Clostridium difficile
Update
July 2016

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Singapore General Hospital
CLOSTRIDIUM DIFFICILE

250,000 INFECTIONS PER YEAR
14,000 DEATHS

$1,000,000,000,000 IN EXCESS MEDICAL COSTS PER YEAR

THREAT LEVEL URGENT
This bacteria is an immediate public health threat that requires urgent and aggressive action.

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These bacteria are immediate public health threats that require urgent and aggressive action.
Clostridium difficile

- Gram positive rod
- Obligate anaerobe
- Spore producing (they can survive 5 months)
- Toxin producing

Paredes Sabja et al, Trends Microbiology 2014;22:406-16
Fig 1. Developmental life cycle of Clostridium difficile during infection.

http://journals.plos.org/plospathogens/article?id=info:doi/10.1371/journal.ppat.1005157
**Clostridium difficile**

- Antibiotic use – biggest risk factor
- 96% of symptomatic patients received antibiotic within 14 days

<table>
<thead>
<tr>
<th>Very commonly related</th>
<th>Less commonly related</th>
<th>Uncommonly related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>Sulfonamides</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Macrolides</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Carbapenems</td>
<td>Tetracycline</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Other penicillins</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>Fluoroquinolons</td>
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<td></td>
</tr>
</tbody>
</table>
Clostridium difficile associated diarrhea

- It is implicated in:
  - 20-30% of cases of antibiotic-associated diarrhea
  - 50-75% antibiotic-associated colitis
  - > 90% of cases of pseudomembranous colitis.
Patient

- Disruption of normal enteric flora
- Acquisition of toxigenic *Clostridium difficile*

40%-60%

**Protective factors:**
- High serum antibody response to toxin A
- Mild underlying disease

40%-60%

**Risk factors:**
- Low serum antibody response to toxin A
- Severe underlying disease

**Asymptomatic *C. difficile* colonization** (carrier state)

**C. difficile diarrhea**

**Treatment**

60%-95%

**Additional protective factors:**
- Age < 65 years
- No exposure to additional antibiotics

5%-40%

**Additional risk factors:**
- Age > 65 years
- Exposure to additional antibiotics

**Low likelihood of *C. difficile* diarrhea**
- May act as reservoir for nosocomial spread of *C. difficile*

**Decreased risk of recurrent *C. difficile* diarrhea after treatment**

**Increased risk of recurrent *C. difficile* diarrhea after treatment**
- 50% due to reinfection
- 50% due to relapse
Toxin A and B and new hyper-virulent strains (ribotype 027)

- TcdC downregulates production of toxins A and B
- Partial deletions in this gene leads to increased production of toxins A and B
- This in turn causes severe disease
Incidence of *C. difficile* in Singapore

**TTSH data 2001 - 2006**  
Lim et al Emerg Infect Dis. 2008 September; 14(9): 1487–1489

<table>
<thead>
<tr>
<th>Singapore TTSH Data</th>
<th>2001</th>
<th>2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence density (cases per 10,000 patient days)</td>
<td>1.49 cases</td>
<td>6.64 cases</td>
</tr>
<tr>
<td>% CDT positive samples</td>
<td>7%</td>
<td>11%</td>
</tr>
<tr>
<td>No. of samples tested for CDT</td>
<td>906</td>
<td>3,508</td>
</tr>
</tbody>
</table>

**SGH**

<table>
<thead>
<tr>
<th>CDAD incidence-density (95% confidence interval)</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th><em>p</em>-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(95% confidence interval)</td>
<td>4.75 (4.16 to 5.43)</td>
<td>3.65 (3.16 to 4.22)</td>
<td>3.06 (2.59 to 3.61)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

References:
Epidemiology in Singapore

Figure 1.30: Incidence density of *C. difficile*, clinical isolates, 2011 to 2014

*Note:* The *C. difficile* detection method may differ between hospitals (EIA, PCR, GDH).
SGH March 2015 till February 2016
Duplicates excluded
Not all nosocomial

- Community associated CDI reported since 2005
- It is often difficult to separate true community associated with healthcare associated but community onset cases
Clinical Practice Guidelines for Clostridium difficile Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA)

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

- Chitnis et al. JAMA 2013;173:1359-67
- Surveillance program in 32 counties, 8 states, USA
- 984 patients with community associated CDI
  - 177 no healthcare exposure
  - 400 low level exposure (physician or dentist visit)
  - 407 high level exposure (day surgery, AE or HCW)
- 35.9% did not receive antibiotics (and 31% of them were on PPIs)
Among those who had a positive toxin assay, 62 (23%) had their positive stool samples collected within 48 hours of admission.

Of these 62, only 2 (3.2%) had no hospital admissions or outpatient clinic attendances within the preceding 12 weeks.
CA CDI in Singapore

- NUH December 2011 to May 2012
- 66 of 158 positive cases were recruited and completed questionnaire

33 of 66 cases were “community onset”

a. 14 of 33 (42.4%) = HCFA-CO
b. 10 of 33 (30.3%) = indeterminate

**c. 9 of 33 (27.3%) = community associated.** This was 13.6% of all 66 cases

*8 of 9 had no recent antibiotic exposure
*All 9 were seen in polyclinic

Tan et al IJAA 2014;43:47-51
Isolation of the first three cases of Clostridium difficile polymerase chain reaction ribotype 027 in Singapore


3 hospitals: TTSH, NUH and SGH
September 2008 till December 2009
240 toxin positive isolates

35 different ribotypes but only 3 isolates of ribotype 027
Ideal test

1. Sensitive (to reliably exclude C dif)
2. Specific (to avoid treating “innocent”)
3. Able to differentiate “active” disease from colonization
4. Fast turnaround time
5. Cheap
Available tests

1. Culture plus toxin confirmation
   - Very good but slow and labor intensive

2. PCR.
   - Detects genes but not toxin (overdiagnosis?)

3. EIA for GDH
   - Very sensitive but present also in non-toxigenic strains. Requires confirmatory testing

4. EIA for toxin
   - Cheap and correlates with severity of disease but sensitivity is low (underdiagnosis?)
Algorithms

- NAAT (PCR) alone
- Screen with GDH, confirm with NAAT
- Screen with GDH, “confirm” with toxin A/B
- Screen with NAAT, “confirm” with toxin A/B
Quick local “survey”

- SGH – PCR only
- NUH – GDH and toxin EIA. GeneXpert PCR for GDH+/toxin negative cases
- TTSH – GDH and toxin EIA. PCR for GDH+/toxin negative cases
- CGH - PCR only; if positive, test for toxin – interpretative comment based on ELISA
Issues in diagnostic testing

Implications for testing

- Test only patients presenting with diarrhea
- Test them early
- Do not repeat a test within the first week of illness due to minimal diagnostic value
- Do not perform tests on specimens from treated patients because of high post-infection asymptomatic carriage rates
Test them early

- For PCR, 14%, 35%, and 45% of positive test converted to negative after 1, 2 and 3 days of treatment, respectively.
- Rate of conversion was similar for PCR, GDH and toxigenic culture.
Over-diagnosis by PCR?

Prospective observational cohort study
1416 hospitalized adults tested for C difficile toxins (reported) and PCR (not reported)
Analyzed as Tox+/PCR+(131 patients), Tox-/PCR+(162 patients) and Tox-/PCR- (1123 patients)

JAMA Intern Med. 2015;175(11):1792-1801
Over-diagnosis by PCR?
Over-diagnosis by PCR?

- Virtually all CDI-related complications and deaths occurred in patients with positive toxin
- Tox-/PCR+ patients had outcomes that were comparable to Tox-/PCR- patients

JAMA Intern Med. 2015;175(11):1792-1801
Treatment depends on severity

- Common classification:
  - Severe CDI: systemic signs, WBC > 15K, creatinine > 1.5 times premorbid
  - Severe complicated CDI: as above plus hypotension, ileus or megacolon
  - Severe CDI is one with SIRS or organ damage or both
Associated signs and symptoms: nausea, dehydration, low-grade fever, cramping and leukocytosis

8-10% death rate for patients >50 years old with co-morbidities
Treatment

- Mild – often stopping precipitating antibiotic is enough
- Mild to moderate – metronidazole or vancomycin
- Severe – vancomycin although fidaxomicin equally effective
- Severe complicated CDI – higher dose of oral vancomycin or vancomycin enema plus IV metronidazole
Fidaxomicin

- Approved by FDA in 2011
- Not registered with HSA
- 200mg BD for 10 days, minimal absorption
- 2 randomized trials showed similar cure rates as vancomycin
- Good activity against Clostridium some against Staphylococcus and Enterococcus
- Sinfully expensive
- May be good choice for recurrent CDI (lower recurrence rates than vancomycin)
Antibiotic resistance and Clostridium difficile

- Highest risk from antibiotics that disrupt bowel flora but spares *Clostridium difficile*

- Development of resistance precedes outbreaks
  - 1970s – clindamycin
  - 1980s and 90s – cephalosporins
  - 2000s – quinolones (RT 027)
Big worry: vancomycin and metronidazole resistance

- Still very uncommon
- More common is reduced susceptibility
- More problematic for metronidazole than vancomycin because of PK PD

Breakpoints
- Sensitive $\leq 2$
- Intermediate $= 4$
- Resistant $\geq 8$
Surveillance study in Israel

- January and February 2014
- 6 GHs and 10 LTCFs
- 208 isolates; RT027 was the most common – 31.8%
- 44.6% isolates were metronidazole non-susceptible

Adler et al, DMID 2015;83;21-4
In Vitro and In Vivo Characterization of CB-183,315, a Novel Lipopeptide Antibiotic for Treatment of Clostridium difficile
A Study of Ridinilazole (SMT19969) Compared With Fidaxomycin for the Treatment of Clostridium Difficile Infection (CDI)

**This study is currently recruiting participants.** *(see Contacts and Locations)*

**Sponsor:** Summit Therapeutics

**Information provided by (Responsible Party):** Summit Therapeutics

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**ClinicalTrials.gov Identifier:**
NCT02784002

**First received:** May 16, 2016

**Last updated:** May 23, 2016

**Last verified:** May 2016

**History of Changes**

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**Tracking Information**

<table>
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<th>Parameter</th>
<th>Date</th>
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<td>First Received Data [ICMJE]</td>
<td>May 16, 2016</td>
</tr>
<tr>
<td>Last Updated Date</td>
<td>May 23, 2016</td>
</tr>
<tr>
<td>Start Date [ICMJE]</td>
<td>December 2014</td>
</tr>
<tr>
<td>Estimated Primary Completion Date</td>
<td>December 2016</td>
</tr>
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</table>
Disruption of normal flora

- The root problem in CDI is the disruption of the normal flora of the intestines caused by antibiotics.
- The ultimate goal of treatment is to discontinue all antibiotics and allow the normal bowel microflora to restore itself.
Restoring the microbial diversity – why not to donate it?

Courtesy of Dr Jasmine Chung
Administration of Faecal Microbiota

**Enema**
- First report in 1958
- Retention enema in use all the way till 1989

**Colonoscopy**

1991

**Duodenal Tube**

1994

**Rectal Tube**

1998

Bakken et al Clinical Gastroenterology And Hepatology 2011;9:1044–1049
Systematic Review of Intestinal Microbiota Transplantation (Fecal Bacteriotherapy) for Recurrent *Clostridium difficile* Infection

Clinical Infectious Diseases 2011;53(10):994–1002

Ethan Gough,¹ Henna Shaikh,² and Amee R. Manges¹,³

Departments of ¹Epidemiology Biostatistics and Occupational Health, and ²Biology, McGill University, and ³Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada

- Meta-analysis of 28 articles published
- Cases published/unpublished between 1957 – 2011
- From North America, Europe and Australia

<table>
<thead>
<tr>
<th></th>
<th>Comments</th>
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<tbody>
<tr>
<td><strong>Average Age</strong></td>
<td>53 years (2-95 years)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>39% male</td>
</tr>
<tr>
<td><strong>Followup duration</strong></td>
<td>36 h – 5 years</td>
</tr>
<tr>
<td><strong>Dx</strong></td>
<td>CDI or Pseudomembranous Colitis</td>
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</table>
**Characteristics of Studies Reviewed**

- Case reports involving small no. of pts
- Age Range: 2-95 yrs
- FMT: Most pts received single infusion.
- Donors: Mainly Family members
- Response rates: 50-100%
- Route of FMT: mainly PR (Enema/colonscopy)
  Others: NG/NJ
Original Investigation

Frozen vs Fresh Fecal Microbiota Transplantation and Clinical Resolution of Diarrhea in Patients With Recurrent Clostridium difficile Infection: A Randomized Clinical Trial

Christine H. Lee, MD; Theodore Steiner, MD; Elaine O. Petrof, MD; Marek Smieja, MD, PhD; Diane Roscoe, MD; Anouf Nematallah, MD; J. Scott Weese, DVM; Stephen Collins, MBBS; Paul Moayyedi, MB; Mark Crowther, MD; Mark J. Ropeleski, MD; Padman Jayaratne, PhD; David Higgins, MB; Yingfu Li, PhD; Neil V. Rau, MD; Peter T. Kim, PhD

Courtesy of Dr Jasmine Chung
Investigations

Stool
- Ova, cysts and parasites
- C. Difficile (Toxin and PCR)
- Cryptosporidium, isospora, microsporidium
- Culture for enteric pathogen
- Helicobacter pylori fecal antigen test

Serum
- HIV
- Hep A/B/C
- VDRL/TPPA

Bakken et al Clinical Gastroenterology And Hepatology 2011;9:1044–1049

SGH has FMT protocol since 2014

- Proposed by Dr Tan Ban Hock
- For patients with CDI that is recurrent, relapsing or not responding to therapy
- Patients with neutropenia and recent (3 months) allogenic BMT are at present excluded
- Patients will sign consent
The specimen

- The stools will be mixed with normal saline, homogenized in a household blender, packaged in syringes and frozen for up to 150 days.
  - The blender will, unfortunately, be discarded after each use.
The procedure

- The default mode of stool instillation will be via a colonoscopy.
- Alternatives - nasoduodenal tube or in case of ileus, by enema or nasogastric tube.
- The following are contraindications to colonoscopy: pregnancy, within 2 weeks of a myocardial infarction, toxic mega-colon, suspected bowel perforation.
Randomized, double-blind, placebo-controlled study of two neutralizing, fully human monoclonal antibodies against *Clostridium difficile* toxins A (CDA1) and B (CDB1).

- Total 200 patients, Single infusion
- Patients on vancomycin or metronidazole

The recurrence rates were significantly lower 25% vs 7%.

The time to the resolution of diarrhea, LOS for the initial episode, and severity of diarrhea during the initial episode were similar in the two study groups.
Please be careful with antibiotics

Figure 2. Targeted antibiotic (Abx) consumption and nosocomial *Clostridium difficile*-associated disease (CDAD) incidence per 1000 patient-days of hospitalization.

Valiquette et al. CID 2007;45:S112-21
Effect of antibiotic stewardship programmes on *Clostridium difficile* incidence: a systematic review and meta-analysis

Leah M. Feazel¹, Ashish Malhotra¹,², Eli N. Perencevich¹,², Peter Kaboli¹,², Daniel J. Diekema¹ and Marin L. Schweizer¹,²*

<table>
<thead>
<tr>
<th>Study of subgroup</th>
<th>log [Risk ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Risk ratio IV, Random, 95% CI</th>
<th>Risk ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligison 2012</td>
<td>-0.37</td>
<td>0.393</td>
<td>5.0%</td>
<td>0.69 [0.32, 1.49]</td>
<td>0.69 [0.32, 1.49]</td>
</tr>
<tr>
<td>Fowler 2007</td>
<td>-1.05</td>
<td>0.372</td>
<td>5.3%</td>
<td>0.35 [0.17, 0.73]</td>
<td>0.35 [0.17, 0.73]</td>
</tr>
<tr>
<td>Frank 1997</td>
<td>0.029</td>
<td>0.522</td>
<td>3.6%</td>
<td>1.03 [0.37, 2.86]</td>
<td>1.03 [0.37, 2.86]</td>
</tr>
<tr>
<td>Guihar 2009</td>
<td>-1.65</td>
<td>0.522</td>
<td>3.6%</td>
<td>0.19 [0.07, 0.53]</td>
<td>0.19 [0.07, 0.53]</td>
</tr>
<tr>
<td>Jones 1997</td>
<td>-0.4</td>
<td>0.205</td>
<td>8.1%</td>
<td>0.67 [0.45, 1.00]</td>
<td>0.67 [0.45, 1.00]</td>
</tr>
<tr>
<td>Ludlam 1999</td>
<td>-0.721</td>
<td>0.177</td>
<td>8.7%</td>
<td>0.49 [0.34, 0.69]</td>
<td>0.49 [0.34, 0.69]</td>
</tr>
<tr>
<td>Malani 2013</td>
<td>-0.755</td>
<td>0.257</td>
<td>7.2%</td>
<td>0.47 [0.28, 0.78]</td>
<td>0.47 [0.28, 0.78]</td>
</tr>
<tr>
<td>Miller 2009</td>
<td>-1.341</td>
<td>0.341</td>
<td>5.8%</td>
<td>0.26 [0.13, 0.51]</td>
<td>0.26 [0.13, 0.51]</td>
</tr>
<tr>
<td>O'Conor 2004</td>
<td>-1.164</td>
<td>0.567</td>
<td>3.2%</td>
<td>0.31 [0.10, 0.95]</td>
<td>0.31 [0.10, 0.95]</td>
</tr>
<tr>
<td>Price 2010</td>
<td>-0.661</td>
<td>0.082</td>
<td>10.1%</td>
<td>0.52 [0.44, 0.61]</td>
<td>0.52 [0.44, 0.61]</td>
</tr>
<tr>
<td>Reinoso 2002</td>
<td>-3.372</td>
<td>1.438</td>
<td>0.7%</td>
<td>0.03 [0.00, 0.57]</td>
<td>0.03 [0.00, 0.57]</td>
</tr>
<tr>
<td>Schön 2011</td>
<td>0.034</td>
<td>0.103</td>
<td>9.8%</td>
<td>1.03 [0.85, 1.27]</td>
<td>1.03 [0.85, 1.27]</td>
</tr>
<tr>
<td>Starks 2008</td>
<td>-0.984</td>
<td>0.309</td>
<td>6.3%</td>
<td>0.37 [0.20, 0.68]</td>
<td>0.37 [0.20, 0.68]</td>
</tr>
<tr>
<td>Stone 1998</td>
<td>-0.546</td>
<td>0.251</td>
<td>7.3%</td>
<td>0.58 [0.35, 0.95]</td>
<td>0.58 [0.35, 0.95]</td>
</tr>
<tr>
<td>Taipaert 2011</td>
<td>-1.079</td>
<td>0.272</td>
<td>6.9%</td>
<td>0.34 [0.20, 0.58]</td>
<td>0.34 [0.20, 0.58]</td>
</tr>
<tr>
<td>Thomas 2002</td>
<td>-0.78</td>
<td>0.19864</td>
<td>8.3%</td>
<td>0.46 [0.31, 0.68]</td>
<td>0.46 [0.31, 0.68]</td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 0.48 [0.38, 0.62]

Heterogeneity: $\tau^2 = 0.14; \chi^2 = 61.27, df = 15 (P<0.00001); I^2 = 76\%$

Test for overall effect: $Z = 5.94 (P<0.00001)$

**Figure 4.** Forest plot of all included studies. IV, inverse variance.
Vaccines
Sanofi Pasteur’s C.diff vaccine candidate

- Targets the key bacterial mechanisms for disease – C.difficile Toxins A and B
- Toxoid vaccines are an approach has been highly effective for other toxin-mediated diseases (tetanus and diphtheria)
- The only vaccine candidate in Phase III efficacy trials…. 
- Ongoing in > 200 sites globally
# Phase III Study overview

<table>
<thead>
<tr>
<th>Title of the Trial (Trial Code)</th>
<th>Efficacy, Immunogenicity, and Safety Study of Clostridium difficile Toxoid Vaccine in Subjects at Risk for C. difficile Infection (H-030-014)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study design</strong></td>
<td>This is a randomized, observer-blind, placebo-controlled, multi-center, multi-national Phase III trial in 15,000 subjects. Adult subjects aged ≥ 50 years who are at risk for CDI will be enrolled. Subjects will be enrolled in 1 of 2 risk strata across the treatment groups. To assess the efficacy of the C. difficile vaccine in preventing the onset of symptomatic primary CDI confirmed by polymerase chain reaction (PCR) in adult subjects aged ≥ 50 years who are at risk for CDI and have received at least 1 injection.</td>
</tr>
<tr>
<td><strong>Primary Objective</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Planned Trial Period</strong></td>
<td>3Q2013 to Dec.2017 (estimated study completion date).</td>
</tr>
<tr>
<td><strong>Main Population (N)</strong></td>
<td>15,000 adult subjects, aged ≥ 50 years who are at risk for C. difficile infection (CDI): Subjects will be enrolled in 1 of 2 risk strata across the treatment groups.</td>
</tr>
<tr>
<td><strong>Vaccine Schedule</strong></td>
<td>Vaccine or placebo will be administered in a 3-dose schedule on days 0, 7, and 30</td>
</tr>
<tr>
<td><strong>Current Status</strong></td>
<td>Enrolment and surveillance ongoing</td>
</tr>
</tbody>
</table>