Hospital - approved prior to admission to Rehab Hospital
- Fidaxomicin - ID or GI attending use only

- Approved fluoroquinolone use per P&T restriction exemptions
Existing Restriction Modification

• “Aztreonam may be used without Infectious Disease approval for up to 72 hours of empiric use. After 72 hours, ID approval required through ID consult or Restricted Antimicrobial Pager (*3333)”
Pilot Results: August 2016

• Pilot Units
  – MICU/SICU FQ use ↓ 70.5%
  – Transplant FQ use ↓ 65.8%

• Non-pilot Units
  – General Medicine and Hospitalist FQ use ↓ 39.7%
  – Overall FQ use at University Hospital ↓ 29.6%
  – Overall FQ use at The American Center ↓ 33.3%
<table>
<thead>
<tr>
<th>Indication</th>
<th>Order Set Utilization N</th>
<th>Alternative compliance N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholangitis</td>
<td>6</td>
<td>4 (67)</td>
</tr>
<tr>
<td>Community-acquired pneumonia</td>
<td>7</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Cystitis</td>
<td>4</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Healthcare-associated pneumonia</td>
<td>24</td>
<td>13 (54)</td>
</tr>
<tr>
<td>Intraabdominal infection</td>
<td>26</td>
<td>21 (81)</td>
</tr>
<tr>
<td>Positive donor culture (renal transplant)</td>
<td>5</td>
<td>4 (80)</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>8</td>
<td>6 (75)</td>
</tr>
<tr>
<td>Sepsis (urinary tract source)</td>
<td>10</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Septic shock – unknown origin</td>
<td>7</td>
<td>3 (43)</td>
</tr>
<tr>
<td>Other infection</td>
<td>41</td>
<td>40 (98)</td>
</tr>
</tbody>
</table>

104/138 = 75% overall compliance
Results: Safety & Efficacy

• Safety
  – 7/138 treatment courses used AG
    • 2 patients developed AKI

• Efficacy
  – 5/124 patients readmitted for same infection
    • 3 intraabdominal
    • 2 cellulitis
Pilot Results: November 2016

Number of HA-CDI cases

Antimicrobial Utilization

Intervention Start Date
## Results: November 2016

<table>
<thead>
<tr>
<th>HA-CDI Cases Per 10,000 Patient Days</th>
<th>Pre-intervention</th>
<th>Post-intervention</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>University Hospital</td>
<td>8.36</td>
<td>5.65</td>
<td>0.05</td>
</tr>
<tr>
<td>Pilot Units</td>
<td>16.8</td>
<td>7.7</td>
<td>0.12</td>
</tr>
</tbody>
</table>
House-Wide Expansion

• March 15th, 2017
• Create general medicine/surgery alternative tables
• Update 66 order sets containing FQs
• Education via institutional Lexicomp®
• Exclusions: Children’s Hospital, Emergency Department, Regional hospitals
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Historical Empiric Therapy</th>
<th>Proposed New Empiric Therapy</th>
<th>Comments/Step Down Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystitis or Uncomplicated Urinary Tract Infection</td>
<td>Ciprofloxacin OR Levofloxacin</td>
<td>Nitrofurantoin Fosfomycin Cefpodoxime</td>
<td>Do not treat asymptomatic bacteriuria</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Base on final culture results: nitrofurantoin, fosfomycin, TMP/SMX, cefpodoxime</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ceftriaxone susceptibility predicts activity for cefpodoxime</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>Ciprofloxacin OR Levofloxacin</td>
<td>No risk for MDRO: cefpodoxime or ceftriaxone</td>
<td>If no oral options, page 3333 for fluoroquinolone approval</td>
</tr>
<tr>
<td></td>
<td></td>
<td>With risk factors for MDRO: cefepime and vancomycin</td>
<td>Tailor therapy based on final culture results</td>
</tr>
<tr>
<td></td>
<td></td>
<td>With risk factors for MDRO and IgE-mediated or severe reaction to β-lactam: gentamicin OR TMP/SMX</td>
<td>Ceftriaxone susceptibility predicts activity for cefpodoxime</td>
</tr>
<tr>
<td>Spontaneous bacterial peritonitis (SBP) prophylaxis</td>
<td>Ciprofloxacin</td>
<td>Oral therapy: TMP/SMX OR cefpodoxime</td>
<td>May transition to oral equivalent of empiric regimen OR to ciprofloxacin at discharge</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intravenous therapy: ceftriaxone</td>
<td>base on final culture results, some examples of potential oral options: cefpodoxime OR cefuroxime PLUS metronidazole, amoxicillin/clavulanic acid</td>
</tr>
<tr>
<td>Intra-abdominal infection – community or healthcare associated</td>
<td>Ciprofloxacin AND metronidazole</td>
<td>No risk factors for MDRO: cefpodoxime AND metronidazole OR ceftriaxone AND metronidazole</td>
<td>If final culture results require fluoroquinolone step down (e.g. Pseudomonas) single oral dose prior to discharge is acceptable</td>
</tr>
<tr>
<td></td>
<td>Vancomycin PLUS Piperacillin/ tazobactam AND Ciprofloxacin</td>
<td>With risk factors for MDRO or severe community-acquired infection: vancomycin PLUS piperacillin/tazobactam OR vancomycin PLUS cefepime AND metronidazole</td>
<td>If final culture results require fluoroquinolone step down (e.g. Pseudomonas) single oral dose prior to discharge is acceptable</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Historical Empiric Therapy</td>
<td>Proposed New Empiric Therapy</td>
<td>Comments/Step Down Therapy</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>---------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| Community-acquired Pneumonia<sup>D</sup>     | Moxifloxacin OR Levofloxacin | No risk factors for MDRO:  
• ceftriaxone PLUS doxycycline OR  
• ceftriaxone PLUS azithromycin  
For patients with IgE-mediated or severe reaction to β-lactam: vancomycin<sup>B</sup> PLUS aztreonam<sup>C</sup> | Potential oral options: cefpodoxime OR cefuroxime PLUS azithromycin OR doxycycline  
If no oral options, page 3333 for fluoroquinolone approval |
| Healthcare-associated Pneumonia<sup>D</sup>  | Vancomycin PLUS Cefepime AND Ciprofloxacin | With risk factors for MDRO:  
vancomycin<sup>B</sup> PLUS cefepime  
If patient in septic shock: ADD tobramycin (Pending transfer to higher care level)  
If concern for atypical bacteria: ADD azithromycin  
For patients with IgE-mediated or severe reaction to β-lactam: vancomycin<sup>B</sup> PLUS aztreonam<sup>C</sup> | Double coverage for *Pseudomonas* is not required in clinically stable, general care patient  
If no oral options, page 3333 for fluoroquinolone approval |
| Sepsis (without septic shock) of urinary origin/pyelonephritis | Vancomycin AND/OR ciprofloxacin | No risk factors for MDRO:  
ceftriaxone  
With risk factors for MDRO:  
vancocycin<sup>B</sup> PLUS cefepime  
For patients with IgE-mediated or severe reaction to β-lactam:  
vancocycin<sup>B</sup> PLUS tobramycin | | |
| Septic Shock – unknown origin empiric coverage of *Pseudomonas* | Vancomycin PLUS Piperacillin/tazobactam AND Ciprofloxacin |  
• Vancomycin<sup>B</sup> PLUS piperacillin/tazobactam PLUS tobramycin OR  
• Vancomycin<sup>B</sup> PLUS cefepime PLUS tobramycin  
For patients with IgE-mediated or severe reaction to β-lactam:  
Vancomycin<sup>B</sup> PLUS aztreonam<sup>C</sup> PLUS tobramycin PLUS metronidazole | |
Ciprofloxacin (Systemic) [Formulary] [Restricted] (UW Health)

P & T Restrictions

Systemic fluoroquinolone use (ciprofloxacin, levofloxacin, and moxifloxacin) is restricted at University Hospital. Systemic fluoroquinolone use will be permitted based on ID consult or approval.

Antibiotic alternatives for use may be found on UConnect

- Intensive Care
- General Care
- Abdominal Transplant
Exemptions

- Fever and neutropenia prophylaxis (oncology)
- 24-hour periprocedural use (urology)
- Cystic fibrosis exacerbation treatment (pulmonary)
- 24-hour perioperative use in selected procedures in patients with severe or immediate IgE-mediated beta-lactam allergy or intolerance
Audience Participation
You Live and You Learn

- Cefepime shortage
- Allergies
- Prior-to-admission medications
- Readmissions
- Facilitating discharge
- Renal transplant / Nephrology
- GI clinic
- Pulmonary
- Emergency Department
- Ophthalmology
- Leeches
- Ebola
<table>
<thead>
<tr>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use at TAC, Rehab, AFCH or Swedish American (FQ restriction only applies to University Hospital)</td>
</tr>
<tr>
<td>Approval via 3333 (restricted drug pager)</td>
</tr>
<tr>
<td>One time dose after hours – use between 2300 and 0700 only</td>
</tr>
<tr>
<td>Current inpatient consult recommendation</td>
</tr>
<tr>
<td><strong>Neutropenic fever prophylaxis</strong></td>
</tr>
<tr>
<td>24-hour perioperative use on Urology service</td>
</tr>
<tr>
<td>Cystic fibrosis exacerbation treatment</td>
</tr>
<tr>
<td>24-hour perioperative use in selected procedures in patients with severe or immediate IgE-mediated beta-lactam allergy or intolerance</td>
</tr>
<tr>
<td>Ruptured globe – ophthalmology service</td>
</tr>
<tr>
<td>Emergency Department for patients being discharged</td>
</tr>
</tbody>
</table>
Expansion Results

<table>
<thead>
<tr>
<th>Month</th>
<th>HA-CDI Cases 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>April</td>
<td>5</td>
</tr>
<tr>
<td>May</td>
<td>5</td>
</tr>
<tr>
<td>June</td>
<td>3</td>
</tr>
</tbody>
</table>
Expansion Results

SIR = 1.016
Expansion Results

FQ use at University Hospital

Days of Therapy (DOT) per 1000 Patient Days (PD)

DOT/1000PD

Days:
- Jan-2015
- Feb-2015
- Mar-2015
- Apr-2015
- May-2015
- Jun-2015
- Jul-2015
- Aug-2015
- Sep-2015
- Oct-2015
- Nov-2015
- Dec-2015
- Jan-2016
- Feb-2016
- Mar-2016
- Apr-2016
- May-2016
- Jun-2016
- Jul-2016
- Aug-2016
- Sep-2016
- Oct-2016
- Nov-2016
- Dec-2016
- Jan-2017
- Feb-2017
- Mar-2017
- Apr-2017
- May-2017
- Jun-2017
- Jul-2017
- Aug-2017
- Sep-2017
Key Takeaways

- It takes a lot to steer a big ship
- Antimicrobial stewardship is a team effort
- “It’s not whether you get knocked down, it’s whether you get up.”
- Fluoroquinolones aren’t great and you can live without them
Evolution of *Clostridium difficile* Testing and Implications for Antimicrobial Stewardship

Tristan T. Timbrook, Pharm.D., M.B.A., BCPS
Antimicrobial Stewardship Pharmacist
University of Utah Health Care
Salt Lake City, Utah

@TimbrookTT
Learning Objectives

- Recognize the differences between rapid diagnostic tests for *Clostridium difficile* infection (CDI) and impact on diagnosis.

- Use various approaches, including multi-step testing algorithms, to potentially improve diagnosis of CDI.
CDI Testing 101: Gold Standard

Anaerobic Toxigenic Culture (TC)

• Isolation of *C. difficile* via culture incubation of 2-7 days

• Not routinely used due to labor and time intensity

• Requires additional test to confirm toxin production
CDI Testing 101: Gold Standard

Cell culture cytotoxicity neutralization assay (CCNA)
- Confirms in vivo toxin production
- Requires 24-48h test time
- Not routinely used due to labor and time intensity
CDI Testing 101:

Toxin Enzyme-linked immunosorbent assay (EIAs)

• Utilizes antibodies directed against *C. difficile* antigens (e.g. proteins) to detect toxins

• Toxin A and B
  – Sensitivity 70%
  – Specificity 98%

Burnham CD, et al. CMR. 2013. • AHRQ 2017 • Image: upload.wikimedia.org/wikipedia/commons/e/e5/Antibody1.jpg
CDI Testing 101:

**Glutamate Dehydrogenase (GDH) EIAs**

- Enzyme produced by both toxogenic and non-toxin producing *C. difficile*
- May require toxin identification by another test
- Sensitivity 90%, specificity 94%

CDI Testing 101:

*Nucleic Acid Amplification Techniques (NAAT/PCR)*

- Detects gene for toxin B (*tcd*B) and/or toxin A (*tcd*A)
- Advantages
  - Limited labor
  - Approximately 1 hour turn-around time
  - Sensitivity 95%, specificity 97%
- Does **not** detect toxin production and therefore may reflect colonization rather than active disease

Burnham CD, et al. CMR. 2013. • AHRQ 2017 • Image: upload.wikimedia.org/wikipedia/commons/e/e5/DNA_Double_Helix.png
Evolution of CDI Testing: A Messy Endeavor

- Increased utilization of NAAT due to high sensitivity
- CDI rates often reported to double after switching to PCR
- When screening all hospitalized patients, 72% of positive CDI tests may be in colonized/ asymptomatic patients

Which type of CDI testing may promote over-diagnosis of CDI?

A. Glutamate Dehydrogenase (GDH) Enzyme-linked immunosorbent assay (EIAs)
B. Nucleic Acid Amplification Techniques (NAAT/PCR)
C. Toxin A&B Enzyme-linked immunosorbent assay (EIAs)
D. A&B
Strategies to Improve CDI Diagnosis

• Creating a “laboratory test utilization committee” can optimize diagnostic test use by involving key stakeholders akin to P&T committees optimization of medication use

• Areas for optimization
  – Pre-analytical: Ensuring appropriate test ordering
  – Analytical: Optimal testing
  – Post-analytical: Improved communication of results

Pre-analytical

Increasing Pre-Test Probability of CDI

EMR Modification Study

• Methods: EMR modified to enforce testing criteria
  – ≥ 3 unformed stools in 24h, absence of laxative use in prior 48h

• Results: In 1 year, 16.2% (375/2,321) of tests canceled for not meeting criteria

• Conclusion: EHR enforced criteria for testing to decrease inappropriate *C. difficile* testing

Pre-analytical

Does Pre-test Probability Correlate to CDI?

CDI Test to Pre-test Probability Study

- Methods: low, medium, and high pre-test probability compared to EIA and TC results

- Results: Of 111 patients, 65% had low pre-test probability. None had + EIA, four had + TC and none developed CDI in following 30 days

- Conclusion: Pre-test probability of disease should be considered when ordering CDI testing

Analytical

European Diagnostic Recommendations on CDI Testing

- Multi-step algorithm
  - High sensitivity test for negative predictive value
  - High specificity test for positive predictive value
  - Combination increases clinical utility of testing

Figure adapted from Crobach MJT, et al. CMI. 2016
# Analytical: Value in Toxin Identification?

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polage et al.</td>
<td>1,416 adults</td>
<td>Testing: EIA Tox, PCR</td>
<td>21% PCR+ (44.7% of those Tox+)</td>
</tr>
<tr>
<td><em>JAMA Intern Med.</em> 2015</td>
<td>Single academic center</td>
<td>PCR reported, tox <strong>not</strong> reported</td>
<td><strong>No CDI-related complications</strong> in Tox−/PCR+ v.s 10 Tox+/PCR+ (p&lt; 0.01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Outcomes: CDI related complications, CDI related mortality</td>
<td></td>
</tr>
</tbody>
</table>
# Analytical: Value in Toxin Identification?

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Planche et al. *Lancet Infect Dis.* 2013 | • 12,420 fecal samples  
  • 4 UK laboratories | • Testing: TC, CCNA, GDH, EIA, PCR  
  • Outcomes: Mortality (adj. for confounding) | • **Increased mortality** associated with detection of toxin production (p=0.04) but **not** in detection of organism w/o toxin |
Analytical: Is There an Optimal Approach?

• Overall, the issue of testing methods is still an evolving subject
  – ECCMID supporting multiple step algorithms
  – IDSA new guidelines will likely support multiple step algorithm

• Take home:
  – Know your labs methods and use with clinical judgement
  – CDI is a clinical diagnosis supported, not defined, by laboratory data

Using sample multistep in handout, how should a positive PCR be used?

A. CDI is likely, initiate CDI therapy
B. Follow-up test with GDH EIA
C. Follow-up test with Toxin A/B EIA
D. Follow-up test with TC
Post-analytical
Communicating & Interpreting Results

- *Clostridium difficile* detected by PCR, EIA Toxin A/B negative

VS

- *Clostridium difficile* detected by PCR, EIA Toxin A/B negative
  - Results suggestive of colonization or possible CDI

Which facilitates interpretation for clinicians?
Post-analytical
Communicating & Interpreting Results

• RDT Mock Case Study
  - Interpretation and prescribing of 156 physicians based on mock cases with rapid diagnostic testing (RDT) results
  - 14-48% incorrect RDT interpretation

• Stewardship teams should work with labs to develop results communications in addition to providing clinician education on interpretation

Key Takeaways

• Work with IT and educate clinical staff on strategies to increase pre-test probability of disease (e.g. no laxatives in last 48h)

• Determine your current testing standards and discuss with microbiolab and other stakeholders if multi-step testing is right for your facility

• Educate clinical staff on facility specific testing methods and result interpretation, provide prospective audit and feedback on positive testing
Pharmacologic and Non-Pharmacologic Interventions That Improve CDI Rates and Patient Outcomes

Jerod Nagel, Pharm.D., BCPS-AQ ID
Clinical Team Lead, Infectious Diseases
Clinical Assistant Instructor
University of Michigan Health System
University of Michigan, College of Pharmacy
Overview

• **Primary vs Secondary Treatment and Prevention**
  – Infection control for pharmacists
    • Going beyond hand hygiene
  – Pharmacologic treatment options
    • Focus on newer options
  – Non-pharmacologic treatment options
    • Probiotics and FMT
  – Multi-faceted approach
Infection Control Practices for Pharmacists

Hands
- Most common source for spread of CDI spores

Shoes
- 10-40% of shoes have CDI spores and other pathogens
  - Shoe covers can reduce spread

Neck Tie

Lab Coat
- Wash at least weekly with on hot cycle

Computer
Predicting and Possibly Preventing Patients From Acquiring CDI

• **Traditional Risk Factors:**
  – Age >65, antibiotics, PPIs, previous CDI, length of hospitalization

• **Targeted Risk Factors:**
  – ICU: SICU admission, ICU length of stay, COPD, mechanical ventilation
  – Oncology: salvage lymphoma chemotherapy
  – Transplant: neutropenia in BMT

• **Screen for Colonization with Toxigenic *C. difficile***
  – Incidence ranges from 2% to 35% depending on population
Prevention Options for Patients at High-Risk

• Practice Good Hand Hygiene and Infection Control Practices
• Evaluate and Minimize Modifiable Risk Factors
  – Avoid antimicrobials (FQs, clindamycin, ceftriaxone, carbapenems)
  – Minimize use of acid suppression with proton pump inhibitors
• Prophylaxis with Anti-CDI Agent for Select Patients
  – Ongoing studies for patients colonized with toxigenic CDI
• Vaccination
  – Currently being developed
• Probiotics for High-risk Patients
# Probiotics in Patient Taking Antibiotics

**Gastroenterology. 2017 Jun;152(8):1889-1900**

<table>
<thead>
<tr>
<th>Study name</th>
<th>Events / total</th>
<th>Relative weight</th>
<th>Risk ratio</th>
<th>Risk ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probiotics</td>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surawicz 1989</td>
<td>3 / 116</td>
<td>5 / 64</td>
<td>5.30</td>
<td>0.33</td>
</tr>
<tr>
<td>McFarland 1995</td>
<td>3 / 97</td>
<td>4 / 96</td>
<td>4.80</td>
<td>0.74</td>
</tr>
<tr>
<td>Thomas 2001</td>
<td>2 / 133</td>
<td>3 / 134</td>
<td>3.30</td>
<td>0.67</td>
</tr>
<tr>
<td>Plummer 2004</td>
<td>2 / 69</td>
<td>5 / 69</td>
<td>4.02</td>
<td>0.40</td>
</tr>
<tr>
<td>Can 2006</td>
<td>0 / 73</td>
<td>2 / 78</td>
<td>1.14</td>
<td>0.21</td>
</tr>
<tr>
<td>Beausoleil 2007</td>
<td>1 / 44</td>
<td>7 / 45</td>
<td>2.46</td>
<td>0.15</td>
</tr>
<tr>
<td>Hickson 2007</td>
<td>0 / 57</td>
<td>9 / 56</td>
<td>1.30</td>
<td>0.05</td>
</tr>
<tr>
<td>Rafiq 2007</td>
<td>5 / 45</td>
<td>22 / 55</td>
<td>13.16</td>
<td>0.28</td>
</tr>
<tr>
<td>Wenus 2008</td>
<td>0 / 34</td>
<td>1 / 29</td>
<td>1.04</td>
<td>0.29</td>
</tr>
<tr>
<td>Safdar 2008</td>
<td>0 / 23</td>
<td>1 / 17</td>
<td>1.05</td>
<td>0.25</td>
</tr>
<tr>
<td>Miller 2008a</td>
<td>4 / 95</td>
<td>7 / 94</td>
<td>7.26</td>
<td>0.57</td>
</tr>
<tr>
<td>Miller 2008b</td>
<td>2 / 157</td>
<td>0 / 159</td>
<td>1.13</td>
<td>5.06</td>
</tr>
<tr>
<td>Gao 2010</td>
<td>9 / 171</td>
<td>20 / 84</td>
<td>18.82</td>
<td>0.22</td>
</tr>
<tr>
<td>Pozzoni 2012</td>
<td>3 / 106</td>
<td>2 / 98</td>
<td>3.32</td>
<td>1.39</td>
</tr>
<tr>
<td>Allen 2013</td>
<td>12 / 1470</td>
<td>17 / 1471</td>
<td>19.16</td>
<td>0.71</td>
</tr>
<tr>
<td>Ouwehand 2014</td>
<td>6 / 304</td>
<td>7 / 146</td>
<td>9.01</td>
<td>0.41</td>
</tr>
<tr>
<td>Wong 2014</td>
<td>0 / 76</td>
<td>1 / 82</td>
<td>1.02</td>
<td>0.36</td>
</tr>
<tr>
<td>Ehrhardt 2016</td>
<td>2 / 146</td>
<td>2 / 146</td>
<td>2.74</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**Summary estimate**

0.42
University of Michigan Experience with Reducing High-Risk Antibiotics

• Focused on Providing Service-Specific Feedback to Pharmacy Teams on Performance and Outcomes Metrics
  – Antibiotic utilization reports for FQs, clindamycin, and ceftriaxone
  – Appropriate prescribing reports
  – Hospital acquired CDI rates by service and pharmacy team

• Evaluated utilization and CDI during 4 periods:
  – Historic control
  – Education session on appropriate utilization of antibiotics and workflow expectations
  – Monthly reports, plus daily stewardship team coaching and feedback to clinical pharmacists
  – Monthly reports without stewardship oversight
Hospital-Wide (All Adult Inpatient) Use of FLUOROQUINOLONES (DOT/1000 Patient Days) and HA-CDI Rates

Overall Historical vs. Intervention Periods: -24.7%

- **Historical Control Period**
  - Apr-16: 29.1
  - May-16: 29.1
  - Jun-16: 29.1
  - Jul-16: 29.1
  - Aug-16: 29.1
  - Sep-16: 29.1
  - Oct-16: 29.1
  - Nov-16: 29.1
  - Dec-16: 29.1
  - Jan-17: 29.1
  - Feb-17: 29.1
  - Mar-17: 29.1
  - Apr-17: 29.1
  - May-17: 29.1
  - Jun-17: 29.1

- **Roll-out Period**
  - DOT/1000 Patient Days:
    - Plot Area: 26.9

- **Intervention – Phase I**
  - DOT/1000 Patient Days:
    - 14.4
    - 14.7
    - 14.3

- **Intervention – Phase II**
  - DOT/1000 Patient Days:
    - 11.5
    - 11.5
    - 11.4

**HA-CDI Rate**
- Apr-16: 5.3
- May-16: 5.3
- Jun-16: 5.3
- Jul-16: 5.3
- Aug-16: 5.3
- Sep-16: 5.3
- Oct-16: 5.3
- Nov-16: 5.3
- Dec-16: 5.3
- Jan-17: 5.3
- Feb-17: 5.3
- Mar-17: 5.3
- Apr-17: 5.3
- May-17: 5.3
- Jun-17: 5.3

**Dashboard HP:**
Hospital-Wide (All Adult Inpatient) Use of CLINDAMYCIN (DOT/1000 Patient Days) and HA-CDI Rates

Overall Historical vs. Intervention Periods: -28.9%
Hospital-Wide (All Adult Inpatient) Use of CEFTRIAXONE (DOT/1000 Patient Days) and HA-CDI Rates

Overall Historical vs. Intervention Periods: -20.9%
Pharmacy Driven Intervention to Minimize PPIs and Promote Probiotics

<table>
<thead>
<tr>
<th></th>
<th>Historic Group</th>
<th>Intervention Group</th>
<th>Difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total PPI (doses/1,000 pt days)</td>
<td>677</td>
<td>581</td>
<td>-14.2%</td>
<td>0.0002</td>
</tr>
<tr>
<td>IV PPI (doses/ 1,000 pt days)</td>
<td>229</td>
<td>158</td>
<td>-31.1%</td>
<td>0.0008</td>
</tr>
<tr>
<td>Total Probiotic (doses/1,000 pt days)</td>
<td>97</td>
<td>223</td>
<td>+129.6%</td>
<td>0.0006</td>
</tr>
<tr>
<td>Hospital CDI (cases/1,000 pt days)</td>
<td>0.49</td>
<td>0.39</td>
<td>-20%</td>
<td>0.04</td>
</tr>
</tbody>
</table>

## IDSA/SHEA CDI Treatment Guidelines

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild-moderate</td>
<td>Oral Metronidazole</td>
</tr>
<tr>
<td>Severe</td>
<td>Oral Vancomycin</td>
</tr>
<tr>
<td>Severe and complicated</td>
<td>Oral Vancomycin +/− IV Metronidazole + PR Vancomycin if ileus or obstruction</td>
</tr>
</tbody>
</table>

- Treatment recommendations are same for index and first recurrence, but metronidazole should be avoided past first recurrence.
- No guidance is provided for treatment of multiple recurrences.
- Guidelines were published in 2010 and do not mention role for fidaxomicin, bezlotoxumab, or fecal microbiota transplant (FMT).
Vancomycin vs. Metronidazole

(A) Recurrence by disease severity

(B) All-cause 30-d mortality by disease severity

*Adjusted relative risk, 0.86; 95% CI, 0.74 to 0.98
Fidaxomicin vs. Vancomycin

Clinical Cure
- Fidaxomicin: 88.2%
- Vancomycin: 85.8%

Recurrance
- Fidaxomicin: 15.4%
- Vancomycin: 25.3%

P = 0.005

Bezlotoxumab

- Monoclonal antibiotic against toxin B
- Prescribed as adjunct therapy with anti-CDI therapy
- Given as a single IV dose of 10 mg/kg infused over 1 hour
- Long half-life of approximately 19 days
- Average wholesale price: $4,560 per 1 gm vial
Bezlotoxumab

- No difference in clinical cure: 80% vs. 73% vs. 80%

N Engl J Med 2017;376:305-17
Multifaceted CDI Initiative

• Real-time notification of CDI result to stewardship team
• Recommend timely appropriate CDI therapy, based on severity
• ID and Surgical consults, for patients with severe disease with complications or multiple recurrences
• Discontinue or de-escalate concomitant antibiotics
• Discontinue or change PPIs
• Education regarding proper testing

## Multifaceted CDI Initiative

### Interventions

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Pre-Intervention (231)</th>
<th>Intervention (227)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI Stopped</td>
<td>13.9%</td>
<td>28.6%</td>
<td>0.0292</td>
</tr>
<tr>
<td>ID Consulted within 72 hours</td>
<td>10.4%</td>
<td>17.2%</td>
<td>0.0349</td>
</tr>
<tr>
<td>Vancomycin order, Severe Disease</td>
<td>59%</td>
<td>87%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Days to Vanco order (mean)</td>
<td>1.70</td>
<td>1.05</td>
<td>0.03</td>
</tr>
</tbody>
</table>

### Clinical Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pre-Intervention (231)</th>
<th>Intervention (227)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attributable 30-day mortality</td>
<td>3.0%</td>
<td>3.1%</td>
<td>0.97</td>
</tr>
<tr>
<td>Attributable 30-day ICU admission</td>
<td>5.6%</td>
<td>5.3%</td>
<td>0.87</td>
</tr>
<tr>
<td>Attributable 30-day surgery</td>
<td>1.7%</td>
<td>0.0%</td>
<td>0.12</td>
</tr>
<tr>
<td>Recurrence</td>
<td>8.7%</td>
<td>8.4%</td>
<td>0.91</td>
</tr>
<tr>
<td>Author (n)</td>
<td>Intervention</td>
<td>Outcomes</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>--------------</td>
<td>----------</td>
<td></td>
</tr>
</tbody>
</table>
| Jury (n=146) | - Clinician education  
- Micro contacted AST, who recommend therapy  
- Order set implementation | - **Improved guideline compliance**  
- **Improved time to appropriate therapy**  
- Clinical outcomes were not evaluated |
| Jardin (n=256) | - Pharmacy prescribing authority for severe CDI | - **Improved compliance with guideline for severe CDI** |
| Yeung (n=424) | - Treatment algorithm  
- Pharmacist consult  
- Education | - **Improved algorithm adherence rates**  
- **No difference in mortality**  
- **Decrease LOS (30 days vs 21 days, p=0.01)** |
| Brumley (n=169) | - Develop guideline and order set (bundle)  
- Education  
- Recommend bundle interventions | - **Improved overall bundle compliance:**  
- **Improved adherence to treatment recommendations**  
- **Discounted concomitant antimicrobials**  
- No difference in mortality, readmission with CDI or LOS |
| Abbett (n=NR) | - Education  
- Prevention and treatment bundle development | - Process measures not reported  
- No Difference in mortality |
| Hammond (n=24) | - Education  
- Treatment guideline | - **Improved algorithm adherence rates**  
- **No difference in hospital LOS**  
- Reduction in ICU LOS (1.5 days vs. 3.5 days, p= 0.01) |
| Knaus (n=351) | - Education  
- Treatment guideline | - **Improved algorithm adherence rates**  
- No difference in mortality or LOS |
Treatment Options for Patients with Multiple Recurrences

• No Guideline Recommendations or Clear Delineation from Published Literature, and Each Option Has Pros and Cons
  – Vancomycin pulse or taper regimen
  – Fidaxomicin taper regimen (following vancomycin or fidaxomicin)
  – Adjunct therapy with bezolotoxumab
  – Fecal microbiota transplant
    • Fresh vs. Frozen
    • GI vs. PR administration
Fidaxomicin Chaser or Taper

- Potential option, but limited comparative data
- 18 patient case series in patients with at least 3 previous CDI, received of various fidaxomicin chaser or taper regimens:
  - 38% recurrence rates with 10-day chaser
  - 18% recurrence rate with 14-33 day taper following treatment
  - Taper resulted in longer time between episodes for patients with recurrence (257 vs. 25 days, p<0.001)
Fecal Microbiota Transplant (FMT)

- Primarily for patients with multiple recurrences failing standard therapy
  - Otherwise, need FDA Investigational New Drug Application

- Several options for getting product:
  - Patient brings in product
    - Auto (self)
    - Donor
  - Purchase screened product from vendor
    - OpenBiome (Medford, MA)
    - AdvancingBio (Sacramento, CA)
Fecal Microbiota Transplant (FMT)

• 83% success rate for patients with multiple recurrences
• 53% success for patients with refractory disease

(Ann Intern Med 2015;162(9):630–8.)
## FMT Preparation

<table>
<thead>
<tr>
<th>Author</th>
<th>Design (sample size)</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Youngster, 2014 | • Randomized controlled trail  
• n=20            | Frozen FMT via NG tube vs. Frozen FMT via colonoscopy                | **Success with 1 treatment:** -60% vs. 80%  
**Success with >1 treatment:** -80% vs. 100% |
| Lee, 2016    | • Double blind, randomized, non-inferiority trail  
• n=232           | Frozen FMT via enema vs. Fresh FMT via enema                        | **Success:** 83.5% vs. 85.1%                |
| Kelly, 2016  | • Multi-center, Double blind, randomized controlled trial  
• n=46              | Fresh FMT via Donor vs. Fresh FMT via Auto (self)                    | **Success:** 91% vs. 63%                  |
<table>
<thead>
<tr>
<th>Author</th>
<th>Design (sample size)</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Nood, 2013</td>
<td>• Open label, randomized trial • n=43</td>
<td>Donor FMT via NG, plus bowel lavage vs. Vancomycin x 14 days vs. Vancomycin x 14 days, plus bowel lavage</td>
<td>No recurrence within 10 weeks: -81% FMT plus lavage -31% Vancomycin -23% Vancomycin plus lavage</td>
</tr>
<tr>
<td>Cammarota, 2015</td>
<td>• Open label, randomized trial • n=20</td>
<td>Vancomycin treatment &amp; taper (minimum 3 weeks) vs. Donor FMT via colonoscopy</td>
<td>No recurrence within 10 weeks: -90% FMT vs. 26% vancomycin</td>
</tr>
<tr>
<td>Hota, 2017</td>
<td>• Single-center, open label, randomized trial • n=30</td>
<td>Vanco x 14D, then Fresh donor FMT vs. Vanco treatment and 6 week taper</td>
<td>No recurrence within 120 days: -56.2% vanco plus FMT -41.7% vanco taper</td>
</tr>
</tbody>
</table>
Efforts to Decrease High-Risk Antibiotics are Strongly Associated with Reductions in Hospital-Acquired CDI Rates

- FQ, Clindamycin, Cephalosporins and Carbapenems

Pharmacists Initiatives to Improve Management of CDI have Consistently Resulted in Significant Improvements:

- Starting prompt anti-CDI therapy
- Starting the correct anti-CDI therapy
- Decreasing unnecessary antibiotics
- Stopping unnecessary PPIs
Key Takeaways

• **Vancomycin should be first line for severe disease**
  – Only CDI treatment option that has demonstrated improvements in clinical cure compared to metronidazole
  – Does not reduce recurrence compared to metronidazole

• **Bezlotoxumab and fidaxomicin have demonstrated reductions in recurrence for patients with initial and/or first recurrence, but limited data for patients with multiple recurrences**

• **Vancomycin taper/pulse dose, bezlotoxumab, fidaxomicin and fecal microbiota transplant are options for patients with multiple recurrences**
Antimicrobial Stewardship Strategies to Reduce Hospital-Acquired Clostridium Difficile Infections