CE IN THE MIDDAY

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

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Disclosures

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• Kevin Garey
  – Merck, Inc., Summit Therapeutics, and Tetraphase: Research Support

• Krishna Rao
  – Merck, Inc.: Research support (Co-investigator)
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.
Side note: Nomenclature Change

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

Volume 3, Issue 1 Winter 2018

Clinical & Laboratory Standards Institute Antimicrobial Susceptibility Testing News Update.
To start: why do we get CDI in the first place?
Welcome to the wonderful world of the microbiome!
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
Welcome to a whole new area of science!

- Metabolomics
- Transcriptomics (RNAseq) and proteinomics
- 16S sequencing
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

Healthy Microbiome

- Colonic epithelium

Recurrent CDI Microbiome

- Colonic epithelium

Enteric flora

Colonic epithelium
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

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

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
## Antibiotics that increase CDI risk

<table>
<thead>
<tr>
<th>Drug</th>
<th>Kills firmicutes</th>
<th>Kills 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

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></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Received PPI?</td>
<td>N</td>
<td>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

We can now update an old slide with newer antibiotics

1. Carbapenems
2. 3rd/4th gen cephalosporin
3. Piperacillin-tazobactam

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

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)
Clinical Practice Guidelines for *Clostridium difficile*
Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA)

Stuart H. Cohen, MD; Dale N. Gerding, MD; Stuart Johnson, MD; Ciaran P. Kelly, MD; Vivian G. Loo, MD; L. Clifford McDonald, MD; Jacques Pepin, MD; Mark H. Wilcox, MD

Clinical Practice Guidelines for *Clostridium difficile*
Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA)

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

IVIG
Monoclonal antibodies vs. C. diff toxins

Ridinilazole
Toxoid vaccines

FMT = fecal microbiota transplantation
<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 (tolevamer phase III RCT).

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

<table>
<thead>
<tr>
<th>CDI severity</th>
<th>Vancomycin</th>
<th>Metronidazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any severity</td>
<td>8.6%</td>
<td>10.6%</td>
</tr>
<tr>
<td>Mild-moderate</td>
<td>5.9%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Severe</td>
<td>15.3%</td>
<td>19.8%</td>
</tr>
</tbody>
</table>

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%).

## 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>6 of 34 (17%)</td>
<td>N/A</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>
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><strong>All strains</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>Karlowsky 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><strong>BI/027/Nap1 strains</strong></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></td>
<td>0.5-1</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 ug/g
- MIC50: 1 ug/mL    MIC90: 2 ug/mL
  - May be higher
- A poor response rate to metronidazole should be expected given these numbers!

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)

## 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><strong>Direct comparisons of metronidazole and vancomycin</strong></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>
<tr>
<td><strong>Direct comparisons of fidaxomicin and vancomycin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resolution at end (10 days) of treatment</td>
<td>1105 (2 studies)</td>
<td>88 (FDX) 86 (VAN)</td>
<td>0.36</td>
<td>High</td>
</tr>
<tr>
<td>Resolution of diarrhea at end of treatment without recurrence**</td>
<td>1105 (2 studies)</td>
<td>71 (FDX) 57 (VAN)</td>
<td>&lt;0.0001</td>
<td>High</td>
</tr>
</tbody>
</table>

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

VAN = vancomycin, MTR = metronidazole, FDX = fidaxomicin

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

IVIG
Monoclonal antibodies vs. C. diff toxins

Ridinilazole

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
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>
<tbody>
<tr>
<td>First recurrence</td>
<td></td>
<td>• VAN SD if metronidazole was used for the first episode OR&lt;br&gt;• Prolonged tapered and pulsed VAN if VAN SD was used for first regimen OR&lt;br&gt;• FDX SD if VAN was used for the initial episode</td>
</tr>
<tr>
<td>Second or subsequent recurrences</td>
<td></td>
<td>• VAN in a tapered or pulsed regimen OR&lt;br&gt;• VAN SD followed by rifaximin 400 mg three times daily for 20 days OR&lt;br&gt;• FDX SD OR&lt;br&gt;• Fecal microbiota transplantation</td>
</tr>
</tbody>
</table>

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

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

*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

FMT for patients with recalcitrant CDI

- FMT (Fecal Microbiota Transplantation)
- Resolution of symptoms
- Healthy individual
- ‘Healthy’ microbiota
- Antibiotics
- Reduced gut microbial species and diversity
- Ingestion of C. difficile spores from the environment
- C. difficile spores germinate
- Bloom of C. difficile
- Dysbiosis of the gut microbiota
- Development of CDI:
  - Severe diarrhea, abdominal pain, nausea and fever
  - C. difficile toxins induce inflammation and cell death
  - CDI can cause pseudomembranous colitis
Recurrent *C. difficile* colitis: case series involving 18 patients treated with donor stool administered via a nasogastric tube

<table>
<thead>
<tr>
<th></th>
<th>Before stool transplant</th>
<th>After stool transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>N/A</td>
<td>2 (unrelated)</td>
</tr>
<tr>
<td># of Recurrence</td>
<td>64 (2-7)</td>
<td>1</td>
</tr>
</tbody>
</table>

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.

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<th>Antibiotic</th>
<th>Metronidazole</th>
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</tr>
</thead>
<tbody>
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<td>Time Course</td>
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<tr>
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</tr>
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<td>Weeks 3-4</td>
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<td>375 mg Q 72h</td>
<td>150 mL TID</td>
</tr>
<tr>
<td>Weeks 5-6</td>
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<td>Weeks 9-15</td>
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</tr>
</tbody>
</table>
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
CDI incidence vs. Clinical Trial Registries

Targets for alternative CDI treatments?

CDI clinical trials vs. treatment goal

So...why do we need alternative treatments?

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

- Hypotension / shock / sepsis
- Ileus / megacolon
- Peritonitis
- Bowel perforation

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

Source: NIH 2011
Recurrent CDI

• 2nd Recurrence: 30-45% of 1st
• 3rd Recurrence: 45-60% of 2nd
• ≤5% of all patients → chronic, recurrent pattern
• No universal treatment algorithm

Can recurrent CDI be prevented with new approaches?

Borrowing old antibiotics for new uses in CDI
Metronidazole and reduced clinical success?

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

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 vancomycin¹
    - 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%, $P =0.11$)

Toxin binders

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

**Tlevamer**
- 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

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

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

Bassères et al. 2016
Ridinilazole (RDZ) effects on microbiome?

Cadazoloid

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

Phase 2 results promising

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cadazoloid 250 mg BID</th>
<th>Cadazoloid 500 mg BID</th>
<th>Cadazoloid 1,000 mg BID</th>
<th>Vancomycin 125 mg QID</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical cure rate [n (%)]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80% CI</td>
<td>58.4, 89.3</td>
<td>63.8, 91.0</td>
<td>51.1, 82.5</td>
<td>52.3, 81.3</td>
</tr>
<tr>
<td><strong>Treatment group P value (right sided)</strong></td>
<td>0.57, 0.41</td>
<td>0.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Recurrence rate [n (%)]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80% CI</td>
<td>4.9, 41.5</td>
<td>9.6, 47.5</td>
<td>5.1, 49.0</td>
<td>30.5, 69.3</td>
</tr>
<tr>
<td><strong>Sustained clinical response rate [n (%)]</strong></td>
<td>11, 12</td>
<td>9, 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>80% CI</strong></td>
<td>40.4, 77.4</td>
<td>37.5, 73.7</td>
<td>28.2, 65.8</td>
<td>19.6, 49.7</td>
</tr>
<tr>
<td><strong>Median time to resolution of diarrhea [h]</strong></td>
<td>141.2</td>
<td>173.6</td>
<td>133.5</td>
<td>133.7</td>
</tr>
<tr>
<td><strong>80% CI</strong></td>
<td>107.3, 180.7</td>
<td>86.7, 212.1</td>
<td>110.8, 286.3</td>
<td>90.7, 190.9</td>
</tr>
</tbody>
</table>


Suromycin

• 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 suromycin 125 mg twice daily, 17.2% for suromycin 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

Table 6. Effect of passive immunotherapy against *Clostridium difficile* infection in human subjects.

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>No. cases with diarrhea/No. in group (%)</th>
<th>Intervention</th>
<th>Control</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juang <em>et al.</em> (2007)</td>
<td>6/18</td>
<td>5/18</td>
<td>1.200</td>
<td>0.446 to 3.232</td>
</tr>
<tr>
<td>Mattila <em>et al.</em> (2008)</td>
<td>8/18</td>
<td>9/20</td>
<td>0.988</td>
<td>0.486 to 2.005</td>
</tr>
<tr>
<td>Lowy <em>et al.</em> (2010)</td>
<td>7/101</td>
<td>24/99</td>
<td>0.286</td>
<td>0.129 to 0.633</td>
</tr>
</tbody>
</table>

Severe CDI
Symptoms
Recurrent CDI

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.

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
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*
  - *Lactobacillus reuteri*
  - *Enterococcus hirae*
  - *Anaerostipes*
  - *Staphylococcus warneri*
  - *Enterorhabdus*

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

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.
KEVIN GAREY PRO – CON debate

• PRO Fidaxomicin
Fidaxomicin has some really cool anti-recurrence properties
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


<table>
<thead>
<tr>
<th>Cost in US dollars; median (IQR)</th>
<th>Without recurrent CDI</th>
<th>With recurrent CDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDI pharmacologic treatment*</td>
<td>$60 (23 - 200)</td>
<td>$140 (30 - 260)</td>
</tr>
<tr>
<td>CDI-attributable hospitalization^</td>
<td>$13,168 (7,525 - 24,455)</td>
<td>$28,218 (15,049 - 47,030)</td>
</tr>
<tr>
<td>Total hospitalization^</td>
<td>$20,693 (11,287 - 41,386)</td>
<td>$45,148 (20,693 - 82,772)</td>
</tr>
</tbody>
</table>
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.

CDI-related readmissions: Fidaxo: 20.4%; Vanco: 41.3%

Real-world evidence that fidaxomicin may reduce these costs?

UK, 2012-13: seven hospitals incorporated fidaxomicin into clinical protocols. Letters below indicate individual hospitals

Before Fidaxo | After fidaxo
--- | ---
A (n=98) | 10.6 | 3.1
B (n=162) | 16.3 | 3.1
D (n=127) | 21.1 | 12.5
C (n=511) | 7.7 | 8.3
E (n=209) | 12.9 | 11.8
F (n=178) | 16.9 | 9
G (n=278) | 5.4 | 5.8

First line, all episodes | First line, R-CDI | Selected episodes only

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)

And last but not least, the patient perspective
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.
Quality of Life (QOL) goes down considerably with recurrent CDI

“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.”
## 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
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>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2005</td>
<td>Ramoplanin</td>
<td>Vancomycin</td>
<td>II</td>
<td>89</td>
<td>Study drug 71</td>
<td>Vanco 78</td>
</tr>
<tr>
<td>2006-08</td>
<td>Fidaxomicin</td>
<td>Vancomycin</td>
<td>III</td>
<td>629</td>
<td>88</td>
<td>90</td>
</tr>
<tr>
<td>2007-09</td>
<td>Fidaxomicin</td>
<td>Vancomycin</td>
<td>III</td>
<td>535</td>
<td>88</td>
<td>87</td>
</tr>
<tr>
<td>2010-11</td>
<td>Surotomycin</td>
<td>Vancomycin</td>
<td>II</td>
<td>209</td>
<td>87-92</td>
<td>89</td>
</tr>
<tr>
<td>2012-15</td>
<td>Surotomycin</td>
<td>Vancomycin</td>
<td>III</td>
<td>608</td>
<td>79</td>
<td>84</td>
</tr>
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<td>Vancomycin</td>
<td>III</td>
<td>608</td>
<td>83</td>
<td>82</td>
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<tr>
<td>2011-12</td>
<td>Cadazolid</td>
<td>Vancomycin</td>
<td>II</td>
<td>84</td>
<td>68-80</td>
<td>68</td>
</tr>
<tr>
<td>2011-12</td>
<td>LFF571</td>
<td>Vancomycin</td>
<td>II</td>
<td>72</td>
<td>85</td>
<td>80</td>
</tr>
<tr>
<td>2014-15</td>
<td>Ridinilazole</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
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)
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)

Recurrence rate (%)

<table>
<thead>
<tr>
<th>Vanco 14d + FMT (n=16)</th>
<th>56.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vanco taper 6 weeks (n=12)</td>
<td>41.7</td>
</tr>
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</table>

Early termination at interim analysis

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

**Clinical cure (%)**

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

**Total treatment duration**
- Every 2nd day pulse: 60±26 days
- Every 3rd day pulse: 86 ±28 days

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

Possibility #2: Use a probiotic
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%)

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)

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

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>
<tr>
<td>Weeks 9-15</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Possibility #3: Improve antibody response

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

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
A. KRISHNA RAO
PRO FIDAXOMICIN
Fidaxomicin: clinical trials

Fidaxomicin: clinical trials

Fidaxomicin: strain specific benefit?

- Reduced relapse (HR 0.40 [0.25–0.66]; \(P = 0.0003\))
- Reduced reinfection (HR 0.33 [0.11–1.01]; \(P = 0.05\))
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 2 Factors associated with probability of lack of fidaxomicin treatment response

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%) of patients with:</th>
<th>Treatment failure (n = 18)</th>
<th>Treatment response (n = 32)</th>
<th>Univariate, OR (95% CI); P value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Multivariate, OR (95% CI); P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60 yr</td>
<td></td>
<td>14 (77.8)</td>
<td>14 (43.8)</td>
<td>4.5 (1.21–16.72); 0.04</td>
<td>4.7 (0.9–23.4); 0.06</td>
</tr>
<tr>
<td>CDI due to NAP1 strain</td>
<td></td>
<td>10 (55.6)</td>
<td>11 (35.5)</td>
<td>2.3 (0.69–7.44); 0.3</td>
<td>1.5 (0.36–6.55); 0.6</td>
</tr>
<tr>
<td>Severe and severe complicated CDI</td>
<td></td>
<td>13 (72.2)</td>
<td>11 (34.4)</td>
<td>4.9 (1.4–17.56); 0.02</td>
<td>5.1 (1.02–25.46); &lt;0.05</td>
</tr>
<tr>
<td>Fever when fidaxomicin therapy commenced</td>
<td></td>
<td>5 (27.8)</td>
<td>11 (34.4)</td>
<td>3.7 (0.77–17.94); 0.1</td>
<td>2.6 (0.27–25.48); 0.4</td>
</tr>
<tr>
<td>Fidaxomicin in combination with other anti-CDI drugs&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>11 (61.1)</td>
<td>7 (21.9)</td>
<td>5.6 (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></td>
<td>8 (44.4)</td>
<td>12 (37.5)</td>
<td>1.3 (0.412–4.31); 0.8</td>
<td>0.8 (0.12–3.74); 0.6</td>
</tr>
</tbody>
</table>

<sup>a</sup> OR, odds ratio; CI, confidence interval.

<sup>b</sup> Including metronidazole (n = 9), oral vancomycin (n = 4), or both (n = 5).
Fidaxomicin: the microbiota

Table 1. Quantification of *Enterococaceae–Lactobacillaceae* (probe Lab158) as a proportion of the total faecal microbiota

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage of total faecal microbiota on day:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Fidaxomicin</td>
<td>4.66 ± 1.37</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>6.04 ± 2.66</td>
</tr>
<tr>
<td>None (healthy controls)</td>
<td>4.72 ± 1.50</td>
</tr>
</tbody>
</table>

Data are means ± se of percentage values. ND, No samples; NA, not applicable.
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

Fidaxomicin: Overview

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

A. KRISHNA RAO
PRO VANCOMYCIN
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

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

| Table 4. Concordance of Severity Score Indices for Severe Clostridium difficile Infection |
|-----------------------------------------------|--------|--------|--------|--------|---------------------|
| Index                                         | Sensitivity, % | Specificity, % | PPV, % | NPV, % | Kappa score (95% CI) |
| Beth Israel                                    | 61.2   | 87.3   | 56.4   | 95.4   | 0.38 (0.26-0.52)    |
| UPMC version 1                                 | 68.4   | 93.9   | 565    | 96.3   | 0.57 (0.45-0.70)    |
| University of Calgary version 1                | 68.4   | 90.3   | 448    | 96.1   | 0.48 (0.34-0.62)    |
| Hines VA                                       | 71.7   | 93.4   | 700    | 97.0   | 0.69 (0.54-0.83)    |
| Modified University of Illinois               | 64.2   | 99.4   | 193    | 97.3   | 0.18 (0.08-0.27)    |
| University of Calgary version 2                | 71.7   | 72.7   | 237    | 96.0   | 0.24 (0.13-0.36)    |
| UPMC version 2                                 | 73.7   | 88.5   | 42.4   | 96.7   | 0.47 (0.33-0.61)    |
| University of Temple                          | 64.2   | 71.5   | 21.7   | 95.2   | 0.20 (0.08-0.32)    |

Note: CI: confidence interval; NPV: negative predictive value; OR: odds ratio; PPV: positive predictive value; UPMC, University of Pittsburgh Medical Center.


Stevens et al., ID Week 2015.
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
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."

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
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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