Update on *C. difficile* infection:
New bugs and new drugs

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Acknowledgements

- Past and/or ongoing research grant support from Merck, Cubist, Summit, and Astellas
- Consultancy for Merck, Summit, and Seres Therapeutics

Objectives

- Take a best guess on what treatment of *C. difficile* infection will look like in the near future
- What does next generation fecal microbiota transplantation (FMT) look like (and is it possible).
- Are there any (less gross) ways to prevent/cure dysbiosis

A History of *C. difficile*

- 1986-2003 CDC reports rate of CDI increased from 31 cases per 100,000 persons to 61 cases per 100,000 persons.

Hypervirulent *C. difficile*

An Epidemi, Toxin Gene-Variant Strain of *Clostridium difficile*

Incidence of hypervirulent strains of *C. difficile*, 2005

<table>
<thead>
<tr>
<th>Health Care Facility</th>
<th>Date of Onset of Disease</th>
<th>No. of Isolates Collected</th>
<th>B/N/AI Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Georgia</td>
<td>Oct 2001</td>
<td>46</td>
<td>29 (60)</td>
</tr>
<tr>
<td>Illinois</td>
<td>July 2003</td>
<td>14</td>
<td>6 (43)</td>
</tr>
<tr>
<td>Maine, Facility A</td>
<td>March 2002</td>
<td>13</td>
<td>9 (69)</td>
</tr>
<tr>
<td>Maine, Facility B</td>
<td>July 2003</td>
<td>36</td>
<td>20 (55)</td>
</tr>
<tr>
<td>New Jersey</td>
<td>June 2001</td>
<td>12</td>
<td>9 (75)</td>
</tr>
<tr>
<td>Oregon</td>
<td>April 2000</td>
<td>10</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Pennsylvania, Facility A</td>
<td>2000-2002</td>
<td>18</td>
<td>7 (39)</td>
</tr>
<tr>
<td>Pennsylvania, Facility B</td>
<td>Oct 2001</td>
<td>6</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>102</td>
<td>36 (35)</td>
</tr>
</tbody>
</table>

Table 1. Incidence of *Clostridium difficile* and the Proportion of Isolates Belonging to the B/N/AI Strains.
Increasing mortality and complications due to CDAD

Table 1: Patients with Clostridium difficile-associated diarrhea (CDAD) in the Eastern region of Quebec who died within 30 days after diagnosis or who had complicated CDAD, 1991–2001

<table>
<thead>
<tr>
<th>Period</th>
<th>No. of patients with CDAD</th>
<th>No. of patients who died within 30 days after diagnosis</th>
<th>Adjusted OR (95% CI)</th>
<th>No. of patients who had complicated CDAD</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991–1992</td>
<td>669</td>
<td>8 (4.7)</td>
<td>1.0</td>
<td>12 (7.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>1993–1994</td>
<td>457</td>
<td>11 (2.4)</td>
<td>1.7 (0.5–5.3)</td>
<td>14 (6.5)</td>
<td>1.6 (0.4–6.7)</td>
</tr>
<tr>
<td>1995–1996</td>
<td>615</td>
<td>15 (2.5)</td>
<td>1.8 (0.5–5.3)</td>
<td>17 (7.0)</td>
<td>1.9 (0.6–5.3)</td>
</tr>
<tr>
<td>1997–1998</td>
<td>152</td>
<td>11 (7.3)</td>
<td>1.5 (0.4–5.3)</td>
<td>13 (8.6)</td>
<td>0.6 (0.2–3.7)</td>
</tr>
<tr>
<td>1999–2000</td>
<td>248</td>
<td>19 (7.7)</td>
<td>1.9 (0.5–6.6)</td>
<td>20 (11.0)</td>
<td>1.2 (0.3–5.9)</td>
</tr>
<tr>
<td>2001–2002</td>
<td>244</td>
<td>21 (8.6)</td>
<td>1.8 (0.5–7.7)</td>
<td>26 (11.0)</td>
<td>1.3 (0.5–3.9)</td>
</tr>
<tr>
<td>2003–2005</td>
<td>390</td>
<td>54 (13.8)</td>
<td>3.0 (1.3–6.4)</td>
<td>71 (18.2)</td>
<td>2.2 (1.0–4.9)</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

Note: OR = odds ratio; CI = confidence interval.

Time course of toxin production by hypervirulent strain compared to control

C difficile nomenclature

• All these are synonymous terms:
  – Toxinotype III: PCR analysis of PaLoc
  – PCR ribotype 027: European typing method
  – REA Group BI (bee eye): Typing method by Dale Gerding (Hines, IL)
  – PFGE: Nap-1: CDC typing method
• Work currently being conducted to make ribotyping the preferred typing method in the USA and Europe

...and there are more ribotypes than just 027

A lot of ribotypes are associated with CDI

Many ribotypes are virulent, including 027

Who you calling “hypervirulent”

Michigan: Derivation (n=310/34 severe) and validation (n=433/45 severe) of predictors of severe CDI (ICU admission, colectomy, or death). After accounting for disease presentation severity, ribotype did not predict outcome

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Derivation OR (95% CI)</th>
<th>P Value</th>
<th>Validation OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypervirulent ribotypes:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>027/078 vs non-027/078 (reference)</td>
<td>0.82 (0.57–1.16)</td>
<td>0.47</td>
<td>1.34 (1.03–1.74)</td>
<td>0.046</td>
</tr>
<tr>
<td>White blood cell count (1 × 10^9 cells/L) (reference)</td>
<td>4.27 (1.94–9.50)</td>
<td>0.013</td>
<td>2.32 (1.07–5.15)</td>
<td>0.038</td>
</tr>
<tr>
<td>Low albumin level (g/dL)</td>
<td>0.25 (0.14–0.49)</td>
<td>0.001</td>
<td>0.67 (0.25–1.87)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Walk et al. CID 2012; doi: 10.1093/CID/CIS78

You are all now expert C diff ribotypers

• 027 is definitely a virulent ribotype
• .....but, there are lots of ribotypes that are equally virulent
  – Treat the patient, not the bug!
• Without a doubt, the ribotype 027 strain has put a large focus on the value of strain typing in C. difficile.
• Now, let’s use some antibiotics!
The Impact of *Clostridium difficile* Infections (CDI)

Of patients with CDI given metronidazole or oral vancomycin, 25% will experience recurrent CDI.


Lessa CF et al. NEJM 2015;372:825-34.

500,000 29,000 New Data Of patients with CDI given metronidazole or oral vancomycin, 25% will experience recurrent CDI.

Britton et al. 2014

Expanding treatment 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

Adams and Lawley. Curr Opin Microbiol 2013

There has been an explosion in treatment possibilities for CDI

**Current:**
- Probiotics
- FMT
- Metronidazole
- IVIG

**Future:**
- 2nd generation FMT
- Surotomycin
- Cadazolid
- Monoclonal antibodies
- Toxoid vaccines

Current European CDI guidelines

Non-severe CDI:
- Metronidazole
- Vancomycin
- Fidaxomicin

(Risk of) first recurrence:
- Metronidazole
- Fidaxomicin
- Vancomycin
- Fidaxomicin

Severe disease or complicated course:
- Metronidazole
- Vancomycin
- Fidaxomicin

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)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Clinical Success</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolevamer (n=278)</td>
<td>0.74</td>
<td>0.045</td>
</tr>
<tr>
<td>Metronidazole (n=259)</td>
<td>0.81</td>
<td>0.21</td>
</tr>
<tr>
<td>Vancomycin (n=259)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Explosion in treatment possibilities for CDI minus 1**

<table>
<thead>
<tr>
<th>Current:</th>
<th>Probiotics</th>
<th>IVIG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>FMT</td>
<td></td>
</tr>
<tr>
<td>Fidaxomicin</td>
<td>FMT</td>
<td></td>
</tr>
</tbody>
</table>

**Future:**
- 2nd generation FMT
- non-tox C diff MD
- Erobiotics
- Surotomycin
- Cadazolid
- SMT-19969
- Monoclonal antibodies vs. C diff toxins
- Toxoid vaccines

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**New antibiotics coming soon for C diff**

- Surotomycin
  - Kissing cousin to daptomycin
  - Great phase II
  - Just finished phase III
- Cadazolid
  - Novel fluoroquinolone-oxazolidinone
  - Great phase II
  - Entering phase III
- SMT-19969
  - Now called ridinilazole. MOA: Unknown
  - Great phase II
  - Entering phase III

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**Surotomycin**

- Novel cyclic lipopeptide antibiotic disrupts bacterial cellular membrane (think dapto)
- Lacks activity against Gram-negative aerobes and facultative anaerobes (Bacteroides)
- Still kills Gram-positives (think dapto)
- Non-absorbable
- Good in a hamster model

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**Surotomycin: No affect on toxins**

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**Surotomycin: No effect on host response**
All of this data justified a phase II study

![Bar chart showing cure and recurrence rates for different treatments.](image1)

Patino et al. ICAAC 2011 Poster B-230

But the phase III study was a total bust!

![Bar chart showing cure and recurrence rates for different treatments.](image2)

Boix et al. ECCMID 2016 Poster P0612

Summary of new drug properties

<table>
<thead>
<tr>
<th>Drug</th>
<th>KIR C diff</th>
<th>Spare microbiota</th>
<th>Decrease toxins</th>
<th>Affects spores</th>
<th>Good phase II</th>
<th>Good phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surotomycin</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cadazolid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ridinilazole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cadazolid

- Protein synthesis inhibitor with weak inhibition of DNA synthesis (think linezolid meets levo)
- Kills other gut bacteria (especially bifidobacteria, a gut anaerobe)
  - But less than previous studies with linezolid or fluoroquinolones for unknown reasons
- Non-absorbable
- Good in a hamster model

Locher et al. AAC 2014;58:892-900
Locher et al. AAC 2014;58:892-900
Chilton et al. JAC 2013;697-705

Cadazolid: Great in vitro activity

![Graph showing in vitro activity.](image3)


Cadazolid: Also affects C. difficile toxins

![Graph showing C. difficile toxins.](image4)

Cadazolid may inhibit spore formation


Cadazolid phase II study

Louie et al. AAC 2015;59:6266-73

Cadazolid phase III

- In progress
- Cadazolid 250 mg BID vs. vancomycin 125 mg QID
- Think it will be successful?

Summary of new drug properties

<table>
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<tr>
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<th>Kill C. diff</th>
<th>Spare microbiota</th>
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<th>Good phase II</th>
<th>Good phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surtomycin</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cadazolid</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>??</td>
</tr>
<tr>
<td>Ridinilazole</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ridinilazole

- MOA: Unknown (but I will show you some cool data)
- Super narrow spectrum (clostridia only)
- Non-absorbable
- Good in a hamster model

Ridinilazole: Great in vitro activity (no affect on spores / not shown)

Goldstein et al. AAC 2013;57:4872-6
Sattar et al. JAC 2015;70:1797-62

Basseres, Endres, et al. JAC 2016;71:1245-51

1.00E+00  1.00E+02  1.00E+04  1.00E+06  1.00E+08
CTR 0.125xMIC 0.25xMIC 0.5 xMIC 1xMIC 4xMIC 40xMIC
log10 CFU total CFU
Ridinilazole: significantly decreases toxin production and affect host response

Ridinilazole phase III
- About to start
- Ridinilazole 200 mg BID vs. vancomycin 125 mg QID
- Can you imagine going into a phase III study without knowing how your drug works?

Ridinilazole is effective at killing C. difficile vegetative cells after 24h treatment

Ridinilazole treatment affects septum formation

Concentration dependent cell lengthening phenotype
Ridinilazole MOA (Best guess)

- Inhibits cell division by prevention of septum formation
- I’m going to take a guess that this is a protein synthesis inhibitor
- Confirmatory experiments: pending!

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<tr>
<td>Surotomycin</td>
<td>Yes</td>
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<td>No</td>
<td>No</td>
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<tr>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>??</td>
</tr>
<tr>
<td>Ridinilazole</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>??</td>
</tr>
</tbody>
</table>

Explosion in treatment possibilities for CDI:

- Augment immune response!

Current: Probiotics FMT
- Vancomycin Fidaxomicin

Future: 2nd generation FMT
- non-tox C diff M3
- Ecobiotics
- Surotomycin Fidaxomicin
- Monoclonal antibodies vs. C diff toxins
- Toxoid vaccines

Serum concentrations of IgG antibodies against toxin A, toxin B, and non-toxin antigens

\[ p = 0.009 \quad p = 0.79 \quad p = 0.19 \]

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

Monoclonal antibody: phase II study

\[ P < 0.001 \]

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

Coming soon to an infusion clinic near you!

- FDA Antimicrobial Drug Advisory Committee (June 9th, 2016)
  - "vote of 10 to 5 with one abstention, that Merck has provided substantial evidence of the safety and effectiveness of bezlotoxumab for the prevention of C. difficile infection recurrence in patients aged 18 years and older."
  - http://www.fda.gov/AdvisoryCommittees/Calendar/ucm496386.htm
- Stay tuned!

Explosion in treatment possibilities for CDI: Correct dysbiosis!

Current: Probiotics FMT Vancomycin Fidaxomycin IVIG

Future: 2nd generation FMT non-tox C diff MS Ecobiotics Surotomyin Cadazolid SMT-19969 Monoclonal antibodies vs. C diff toxins Toxoid vaccines

FMT for patients with recalcitrant CDI

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>

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

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*
  - SER-109, Seres Therapeutics

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.

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

CDI patients given NTCD or placebo immediately after finishing antibiotic therapy

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>NTCD 10(4)</th>
<th>NTCD 10(7)</th>
<th>NTCD 10(7)</th>
<th>Placebo X 10d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Course</td>
<td>spores X 7 d (n=43)</td>
<td>spores X 7 d (n=42)</td>
<td>spores X 10d (n=42)</td>
<td>X 10d (n=44)</td>
</tr>
<tr>
<td>Weeks 1-2</td>
<td>10mg Q 14h</td>
<td>375mg Q 14h</td>
<td>10mg Q 14h</td>
<td>10mg Q 14h</td>
</tr>
<tr>
<td>Weeks 3-4</td>
<td>750mg Q 72h</td>
<td>375mg Q 72h</td>
<td>10mg Q 14h</td>
<td>10mg Q 14h</td>
</tr>
<tr>
<td>Weeks 5-6</td>
<td>750mg Q 72h</td>
<td>375mg Q 72h</td>
<td>10mg Q 14h</td>
<td>10mg Q 14h</td>
</tr>
<tr>
<td>Weeks 7-8</td>
<td>750mg Q 72h</td>
<td>375mg Q 72h</td>
<td>10mg Q 14h</td>
<td>10mg Q 14h</td>
</tr>
<tr>
<td>Weeks 9-10</td>
<td>750mg Q 72h</td>
<td>375mg Q 72h</td>
<td>10mg Q 14h</td>
<td>10mg Q 14h</td>
</tr>
</tbody>
</table>

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.
Expanding the Role of FMT

- Case reports and case series have documented positive effects of FMT in the following conditions:
  - GI diseases
    - Ulcerative colitis, Crohn’s disease, irritable bowel syndrome, idiopathic constipation
  - Not traditional GI diseases
    - Insulin resistance, metabolic syndrome, morbid obesity, Parkinson’s disease, autism

FMT and obesity

- Energy metabolism is a well-recognized function of gut microbiota
  - Low dose antibiotics increases farming animal weight for unknown reasons (via killing of gut microbiota?).
- Similar effects have been shown in humans
  - Antibiotic prophylaxis for streptococcal infections in the 1950’s increased weight of these otherwise, young healthy males compared to placebo-treated males
    - J Nutr 1955;56:151-61


An obesity-associated gut microbiome with increased capacity for energy harvest

- Germ-free mice given FMT from obese and non-obese mice.
- Weight gain assessed
- Transplanting stool from an obese mouse lead to increased weight gain in the mouse vs. transplant from the non-obese mouse

Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome

18 patients with metabolic syndrome underwent bowel lavage by random assignment with an allogenic (from lean donor) or autologous gut microbiota transplant (autologous: reinfusion of own collected feces)

Vrieze et al. Gastroenterol 2012 Jun 20

Insulin sensitivity improved after FMT from allogenic donors

But, let’s not get carried away. Let’s start wrapping this up

- Remember, only about 1 in 5 antibiotics that enter phase I trials make it to an indication
- But, I think the higher urgency to discover new anti-infectives for C diff is producing viable candidates
- I think the future of ID may be as much host augmentation as it is bug killing.
I do see a world where this is commonplace for most infectious diseases!

Update on *C. difficile* infection: New bugs and new drugs

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