Get Your CE IN THE MIDDAY

A Midday Symposium and Live Webinar conducted at the 2018 Midyear Clinical Meeting and Exhibition

Improving the Lives of Patients with Clostridium Difficile Infection One Case at a Time

Monday, December 3, 2018
11:30 a.m. – 1:00 p.m.
Anaheim, California

Provided by ASHP
Supported by an educational grant from Merck

Agenda

11:30 a.m. – 11:35 a.m.
Welcome and Introductions
Kevin W. Garey, Pharm.D., Activity Chair

11:35 a.m. – 11:40 a.m.
Correlation of Clostridium difficile Infection (CDI) and Antibiotic Use
Kevin W. Garey, Pharm.D.

11:40 a.m. – 11:55 a.m.
Applying New Treatment Guidelines for Patients with CDI
Kevin W. Garey, Pharm.D.

11:55 a.m. – 12:20 p.m.
Vancomycin and Fidaxomicin for the Primary Treatment of CDI
Kevin W. Garey, Pharm.D. and A. Krishna Rao, M.D.

12:20 p.m. – 12:45 p.m.
Role of Newer Therapies in the Treatment of CDI
A. Krishna Rao, M.D.

12:45 p.m. – 1:00 p.m.
Faculty Discussion and Audience Questions
Kevin W. Garey, Pharm.D. and A. Krishna Rao, M.D.
Improving the Lives of Patients with *Clostridium difficile* Infection
One Case at a Time

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Professor and Chair
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Assistant Professor of Internal Medicine
University of Michigan
Ann Arbor, Michigan

Disclosures

In accordance with ACCME and ACPE Standards for Commercial Support, ASHP policy requires that all faculty, planners, reviewers, staff, and others in a position to control the content of this presentation disclose their financial relationships. In this activity, only the individuals below have disclosed a financial relationship. No other persons associated with this presentation have disclosed any relevant financial relationships.

- Kevin Garey
  - Merck, Inc., Summit Therapeutics, and Tetraphase: Research Support
- Krishna Rao
  - Merck, Inc.: Research support (Co-investigator)
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One Case at a Time

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**Learning Objectives**

- Describe the correlation of *Clostridium difficile* Infection (CDI) and overuse of antibiotics.
- Apply new treatment guidelines to treat patients with CDI.
- Evaluate the use of vancomycin and fidaxomicin for the primary treatment of CDI.
- Discuss the role of newer therapies in the treatment of CDI.

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**Side note: Nomenclature Change**

Updated CLSI AST Documents Are Here! So what’s new?

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To start: why do we get CDI in the first place? Welcome to the wonderful world of the microbiome!

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It’s your first day on the job as the antimicrobial stewardship pharmacist

You get called into the boss’s office:

Why is *C. difficile* the #1 healthcare pathogen in my hospital (and in the U.S.)?

….what are you going to do to decrease the number of infections we see?


What antibiotic are you going to target to decrease your CDI rates?

- a. Clindamycin
- b. Cefepime
- c. Meropenem
- d. Minocycline
- e. Piperacillin-tazobactam

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Welcome to a whole new area of science!

Transcriptomics (RNAseq) and proteinomics

16S sequencing

Metabolomics

Gut microbiota

Genes & proteins

Mucous layer

Energy balance

Bottom-up approach

Top-down approach

Unresolved Compromise inflammation gut barrier

Epithelial cells

Lymphoid follicles

Cells with recognition receptors

Dendritic cells

No inflammation (healthy gut barrier)

Microbiome analysis is all about abundance, diversity, and types of organisms present

Microbiome of non-CDI patients vs. CDI patients

- Total colony forming units (CFU) abundance
- Diversity of microbiologic species
- Other pathogenic organisms

Colonic epithelium

Healthy Microbiome

Colonic epithelium

Recurrent CDI Microbiome

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**Gut microbiota: 16S RNA sequencing**

**Firmicutes**
- Mostly good (*C. diff* is a firmicute)
- Mostly spore formers (think: probiotic)
- Usually largest component of microbiota

**Bacteroidetes**
- Mostly good *(Bacteroides predominates)*
- Non-spore forming
- Usually tied for largest component

**Actinobacteria**
- Mostly good
- Not very common, sort of the ugly stepsister of the healthy microbiota

**Proteobacteria**
- Good in small quantities (this is *E. coli*, *Klebsiella*, etc)
- This is where the ‘overgrowth’ occurs after antibiotic therapy

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**Mice exposed to a variety of antibiotics for 5 days**

5 days of antibiotics are more than enough to completely change the microbiota

...and this disruption is more than enough to support *C. diff* colonization

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The effect on the microbiome starts almost immediately

- 14 healthy volunteers given ceftaroline-avibactam X 7 days
- Changes in microbiota assessed over 21 days


We are now able to predict the antibiotics most likely to cause CDI!!

- Any antibiotic that kills firmicutes and/or bacteroides will almost immediately increase CDI risk
- Thus: the most common antibiotic used with these properties will be the most likely to be associated with CDI
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**Antibiotics that increase CDI risk**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Kills f Firmicutes</th>
<th>Kills b Bacteroidetes</th>
<th>Commonly used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin-sulbactam</td>
<td>Yes</td>
<td>Yes</td>
<td>Medium</td>
</tr>
<tr>
<td>Cefepime</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes and increasing</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Yes</td>
<td>Yes</td>
<td>Not as much</td>
</tr>
</tbody>
</table>

**30-day risk of CDI among 97,130 hospitalized patients 1,481 of whom developed CDI**

<table>
<thead>
<tr>
<th>Individual Antibiotic</th>
<th>OR (ABX Received (Y/N))</th>
<th>P-Value</th>
<th>Antibiotic Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin/Sulbactam</td>
<td>1.640</td>
<td>0.012</td>
<td>1.7%</td>
</tr>
<tr>
<td>Cefepime</td>
<td>1.673</td>
<td>&lt; 0.001</td>
<td>16.1%</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1.464</td>
<td>&lt; 0.001</td>
<td>21.8%</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>1.864</td>
<td>&lt; 0.001</td>
<td>3.6%</td>
</tr>
<tr>
<td>Imipenem</td>
<td>2.077</td>
<td>&lt; 0.001</td>
<td>3.2%</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1.335</td>
<td>0.020</td>
<td>2.8%</td>
</tr>
<tr>
<td>Piperacillin/Tazobactam</td>
<td>1.655</td>
<td>&lt; 0.001</td>
<td>16.6%</td>
</tr>
<tr>
<td>Age</td>
<td>1.009</td>
<td>&lt; 0.001</td>
<td>N/A</td>
</tr>
<tr>
<td>Proton Pump Inhibitor (Y/N)</td>
<td>1.375</td>
<td>&lt; 0.001</td>
<td>N/A</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>1.208</td>
<td>&lt; 0.001</td>
<td>N/A</td>
</tr>
</tbody>
</table>

OR – odds ratio; ABX - antibiotic

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Risk of CDI increased from 0.14% to 6.21% in comorbid patients who received high risk antibiotics and a proton pump inhibitor

<table>
<thead>
<tr>
<th>Received High Risk Antibiotic?</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charlson Comorbidity Index</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Received PPI?</td>
<td>N Y</td>
<td>N Y</td>
</tr>
<tr>
<td>CDI Incidence (%)</td>
<td>0.14</td>
<td>0.58</td>
</tr>
</tbody>
</table>

- Independent of receipt of high risk antibiotic, more severe Charlson comorbidity index increases CDI risk


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**We can now update an old slide with newer antibiotics**

- Carbapenems
- 3rd/4th gen cephalosporin
- Piperacillin-tazobactam

If I was a betting man, I would guess that carbapenems will be the ‘cause’ of the next *C. diff* epidemic.

Despite our best efforts, CDI will be hard to prevent!

Betty B

71-year-old female with congestive heart failure, gastroesophageal reflux disease, diabetes mellitus, and a history of breast cancer.

Recently discharged after a 2-week hospitalization for bacterial pneumonia.

She now presents to the emergency department with watery diarrhea, leukocytosis (11,000 cells/mL) and elevated serum creatinine (1.1 mg/dL).

Stool is sent to the clinical microbiology lab and tests positive for *C. difficile* toxins.

How do you want to treat Betty B?

a. Metronidazole 500 mg orally three times daily
b. Vancomycin 125 mg orally four times daily
c. Vancomycin 250 mg orally four times daily
d. Fidaxomicin 200 mg orally twice daily
e. Vancomycin + metronidazole

*Treat for 10 days (usually)*
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There has been an explosion in treatment possibilities for CDI

**Current:** Probiotics, FMT, Use narrow-spectrum antibiotics

**Future:** 2nd generation FMT, non-toxigenic *C. diff* M3, Ecobiotics

- Metronidazole
- Vancomycin
- Fidaxomicin
- Ridinilazole
- IVIG
- Monoclonal antibodies vs. *C. diff* toxins
- Toxoid vaccines

FMT = fecal microbiota transplantation

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### IDSA/SHEA CDI Guidelines 2010

<table>
<thead>
<tr>
<th>Episode</th>
<th>Clinical Signs</th>
<th>Severity</th>
<th>Recommended agent</th>
<th>Dosing Regimen</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>WBC &lt; 15,000 and SCr &lt; 1.5 X premorbid level</td>
<td>Mild or moderate</td>
<td>Metronidazole</td>
<td>500 mg PO three times daily 10-14 days</td>
<td>A-I</td>
</tr>
<tr>
<td>Initial</td>
<td>WBC ≥ 15,000 or SCr ≥ 1.5 X premorbid level</td>
<td>Severe</td>
<td>Vancomycin</td>
<td>125 mg PO four times daily 10-14 days</td>
<td>B-I</td>
</tr>
<tr>
<td>Initial</td>
<td>Hypotension, shock, ileus, megacolon</td>
<td>Severe, complicated</td>
<td>Vancomycin + metronidazole IV</td>
<td>Vancomycin: 500 mg PO or NG four times daily + Metronidazole: 500 mg IV every 8 hr. For ileus, consider adding rectal instillation of vancomycin</td>
<td>C-III</td>
</tr>
<tr>
<td>Second (1st recurrence)</td>
<td></td>
<td></td>
<td>Same as initial</td>
<td>Same as initial</td>
<td>A-II</td>
</tr>
<tr>
<td>Third (2nd recurrence)</td>
<td></td>
<td></td>
<td>Vancomycin</td>
<td>PO tapered and/or pulsed</td>
<td>B-III</td>
</tr>
</tbody>
</table>


More recently, metronidazole has been shown to be globally inferior to vancomycin (televamer phase III RCT)


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Increased failure rate of metronidazole also associated with increased 30-day mortality

VA dataset (vancomycin: n=2068; metronidazole: n=8069 propensity matched). Patients given vancomycin had a significantly lower 30-day mortality (RR: 0.86, 95% CI: 0.74-0.98). No difference in CDI recurrence regardless of disease severity or choice of antibiotic (16.3-22.8%).


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**Summary of metro vs. vanco clinical studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Location</th>
<th>n</th>
<th>Single center</th>
<th>Blinded</th>
<th>Randomized</th>
<th>Metro dose</th>
<th>Vanco dose</th>
<th>Clinical failure</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teasley, 1983</td>
<td>82-83</td>
<td>MN</td>
<td>101</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>250 mg QID</td>
<td>500 mg QID</td>
<td>2 of 37 (5.4%)</td>
<td>0 of 45 (0%)</td>
</tr>
<tr>
<td>Wenisch, 1996</td>
<td>93-95</td>
<td>Austria</td>
<td>62</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>500 mg TID</td>
<td>500 mg TID</td>
<td>2 of 31 (6%)</td>
<td>2 of 31 (6%)</td>
</tr>
<tr>
<td>Musher, 2006</td>
<td>02-04</td>
<td>USA (Houston)</td>
<td>34</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>250 mg QID</td>
<td>125 mg QID</td>
<td>N/A</td>
<td>9 of 28 (32%)</td>
</tr>
<tr>
<td>Zar, 2007</td>
<td>94-02</td>
<td>Chicago</td>
<td>150</td>
<td>Yes</td>
<td>yes</td>
<td>yes</td>
<td>250 mg QID</td>
<td>125 mg QID</td>
<td>13 of 79 (16%)</td>
<td>2 of 71 (3%)</td>
</tr>
<tr>
<td>Johnson, 2013</td>
<td>05-07</td>
<td>World</td>
<td>552</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>375 mg QID</td>
<td>125 mg QID</td>
<td>76 of 278 (27%)</td>
<td>49 of 259 (19%)</td>
</tr>
</tbody>
</table>

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There may have been a MIC creep with metronidazole over the decades

<table>
<thead>
<tr>
<th>Author</th>
<th>Location</th>
<th>Time period</th>
<th>Isolates</th>
<th>MIC50</th>
<th>MIC90</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hecht et al</td>
<td>Various</td>
<td>1983–2004</td>
<td>110</td>
<td>0.125</td>
<td>0.25</td>
<td>0.025–0.5</td>
</tr>
<tr>
<td>Edlund et al</td>
<td>Sweden</td>
<td>1998</td>
<td>50</td>
<td>0.125</td>
<td>0.25</td>
<td>0.125–0.25</td>
</tr>
<tr>
<td>Betriu et al</td>
<td>Spain</td>
<td>2001</td>
<td>55</td>
<td>0.5</td>
<td>1</td>
<td>≤0.06–1</td>
</tr>
<tr>
<td>Citron et al</td>
<td>USA</td>
<td>2003</td>
<td>18</td>
<td>0.5</td>
<td>1</td>
<td>0.25–1</td>
</tr>
<tr>
<td>Finegold et al</td>
<td>USA (CA)</td>
<td>2003</td>
<td>72</td>
<td>0.5</td>
<td>1</td>
<td>0.25–2</td>
</tr>
<tr>
<td>Karloowsky et al</td>
<td>Canada (Manitoba)</td>
<td>2007</td>
<td>208</td>
<td>0.5</td>
<td>1</td>
<td>0.25–4</td>
</tr>
<tr>
<td>Debast et al</td>
<td>Europe</td>
<td>2008</td>
<td>398</td>
<td>0.25</td>
<td>0.5</td>
<td>&lt;0.06–2</td>
</tr>
<tr>
<td>Reigadas et al</td>
<td>Spain</td>
<td>2013</td>
<td>100</td>
<td>0.25</td>
<td>0.5</td>
<td>0.06–1</td>
</tr>
<tr>
<td>Snydman et al</td>
<td>USA</td>
<td>2011–12</td>
<td>925</td>
<td>1</td>
<td>2</td>
<td>&lt;0.06–4</td>
</tr>
<tr>
<td>BI/027/Nap1 strains</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citron et al</td>
<td>USA</td>
<td>2004–2005</td>
<td>NR</td>
<td>2</td>
<td></td>
<td>0.5–2</td>
</tr>
<tr>
<td>Debast et al</td>
<td>Europe</td>
<td>2008</td>
<td>0.5</td>
<td>1</td>
<td>0.5–1</td>
<td></td>
</tr>
<tr>
<td>Snydman et al</td>
<td>USA</td>
<td>2011–12</td>
<td>2</td>
<td>2</td>
<td></td>
<td>&lt;0.06–4</td>
</tr>
</tbody>
</table>

MIC=minimum inhibitory concentration


**Bottom line:**
This may simply be a PK/PD problem

- Mean concentrations of metronidazole in stool: 
  - <0.25-9.5 μg/g
- MIC50: 1 μg/mL  
  - MIC90: 2 μg/mL
  - May be higher
- A poor response rate to metronidazole should be expected given these numbers!

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Fidaxomicin: Equal efficacy at vancomycin to cure patients and lessens the risk of recurrence

The second phase III study showed similar results (Crook et al. Lancet ID)


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### Comparative Treatment Efficacy in CDI

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants</th>
<th>Resolution, %</th>
<th>P Value</th>
<th>Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct comparisons of metronidazole and vancomycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resolution at end (10 days) of treatment</td>
<td>843 (5 studies)</td>
<td>87 (VAN) 78 (MTR)</td>
<td>0.0008</td>
<td>High</td>
</tr>
<tr>
<td>Resolution of diarrhea at end of treatment without recurrence*</td>
<td>843 (5 studies)</td>
<td>73 (VAN) 63 (MTR)</td>
<td>0.003</td>
<td>High</td>
</tr>
</tbody>
</table>

| Direct comparisons of fidaxomicin and vancomycin |                     |               |         |                     |
| Resolution at end (10 days) of treatment        | 1105 (2 studies)    | 88 (FDX) 86 (VAN) | 0.36    | High               |
| Resolution of diarrhea at end of treatment without recurrence** | 1105 (2 studies) | 71 (FDX) 57 (VAN) | <0.0001 | High               |

*1 month after treatment; **56 days after treatment

VAN = vancomycin, MTR = metronidazole, FDX = fidaxomicin

Improving the Lives of Patients with *Clostridium difficile* Infection
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### Explosion in Treatment Possibilities for CDI Minus 1

**Current:**
- Probiotics
- FMT
- Use narrow-spectrum antibiotics

**Future:**
- 2nd generation FMT
- non-toxigenic *C. diff* M3
- Ecobiotics

- **Vancomycin**
- **Fidaxomicin**
- **Ridinilazole**
- **IVIG**
- Monoclonal antibodies vs. *C. diff* toxins
- Toxoid vaccines

### Recommendation for initial treatment of CDI in adults

<table>
<thead>
<tr>
<th>Clinical definition</th>
<th>Supportive clinical data</th>
<th>Recommended treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial episode, non-severe</td>
<td>WBC &lt; 15,000 cells/mL and serum creatinine &lt; 1.5 mg/dL</td>
<td>VAN 125 mg given four times daily for 10 days, or FDX 200 mg given twice daily for 10 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alternate if above agents are not available: metronidazole 500 mg three times daily by mouth for 10 days</td>
</tr>
<tr>
<td>Initial episode, severe</td>
<td>WBC &gt; 15,000 cells/mL or a serum creatinine &gt; 1.5 mg/dL</td>
<td>VAN 125 mg given four times daily for 10 days, or FDX 200 mg given twice daily for 10 days</td>
</tr>
<tr>
<td>Initial episode, fulminant</td>
<td>Hypotension or shock, ileus, megacolon</td>
<td>VAN 500 mg given four times daily by mouth or nasogastric tube. If ileus, consider adding rectal instillation of VAN. Add intravenous metronidazole 500 mg every 8 hr if ileus present</td>
</tr>
</tbody>
</table>

VAN: vancomycin, FDX: fidaxomicin; SD: standard dose

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**Recommendation for recurrence of CDI in adults**

<table>
<thead>
<tr>
<th>Clinical definition</th>
<th>Supportive clinical data</th>
<th>Recommended treatment</th>
</tr>
</thead>
</table>
| First recurrence    |                          | • VAN SD if metronidazole was used for the first episode OR  
|                     |                          | • Prolonged tapered and pulsed VAN if VAN SD was used for first  
|                     |                          | regimen OR  
|                     |                          | • FDX SD if VAN was used for the initial episode |

Second or subsequent recurrences

|                      |                          | • VAN in a tapered or pulsed regimen OR  
|                      |                          | • VAN SD followed by rifaximin 400 mg three times daily for 20  
|                      |                          | days OR  
|                      |                          | • FDX SD OR  
|                      |                          | • Fecal microbiota transplantation |

VAN: vancomycin, FDX: fidaxomicin; SD: standard dose

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**Extended-Pulsed Fidaxomicin vs. Standard Dose Vancomycin**

in Patients >60 years of age

*EXTEND: randomized, controlled, open-label, phase 3b/4 trial in 181 patients
≥60 years old with initial or recurrent CDI confirmed by presence of toxin A or B in stool sample*

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Recurrence</th>
<th>Sustained clinical cure</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fidaxomicin*</td>
<td>Standard dose vancomycin**</td>
<td></td>
</tr>
<tr>
<td>Day 12</td>
<td>10.0/92.3</td>
<td>8.0/92.0</td>
<td>67%</td>
</tr>
<tr>
<td>2 days after</td>
<td>2.7/90.9</td>
<td>4.0/91.0</td>
<td>6%</td>
</tr>
<tr>
<td>Day 40</td>
<td>2.7/90.9</td>
<td>4.0/91.0</td>
<td>6%</td>
</tr>
<tr>
<td>Day 90</td>
<td>6.2/90.7</td>
<td>6.2/90.7</td>
<td>71%</td>
</tr>
</tbody>
</table>

---

*Fidaxomicin: 200 mg oral tablets, twice daily on days 1–5, then once daily on alternate days on days 7–25
**Vancomycin: 125 mg oral capsules, four times daily on days 1–10

---


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Improving the Lives of Patients with *Clostridium difficile* Infection
One Case at a Time

**FMT for patients with recalcitrant CDI**

- Before stool transplant
  - Deaths: N/A
  - # of Recurrence: 64 (2-7)

- After stool transplant
  - Deaths: 2 (unrelated)
  - # of Recurrence: 1

Recurrent *C. difficile* colitis: case series involving 18 patients treated with donor stool administered via a nasogastric tube


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**Duodenal infusion of donor feces for recurrent *C. difficile* infection**

RCT of PO vanco + FMT (n=16), PO vanco alone (n=13), or PO vanco + bowel lavage (n=13). Study stopped prematurely due to superiority of FMT

Resolution: no diarrhea without relapse after 10 weeks


---

**Protocol utilizing a staggered and tapered antibiotic regimen for the treatment of recurrent *Clostridium difficile* infection that has failed to respond to standard antibiotic therapy.**

25 patients with recurrent CDI that were not able to perform FMT. Twenty-one of the 25 patients (84%) remained free of diarrhea during the following 9 months. The 4 patients who relapsed permanently resolved their diarrhea after a conventional 2-week course of oral vancomycin 125 mg 4 times daily followed by a 2-week course of rifaximin 200 mg twice daily. All 4 patients remained symptom-free at 12 months of follow-up.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Metronidazole Dose/Frequency</th>
<th>Vancomycin Dose/Frequency</th>
<th>Kefir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Course</td>
<td>OR</td>
<td>PLUS</td>
<td></td>
</tr>
<tr>
<td>Weeks 1-2</td>
<td>250 mg Q 6h</td>
<td>125 mg Q 6h</td>
<td>150 mL TID</td>
</tr>
<tr>
<td>Weeks 3-4</td>
<td>750 mg Q 72h</td>
<td>375 mg Q 72h</td>
<td>150 mL TID</td>
</tr>
<tr>
<td>Weeks 5-6</td>
<td>500 mg Q 72h</td>
<td>250 mg Q 72h</td>
<td>150 mL TID</td>
</tr>
<tr>
<td>Weeks 7-8</td>
<td>250 mg Q 72h</td>
<td>125 mg Q 72h</td>
<td>150 mL TID</td>
</tr>
<tr>
<td>Weeks 9-15</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>


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Improving the Lives of Patients with Clostridium difficile Infection
One Case at a Time

Alternative Therapies for Clostridium difficile Infection:
Antibiotics, Immune Therapy, and Beyond

A. Krishna Rao, M.D., M.S.
Assistant Professor of Internal Medicine
University of Michigan

Outline

• Overview of new CDI treatment landscape
• Why we need alternative treatments for CDI
• Borrowing old antibiotics for new uses in CDI
• New antimicrobial approaches to CDI treatment
• Novel non-antibiotic approaches to CDI treatment
Improving the Lives of Patients with *Clostridium difficile* Infection One Case at a Time

**CDI incidence vs. Clinical Trial Registries**


**Targets for alternative CDI treatments?**

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One Case at a Time

So...why do we need alternative treatments?

- Clinical failure / persistent symptoms
- Severe and complicated disease
- Recurrence

Dieterle MG et al. *Ann NY Acad Sci.* 2018. DOI: [https://doi.org/10.1111/nyas.13958](https://doi.org/10.1111/nyas.13958)
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Clinical failure

- Continued or worsening symptoms by day 5 of therapy
- Initial resolution but early (<2 weeks) relapse of symptoms
- Failure to achieve 2 consecutive days with absence of symptoms
- Common: up to 1/3 in some studies
- **Can clinical failure be reduced by alternative treatments?**

Severe CDI

- Age >65 yr
- WBC >15,000 cells/mL
- Albumin <2.5 mg/dL
- Fever
- Colonic thickening / Severe abdominal pain
- Acute kidney injury (Cr >1.5 x premorbid level)
- Pseudomembranous colitis (rare in IBD)
- **Can severe CDI be prevented with alternative approaches?**

Source: Samir, Wikipedia 2009
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One Case at a Time

**Complicated CDI**

- Hypotension / shock / sepsis
- Ileus / megacolon
- Peritonitis
- Bowel perforation
- **Can complicated CDI be prevented with new approaches?**

**Recurrent CDI**

- 2\textsuperscript{nd} Recurrence: 30-45% of 1\textsuperscript{st}
- 3\textsuperscript{rd} Recurrence: 45-60% of 2\textsuperscript{nd}
- ≤5% of all pa. ents → chronic, recurrent pattern
- No universal treatment algorithm

**Can recurrent CDI be prevented with new approaches?**

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One Case at a Time

Borrowing old antibiotics for new uses in CDI

- Metronidazole inferior to vancomycin for clinical success
- Some high-risk populations may benefit from vancomycin up front
- Guidelines now advise against metronidazole

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**Rifaximin**

- Non-absorbable rifamycin antibiotic
- Approved for traveler’s diarrhea
- Excellent in-vitro activity against *C. difficile*, but resistance develops rapidly
- Guidelines for ≥2nd recurrence:
  - Recent RCT testing “chaser” following vancomycin\(^1\)
    - Rifaximin 400 mg three times a day for 2 weeks, reduced to 200 mg three times a day for a further 2 weeks
    - 12-week recurrence 29.5% (18/61) placebo vs. 15.9% (11/69) rifaximin: RR 0.54 (0.28-1.05, P=0.07)


**Rifaximin**

- Garey et al. 2011
  - Double-blind, placebo-controlled, RCT 68 patients
  - 20 days of 400 mg TID following standard therapy
  - Less recurrent diarrhea (21% vs. 49%, \(P = 0.002\))
  - Trend to less CDI recurrence (15% vs. 31%, \(P =0.11\))


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Toxin binders

**Cholestyramine & colestipol**
- Non-absorbable anionic polymers
- No efficacy demonstrated
- **WARNING:** may actually bind vancomycin! Do not co-administer!

**Tolevamer**
- Johnson et al. 2014: Inferior to metronidazole / vancomycin (cure 44.2% vs. 72.7% and 81.1%, $P = 0.02$)

---

**Linezolid**

- **✓** HAS IN VITRO ACTIVITY AGAINST CDI
- **✓** CASE REPORTS PUBLISHED WITH SUCCESS
- **✗** FAILURES ALSO PUBLISHED, INCLUDING A FATALITY WHERE LINEZOLID WAS IMPLICATED
- **✗** AT THIS TIME: NOT RECOMMENDED

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One Case at a Time

### Tigecycline

- Good in-vitro activity
- High fecal concentrations
- Low risk for development of CDI

#### Systematic review: Larson et al. 2011:
- Six case reports
- All but one refractory to metronidazole and/or vancomycin
- Success with tigecycline in all 6 cases
- No recurrence

- Four retrospective cohort studies\(^1\) in past 3 years differ, but possible benefit in severe CDI as adjunctive treatment
- Conclusion: shows promise; in need of better data


### Nitazoxanide

- Used to treat intestinal parasites (*Cryptosporidium parvum*)
- Blocks anaerobic metabolism
- Inhibits *C. difficile* in vitro at low concentrations, including metronidazole-resistant strains
- Similar efficacy to metronidazole and vancomycin in two RCTs (Musher et al., 2006 and 2009)
- Jury is out on recommending for clinical use

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One Case at a Time

New Antimicrobial Approaches to CDI Treatment

Ridinilazole

- Narrow spectrum, non-absorbable antibiotic
- Potent anti-*C. difficile* activity
- Decreased inflammation (calprotectin/lactoferrin)
  - Multicenter, double-blind RCT
  - 1° endpoint: sustained clinical response
  - Noninferiority to vancomycin design
  - Superiority demonstrated: 66.7% vs. 42.4% (difference in treatment proportions 21.1%; 90% CI 3.1, 39.1 )
  - 50% reduction in recurrence


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**Ridinilazole (RDZ) effects on microbiome?**

![Graph showing microbiome effects](image)


**Cadazolid**

- Non-absorbable, narrow-spectrum protein synthesis inhibitor
- Potent, but similar to vancomycin

**Phase 2 results promising**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Cadazolid (mg)</th>
<th>Vancomycin (1 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical cure rate (n=90)</td>
<td>13 (96.7)</td>
<td>16 (88.9)</td>
<td>18 (100)</td>
</tr>
<tr>
<td>80% CI</td>
<td>8.6, 13.2</td>
<td>4.0, 18.3</td>
<td>7.0, 21.4</td>
</tr>
<tr>
<td>Treatment group P value (right sided)</td>
<td>0.57</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>Recurrence rate (n=90)</td>
<td>2 (22.2)</td>
<td>0 (0.0)</td>
<td>3 (16.7)</td>
</tr>
<tr>
<td>80% CI</td>
<td>4.8, 13.5</td>
<td>4.0, 7.5</td>
<td>10.0, 22.5</td>
</tr>
<tr>
<td>Sustained clinical response rate (n=90)</td>
<td>40% (4/10)</td>
<td>70% (7/10)</td>
<td>28.2, 65.8</td>
</tr>
<tr>
<td>80% CI</td>
<td>37.9, 73.1</td>
<td>65.0, 76.8</td>
<td>40.0, 60.0</td>
</tr>
<tr>
<td>p</td>
<td>0.05</td>
<td>0.01</td>
<td>0.03</td>
</tr>
</tbody>
</table>


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One Case at a Time

**Surotomycin**

- Potent in vitro activity
- Louie et al. (ASM Microbe 2016)
  - Phase 3, double-blind RCT
  - Clinical response compared to vancomycin
  - Noninferiority design
  - Cure 83.4% vs. 82.1% \((P = .281)\)
  - Sustained clinical response no different (63.3% vs. 59%)
- Recurrence 27.9% for surotomycin 125 mg twice daily, 17.2% for surotomycin 250 mg twice daily and 35.6% for vancomycin \((P = .035)\).
- Minimal disruption of *B. fragilis* and *Bacteroides/Prevotella* groups and decreased VRE counts compared with vancomycin (Chesnel et al., ASM Microbe 2016)

---

**Novel non-antibiotic approaches to CDI treatment**

immune therapy
Immunoglobulins: animal data

• RR 0.18


Immunoglobulins: human data

• Most case series and studies show a benefit
• 17 studies included, but only three met criteria for meta-analysis

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One Case at a Time

### Monoclonal antibodies

- Two candidates: actoxumab (ACT) and bezlotoxumab (BEZ)
- Two phase 3 RCTs: MODIFY I and MODIFY II
  - ACT study arm stopped early: lack of efficacy
  - Pooled analysis of 2327 patients who received either ACT + BEZ or BEZ alone
  - rCDI in 15.4% and 16.5%, respectively, versus 26.6% in the placebo arm (P <.001)
  - Held across subgroups: age ≥65 years, history of CDI, ribotype 027 infection, and severity


### Vaccines: In development for 20 years—many candidates

- **Vla84**: *C. difficile* vaccine candidate (Bezay et al., Vaccine. 2016)
  - Targets cell-binding domains of TcdA and TcdB
  - Phase 2 single-blind, placebo-controlled RCT
  - Seroconversion 60–83% against both toxins
  - Seroconversion 92–97% against TcdA
  - The antibodies were toxin neutralizing
  - Safe and well-tolerated

- **PF-06425090**: phase III
  - Genetically modified *C. difficile* toxins A and B
  - Given IM induces antitoxin antibody production.

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Novel non-antibiotic approaches to CDI treatment

bacteriotherapy* and beta-lactamases

*excluding fecal transplant

Nontoxigenic *C. difficile* spores

- Gerding et al. 2015, phase 2 trial
  - Strain M3 (VP20621; NTCD-M3)
  - Double-blind, placebo-controlled RCT
  - Secondary outcome: 6-week recurrence

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One Case at a Time

Defined microbial communities

- Lawley et al. 2012
  - Mice with CDI treated with FMT had resolution of symptoms
  - Studied community structure of healthy feces
  - Rational, stepwise approach to develop a product
  - Developed many combinations of the bacterial phyla and tested them in lieu of standard FMT
  - Most of these mixtures did not work....


Defined microbial communities

- Mixture B:
  - *Bacteroidetes* novel species
  - *Lactobacillus reuteri*
  - *Enterococcus hirae*
  - *Anaerostipes* novel species
  - *Staphylococcus warneri*
  - *Enterorhabdus* novel species

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Ser-262: defined microbial community
- Spores of anaerobic, indigenous microbes
- Produced by in-vitro fermentation
- Phase I testing underway for rCDI (NCT02830542)


Ribaxamase: an oral β-Lactamase to Prevent *Clostridium difficile*
- Ribaxamase(Syn-004), a novel, oral, recombinant β-lactamase
- Given during treatment with IV β-lactam antibiotics
- Phase 2a trials in patients with ileostomy for sampling of intestinal chyme
- In vivo, syn-004 degrades ceftriaxone excreted in the human intestine
- No systemic absorption and no change in systemic ceftriaxone levels
- Proton pump inhibitor administration did not change the effect

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One Case at a Time

And many more...


Future of CDI treatment?

- Substantial near-term impact: narrow-spectrum, non-absorbable antibiotics
- Long-term: pharmaceutical grade, FDA-approved filtered stool products and defined communities
- Better risk-stratification models to assign expensive or experimental treatments
PART 2: THE BIG QUESTION!

• Should fidaxomicin or vancomycin be considered the front-line antibiotic for CDI
• PRO-CON Debate time!

Who do you want to present each side of the debate?

a. Option 1
   Vanco PRO: Kevin Garey, Pharm.D.
   Fidaxo PRO: Krishna Rao, M.D.

b. Option 2:
   Fidaxo PRO: Kevin Garey, Pharm.D.
   Vanco PRO: Krishna Rao, M.D.
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One Case at a Time

KEVIN GAREY PRO – CON debate

- PRO Fidaxomicin

Fidaxomicin has some really cool anti-recurrence properties
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One Case at a Time

Recurrent CDI is costly:
Healthcare utilization for recurrent CDI

* Of disease-attributable readmission, 85% returned to the initial hospital for care

Increased healthcare utilization = increased healthcare costs

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**Any evidence that fidaxomicin may reduce these costs?**
Patients who received oral vancomycin (n=46) or fidaxomicin (n=49) for the treatment of CDI via a protocol that encouraged fidaxomicin for selected patients.


**Real-world evidence that fidaxomicin may reduce these costs?**
UK, 2012-13: seven hospitals incorporated fidaxomicin into clinical protocols. Letters below indicate individual hospitals

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One Case at a Time

**Real-world evidence that fidaxomicin may reduce these costs?**

UK, 2012-13: seven hospitals incorporated fidaxomicin into clinical protocols. Letters below indicate individual hospitals. Mortality rates decreased from 18.2% and 17.3% to 3.1% and 3.1% in hospitals A and B, respectively (p<0.05, each)

- **Before Fidaxo**
- **After fidaxo**

<table>
<thead>
<tr>
<th></th>
<th>Re-admission within 30 days or primary CDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n=98)</td>
<td>35</td>
</tr>
<tr>
<td>B (n=162)</td>
<td>15</td>
</tr>
<tr>
<td>D (n=127)</td>
<td>20</td>
</tr>
<tr>
<td>C (n=511)</td>
<td>25</td>
</tr>
<tr>
<td>E (n=209)</td>
<td>10</td>
</tr>
<tr>
<td>F (n=178)</td>
<td>15</td>
</tr>
<tr>
<td>G (n=278)</td>
<td>20</td>
</tr>
</tbody>
</table>

And last but not least, the patient perspective

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One Case at a Time

I wonder if we are missing the most important endpoints?


The driver for decreased quality of life (QOL) is not so much physical as a worry/anxiety of transmissibility or symptom persistence

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One Case at a Time

Quality of Life (QOL) goes down considerably with recurrent CDI

Primary or recurrent CDI
- Primary
- Recurrent


Patient perspective

“It was a little over a year ago I was diagnosed and treated with metronidazole, then treated again in April with vancomycin for it as tested positive again, and am 50 years old and otherwise healthy except for hypertension issues. I think I acquired it as a caretaker for my elderly mother (who has since passed away), and having antibiotics for dental issues. I wouldn't wish this illness on my worst enemy, and it's been a life changer for me.”

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## Should fidaxomicin be used first-line?

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
<th>Why</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is fidaxomicin a superior drug?</td>
<td>Yes</td>
<td>Decreased recurrence rate by 50%</td>
</tr>
<tr>
<td>Is fidaxomicin a safer drug?</td>
<td>Yes</td>
<td>Decreased VRE colonization</td>
</tr>
<tr>
<td>Is fidaxomicin a more cost-effective drug?</td>
<td>Yes</td>
<td>Decreased hospitalization costs due to recurrent CDI</td>
</tr>
<tr>
<td>Is patient satisfaction higher if you don’t have recurrence?</td>
<td>Yes</td>
<td>Significantly increased anxiety in patients with recurrent CDI</td>
</tr>
</tbody>
</table>

## Kevin GAREY PRO – CON debate

- PRO Vancomycin
Improving the Lives of Patients with *Clostridium difficile* Infection
One Case at a Time

**Vancomycin is remarkably effective at day 7-10 cure rates**

<table>
<thead>
<tr>
<th>Study years</th>
<th>Study drug</th>
<th>Comparator</th>
<th>Study phase</th>
<th>N</th>
<th>Clinical cure rate (%)</th>
<th>Recurrence rate (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Study drug</td>
<td>Vanco</td>
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<tr>
<td>&lt;2005</td>
<td>Ramoplanin</td>
<td>Vancomycin</td>
<td>II</td>
<td>89</td>
<td>71</td>
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<td>2006-08</td>
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<td>III</td>
<td>629</td>
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<td>90</td>
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<td>2007-09</td>
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<tr>
<td>2010-11</td>
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<td>Vancomycin</td>
<td>II</td>
<td>209</td>
<td>87-92</td>
<td>89</td>
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<tr>
<td>2012-15</td>
<td>Surotomyce</td>
<td>Vancomycin</td>
<td>III</td>
<td>608</td>
<td>79</td>
<td>84</td>
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<tr>
<td>2012-15</td>
<td>Cadazolid</td>
<td>Vancomycin</td>
<td>II</td>
<td>84</td>
<td>68-80</td>
<td>68</td>
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<td>2011-12</td>
<td>LFF571</td>
<td>Vancomycin</td>
<td>II</td>
<td>72</td>
<td>85</td>
<td>80</td>
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<td>2014-15</td>
<td>Ridinilazo</td>
<td>Vancomycin</td>
<td>II</td>
<td>100</td>
<td>78</td>
<td>70</td>
</tr>
</tbody>
</table>

Basseres et al. *Curr Opin Gastroenterol.* 2017; 33:1-7

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**I would use vancomycin routinely if:**

- I could get the recurrence rate similar to fidaxomicin or other ‘newer’ antibiotics
- Is this possible?
- (I’m ignoring the VRE overgrowth stuff)
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One Case at a Time

Can we use our knowledge of CDI treatment goals to better use vanco (aka, drop recurrence rate)?

**Current:** Can we combine with a probiotic

Are there novel ways to use vanco?

Vanco + immune stimulation?

---

**Six week taper of vanco was as good as an FMT enema**

Ontario, Canada. Patients experiencing recurrent CDI randomized to standard course vanco + FMT enema vs. vanco taper regimen (6 weeks)

![Graph showing recurrence rate comparison](#)

- Vanco 14d + FMT (n=16): 56.2%
- Vanco taper 6 weeks (n=12): 41.7%

Early termination at interim analysis

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One Case at a Time

**Possibility #1:** Extend out the pulse taper regimen to every 3rd day

![Bar chart showing clinical cure and total treatment duration](chart)

- **Clinical cure ( enrolment)**
  - Every 2nd day pulse (n=36): 61%
  - Every 3rd day pulse (n=64): 81%

- **Total treatment duration**
  - 60±26 days
  - 86 ±28 days

Chicago, IL: 100 patients with recurrent CDI treated with vanco pulse taper regimen


**Possibility #2:** Use a probiotic

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**Non-toxigenic C. diff (NTCD): phase II study**

CDI patients given NTCD or placebo immediately after finishing antibiotic therapy (metro only: 53-60%; vanco only: 14-32%; metro+vanco: 12-26%)

![Recurrence Graph](https://example.com/graph.png)


---

**SER-109. Fractionated and encapsulated spores from healthy donor stools**

CDI patients given SER-109 immediately after finishing antibiotic therapy (vanco: n=23; fidaxomicin: n=5; metro: n=1; rifaximin: n=1)

![Recurrence Graph](https://example.com/graph.png)


---

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A probiotic formula of Lactobacillus acidophilus CL1285 and Lactobacillus casei LBC80R decreased CDI rates

![Bar chart showing CDI rates](chart.png)


Protocol utilizing a staggered and tapered antibiotic regimen for the treatment of recurrent *Clostridium difficile* infection that has failed to respond to standard antibiotic therapy.

25 patients with recurrent CDI that were not able to perform FMT. Twenty-one of the 25 patients (84%) remained free of diarrhea during the following 9 months. The 4 patients who relapsed permanently resolved their diarrhea after a conventional 2-week course of oral vancomycin 125 mg 4 times daily followed by a 2-week course of rifaximin 200 mg twice daily. All 4 patients remained symptom-free at 12 months of follow-up.

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</tr>
</thead>
<tbody>
<tr>
<td>Weeks 1-2</td>
<td>250 mg Q 6h</td>
<td></td>
<td>125 mg Q 6h</td>
<td></td>
<td>150 mL TID</td>
</tr>
<tr>
<td>Weeks 3-4</td>
<td>750 mg Q 72h</td>
<td></td>
<td>375 mg Q 72h</td>
<td></td>
<td>150 mL TID</td>
</tr>
<tr>
<td>Weeks 5-6</td>
<td>500 mg Q 72h</td>
<td></td>
<td>250 mg Q 72h</td>
<td></td>
<td>150 mL TID</td>
</tr>
<tr>
<td>Weeks 7-8</td>
<td>250 mg Q 72h</td>
<td></td>
<td>125 mg Q 72h</td>
<td></td>
<td>150 mL TID</td>
</tr>
<tr>
<td>Weeks 9-15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>150 mL TID</td>
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</tbody>
</table>


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One Case at a Time

**Possibility #3: Improve antibody response**

Combined phase III clinical trial results of bezlotoxumab in patients who received vancomycin as standard therapy

- Vancomycin + placebo (n=297)
- Vancomycin + bezlotoxumab (n=292)

Dubberke et al. ID-week 2017.

---

**Should vancomycin be used first line?**

- Remarkably effective for initial clinical cure
- Decades of experience, has withstood the tests of time
- With a little creativity, can lower recurrence rates similar to what is observed with fidaxomicin
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A. KRISHNA RAO
PRO FIDAXOMICIN

Fidaxomicin: clinical trials

![Image of a table showing clinical trial data for Fidaxomicin](image)

Fidaxomicin: clinical trials


Fidaxomicin: strain specific benefit?

- Reduced relapse (HR 0.40 [0.25–0.66]; \( P = .0003 \))
- Reduced reinfection (HR 0.33 [0.11–1.01]; \( P = .05 \))

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**Fidaxomicin for the critically ill?**

- Penziner et al. 2014:
  - 30 patients on the wards compared with 20 in ICUs
  - All received fidaxomicin for CDI

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment failure</th>
<th>Treatment response</th>
<th>Univariate, OR (95% CI); P value</th>
<th>Multivariate, OR (95% CI); P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60 yr</td>
<td>(n = 18)</td>
<td>(n = 32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDI due to NAP1 strain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe and severe complicated CDI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever when fidaxomicin therapy commenced</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fidaxomicin in combination with other anti-CDI drugs(^b)</td>
<td>11 (61.1)</td>
<td>7 (21.9)</td>
<td>3.6 (1.58–19.87) ; 0.014</td>
<td>4.9 (0.95–25.43) ; 0.06</td>
</tr>
<tr>
<td>CCU level of care during fidaxomicin treatment</td>
<td>8 (44.4)</td>
<td>12 (37.5)</td>
<td>1.3 (0.41–4.31) ; 0.8</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) OR, odds ratio; CI, confidence interval.

\(^b\) Including metronidazole (n = 9), oral vancomycin (n = 4), or both (n = 5).

**Fidaxomicin: the microbiota**

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Fidaxomicin: no resistance...yet

- Snydman et al. 2015
  - 7 geographically dispersed medical centers 2011-2012
  - 925 isolates
  - MIC90 ≤ 0.5 μg/mL across regions and over 1 year after licensure


Fidaxomicin: cost-effective? probably...

- Bartsch et al. 2013
  - Incremental cost-effectiveness ratio (ICER) >$43.7 million per quality-adjusted life year (QALY)
  - Assuming 50% ribotype 027, not cost-effective until ≤$150 per course
- Stranges et al. 2013
  - ICER $67,576 per QALY
  - Simulation: 80% chance of being cost-effective at $100K threshold
- Nathwani et al. 2014
  - ICER £16,529 ($23,952) per QALY for severe CDI
  - Dominant (more effective & less costly) for 1st recurrence
  - Simulation: 60% probability of cost-effectiveness for severe CDI and 68% for first recurrence at £30,000 threshold

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### Fidaxomicin: Overview

- Narrow spectrum, non-absorbable antibiotic
- Studied for 1*st* or 2*nd* episode
- Noninferior to vancomycin for cure\(^1\)
- 50% reduction in recurrent CDI\(^1\)
- Possible role at the end of a taper (chaser) in place of rifaximin\(^2\)


---

**A. KRISHNA RAO**

**PRO VANCOMYCIN**
Improving the Lives of Patients with *Clostridium difficile* Infection
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Fidaxomicin is too expensive

- Outpatients:
  - Fidaxomicin cost is over $2000 out of pocket in most settings
  - There are still many insurers that will not cover it without prior authorization / failure of other agents
  - There is a coupon program but many patients do not qualify for it
- Inpatients:
  - Too costly to keep on most formularies without restriction
  - Many programs restrict only to failures / multiple recurrences (less evidence in this setting)
  - There is a special incentive through CMS: new technology add-on payment, but remaining cost is still over $1000
- Vancomycin oral can be compounded from the IV formulation
  - Resulting cost is essentially nominal for most insurers
- Even vancomycin oral tablets are usually several fold less expensive

Fidaxomicin is not necessarily cost effective at the individual hospital level

- Bartsch et al. 2013
  - Incremental cost-effectiveness ratio (ICER) >$43.7 million per quality-adjusted life year (QALY)
  - Assuming 50% ribotype 027, not cost effective until ≤$150 per course
- Stranges et al. 2013
  - ICER $67,576 per QALY
  - Simulation: 80% chance of being cost-effective at $100K threshold
- Gallagher et al. 2015
  - Fidaxomicin costs totaled $62,112
  - Vancomycin costs totaled $6,646
  - Hospital lost $3,286 per fidaxomicin-treated patient and $6,333 per vancomycin-treated patient
  - However, savings depend on local epidemiology and rates of recurrence, readmission to the same facility

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**Precision health is not mature enough to move away from vancomycin yet**

- Cost is an issue but what if we could risk stratify people better?
- Severity/Complications? Nope

- Recurrence? Double nope.
  - Retrospective cohort
  - Entire VA 2006-2012
  - 56,273 CDI cases, 7446 rCDI
  - Overall results were not encouraging

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<table>
<thead>
<tr>
<th>Table 4. Concordance of Severity Score Indicators for <em>Clostridium difficile</em> Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index</td>
</tr>
<tr>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Birth Island</td>
</tr>
<tr>
<td>UFHC cohort 1</td>
</tr>
<tr>
<td>University of Calgary cohort 1</td>
</tr>
<tr>
<td>Biosyn II University of Illinois</td>
</tr>
<tr>
<td>University of Colorado</td>
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<tr>
<td>University of Arizona</td>
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<tr>
<td>University of Utah</td>
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<tr>
<td>University of Texas</td>
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<tr>
<td>University of Temple</td>
</tr>
</tbody>
</table>

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Stevens et al., ID Week 2015.

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Vancomycin is more versatile

1. Capsules that can be opened
2. Liquid formulation upon compounding the IV form
3. Varying doses from 125-500 mg
4. Used orally and can be infused rectally for ileus
5. Useful in severe AND complicated CDI

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### We have more evidence and experience with vancomycin

- Has been used for CDI for three decades now
- Non-inferior for cure compared with fidaxomicin
- Many edge cases have been tested
  - Severe, complicated with multiple recurrences
  - Immune compromised patients
- Can be given as a taper for recurrence and may be even better than FMT?
  - FMT no better than vancomycin taper in recent RCT\(^1\) of acute CDI patients, although enema only
  - The authors on difference with prior RCTs not using a placebo control arm (emphasis mine):
    
    “Without a control arm in either trial, it is not known what proportion of patients would have been symptom-free had their antibiotics been simply discontinued.”


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### Audience response question (for rebuttal period only)

You are treating a 50-year-old man with his initial episode of CDI. He started fidaxomicin but by day 5 is not doing much better with continued diarrheal stools 7-10 times per day. Against the advice of your colleagues in ID, you sent a repeat test and it was positive for toxin A/B by ELISA again. What do you do next?

- a. Continue fidaxomicin and reassess in a couple of days
- b. Stop fidaxomicin and start vancomycin 125 mg orally four times daily
- c. Stop antibiotics and move to fecal transplant
- d. Send for endoscopy to look for alternative diagnoses

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Which of these practice changes will you consider making?

- Discuss with colleagues the disease burden of CDI
- Educate staff on the emerging and current treatment options for managing patients with CDI
- Incorporate most current evidence-based guidelines into practice when treating patients with CDI
- Apply emerging evidence and treatment recommendations for managing patients with CDI
- Collaborate with other healthcare professionals to achieve optimal outcomes for preventing and treating patients with CDI

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- **elearning.ashp.org**
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- Additional instructions in handout

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- Available early March 2019

E-Newsletter
- Spring 2019

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Questions? Contact EducServ@ashp.org!
A. Krishna Rao, M.D., M.S.
Assistant Professor of Internal Medicine
University of Michigan
Ann Arbor, Michigan

A. Krishna Rao, M.D., M.S., is Assistant Professor of internal medicine at Michigan Medicine in Ann Arbor, Michigan. He received his Doctor of Medicine degree from Rush University Medical Center in Chicago, Illinois and completed a pediatrics residency and an infectious diseases fellowship at the University of Michigan in Ann Arbor. He also received a Master of Science degree in Clinical Research Design and Statistical Analysis from the University of Michigan School Of Public Health.

Dr. Rao’s clinical, administrative, and research interests include the diagnosis and management of healthcare-associated infections, especially *Clostridium difficile* infection. His clinical work includes managing the University of Michigan Fecal Microbiota Transplantation (stool transplant) program for recurrent *Clostridium difficile* infection, a program that he co-founded. His primary research goal is to investigate how biochemical, microbiological, and clinical factors can help clinical decision-making in healthcare-associated infections, and he hopes to ultimately integrate these factors into robust risk-prediction algorithms for use by clinicians. He is currently funded by the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) on studies pertaining to *C. difficile* infection, the effect of antibiotics on the gut microbiota, and infections from Gram-negative bacteria, including multi-drug resistant organisms, such as *Klebsiella pneumoniae*.

Kevin W. Garey, Pharm.D., M.S., FASHP, Activity Chair

Professor and Chair
Department of Clinical Sciences and Administration
University of Houston College of Pharmacy
Houston, Texas

Kevin W. Garey, Pharm.D., M.S., FASHP is Professor at the University of Houston College of Pharmacy and Chair of the Department of Clinical Sciences and Administration at the University of Houston College of Pharmacy in Houston, Texas. Dr. Garey is an Adjunct Professor at the University of Texas School of Public Health and a Clinical Specialist and Researcher at Baylor St. Luke’s Medical Center in Houston, Texas. He received a Bachelor of Science in Pharmacy degree from Dalhousie University in Halifax, Nova Scotia, Canada, a Doctor of Pharmacy from the State University of New York in Buffalo, New York, and Master of Science in Biometry from the University of Texas School of Public Health in Austin, Texas. He completed a pharmacy practice residency at Bassett Healthcare, Cooperstown, NY and infectious disease specialty residency and fellowship training at the University of Illinois at Chicago College of Pharmacy in Chicago, Illinois.

Dr. Garey has numerous publications in infectious diseases topics and has presented extensively at national and international professional conferences. He has received numerous professional awards including the ASHP Drug Therapy Research Award, ASHP Best Practices Award in Health-System Pharmacy, the Society of Infectious Diseases Pharmacists Impact Paper in Infectious Diseases Pharmacotherapy Award and the University of Houston Faculty Leadership award. He is a Fellow of ASHP.

Dr. Garey’s research interests involve clinical and translational research involving healthcare-associated infections including post-surgical infections, candidemia, and *Clostridium difficile* infection.

Learning Opportunities

- On-Demand activity Best practice update on *Clostridium difficile* Infection (CDI): Focus on Prevention, Treatment and Recurrence available now
- On-Demand activity of today’s live symposium coming in March 2019
- E-newsletter coming in 2019

[www.ashpadvantage.com/cdiff](http://www.ashpadvantage.com/cdiff)

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