Solving the Mysteries of C. difficile Infection

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Disclosures

• Research grant support paid to the University of Houston
  – For Profit: Merck & Co, Summit PLC
  – State/Federal: Houston Department of Health, NIH (NIAID 1U01 AI24290-01)

• Consulting
  – For Profit: Merck & Co, Summit PLC, Seres Therapeutics
The Twitter-verse has spoken

• Celebrity Death Match among fidaxo, bezlo, and FMT for recurrent CDI? Which one wins?

Antibody response
Pathogenesis of *Clostridium difficile*-associated diarrhea in adults

*Clostridium difficile* spores and vegetative cells are ingested

- Spores
- Vegetative cells

Most vegetative cells are killed in the stomach, but spores can survive the acid environment.

*Clostridium difficile* spores germinate in the small bowel upon exposure to bile acids.

Flagellae facilitate *C. difficile* movement; a polysaccharide capsule discourages phagocytosis.

*C. difficile* multiplies in the colon.

Gut mucosa facilitates adherence to the colonic epithelium.

Therapeutic goals for CDI

**Essential:**
- Correct dysbiosis
- Kill the organism
- Adaptive immunity

**Optional but nice:**
- Safe and convenient
- Also affects toxins and spores
- Short vs. long-term
- Also affects toxins

Adamu and Lawley. Curr Opin Microbiol 2013

There has been an explosion in treatment possibilities for CDI

**Current:**
- Probiotics
- FMT
- Use narrow-spectrum antibiotics
- Metronidazole
- Vancomycin
- Fidaxomicin
- IVIG
- Monoclonal antibodies vs. C diff toxins

**Future:**
- 2nd generation FMT
- non-tox C diff M3
- Ecobiotics
- Ridinilazole
- Toxoid vaccines
### Current US IDSA 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 SrCr &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 SrCr ≥ 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 q8hours. For ileus, consider adding rectal instillation of vancomycin</td>
<td>C-III</td>
</tr>
<tr>
<td>Second (1st recurrence)</td>
<td></td>
<td>Same as initial</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>Vancomycin</td>
<td>PO tapered and/or pulsed</td>
<td>Vancomycin</td>
<td>B-III</td>
</tr>
</tbody>
</table>

Cohen SH, Gerding DN, et al. Infection control and hospital epidemiology. 2010 (May); 31(5)

### Current European CDI guidelines

- **CDI**
  - **Non-severe CDI**
    - **Metronidazole**
    - **Vancomycin**
    - **Fidaxomicin**
  - **(Risk of) first recurrence**
    - **Vancomycin**
    - **Fidaxomicin**
    - **Metronidazole**
  - **Severe disease or complicated course**
    - **Vancomycin**
    - **Fidaxomicin**
    - **Metronidazole**

Green: strongly supports use; Blue: moderately supports use; Grey: Minimally supports use; Red: recommend to not use

Clin Microbiol Infect 2014
More recently, metronidazole has been shown to be globally inferior to vancomycin (tolevamer phase III RCT)

VA dataset (vancomycin: n=2,068; metronidazole: n=8,069 propensity matched). Patients given vancomycin had a significantly lower risk of 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%)

Stevens et al. JAMA Int Med 2017
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>04-05</td>
<td>Chicago</td>
<td>150</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>500 mg QID</td>
<td>125 mg qid</td>
<td>13 of 79 (16%)</td>
<td>2 of 71 (1%)</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>575 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>All strains</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>Snyderman 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</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>0.5–2</td>
<td></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>Snyderman et al</td>
<td>USA</td>
<td>2011-12</td>
<td>2</td>
<td>2</td>
<td>&lt;0.06-4</td>
<td></td>
</tr>
</tbody>
</table>

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!

Explosion in treatment possibilities for CDI minus 1

Current: Probiotics  
FMT  
Use narrow-spectrum antibiotics

Future: 2nd generation FMT  
non-tox C diff M3  
Ecobiotics

Vancomycin  
Fidaxomicin

IVIG  
Monoclonal antibodies vs. C diff toxins

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

![Graph showing comparison of Fidaxomicin and Vancomycin](image)

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


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However, this drug is quite costly: Fidaxomicin Use By Region

![Map showing Fidaxomicin use by region](image)

Shah, Chan, Garey. Springer Plus 2016
Appropriate use of fidaxomicin

- Because of high acquisition cost, fidaxomicin has been reserved for a very select patient population (my best guess)
- Remember: fidaxomicin’s primary MOA is its narrow spectrum of activity preserving host microbiota
- Has reserving fidaxomicin for the worst cases been a good idea?
- Answer: No

We really have to do a better job of using fidaxomicin correctly

<table>
<thead>
<tr>
<th></th>
<th>Early episodes</th>
<th>Later episodes</th>
<th>Overall (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Episode 1 (n=37)</td>
<td>Episode 2 (n=32)</td>
<td>Total (n=69)</td>
</tr>
<tr>
<td>Mild-Moderate CDI; n(%)</td>
<td>10 (27%)</td>
<td>12 (37.5%)</td>
<td>22 (32%)</td>
</tr>
<tr>
<td>Severe CDI; n(%)</td>
<td>27 (73%)</td>
<td>20 (62.5%)</td>
<td>47 (68%)</td>
</tr>
<tr>
<td>1. FDX monotherapy; n (%)</td>
<td>3 (8%)</td>
<td>4 (12.5%)*</td>
<td>7 (12%)</td>
</tr>
<tr>
<td>2. Other CDI therapy; n (%)</td>
<td>34 (92%)</td>
<td>27 (84%)</td>
<td>61 (88%)</td>
</tr>
<tr>
<td>I. Subsequent; n</td>
<td>18</td>
<td>14</td>
<td>32</td>
</tr>
<tr>
<td>II. Subsequent and combination; n</td>
<td>8</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>III. Combination; n</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>IV. Unable to categorize; n</td>
<td>6</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Concomitant non-CDI antibiotics; n (%)</td>
<td>25 (68%)</td>
<td>10 (31%)</td>
<td>35 (51%)</td>
</tr>
</tbody>
</table>

Multicenter, 11 hospital chart review study of hospitalized patients with CDI that received fidaxomicin between 2011 and 2013.

Shah, Chan, Garey. Springer Plus 2016
Appropriate use of fidaxomicin

- Because of high acquisition cost, fidaxomicin has been reserved for a very select patient population almost always in combination with other C diff or other antibiotics
- Remember: fidaxomicin’s primary MOA is its narrow spectrum of activity preserving host microbiota
- Can the anti-recurrence effect of fidaxomicin offset its high acquisition cost?

Shah, Chan, Garey. Springer Plus 2016

Recurrent CDI is costly:
Healthcare utilization for recurrent CDI

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

Aitken, DuPont, Garey. PLOS One 2014 July 24;9(7)
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>

Shah et al. ICAAC 2014 Poster #K-356, Sat, Sept 6, 2014

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 select patients.

CDI-related re-admissions: Fidaxo: 20.4%; Vanco: 41.3%

Gallagher et al. AAC 2015
Real-world evidence that fidaxomicin may reduce these costs?


<table>
<thead>
<tr>
<th>Hospital</th>
<th>Before Fidaxo</th>
<th>After fidaxo</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n=98)</td>
<td>10.6</td>
<td>3.1</td>
</tr>
<tr>
<td>B (n=162)</td>
<td>16.3</td>
<td>7.7</td>
</tr>
<tr>
<td>C (n=511)</td>
<td>21.1</td>
<td>12.9</td>
</tr>
<tr>
<td>D (n=127)</td>
<td>12.5</td>
<td>11.8</td>
</tr>
<tr>
<td>E (n=209)</td>
<td>5.4</td>
<td>9</td>
</tr>
<tr>
<td>F (n=178)</td>
<td>5.8</td>
<td>5.4</td>
</tr>
<tr>
<td>G (n=278)</td>
<td>12.5</td>
<td>3.1</td>
</tr>
</tbody>
</table>

90-day hospital recurrence rate


Real-world evidence that fidaxomicin may reduce these costs?

UK, 2012-13: seven hospitals incorporate 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).

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Before Fidaxo</th>
<th>After fidaxo</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n=98)</td>
<td>P&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>B (n=162)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C (n=511)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D (n=127)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E (n=209)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F (n=178)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G (n=278)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Re-admission within 30 days of primary CDI

It’s important to remember that recurrent CDI is more than about cost

Microbiome of non-CDI patients vs. CDI patients

The microbiome of recurrent CDI patients is much less diverse

Boston, USA: Decreased microbiome diversity observed in patients with recurrent CDI

The microbiome “organ” continues to be damaged with recurrent CDI

Michigan: 93 patients with CDI. Fecal microbiome diversity during initial infection (A) and during follow up period. All patients treated with metronidazole or vancomycin

What else do we have in our damaged microbiome?

Canada: Number of antibiotic resistant genes (ABR) present in stool samples from patients with recurrent CDI before and after FMT (n=8)
And last but not least, the patient perspective

I wonder if we are missing the most important endpoints?

Aitken et al. ICAAC 2014 Poster #K-360, Sat, Sept 6, 2014
The driver for decreased QOL is not so much physical as a worry/anxiety of transmissibility or symptom persistence

Goddu S, Bozorgui S et al. Ispor 2015

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

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.”

Explosion in treatment possibilities for CDI: 
**Augment immune response!**

<table>
<thead>
<tr>
<th>Current</th>
<th>Future</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probiotics</td>
<td>2nd generation FMT</td>
</tr>
<tr>
<td>FMT</td>
<td>non-tox C diff M3</td>
</tr>
<tr>
<td>Use narrow-spectrum antibiotics</td>
<td>Ecobiotics</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Ridinilazole</td>
</tr>
<tr>
<td>Fidaxomicin</td>
<td>Toxoid vaccines</td>
</tr>
<tr>
<td>IVIG</td>
<td>Monoclonal antibodies vs. C diff toxins</td>
</tr>
</tbody>
</table>
Serum concentrations of IgG antibodies against toxin A, toxin B, and non-toxin antigens

Kyne et al. Lancet 2001;357:189-93

Monoclonal antibody: phase II study

Phase III studies of actoxumab (acto) and bezlotoxumab (bezlo): Overall


BEZLO was also shown to reduce hospital readmissions (European population)
Explosion in treatment possibilities for CDI: 

Correct dysbiosis!

**Current:**
- Probiotics
- FMT
- Use narrow-spectrum antibiotics
- Vancomycin
- Fidaxomicin
- IVIG
- Monoclonal antibodies
- vs. C diff toxins

**Future:**
- 2nd generation FMT
- non-tox C diff M3
- Ecobiotics
- Ridinilazole
- Toxoid vaccines

FMT for patients with recalcitrant CDI
Recurrence of *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>

Aas. CID 2003;36:580-5

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

Resolution: no diarrhea without relapse after 10 weeks

Changes in the Composition of the Human Fecal Microbiome After Bacteriotherapy for Recurrent CDI

A. Dendrogram of the 16S-based T-RFLPs obtained from fecal material from the patient and the donor before and after fecal transplantation. B, Distribution of bacterial species in feces of the donor and the patient before and after fecal transplantation.

Next Generation FMT

- Probiotic cocktails (Kefir)
- Designer biotherapeutics
  - Non-toxigenic C. difficile
Non-toxigenic C. diff (NTCD): phase II study

CDI patients given NTCD or placebo immediately after finishing antibiotic therapy

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

CDI patients given SER-109 immediately after finishing antibiotic therapy
Patients given SER-109 had a microbiome that looked like the average population

Red represents microbiome prior to SER-109, yellow represents after SER-109, and blue represents samples from the human microbiome project

Protocol utilizing a staggered and tapered antibiotic treatment 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</th>
<th>Vancomycin</th>
<th>Kefir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Course</td>
<td>Dose/Frequency</td>
<td>Dose/Frequency</td>
<td>150 mL TID</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>150 mL TID</td>
</tr>
</tbody>
</table>
So: who wins the celebrity death match?

1. Fidaxomicin: As far as I can tell, you always need to kill the bug. Find some $$ and start using more of this drug
2. Bezlo: With insurance on an outpatient basis, this can’t be beat. If need to reserve: >65 yo
3. FMT: Upon discharge, get patients to stop by the grocery store on the way home and pick up some Kefir!
Thank You!

To Receive CE Credit

• Complete the Post-Test and Evaluation
• Score of ≥ 70% is required to receive credit
• Your CE credit will be sent to NABP/CPE Monitor