Clostridium difficile, changing perspectives on a running problem

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Objectives

• Identify three steps to reduce a patient’s risk for CDI
• Describe three challenges in implementing a biotherapy treatment program
• State the most effective approach to limiting the spread of *C. difficile*
Clostridium difficile 2014
Forget a lot of what we told you in early 2013

• What is still true
C. Difficile
The basics

• C. difficile disease is caused by a toxin
  – Toxin A (not bad), toxin B and binary toxin
  – Some strains produce logs more of toxin than others
  – Not all C. difficile makes toxin

• Neonates do not get ill from C. difficile but colonization rates are very high (should babies visit?)

• C. difficile is acquired via fecal-oral transmission
  – HCW hands
  – Health environment
  – Food
What are *C. difficile*-associated diseases?

- They are diseases that result from *C. difficile* infections including:
  - pseudomembranous colitis (PMC)
  - toxic megacolon
  - perforations of the colon
  - sepsis
  - death (rarely)
What are the main clinical symptoms of \textit{C. difficile}-associated disease?

- Clinical symptoms include:
  - watery diarrhea
  - fever
  - loss of appetite
  - nausea
  - abdominal pain/tenderness
Which patients are at increased risk for *C. difficile*-associated disease?

- The risk for disease increases in patients with:
  - antibiotic exposure
  - gastrointestinal surgery/manipulation
  - long length of stay in healthcare settings
  - a serious underlying illness
  - immunocompromising conditions
  - advanced age
C. Difficile
Background

• Generally patients with non-altered normal gut flora do not get sick from C. difficile

• Alteration of gut flora
  – Antibiotics
  – PPI and H2 antagonists
  – Surgery
  – Prolonged GI illness (salmonella)

• Prolonged colonization with C. difficile is protective against disease
  – Median incubation period 3 days!
Microbiome

You are surrounded and outnumbered

- 10 bacteria live in you or on you for every one cell of you

- Alteration of your microbiome has direct consequences to you
  - C. difficile
  - Obesity
  - Metabolic syndrome
  - Asthma
Helicobacter pylori

• Dramatically proven to cause peptic ulcer disease
• Dramatically increases the rate of gastric cancer
• Is curable and can be eliminated from the food supply
• Also can be controlled or decreased by changes in diet
• Victory!!!!!!! Its rates are going down dramatically worldwide as sanitation improves
Helicobacter pylori

• *H. pylori* infection leads to a decrease in circulating ghrelin through a reduction in ghrelin-producing cells in the gastric mucosa and to an increase in gastric leptin

• Leptin controls appetite therefore failure to have *H pylori* as normal flora dramatically increases your chances for obesity

• OH and it might protect against something else
Microbiome

• Ecology of the body is like the ecology of a habitat complex and interrelated and poorly understood
  – Changing the flora is like killing wolves in Europe in the 13-14 century
  – Argggghhhhh bunnies!

• Reintroduction of “normal flora “ has been shown to reverse C difficile, obesity, metabolic syndrome, rheumatoid arthritis. Promising for MS

• Fecal transplants made Crohn’s disease worse
Will vaccines alter my biome

- The ones approved to date do not as they target only pathogenic transient bacteria
- But what about a C. difficile vaccine?
C. Difficile

**Background**
- Generally patients with normal gut flora do not get sick from C. difficile.
- Alteration of gut flora:
  - Antibiotics
  - PPI and H2 antagonists
  - Surgery
  - Prolonged GI illness (salmonella)
- Prolonged colonization with C. difficile is protective against disease.
  - Median incubation period 3 days!

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### Sites of Attack for Prevention and Management of CDI

1. **Keep patients out of the hospital.**
2. **Barrier precautions and environmental cleaning.**
3. **Stop unnecessary antimicrobial use.**
4. **Restore flora or colonize with nontoxigenic C. difficile.**
5. **Bolster immunity with vaccines or passive antibody strategies.**
6. **Antibiotic Rx ± Nonantibiotic Rx.**

**Asymptomatic C. difficile colonization**

**CDI**

*Gerding and Johnson Clin Infect Dis. 2010;51:1306-13*
National Estimates of US Hospital Stays With *C. difficile* as First-Listed or Any Diagnosis

C. Difficile
Fun facts

• Exists in two states
  – Vegetative (vastly most common) normal state needs to eat and can reproduce
  – Spore (rarer) can not absorb nutrients or reproduce but can survive most disinfectants, and drying and lack of food
  – Moves between these two states but can not do so quickly
Strain Type is EVERYTHING

• Determines
  – How sticky it is in the environment
  – How likely it is to make a patient sick
    • Toxin producing and adherence to cell wall
  – How likely it is to sporulate
  – How likely it will be to germinate from a spore
  – How sick the patient will get
  – How long it takes for bleach to kill it in the spore state
  – How likely it is the patient will have a recurrence
### Changing Prevalence of the 10 Most Common *Clostridium difficile* Ribotypes in England, 2007–2010

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>027*</td>
<td>1044 (55)</td>
<td>1504 (36)</td>
<td>1102 (21)</td>
</tr>
<tr>
<td>106*</td>
<td>253 (13)</td>
<td>518 (12)</td>
<td>364 (7)</td>
</tr>
<tr>
<td>001</td>
<td>162 (9)</td>
<td>299 (7)</td>
<td>371 (7)</td>
</tr>
<tr>
<td>014/020a</td>
<td>54 (3)</td>
<td>20 (5)</td>
<td>33 (8)</td>
</tr>
<tr>
<td>015*</td>
<td>46 (2)</td>
<td>224 (5)</td>
<td>330 (6)</td>
</tr>
<tr>
<td>002*</td>
<td>57 (3)</td>
<td>238 (6)</td>
<td>302 (6)</td>
</tr>
<tr>
<td>078*</td>
<td>35 (2)</td>
<td>149 (4)</td>
<td>285 (5)</td>
</tr>
<tr>
<td>005*</td>
<td>27 (2)</td>
<td>118 (3)</td>
<td>213 (4)</td>
</tr>
<tr>
<td>023*</td>
<td>21 (1)</td>
<td>112 (3)</td>
<td>149 (3)</td>
</tr>
<tr>
<td>016*</td>
<td>0</td>
<td>79 (2)</td>
<td>139 (3)</td>
</tr>
<tr>
<td>Others*</td>
<td>201 (11)</td>
<td>731 (17)</td>
<td>1514 (29)</td>
</tr>
</tbody>
</table>

CDI Publically report in CA soon to be the U.S.

- Patient acuity
- Burden of C. diff cases coming in
- Test performance issues (toxin versus PCR)
- New report coming out soon!
- Acute care infection prevention and antimicrobial stewardship will soon be expanded to SNFs based on readmission prevention
FIGURE 1. Percentage of *Clostridium difficile* infection (CDI) cases (N = 10,342), by inpatient or outpatient status at time of stool collection and type/location of exposures* — US, Emerging Infections Program, 2010
The environment

• Being is a hospital room that was previously occupied by a patient with *C. difficile* is a risk factor for acquiring it

• Contamination of the room with occurred in:
  – 49% of the rooms with symptomatic patients
  – 29% in carriers
  – <10% of rooms with patients who were not colonized or ill with CDAD
Killing *C. difficile* spores

- There are now a number of disinfectants that kill *C. difficile* spores not just bleach
  - Compatibility with equipment material is an issue
- Do we need to kill spores?
- Should we be killing spores on equipment?
Does Bleach Matter?

• Lessons learned from endoscopes
  – High level disinfection can’t kill spores
  – Endoscopes are largely high level disinfected
  – Endoscopes are used to diagnose pseudomembranous colitis in C. Diff patients
  – No outbreaks of *C. difficile* in the next patient
Activity of selected oxidizing microbicides against the spores of *Clostridium difficile*: Relevance to environmental control

Justo Perez, V. Susan Springthorpe, Syed A. Sattar AJIC 2005:33:320-325
C. difficile sporulation caused cleaning agents

Wilcox and Fawley THE LANCET • Vol 356 • October 14, 2000
SHEA compendium

• Perform environmental decontamination of rooms housing patients with CDI, using Sodium hypochlorite (household bleach) diluted 1 : 10 with water, in an outbreak setting or setting of hyperendemicity
• Facilities should consider using a 1 : 10 dilution of sodium hypochlorite (household bleach) for environmental disinfection in outbreak settings and settings of hyperendemicity in conjunction with other infection prevention and control measures. Bleach should have a contact time of at least 10 minutes.
SHEA on cleaning

• Assess the adequacy of cleaning before changing to a new cleaning product (eg, bleach). If cleaning is not adequate, address this before changing products.
Currently there is no approved EPA-registered detergent/disinfectant that is effective in killing C. difficile spores(*). Therefore a 1:10 dilution of 5.25% sodium hypochlorite (household bleach) and water freshly mixed daily should be used to disinfect the rooms of those residents with symptomatic (e.g., diarrhea) infection. If there is evidence of ongoing C. difficile transmission, the facility should consider using a bleach solution daily in all resident rooms until transmission has ceased.

(*) The technical term for this is “wrong” there are a few.
Bleach and pitting
Stainless steel after 1 exposure to bleach
Vapors, Ultra Violet light and *Clostridium difficile*

Hydrogen peroxide vapor

- Depends on room cleaning prior to be effective
- Studies are done in institutions with outbreaks or high endemic rates
Could the Reduction Attributed to the Impact of Hydrogen Peroxide Vapor Room Decontamination in Clostridium difficile been Attributable to better Antibiotic Stewardship?

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Preintervention (Jun 2004 to Mar 2005)</th>
<th>Intervention (Jun 2005 to Mar 2006)</th>
<th>Subperiods when epidemic strain was present&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>All antibiotics</td>
<td>805.7</td>
<td>764.1</td>
<td>814.6</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>300.4</td>
<td>298.9</td>
<td>300.6</td>
</tr>
<tr>
<td>All fluoroquinolones</td>
<td>158.9</td>
<td>146.0</td>
<td>158</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>138.5</td>
<td>140.5</td>
<td>142.2</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second generation</td>
<td>10.2</td>
<td>7.5</td>
<td>10.8</td>
</tr>
<tr>
<td>Third generation</td>
<td>31.5</td>
<td>39.1</td>
<td>31.6</td>
</tr>
<tr>
<td>Fourth generation</td>
<td>32.0</td>
<td>29.7</td>
<td>33</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>10.5</td>
<td>8.5</td>
<td>9.8</td>
</tr>
</tbody>
</table>

Note: DDD, defined daily dose.
<sup>a</sup> *Clostridium difficile* North American pulsed-field 1 (NAP1) strain.

The impact of the outbreak may have made HPV look better at *Clostridium difficile* reduction than it was.

**Figure 3.** Hospital-wide incidence of nosocomial *Clostridium difficile*–associated disease, by month, during the preintervention period (gray bars; June 2004 through March 2005) and the intervention period (black bars; June 2005 through March 2006).
Other HPV UV concerns

- Turnaround times on rooms
- Cost
- Safety (making sure room is sealed no risk to machines or byproducts or staff accidently exposed to UV)
## Is Cleaning the Issue (Or is it contact precautions?!?)

<table>
<thead>
<tr>
<th>Conditions</th>
<th>% Toilets clean</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolation: signoff to document cleaning</td>
<td>64.7%</td>
<td>(9 patients each day for duration of stay)</td>
</tr>
<tr>
<td>Isolation: routine cleaning</td>
<td>56.5%</td>
<td>(7 patients for duration of hospitalization)</td>
</tr>
<tr>
<td>No Isolation: routine cleaning</td>
<td>72.9%</td>
<td>(10 patients over duration of hospitalization)</td>
</tr>
</tbody>
</table>
Contaminated environments Result in spread of disease
What’s wrong with this picture?
We should wash our hands and not use alcohol right?

- Alcohol doesn’t kill spores
- Soap doesn’t kill spores
  - They do probably go down the drain
- Again with the endoscopes Frank?
- CDC Hand hygiene guidelines does not recommend soap and water to the exclusion of alcohol with *C. difficile* cases
  - ANTHRAX?!?
- SHEA guideline appeared to
“In conclusion, although soap and water is superior to removing *C. difficile* spores from hands of volunteers compared to alcohol-based hand hygiene products, there have been no studies in acute care settings that have demonstrated an increase in CDI with alcohol-based hand hygiene products or a decrease in CDI with soap and water. This is why preferential use of soap and water for hand hygiene after caring for a patient with CDI is not recommended in non-outbreak settings. The recommendation to use soap and water preferentially in outbreak settings after caring for a patient with CDI is based on expert opinion as there are no data that demonstrate preferential use of soap and water for hand hygiene after caring for a patient with CDI in an outbreak setting is effective at preventing CDI.”
# Hand Wash Products and Prototypes Tested for Reducing *C. difficile* Spores

<table>
<thead>
<tr>
<th>Test Product</th>
<th>No. Samples</th>
<th>Log10 Decrease</th>
<th>Standard Deviation</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tap Water</td>
<td>18</td>
<td>0.76</td>
<td>0.11</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>4% Chlorhexidine hand wash</td>
<td>18</td>
<td>0.77</td>
<td>0.11</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Nonantimicrobial hand wash</td>
<td>6</td>
<td>0.78</td>
<td>0.16</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Nonantimicrobial body wash</td>
<td>18</td>
<td>0.86</td>
<td>0.22</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>0.5% bleach/surfactant prototype</td>
<td>6</td>
<td>0.98</td>
<td>0.13</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>0.3% triclosan hand wash</td>
<td>6</td>
<td>0.99</td>
<td>0.13</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>8% H2O2/surfactant prototype</td>
<td>6</td>
<td>0.99</td>
<td>0.72</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Peracetic acid wipe</td>
<td>6</td>
<td>1.08</td>
<td>0.29</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Na tetraborate decahydrate (Borax)</td>
<td>6</td>
<td>1.18*</td>
<td>0.31</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Ink and stain remover</td>
<td>12</td>
<td>1.21*</td>
<td>0.22</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ink and stain remover with brush</td>
<td>6</td>
<td>1.47*</td>
<td>0.10</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Peracetic acid/surfactant prototype</td>
<td>6</td>
<td>1.51*</td>
<td>0.42</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

* Significantly better than water at p < 0.05.
But Wait the UK weighs in

- Each additional mL of alcohol hand rub procured per patient bed day was associated with a rise in *C difficile* infection which changed over time, being most marked during periods of high incidence of *C difficile* infection. Further analyses showed strong correlations between soap and alcohol hand rub procurement (web appendix). When included separately in a simplified model, each consumable was associated with a reduction in *C difficile* infection. Inclusion of both consumables removed the association with alcohol hand rub, *suggesting that only soap was independently associated with reduced C difficile infection. (speaker’s emphasis)*

- BMJ. 2012; 344: e3005. Published online 2012 May 3. doi: [10.1136/bmj.e3005](https://doi.org/10.1136/bmj.e3005) PMCID: PMC3343183

*Evaluation of the national Cleanyourhands campaign to reduce *Staphylococcus aureus* bacteraemia and *Clostridium difficile* infection in hospitals in England and Wales by improved hand hygiene: four year, prospective, ecological, interrupted time series study*
C difficile prevention

• Clearly moving from an infection prevention issue to an antimicrobial stewardship issue
  – Antimicrobial stewardship reduces C. difficile cases dramatically
  – Endemic strains are susceptible to formulary changes (not that the C difficile is susceptible but that their niche in the microbiome is defined by the niche carved by the front line antibiotic).
Food C. difficile

• Pathogenic strains are in our food supply
• Cases with those strains are very rare
• Cooking kills C. difficile
• Some have been found in our lettuce or non cookable food
• Walk away
  – Don’t worry on this yet
Pediatric C difficile

• Study at Hopkins found
  – Youths over 1 yo more likely to get C difficile than those over 21 per dose of antibiotic given
  – Community cases dwarf HAI cases
  – May be more likely to get recurrences (methodology issue)

• Neonates?

• Clindamycin for youth MRSA
Probiotics for Prevention

- Problems with probiotics as a class
  - Different formulations
  - Concentrations
  - Doses
  - Organisms chosen (not all L. acidophilus and L. casei are the same)
  - One product has data showing it works for prevention of CDAD but not treatment
  - Side effects in certain populations (BMT)
<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Experimental Group, n</th>
<th>Control Group, n</th>
<th>Weight, %</th>
<th>Relative Risk (95% CI) M–H Random</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arvola et al, 1999 (32)</td>
<td>1 61</td>
<td>1 58</td>
<td>1.7</td>
<td>0.95 (0.06–14.85)</td>
</tr>
<tr>
<td>Beausoleil et al, 2007 (33)</td>
<td>1 44</td>
<td>7 45</td>
<td>3.0</td>
<td>0.15 (0.02–1.14)</td>
</tr>
<tr>
<td>Bravo et al, 2008 (34)</td>
<td>0 41</td>
<td>0 45</td>
<td>–</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Can et al, 2006 (35)</td>
<td>0 73</td>
<td>2 78</td>
<td>1.4</td>
<td>0.21 (0.01–4.37)</td>
</tr>
<tr>
<td>Duman et al, 2005 (36)</td>
<td>0 196</td>
<td>1 180</td>
<td>1.2</td>
<td>0.31 (0.01–7.47)</td>
</tr>
<tr>
<td>Gao et al, 2010 (37)</td>
<td>9 171</td>
<td>20 84</td>
<td>23.0</td>
<td>0.22 (0.11–0.46)</td>
</tr>
<tr>
<td>Hickson et al, 2007 (38)</td>
<td>0 56</td>
<td>9 53</td>
<td>1.6</td>
<td>0.05 (0.00–0.84)</td>
</tr>
<tr>
<td>Kotowska et al, 2005 (39)</td>
<td>3 119</td>
<td>10 127</td>
<td>7.9</td>
<td>0.32 (0.09–1.14)</td>
</tr>
<tr>
<td>Lönnemark et al, 2010 (40)</td>
<td>1 80</td>
<td>0 83</td>
<td>1.3</td>
<td>3.11 (0.13–75.26)</td>
</tr>
<tr>
<td>McFarland et al, 1995 (41)</td>
<td>3 97</td>
<td>4 96</td>
<td>5.9</td>
<td>0.74 (0.17–3.23)</td>
</tr>
<tr>
<td>Miller et al, 2008 (47)</td>
<td>4 95</td>
<td>7 94</td>
<td>8.9</td>
<td>0.57 (0.17–1.87)</td>
</tr>
<tr>
<td>Miller et al, 2008 (47)*</td>
<td>2 157</td>
<td>0 159</td>
<td>1.4</td>
<td>5.06 (0.25–104.63)</td>
</tr>
<tr>
<td>Plummer et al, 2004 (42)</td>
<td>2 69</td>
<td>5 69</td>
<td>4.9</td>
<td>0.40 (0.08–1.99)</td>
</tr>
<tr>
<td>Psaradellis et al, 2010 (48)</td>
<td>1 216</td>
<td>4 221</td>
<td>2.7</td>
<td>0.26 (0.03–2.27)</td>
</tr>
<tr>
<td>Rafiq et al, 2007 (49)</td>
<td>5 45</td>
<td>22 55</td>
<td>16.1</td>
<td>0.28 (0.11–0.67)</td>
</tr>
<tr>
<td>Ruszczyński et al, 2008 (43)</td>
<td>3 120</td>
<td>7 120</td>
<td>7.2</td>
<td>0.43 (0.11–1.62)</td>
</tr>
<tr>
<td>Safdar et al, 2008 (44)</td>
<td>0 23</td>
<td>1 17</td>
<td>1.3</td>
<td>0.25 (0.01–5.79)</td>
</tr>
<tr>
<td>Selinger et al, 2011 (50)</td>
<td>0 62</td>
<td>0 62</td>
<td>–</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Surawicz et al, 1989 (45)</td>
<td>3 116</td>
<td>5 64</td>
<td>6.5</td>
<td>0.33 (0.08–1.34)</td>
</tr>
<tr>
<td>Thomas et al, 2001 (46)</td>
<td>2 133</td>
<td>3 134</td>
<td>4.0</td>
<td>0.67 (0.11–3.96)</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>1974</strong></td>
<td><strong>1844</strong></td>
<td><strong>100.0</strong></td>
<td><strong>0.34 (0.24–0.49)</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: τ² = 0.00; chi-square = 12.09; P = 0.79; I² = 0%
Test for overall effect: Z = 5.87; P < 0.001

When We are Talking about *C* difficile
There is Always a But

- The Lancet published the largest test of probiotic to date and found no effect
  - Carefully measured dose of lactobacilli and bifidobacteria
  - Rare *C* diff cases in both control and placebo arm

H2 Antagonists and PPI

• Used to prevent and treat peptic ulcer disease
• Usage in hospitals in SD at baseline was between 60%->95% of patients on them
• 2 to 5 fold increase in patients getting C. difficile when on them
• Alternatives exist (Tums)
• But these do not increase your risk of recurrence
Who is related to who

THE BREAK THROUGH!!!!!!

- Diverse Sources of *C. difficile* Infection Identified on Whole-Genome Sequencing N Engl J Med 2013; 369:1195-1205*September 26, 2013*

- **Results**

  - Of 1250 *C. difficile* cases that were evaluated, 1223 (98%) were successfully sequenced. In a comparison of 957 samples obtained from April 2008 through March 2011 with those obtained from September 2007 onward, a total of 333 isolates (35%) had no more than 2 SNVs from at least 1 earlier case, and 428 isolates (45%) had more than 10 SNVs from all previous cases. Reductions in incidence over time were similar in the two groups, a finding that suggests an effect of interventions targeting the transition from exposure to disease. Of the 333 patients with no more than 2 SNVs (consistent with transmission), 126 patients (38%) had close hospital contact with another patient, and 120 patients (36%) had no hospital or community contact with another patient. Distinct subtypes of infection continued to be identified throughout the study, which suggests a considerable reservoir of *C. difficile*.

- This is a replication of a CID article published earlier in 2013
WHAT YOU TOLD ME

• 1) The longer you have C diff the more you are protected against it
• 2) Most babies get C diff (even toxin producing strains)
• 3) Only people actively sick with C diff cause great room contamination
• SO how are colonized patients causing most of the transmission?
  – There are a lot more of them?
  – It is a spore?
  – It is their own biome?
Reductions in intestinal Clostridiales precede the development of nosocomial *Clostridium difficile* infection

Caroline Vincent¹,², David A Stephens³, Vivian G Loo⁴, Thaddeus J Edens⁵, Marcel A Behr¹,⁴, Ken Dewar²,⁴,⁶ and Amee R Manges⁷

Abstract

Background: Antimicrobial use is thought to suppress the intestinal microbiota, thereby impairing colonization resistance and allowing *Clostridium difficile* to infect the gut. Additional risk factors such as proton-pump inhibitors may also alter the intestinal microbiota and predispose patients to *Clostridium difficile* infection (CDI). This comparative metagenomic study investigates the relationship between epidemiologic exposures, intestinal bacterial populations and subsequent development of CDI in hospitalized patients. We performed a nested case–control study including 25 CDI cases and 25 matched controls. Fecal specimens collected prior to disease onset were evaluated by 16S rRNA gene amplification and pyrosequencing to determine the composition of the intestinal microbiota during the at-risk period.

Results: The diversity of the intestinal microbiota was significantly reduced prior to an episode of CDI. Sequences corresponding to the phylum Bacteroidetes and to the families Bacteroidaceae and Clostridiales Incertae Sedis XI were depleted in CDI patients compared to controls, whereas sequences corresponding to the family Enterococcaceae were enriched. In multivariable analyses, cephalosporin and fluoroquinolone use, as well as a decrease in the abundance of Clostridiales Incertae Sedis XI were significantly and independently associated with CDI development.

Conclusions: This study shows that a reduction in the abundance of a specific bacterial family - Clostridiales Incertae Sedis XI - is associated with risk of nosocomial CDI and may represent a target for novel strategies to prevent this life-threatening infection.

Keywords: Intestinal microbiota, *Clostridium difficile* infection, 16S rRNA gene sequencing, Clostridiales Incertae Sedis XI
Role of Leptin-mediated Colonic Inflammation in Defense against C. difficile Colitis

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ABSTRACT

The role of leptin in the mucosal immune response to Clostridium difficile colitis, a leading cause of nosocomial infection, was studied in humans and in a murine model. Previously a mutation in the receptor for leptin (LEPR) was shown to be associated with susceptibility to infectious colitis and liver abscess due to Entamoeba histolytica as well as to bacterial peritonitis. Here we discovered that European–Americans homozygous for the same LEPR Q223R mutation (rs1137101), known to result in decreased STAT3 signaling, were at increased risk of C. difficile infection (odds ratio 3.03, p = 0.015). The mechanism of increased susceptibility was studied in a murine model. Mice lacking a functional leptin receptor (db/db) had decreased clearance of C. difficile from the gut lumen and diminished inflammation. Mutation of tyrosine 1138 in the intracellular domain of LepRb that mediates signaling through STAT3/SOCS3 pathway also resulted in decreased mucosal chemokine and cell recruitment. Collectively these data support a protective mucosal immune function for leptin in C. difficile colitis partially mediated by a leptin–STAT3 inflammatory pathway that is defective in the LEPR Q223R mutation. Identification of the role of leptin in protection from C. difficile offers the potential for host-directed therapy and demonstrates a connection between metabolism and immunity.
Never become known as a biotherapy “expert”

INFECTION DISEASE

Recurrence of C. difficile Therapy

Feces Is Usually Understood As Something to Avoid

BY FRANK MEYERS

Even in societies with a strong understanding of medicine, feces is usually understood as something to avoid. In the field of infectious disease, antibioticinduced diarrheal transmission has frequently been linked to loss of normal gut flora and destruction of the normal flora. It is therefore with great amounts of irony that one of the most successful therapies for recurrent C. difficile is fecal microbiota therapy (FMT) in the literature. It is not surprising that this year, the FDA approved the new treatment for recurrent C. difficile, as it is an oral biologically active agent that is effective at restoring the normal flora. The treatment is typically administered after several courses of antibiotics fail to work, and is given as a single dose. The goal of the therapy is to restore the normal flora, which is essential for the proper functioning of the digestive system. The therapy is usually well tolerated and is effective in the majority of patients. The success rate of the therapy is around 80-90%, and the recurrence rate of C. difficile is reduced to less than 10% in most patients.
Fecal Transplants: Repoopulating the gut for treatment of recurrent C. Difficile

- Very effective at preventing recurrence
- Screening needs done on donor (family or spouse)
- Supported by IDSA
- FDA initially had many guidelines to prevent enforcement
  - Poop police offer enforcement discretion
  - No more IRB
  - Still open for comment

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March 2014

I. Introduction

We, FDA or agency, are informing members of the medical and scientific community, and other interested
Minimum standards for fecal microbiota transplant therapy

- The licensed health care provider treating the patient obtains adequate informed consent from the patient or his or her legally authorized representative for the use of FMT products. The informed consent should include, at a minimum, a statement that the use of FMT products to treat *C. difficile* is investigational and a discussion of its potential risks.

- The FMT product is obtained from a donor known to either the patient or the treating licensed health care provider.

- The stool donor and stool are qualified by screening and testing performed under the direction of the licensed health care provider for the purpose of providing the FMT product to treat his or her patient.
Challenges of make your own biome

• Filtering
• Are you using this blender?
• Fresher is better: Timing in the age of the busy healthcare environment
  – Does bran help or hurt?
• Milk? Got it?
U.S.’s first stool bank supplies hospitals with fecal transplants for C. difficile treatment

February 22, 2014 8:00 am by Deanna Pogorelc | 1 Comments

If you’re eating, you might want to stop before you read this.

A nonprofit called OpenBiome is operating the U.S.’s first human stool bank. Yes, read that right.

In a lab at MIT, OpenBiome collects, processes, stores and delivers donated fecal flora for use at hospitals performing fecal transplants for patients with Clostridium difficile.

C. diff is itself pretty nasty – it’s a bacterial infection that causes diarrhea sometimes accompanied by fever, nausea or inflammation of the colon. It’s one of the most common hospital-acquired infections in the U.S. and can develop from heavy use of
Screening of donors

- Universal
  - HIV, Hepatitis B, HCV
- Standard of Care
  - Hepatitis A, CMV, Epstein Barr
- Others include
  - Enteric pathogens (O&P, salmonella, hemorrhagic E. coli, shigella)
- Irritable Bowel Syndrome? Abdominal issues?
Risks of transmission

• First donor unscreened (surgeon 1950’s toxic megacolon)
• No cases of transmission from donors
• No patient adverse events
• Route of administration
  – Outcomes do not vary patient preference dictates
• Anaerobes? Back seat of the car for transport?
The future of the biome

• Vaccines phase II for prevention
• Pills not endoscopes
  – Unofficial trials for certain microbiome mixtures
  – What is the profit margin on gut flora?
Fidaxomicin inhibits toxin production in Clostridium difficile

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Abstract