Clostridium difficile Infection 2017
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Disclosures

• Mayo Clinic has received funding from my role as an investigator on several clinical trials of new products for CDI
  • Rebiotix
  • Crestovo
  • Merck

• I have been an advisor for ReBiotix

• I will discuss off label uses of several drugs and discuss several investigational agents including FMT
Goals

At the end of this talk participants will

- Know the current epidemiology of *C. difficile* and how it impacts hospital practice
- Know the limitations of diagnostic testing for *C. difficile* infection
- Know the pathogenesis of CDI
- Name the new and upcoming therapeutics for CDI
- Know the role of Biotherapeutic approaches to prevent CDI
Rates of CDI related hospitalization in USA

12% of HAIs in USA
#1 HAI
Incidence of CDI

Leffler NEJM 2015:372;1539

500,000 cases
$5 billion in excess costs
30,000 death per year
How Common is C. difficile?

• It depends
  • Colonization vs infection
  • Outpatients vs inpatients
  • SNF vs free living
**Clostridium difficile** acquisition, germination and infection

What are the risk factors?

- Older age (>65)
- Low levels of Ab to CD toxin B
- **Alteration of the gut microbiota** - diet
  - Role of excess Zinc - calprotectin
- Antimicrobials (more and longer)
  - Clinda, FQ, Amino-PCNS, Cephs
  - Rare w/Dapto, Tige, TCN, MTN, AG
- Hospitalization/Institutionalization
- Critical Care
### Epidemiology of CDI Olmsted County
15 years 1991-2005

<table>
<thead>
<tr>
<th></th>
<th>Community-acquired (n=157)</th>
<th>Healthcare facility acquired (n=192)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median</td>
<td>50</td>
<td>72</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female gender</td>
<td>76%</td>
<td>60%</td>
<td>0.002</td>
</tr>
<tr>
<td>Antibiotic exposure</td>
<td>78%</td>
<td>94%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>H2B/PPI</td>
<td>22%</td>
<td>47%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cancer</td>
<td>17%</td>
<td>32%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Recurrent CDI</td>
<td>28%</td>
<td>30%</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Mechanisms of Colonization w/ CDiff

• Ingestion of spores from the environment
• Interaction with gastric acid
• Interaction with bile acids – uncoating of spores
• Vegetative Cdiff cells penetrate mucus layer in the colon and adhere to epithelial cells
• Disruption of the normal flora - breakdown of colonization resistance
• Colonization may be long standing – months
• Spores can be shed for 6 weeks in sxtic CDI after resolution
Where is *C. difficile* coming from?

- 40-60% neonates carry this
  - by age 1 only 2-3% of normal people carry this bug in their colon
- Widespread in environment, cats and dogs, farm animals
- 20-30% of hospitalized patients carry *C. difficile* and increases with duration of stay
- 4-20% of long-term care residents
- Conn/MD study – 3.9% with sx CDI EID Oct 2011
Asymptomatic Colonization

• 320 participants screened at hospital entry
• 9.7% were positive by PCR for Cdiff
• Independent Risk Factors were:
  • *Recent hospitalization*
  • *Chronic dialysis*
  • *Corticosteroid use*
• Screening these 3 risks - identifies 74% of CD carriers at admission

Leekha S  *Am J Infect Control* 2013;41:390-3
Prevalence of C. diff Colonization

- Healthy neonates/infants: 18-90%
- Healthy adults: 0-15%
- Elderly LTC: 0-51%
- Hospital
  - Elderly: 0.6-15%
  - Inpts: 4-29%
  - Rehab units: 11-50%
  - Surgical pts on px: 17%
  - ICU: 2-7%
  - IBD: 11%
  - Heme CA: 8%

Furuya-Kanamori L et al BMC Infect Disease 2015;15:1516
C difficile and the Hospital

• Where is C. diff coming from? Colonization
  • Prevalence of toxigenic CD 8-10%
  • 6-fold risk of infection vs non-colonized
    • 20-50% of adults in LTC are colonized
    • 20-30% of HSCT at admission
      • 12% toxigenic 17% non
      • 61% w/toxigenic dev CDI – median 12d
  • Hospital pts transmit at rate 15X asxtic
  • LTC transmit at 27% of hospital pt
  • Community at 0.1% of hospital pts
What about Carriers?

- 2/3 of patients with fecal CD colonization become asymptomatic carriers.
- Over a 3-month period - 73 long-term care residents.
  - Five (7%) patients were found to have CDAD.
  - Of the remaining 68 patients, 35 (51%) were asymptomatic carriers, and 13 (37%) of these 35 patients carried epidemic NAP1 strain.
  - Nine of the 35 carriers had a history of CDAD.

Asymptomatic carriers were associated with significantly higher rates of skin and environmental contamination than were noncarriers.
Relationship of *C Diff* Carrier State to Antibiotics and Shedding

**carrier state**
- complex microbiota
- low spore excretion
- low transmission

**C. difficile**
**microbiota**

**supershedding state**
- triggered by antibiotics
- simplified microbiota
- high spore excretion
- high transmission
- epithelial damage

Wt and lgh6-deficient
self-limiting disease

Myd88-deficient
severe disease

## Diagnosis of Clostridium difficile infection

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Advantage</th>
<th>Disadvant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytotoxin assay</td>
<td>80-90%</td>
<td>99-100%</td>
<td>Gold standard</td>
<td>Requires Cx, 48h; toxin B only</td>
</tr>
<tr>
<td>EIA toxin A/B</td>
<td>65-85%</td>
<td>95-100%</td>
<td>Rapid 2-6h</td>
<td>Less sens</td>
</tr>
<tr>
<td>GDH by LA</td>
<td>58-68%</td>
<td>80-96%</td>
<td>Rapid, easy</td>
<td>Requires confirmn</td>
</tr>
<tr>
<td>PCR toxin gene</td>
<td>92-97%</td>
<td>100%</td>
<td>Rapid, sensitive</td>
<td>Detects colonized, not toxin effect</td>
</tr>
<tr>
<td>Stool Culture</td>
<td>90-100%</td>
<td>98-100%</td>
<td>Strain type</td>
<td>2-5 days</td>
</tr>
</tbody>
</table>
## Selected test performances - MCA

<table>
<thead>
<tr>
<th>Test</th>
<th>Sens, %</th>
<th>Spec, %</th>
<th>NPV</th>
<th>PPV</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDH</td>
<td>93 (56/60)</td>
<td>93</td>
<td>99</td>
<td>64</td>
<td>Missed 4 Positives</td>
</tr>
<tr>
<td>Xpert</td>
<td>100 (60/60)</td>
<td>98</td>
<td>100</td>
<td>88</td>
<td>4 Pos unconfirmed</td>
</tr>
<tr>
<td>GDH → Xpert</td>
<td>93 (56/60)</td>
<td>99</td>
<td>99</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>Focus</td>
<td>93 (56/60)</td>
<td>99</td>
<td>99</td>
<td>95</td>
<td>Missed 4 Positives</td>
</tr>
<tr>
<td>GDH → Focus</td>
<td>93 (56/60)</td>
<td>99</td>
<td>98</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>
Testing for the diagnosis of CDI

Martin, J. S. H. et al. (2016) Clostridium difficile infection: epidemiology, diagnosis and understanding transmission
Over diagnosis of C. difficile

- Treated pts may shed for 6 weeks
- After treatment tests can remain + for months
- Repeat testing is discouraged
- Up to 1/3 pts have post CDI IBS (mixed or d)
  - Longer CDI duration, current anxiety and higher BMI
- Review all meds, laxatives etc

Wadgwa A et al Aliment Pharmacol Ther 2016;44:576-82
PCR and Overdiagnosis

- PCR+/Toxin - vs Toxin +/PCR+
  - Less diarrhea at time of test
  - More rapid resolution of diarrhea
  - Fewer CDI complications or death

- PCR Sensitivity near 100% but Specificity in 80% range; PPV 44-47%

- Negative predictive value of toxin EIAs is at least 95%

- CDC – increase in CDI by 43-67% in PCR era

- 20% to 44% of patients tested on a laxative regimen.

Polage CR JAMA Intern Med 2015;1751792
Burden of recurrent CDI

- Median risk for 1 recurrence is 22%-25%
  - Second episode – 38%
  - Third 29%
  - Fourth of more - 27%
- 34% with rCDI required hospitalization
- 28% developed severe CDI, 4% complication
Development of Disease is a 2 Hit Event

Antibiotics alone do not cause C. difficile disease

- Disruption of the protective microbiota
- Consumption of C. difficile

These can be independent and separated in time
Secondary Bile Acids made by colonic bacteria

[Chemical structures and reactions showing the conversion of primary bile acids to secondary bile acids and their conversion into different forms such as cholic, chenodeoxycholic, deoxycholic, lithocholic, and ursodeoxycholic are depicted.]
C. scindens 7a-dehydroxylation prevents C. difficile growth
Strategies to Prevent and Treat CDI

Kociolek, L. K. & Gerding, D. N. (2016) Breakthroughs in the treatment and prevention of Clostridium difficile infection
Time to Improvement
Vancomycin versus Metronidazole

A

Proportion with diarrhea per day
0% 25% 50% 75% 100%
0 2 4 6 8 10
Days of Treatment

Vancomycin
Metronidazole

B

Proportion with detectable C. difficile
0% 25% 50% 75% 100%
0 2 4 6 8 10
Days of Treatment

Vancomycin
Metronidazole
The Vulnerability Zone

- Vancomycin maintains inhibitory activity 4-5 days after completed
- Metronidazole – no late activity
- 14-21 days after treatment stools support CD growth
- 21-28 days after – most inhibit
- 3 phyla are associated with intact colonization resistance
  - Actinobacteria
  - Firmicutes
  - Tenericutes

Abujamel T *Plos One* Oct 2013;8
What happens to C. diff when you stop Metronidazole or Vancomycin treatment
Vancomycin, Metronidazole or Fidaxomicin

• Studies now indicate Metronidazole less effective than Vancomycin
• Increased short term mortality in MTN treated
• MTN - Not recommended in mod-severe disease nor in IBD
• Fidaxomicin – less recurrence, more expensive
• Vancomycin DOC for most
Fidaxomicin in the real world

• Used after first recurrence rather than primary

• High rate of recurrence CDI (40%) in patients who received fidaxomicin (Stony Brook study)
Is there Benefit to **Combination** Therapies or High Dose Antimicrobials?

• Combination therapy – Vanco + Metro
  • No difference in cure rates (57.1 v 65%)  
  • No difference in time to cure (7 vs 8 d)
  • No difference in recurrence
  • More complications in combination
  Bass SN *J Hosp Infect* 2013;85:22-27

• High dose Vancomycin vs Standard
  • No difference in cure rates, time to response
  • Trend toward more recurrence with low dose
  Lam SW *International J Antimicrob Agents* 2013

I use combination when concerned about oral administration reaching colon
Administration of Antibiotics After Initial CDI Therapy

***Continued Use of Antibiotics is Associated with Recurrence***

- Continued use of non-\textit{C. diff} antibiotic after diagnosis of CDI carries a with \textbf{4.23 (P<0.001) risk} for recurrent disease
- Phase 3 study of fidaxomicin vs vancomycin linked concomitant antibiotics with lower rates of cure without recurrence at 30d

Options for Antibiotics to treat infections in those with prior C difficile Infection

• Limited data
• Doxycycline – most data
  • Use for URTI, LRTI, SSTI
• UTI
  • Fosfomycin, Nitrofurantoin
• Shortest possible course
AntiBx Prophylaxis to prevent rCDI

MTN 1-3 days prior – retrospective cohort

- The rate of *C. difficile* infection was 1.4% in the patients who received metronidazole and 6.5% in those who did not (*P*<0.001). In a multivariable analysis accounting for age, sex, and comorbidities, patients receiving metronidazole had an 80% reduced risk for developing *C. difficile* infection.

Rodriguez S et al *Clin Gastroenterol Hepatol* 2014

Oral Vancomycin prophylaxis vs SOC

- 4.2% vs 26.6%
- 125 or 250 mg BID
- Recur defined by PCR+, diarrhea <4 weeks

Van Hise *Clin Infect Dis* 2016
Abx Prophylaxis and CDI

- *Wong ICAAC 2015* secondary prophylaxis of CDI in high-risk patients. This study included patients who were treated with antibiotics for a non-CDI indication 14 to 90 days following an initial CDI diagnosis. Patients receiving prophylaxis relapsed less often than the control group (6.25% vs. 19.3%; \( P = .003 \)) — a 67.6% risk reduction.

- *King ICAAC 2015*, a retrospective cohort study that compared either oral vancomycin, or metronidazole (IV or oral) with no prophylaxis. Patients were included if they had a positive PCR for *C. difficile* toxin between 2011 and 2013 and subsequently received a minimum 5 days of broad-spectrum antibiotics at least 2 weeks after completion of CDI therapy. The study included 339 eligible patients. The patients who received prophylaxis had a CDI relapse rate of 1.8% vs. 5.7% for the control group. There was no difference in relapse rates between vancomycin- and metronidazole-treated patients.
What about C. difficile in patients with IBD?

- Test pts with a flare for CDI
- Test for rCDI if sx recur
- Treat with Vancomycin not Metronidazole
- Hospitalize those with severe symptoms
- Postpone steroid escalation during acute CDI
- Refer for FMT if recurrent disease

Management of Clostridium difficile Infection in Inflammatory Bowel Disease: Expert Review from the Clinical Practice Updates Committee of the AGA Institute
CDI and IBD

Patient with inflammatory bowel disease

Younger age
Antibiotic exposure less likely
More often community onset

Patient characteristics for *Clostridium difficile* infection

Risk of *C. difficile* recurrence
Higher recurrence than non-IBD

Patient without inflammatory bowel disease

Older age
Antibiotic exposure more likely
More often hospital onset

Lack of ongoing antibiotic exposure
Lower recurrence than non-IBD

Persistent dysbiosis due to underlying IBD
Managing CDI in IBD

Always test for CDI in IBD patients presenting with a flare

Positive stool test for CDI

Uncomplicated CDI*

Vancomycin 125 mg q6h
Consider fidaxomicin 200 mg q12h

Improvement in 3-4 days

Continue for 10 days

First recurrence

Treat with vancomycin or fidaxomicin

Consider fecal microbiota transplant

Severe-complicated CDI*

Oral vancomycin 500 mg q6h and IV Metronidazole 500 mg q8h
Consider rectal vancomycin
Surgery consult

Consider escalation of immunosuppression

Continue immunosuppression

Ongoing signs of active colitis without improvement in 3-4 days

Fidaxomicin
Vancomycin taper
Fecal microbiota transplant

Multiple recurrences
Emerging Treatment Options for CDI

## Antibiotics in development for CDI treatment

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Mechanism of action</th>
<th>Clinical status (ClinicalTrials.gov identifier)</th>
<th>Published clinical data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surotomycin (CB-183315)</td>
<td>Disrupts bacterial cell membrane</td>
<td>Phase III NCT01597505 and NCT01598311</td>
<td>Phase II trial results: rates of CDI recurrence among 210 adults with CDI were 36%, 28% and 17% within 28 days post-treatment with vancomycin 125 mg four times daily, surotomycin 125 mg twice daily and surotomycin 250 mg twice daily, respectively(^{37})</td>
</tr>
</tbody>
</table>
| Cadazolid                   | Protein synthesis inhibitor primarily Fluoroquinolone moiety also confers weak inhibition of DNA synthesis | Phase III NCT01983683 and NCT01987895           | • Phase II trial results: clinical CDI cure rates among 84 adults receiving vancomycin or one of three different doses of cadazolid were similar  
  • All three doses of cadazolid resulted in lower recurrence rates than vancomycin (18–25% versus 50\(^{43}\))                                                                 |
| Ridinilazole (SMT19969)     | DNA synthesis inhibitor                                   | Phase II NCT02092935                            | Phase I trial results: among healthy adults, SMT19969 resulted in high faecal drug levels, low plasma drug levels, and no reported serious adverse events\(^{33}\) |

CDI, *Clostridium difficile* infection.

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Fecal Microbiota Transplantation

- Instillation of stool from a healthy person into an ill person in order to cure a certain disease
- Instillation of stool from a healthy person into another person at risk for a disease in order to prevent that disease
Current Indication for FMT

- Recurrent infections that have failed >2 courses of therapy (ie 3rd episode)
  - responded to Vancomycin
  - Presence of >3 unformed stools/d for at least 2 days
- Recent positive C. difficile test
  - Presence of diarrhea off antibiotic therapy
- 2nd episode of Severe CDI
- Refractory CDI
The Forest Analogy

FMT =
# Donor testing for FMT – Open Biome

## Figure 1: Stool and Serology Investigations

<table>
<thead>
<tr>
<th>Stool testing</th>
<th>Serological testing</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Clostridium difficile</em> Toxin B, PCR</td>
<td>HIV 1/2, antigen and antibody</td>
</tr>
<tr>
<td><em>Salmonella</em>, Culture</td>
<td>Hepatitis A, IgM antibody</td>
</tr>
<tr>
<td><em>Shigella</em>, Culture</td>
<td>Hepatitis B, (IgM anti-HBc, anti-HBsAg)</td>
</tr>
<tr>
<td><em>Campylobacter</em>, Culture</td>
<td>Hepatitis C, antibody</td>
</tr>
<tr>
<td>Shiga Toxin, EIA (with reflex to <em>E. coli</em> O157, Culture)</td>
<td>Treponema pallidum, antibody</td>
</tr>
<tr>
<td><em>Vibrio</em>, Culture</td>
<td>HTLV-I/II, antibody</td>
</tr>
<tr>
<td><em>Cryptosporidium</em>, EIA</td>
<td>Complete Blood Count (CBC)</td>
</tr>
<tr>
<td><em>Helicobacter pylori</em>, EIA</td>
<td>Hepatic Function Panel</td>
</tr>
<tr>
<td>Norovirus, EIA</td>
<td></td>
</tr>
<tr>
<td>Rotavirus, EIA</td>
<td></td>
</tr>
<tr>
<td>Adenovirus, EIA</td>
<td></td>
</tr>
<tr>
<td>Vancomycin-resistant Enterococcus (VRE), Culture</td>
<td></td>
</tr>
<tr>
<td><em>Giardia</em>, EIA</td>
<td></td>
</tr>
<tr>
<td>Microsporidia Exam</td>
<td></td>
</tr>
<tr>
<td>Cyclospora and Isospora Examination</td>
<td></td>
</tr>
<tr>
<td>Ova and Parasites Exam</td>
<td></td>
</tr>
</tbody>
</table>

Mayo – GI pathogen panel
Success of FMT at Mayo Clinic in Arizona

**MCA ARIZONA: 94.7 % Success (Dec 2016)**

Success by procedure 88.6%

- 231 – single FMT – 221 cured, 9 failures, 1 LTFU
- 264 procedures on 247 patients
- 231 single; 15 – 2; 1 3 FMT repeat pts.
- Avg. Age: 62.6 years (19-93)
- Females 163 (66%) Males 84 (34%)
- Colonoscopy 232 EGD 17 NJ 4 Stoma 6 Combo 5

**National Average: 90-100%**
Fecal Microbiota Transplant Prevents Recurrence

- Overall for 4 RCT one time 72%
  - Dutch Nasogastric trial – 43 pt – 81% vs Vanco 31%
  - Italy – *Cammarota* 39 pts Colonoscopy FMT vs oral Vanco taper – 65% vs 26%
  - US – Youngster – frozen NG vs Colon (20 pts)
    - 70% overall (8/10 colon, 6/10 in ng)
  - US – *Kelly* Colonoscopic (pt) – RCT
    - 91% cure vs placebo 63% (p 0.024)
  - US – *Orenstein* ReBiotix Phase 2b Trial - *86%*
Role of FMT to Prevent Multiply Recurrent CDI

Rates of clinical cure in the intention-to-treat population, overall and by site. Error bars represent 95% CIs. FMT = fecal microbiota transplantation.
Safety and Efficacy of FMT from Stool Bank 2050 treated subjects – overall efficacy 84%

Figure 1: Efficacy of FMT by *Clostridium difficile* infection classification and fecal microbiota preparation type

<table>
<thead>
<tr>
<th><em>Clostridium difficile</em> infection Classification</th>
<th>Total</th>
<th>250 mL</th>
<th>30mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Efficacy (%)</td>
<td>P-value</td>
</tr>
<tr>
<td>Recurrent</td>
<td>1542</td>
<td>85.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mixed (e.g. recurrent and severe)</td>
<td>259</td>
<td>79.2</td>
<td>0.021</td>
</tr>
<tr>
<td>Refractory</td>
<td>159</td>
<td>74.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severe</td>
<td>90</td>
<td>83.3</td>
<td>0.85</td>
</tr>
</tbody>
</table>
Colectomy for Severe CDI

- Used in severe disease
- Rates of 1-3%
- Systematic review 31 studies – 1433 pts
- 1.1% CDI cases required colectomy
- 30% were severe disease
- 30 day mortality – 41%

Bhangu A et al *Br J Surg* 2012;29:1525
Diverting Loop Ileostomy & Colon Lavage

• Alternate to total colectomy
• 8 liters of warmed PEG and Vancomycin
• Post-op Vanco 500mg/500 ml q8H x 10d
  • Deliver via Malecot cath in efferent limb
  • Also receive IV Metronidazole

Neal et al Am Surg 2011;254:423
Can FMT Help in Severe *C. difficile* Disease?

- CDI refractory to po +/- rectal Vanco and IV MTN
  - Prospective series 29 pts – 27/29 (93%) resolved
  - 100% cure for severe
  - 89% for severe complicated
  - 2 died – sepsis
  - 76% survival at 3 months

*Challenge is the logistics – access to therapeutic microbiota*

Fischer M et al Aliment Pharmacol Ther 2015;42:470-6
The pipeline of products for CDI
ReBiotix
RBX 2660 - enema and 7455 – oral cap

• In Phase 3 – Commercialized Microbiota
• Phase 2 – 52% 1\textsuperscript{st} enema 78.6% 2\textsuperscript{nd}
• Overall success 27/31 – 87.1%
• Phase 2b data being reported
  • Placebo 45.5% (20/24) vs 67% 1 enema
  • 87.5% all comers – inc open label
• Phase 3 Upcoming summer 2017
  • 1 enema, no prep
• Phase 1 RBX 7455 – capsule – $10^9$ cfu
• 8 caps/day = 1 enema – 4 d BID vs 2d BID
CP101 - Crestovo

- Oral full spectrum *lyophilized* capsules
  - 1\textsuperscript{st} trial non-frozen oral
- Phase 2 trial starting in May 2017
  - $6 \times 10^{11}$ vs $3 \times 10^{11}$
  - 10 caps one time vs placebo
SERES Products – spores

- SERES 109
  - Phase 2 multiply recurrent CDI – $1 \times 10^8$ spores
  - 59 S109 vs 30 placebo – 44% vs 53% recur
  - Not statistically significant
  - Re-entering Phase 2 - ECOSPOR III
  - 4 caps daily x 3 days oral ($3 \times 10^7$ scfu)

- SERES 262 – Phase 1b
  - Synthetic oral capsule 12 bacterial strains in spore form
Viropharma
Non-toxigenic C. difficile Spores
CDI Recurrence w/in 6 Weeks

Table 4. CDI Recurrence Within 6 Weeks as Defined by Diarrhea Criteria and by Investigator Decision to Re-treat for Recurrent CDI

<table>
<thead>
<tr>
<th>Events in Intention-to-Treat Safety Population</th>
<th>NTCD-M3 Dosage</th>
<th>Placebo (n = 43)</th>
<th>10⁴ Spores/d for 7 d (n = 41)</th>
<th>10⁵ Spores/d for 7 d (n = 43)</th>
<th>10⁷ Spores/d for 14 d (n = 41)</th>
<th>All (n = 125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDI recurrence, No. (%)</td>
<td></td>
<td>13 (30)</td>
<td>6 (15)</td>
<td>2 (5)</td>
<td>6 (15)</td>
<td>14 (11)</td>
</tr>
<tr>
<td>Unadjusted comparison with placebo, P value⁸</td>
<td></td>
<td>.09</td>
<td>.002</td>
<td>.09</td>
<td>.003</td>
<td></td>
</tr>
<tr>
<td>Adjusted comparison with placebo⁹</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td></td>
<td>0.4 (0.1-1.2)</td>
<td>0.1 (0.0-0.6)</td>
<td>0.4 (0.1-1.2)</td>
<td>0.28 (0.11-0.69)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>.11</td>
<td>.01</td>
<td>.10</td>
<td>.006</td>
<td></td>
</tr>
<tr>
<td>Use of antibacterial treatment for CDI, No. (%)</td>
<td></td>
<td>14 (33)</td>
<td>6 (15)</td>
<td>4 (9)</td>
<td>7 (17)</td>
<td>17 (14)</td>
</tr>
<tr>
<td>Unadjusted comparison with placebo, P value⁸</td>
<td></td>
<td>.05</td>
<td>.008</td>
<td>.10</td>
<td>.006</td>
<td></td>
</tr>
<tr>
<td>Adjusted comparison with placebo⁹</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odds ratio (95% CI)</td>
<td></td>
<td>0.3 (0.1-1.1)</td>
<td>0.2 (0.1-0.8)</td>
<td>0.4 (0.1-1.3)</td>
<td>0.32 (0.14-0.75)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>.07</td>
<td>.02</td>
<td>.14</td>
<td>.009</td>
<td></td>
</tr>
<tr>
<td>CDI recurrence based on NTCD colonization, No./total (%)⁵</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colonized with NTCD</td>
<td></td>
<td>0/4 (0)</td>
<td>1/26 (4)</td>
<td>1/31 (3)</td>
<td>0/29 (0)</td>
<td>2/86 (2)⁴</td>
</tr>
<tr>
<td>Not colonized with NTCD</td>
<td></td>
<td>13/39 (33)</td>
<td>5/15 (33)</td>
<td>1/12 (8)</td>
<td>6/12 (50)</td>
<td>12/39 (31)⁴</td>
</tr>
<tr>
<td>CDI recurrence based on presence of toxin-positive C. difficile on day 1, No./total (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1 toxin-positive C. difficile</td>
<td></td>
<td>1/6 (17)</td>
<td>3/12 (25)</td>
<td>2/9 (22)</td>
<td>3/9 (33)</td>
<td>8/30 (27)</td>
</tr>
<tr>
<td>No day 1 toxin-positive C. difficile</td>
<td></td>
<td>12/37 (32)</td>
<td>3/29 (10)</td>
<td>0/34 (0)</td>
<td>3/32 (9)</td>
<td>6/95 (6)</td>
</tr>
</tbody>
</table>

Abbreviations: CDI, Clostridium difficile infection; NTCD, nontoxigenic C. difficile; NTCD-M3, nontoxigenic C. difficile strain M3.

⁴ Treatment comparison with placebo using 2-sided χ² test at a significance level of P = .05.

⁵ Logistic regression model analysis adjusting for relevant covariates: use of metronidazole, use of vancomycin, and primary episode vs first recurrence for odds ratios, 95% CIs, and the corresponding P values for model-adjusted treatment comparison with placebo. Odds ratios of less than 1 indicate a lower risk in NTCD-M3 dosage groups compared with placebo.

⁶ Colonization was defined as NTCD in stool culture at any time after the end of study drug therapy to week 6.

⁷ Recurrence rate of 2% vs 31% is significantly different (odds ratio, 0.01; 95% CI, 0.00-0.05; P < .001) for colonized vs not colonized with NTCD.
Stool Bank
OpenBiome (501c3)

- $385/bottle
- $385/dose
- $535/dose – 30 caps
Monoclonal Antibody vs Toxin B

• **Bezlotoxumab (Zinplava)**
  - Humanized monoclonal IgG1/kappa Ab vs CD tB
  - Single IV dose 10mg/kg over 60 min
  - In both MODIFY I and MODIFY II, the rate of C. difficile infection recurrence through week 12 was significantly lower in the bezlotoxumab arms (17.4%, \( p=0.0003 \)) compared to the placebo arms (27.6%) and (25.7%), respectively.
  - Half life 19 days
  - most common adverse reactions through four weeks after infusion (nausea, diarrhea and pyrexia)
  - FDA Concern regarding endpoints – delay review
  - Cost – 3500$
Participants with Recurrent *Clostridium difficile* Infection during the 12-Week Follow-up Period.

**MODIFY 1 and 2 Studies**

### Future Preventive Strategies for CDI

**Table 3 | Characteristics of potential interventions for prevention of CDI**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Effectiveness in humans</th>
<th>Time to prevention onset</th>
<th>Duration of prevention</th>
<th>Use for primary CDI prevention</th>
<th>Use for recurrent CDI prevention</th>
<th>Projected cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>FMT or derivatives</td>
<td>Excellent for prevention of multiply recurrent CDI</td>
<td>Rapid (1–2 days)</td>
<td>Likely to be effective until further antibiotics are given</td>
<td>Untested</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Nontoxigenic <em>C. difficile</em></td>
<td>Excellent for first and second CDI recurrence prevention</td>
<td>Rapid (1–2 days)</td>
<td>Effective for duration of colonization and thereafter until further antibiotics</td>
<td>Untested, but effective in animal models</td>
<td>Yes</td>
<td>Low</td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td>Excellent for first and second CDI recurrence prevention</td>
<td>Very rapid (immediate)</td>
<td>Unknown, but not expected to persist beyond several half-lives</td>
<td>Untested</td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td>Injectable vaccine</td>
<td>Unknown, only 3 patients tested</td>
<td>Slow (weeks to months)</td>
<td>Unknown, but expected to be long</td>
<td>Yes</td>
<td>Unknown, depends upon time required for antibody response</td>
<td>Low</td>
</tr>
<tr>
<td>Oral vaccine</td>
<td>Unknown, no patients tested</td>
<td>Slow (weeks to months)</td>
<td>Unknown, but expected to be long</td>
<td>Yes</td>
<td>Unknown, depends upon time required for antibody response</td>
<td>Low</td>
</tr>
</tbody>
</table>

CDI, *Clostridium difficile* infection; FMT, faecal microbiota transplantation.
The Bottom line

*C diff* is bad...you can get it at home; if you take acid suppression, use chemo, or were hospitalized in the past 60 days - you may be asymptptomatically colonized; if you are old - 2% per year after age 18; take antibiotics or acid suppression you are at risk for healthcare acquired CDI. The longer you stay hospitalized the greater the risk of infection.

- if you are old; get infected with the NAP 1 strain and take PPIs and are hospitalized >1 week - you're in deep poo - *literally.*
What’s in YOUR Wallet?
Your Name Here

7 extra hospital days for c-dif from the neighbor .................. $7,000
200 Chux pads ................................................................. $600
Hand washing................................................................. Priceless
Coming Attractions