Overview of Therapeutic Advances in *Clostridium difficile* Infection

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Boston
## Disclosures

<table>
<thead>
<tr>
<th>Company</th>
<th>Relationship</th>
<th>Content area</th>
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<tbody>
<tr>
<td>Astellas</td>
<td>Speaker</td>
<td>Clostridium difficile</td>
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<tr>
<td>Claremont BioSolutions</td>
<td>Scientific advisor &amp; Research</td>
<td>Clostridium difficile</td>
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<td>CSL Behring</td>
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<td>Scientific advisor</td>
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<tr>
<td>ViroPharma</td>
<td>Scientific advisor</td>
<td>Clostridium difficile</td>
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</table>

**Non-FDA approved indications/agents:** Only oral vancomycin and oral fidaxomicin are FDA approved for CDI therapy - all other agents mentioned are not.
C. difficile infection – increasing incidence, severity and recurrence rates

**Host factors**
- Age
- Immune response
- Underlying disease

**Bacterial factors**
- Virulence
- Sporulation
- Antibiotic resistance

**Environment**
- Antibiotic use
- PPI use
- Burden of contamination by C. difficile spores

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Increases in *C. difficile*-related deaths

In US in 2006 reported deaths related to CDI were:
- x 4 deaths related to MRSA
- x 6 deaths related to all other enteric pathogens combined
Frequency of IL-8 Polymorphisms Differ Between Caucasians and non-Caucasians

For TT: P=0.002

Advances in CDI therapy

- Unmet medical needs
  - High (rising) incidence
  - High (rising) death rates
  - Frequent recurrences
CDI: Basic Principles of Therapy

- Discontinue offending antimicrobial agents whenever possible
- Test stool for *C. difficile* or its toxins
- Initiate CDI therapy
  - empirically or after confirmation of diagnosis (depending on clinical urgency)
  - Pharmacotherapy
    - Vancomycin (only FDA-approved treatment)
    - Metronidazole (most commonly used treatment)
  - Supportive treatment

Use of non-\textit{C. difficile} antibiotics & response to CDI therapy: New data for an old rule


**With concomitant antibiotic therapy**

- **Response at Day 10:**
  - 84%* vs 93%
  - \(P < .001\)

- **Sustained response:**
  - Any additional Abx - 66%
  - No additional Abx - 75%
  - \(P = .005\)

**Without concomitant antibiotic therapy**

- **Response at Day 10:**
  - 79% for Vanco, 90% for Fidaxo
  - \(P = 0.04\)

* 79% for Vanco, 90% for Fidaxo

\(P = 0.04\)
# Management of CDI

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)

<table>
<thead>
<tr>
<th>CDI Severity</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to moderate</td>
<td><strong>Metronidazole</strong> 500 mg 3 times per day PO for 10-14 days</td>
</tr>
<tr>
<td>Severe</td>
<td><strong>Vancomycin</strong> 125 mg 4 times per day PO for 10-14 days</td>
</tr>
<tr>
<td>Severe, complicated</td>
<td><strong>Vancomycin</strong> 500 mg 4 times per day PO or by nasogastric tube plus <strong>metronidazole</strong> 500 mg IV q 8 hrs</td>
</tr>
</tbody>
</table>
Markers of Severe CDI

- Severe diarrhea
  - >10 bowel movements/day
- Fever >101°F
- Marked leukocytosis
  - > 15,000 in severe CDI
  - > 25,000 increased fatality
- High or rising (50% increase) serum creatinine
- Low serum albumin (<2.5)
- Ileus or toxic megacolon
- Colonic thickening on CT scan
- Ascites on CT scan
- Pseudomembranes on endoscopy
- Severe abdominal distension, pain
- Hemodynamic instability
- Organ failure
- High Horn’s index

CDSS: Validated clinical prediction rule for severe outcomes of CDI

Severe outcome = ICU admission, colectomy or death.

630 CDI patients
3 sites (Boston, Houston & Dublin)

Derivation cohort:
1 for age > 60 years
1 for creatinine* ≥ 2.0 mg/dL
1 for WBC* ≥ 20,000 μL

Validation cohort:
Score 0 or 1 versus 2 or 3
72% Predictive accuracy


* Peak during week of CDI diagnosis
Fidaxomicin versus Vancomycin for Clostridium difficile Infection

- Initial response
- Recurrence
- Sustained response


FDA approved for CDI therapy 2011
**Bacteroides** group counts in feces before, during and after 10 days of treatment with Fidaxomicin* or Vancomycin*
Recurrent *C. difficile* infection

- **Common** (~25% of treated patients)

- The strain causing recurrence may be the same as for the initial episode (relapse) or a new strain (re-infection)

- Mechanisms of recurrence:
  - NOT primarily due to antimicrobial resistance
  - Instead, antimicrobial therapy can perpetuate loss of colonization resistance

Decreased Diversity of Fecal Microbiome in Recurrent CDI

Chang JY. J Infect Dis 2008;197:435
### Management of Recurrent CDI

<table>
<thead>
<tr>
<th>Episode of CDI</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>First recurrence</td>
<td>• Treat as first episode according to disease severity</td>
</tr>
<tr>
<td></td>
<td>• Fidaxomycin??</td>
</tr>
<tr>
<td>Second recurrence</td>
<td>• Prolonged oral vancomycin (tapering and pulse-dosed)</td>
</tr>
<tr>
<td></td>
<td>• Fidaxomicin?</td>
</tr>
<tr>
<td>Third and subsequent recurrences</td>
<td>• Prolonged oral vancomycin (tapering and pulse-dosed)</td>
</tr>
<tr>
<td></td>
<td>• Fidaxomicin?</td>
</tr>
<tr>
<td></td>
<td>• Rifaximin “chaser”</td>
</tr>
<tr>
<td></td>
<td>• Fecal microbial transplant (FMT aka “stool transplant”)</td>
</tr>
<tr>
<td></td>
<td>• IVIG</td>
</tr>
</tbody>
</table>
Oral vancomycin for recurrent CDI: Taper & pulsed dosing


- 125 mg QID x 10-14 days
- 125 mg BID x 7 days
- 125 mg daily x 7 days
- 125 mg once every 2 days x 8 days
- 125 mg once every 3 days x 15 days

Efficacy

P=0.01
P=0.02

Recurrent CDI following Fidaxomicin versus Vancomycin therapy for a first CDI recurrence

Recurrences to 14 days post therapy
- Fidaxomicin: 7.6% (5/66)
- Vancomycin: 27.4% (17/62)
- P=0.003

Recurrences 15-28 days post therapy
- Fidaxomicin: 13.1% (8/61)
- Vancomycin: 11.1% (5/45)
- NS

Total recurrences to 28 days post therapy
- Fidaxomicin: 19.7% (13/66)
- Vancomycin: 35.5% (22/62)
- P=0.045

Day 0 = last day of therapy

Cornely, OA et al. CID 2012:55 (Suppl 2); 154-61
Rifaximin “chaser” in recurrent CDI

Standard therapy (M in 82%; V in 18%) x 10-14 days
PLUS:
Placebo or Rifaxamin 400 mg tid x 20 days

<table>
<thead>
<tr>
<th></th>
<th>Rifaximin (n=33)</th>
<th>Placebo (n=35)</th>
<th>Recurrent CDI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15%</td>
<td>31%</td>
<td>P = 0.11</td>
</tr>
</tbody>
</table>

### Predictors of recurrent CDI in derivation cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>β coefficient</th>
<th>OR</th>
<th>95% CI</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 y</td>
<td>1.81</td>
<td>6.12</td>
<td>1.03–36.58</td>
<td>1</td>
</tr>
<tr>
<td>Horn’s index severe or fulminant</td>
<td>2.26</td>
<td>9.56</td>
<td>1.19–76.68</td>
<td>1</td>
</tr>
<tr>
<td>Additional antibiotic use</td>
<td>2.31</td>
<td>10.03</td>
<td>1.47–68.26</td>
<td>1</td>
</tr>
<tr>
<td>Anti-toxin A IgG &lt;1.29</td>
<td>3.96</td>
<td>52.54</td>
<td>1.49–1000</td>
<td>2</td>
</tr>
</tbody>
</table>

**NOTE:** The clinical prediction model excluded anti-toxin A IgG

Risk of recurrent *Clostridium difficile* infection compared to score on clinical prediction rule

<table>
<thead>
<tr>
<th>Score</th>
<th>Derivation cohort (n = 44; 50% recurrence)</th>
<th>Validation cohort (n = 64; 20% recurrence)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>0</td>
<td>0/7</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>5/15</td>
<td>33.3</td>
</tr>
<tr>
<td>2</td>
<td>10/14</td>
<td>71.4</td>
</tr>
<tr>
<td>3</td>
<td>7/8</td>
<td>87.5</td>
</tr>
</tbody>
</table>

NOTE. Patients with scores ≥2 were classified as high risk

Diagnostic accuracy in validation cohort 71.9%

Use of clinical prediction rule for recurrent *Clostridium difficile* infection

- Identify high versus low risk patients
- Minimize recurrence risk (e.g. avoid concomitant antibiotics, avoid PPIs)
- Heighten awareness to facilitate prompt diagnosis and treatment of recurrences
- Consider newer (more costly) interventions for high risk subjects
  - Goal:
    - Maximize clinical benefit
    - Offset higher cost by preventing costly recurrence

Predictors of recurrence:
- 1 for age >65 y
- 1 for severe underlying disease (Horn’s index)
- 1 for additional antibiotic use


![Graph showing recurrence risk and cost implications](Image)
Prevention & treatment approaches for *C. difficile* infection (CDI)

- Colonization resistance impaired
- *C. difficile* exposure & colonization
- Toxin production
- Diarrhea & colitis
- Recurrent diarrhea

Host susceptibility

- Passive: IVIG, HuMAbs, Hyperimmune globulin
- Toxoid vaccine
- Anti-toxin immune response
- Protection

Antibiotic husbandry
Infection control
Bacteriotherapy & probiotics
Anti-colonization vaccine
CAMPs, Bacteriocins
Inhibit germination
Antibiotics
Block toxin transcription
Inhibit sporulation
Block toxin activation
Bind toxins
Surgery
Lactobacillus-containing probiotic mixture in Antibiotic-Associated Diarrhea & in CDI: Study 2

Prospective, RCT in 255 hospital subjects receiving antibiotics

Placebo v 1 capsule v 2 capsules

Capsule – 50 billion cfu combined of Lactobacillus acidophilus
Lactobacillus casei

During & 5 days after antibiotics

Non-toxinogenic *C. difficile*  
Nature’s probiotic?

- Occupy niche to block colonization by toxinogenic *C. difficile*
- Protects against CDI in animals
- Currently in Phase II for secondary prevention
- Also suitable for primary prevention
- Environmental enrichment for non-toxinogenic spores probable – potential for “herd” effect
Fecal microbiota transplantation (FMT) for recurrent CDI

- Ancient treatment for food poisoning and diarrheal illness (4th century Chinese Medicine)
- 1st reported for treatment of PMC in 1958.
- Overall reported efficacy of ~90%*
  - 92% overall (range 81% - 100% in recent systematic review)
- Results of recent multi-center European controlled trial awaited.
- FMT also reported other disorders:
  - GI: Refractory IBD, IBS, chronic constipation
  - Non-GI: Case reports in non-GI disorders (ITP, myoclonus-dystonia, obesity, chronic fatigue, autism).

FMT techniques: bringing method to the madness:

- Multiple methods of administration
  - Overall ~75% by colonoscopy or retention enema
  - ~25% by nasogastric tube or upper GI endoscopy
  - Reported efficacy >90% for lower versus 80% for upper routes

- Recent publications provide recommendations for:
  - Donor screening
  - Processing of donor feces
  - Methods of administration

- “Stool bank” approach effective and can increase accessibility

BACTERIOThERAPY FOR CHRONIC RELAPSING CLOSTRIDIUM DIFFICILE DIARRHOEA IN SIX PATIENTS

M. Tvede1 J. Rask-Madsen2

Department of Clinical Microbiology, Rigshospitalet, Statens Seruminstitut,1 and Section of Gastroenterology, Department of Medicine G, Bispebjerg Hospital, University of Copenhagen, Denmark2

Summary Six patients with chronic relapsing diarrhoea caused by Clostridium difficile were treated with rectal instillation of homologous faeces (one patient) or a mixture of ten different facultatively aerobic and anaerobic bacteria diluted in sterile saline (five patients). The mixture led to a prompt loss of Cl difficile and its toxin from the stools and to bowel colonisation by Bacteroides sp, which had not been present in pre-treatment stool samples. Strains of Escherichia coli, Cl bifermentans, and Peptostreptococcus productus in the mixture inhibited the in-vitro growth of Cl difficile, which in turn inhibited the growth of Bacteroides ovatus, Bacteroides vulgatus, and Bacteroides thetaiotaomicron. The finding that Bacteroides sp had been absent during the patients’ illness but was present after recovery suggests that the absence of Bacteroides sp may result in chronic relapsing Cl difficile diarrhoea, and that its presence may prevent colonisation by Cl difficile.

Toxin binders
Some not-so-hot novel treatments

Diatomaceous earth
- A toxin “decoy”
  (Synsorb)

Colostrum of cows vaccinated against *C. difficile* toxins
  “BIC-C. difficile”
  (Galagen)

Toxin binding polymer
  (Tolevamer – Genzyme)
Diverting loop ileostomy and colonic lavage: an alternative to total abdominal colectomy in severe, complicated CDI.

**Colectomy versus:**

- Loop ileostomy
- Intraoperative *colonic lavage* with warmed polyethylene glycol 3350/electrolyte via the ileostomy
- Post-op Antegrade *vancomycin* instillation via ileostomy

42 patients
- 83% laparoscopically
- 93% colon preserved
- 19% mortality vs 50% in historical controls (odds ratio, 0.24; $P = 0.006$).

Anti-toxin immunity protects against CDI

- High serum anti-toxin in symptomless carriers

- Serum anti-toxin response & protection against recurrent CDI

Serum IgM anti-C. difficile antibody levels are lower in patients with recurrent C. difficile diarrhea.

Lancet 2001;357:189-93
Intravenous Immunoglobulin Therapy for Recurrent *C. difficile* Diarrhea

**Serum IgG anti-toxin A (Optical density units)**

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls</th>
<th>Pediatric</th>
<th>Pre-IVIG</th>
<th>Post-IVIG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult</td>
<td>0.4</td>
<td>0.4</td>
<td>0.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Pediatric</td>
<td>0.2</td>
<td>0.2</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Healthy controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children with recurrent <em>C. difficile</em> diarrhea</td>
<td></td>
<td></td>
<td>0.0</td>
<td>1.4</td>
</tr>
</tbody>
</table>

P = 0.03

P = 0.01

Also used in severe & refractory disease

**Efficacy not proven – no RCT**

Treatment with monoclonal antibodies against *C. difficile* toxins A and B prevents recurrence.

Single dose iv infusion used as an adjuvant to standard of care antibiotics.

The potential value of *Clostridium difficile* vaccine: An economic computer simulation model

Bruce Y. Lee\textsuperscript{a,b,c,*}, Michael J. Popovich\textsuperscript{a,b,c}, Ye Tian\textsuperscript{a,b,c}, Rachel R. Bailey\textsuperscript{a,b,c}, Paul J. Ufberg\textsuperscript{a,b,c}, Ann E. Wiringa\textsuperscript{a,b,c,d}, Robert R. Muder\textsuperscript{d}

\textsuperscript{a}Applied Modeling, Public Health Computational and Operations Research Group (PHICOR), University of Pittsburgh, Pittsburgh, PA, United States
\textsuperscript{b}Department of Biomedical Informatics, University of Pittsburgh, Pittsburgh, PA, United States
\textsuperscript{c}Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, United States
\textsuperscript{d}Division of Infectious Diseases, VA Pittsburgh Health System, University of Pittsburgh, Pittsburgh, PA, United States

“*Our results suggest that a *C. difficile* vaccine could be cost-effective over a wide range of *C. difficile* risk, vaccine costs, and vaccine efficacies … … especially prevention of recurrence*”

A *C. difficile* toxoid vaccine (inactivated toxins A and B)
Induces high serum IgG anti-toxin

Patients

Vaccine recipients

50 times levels in patients with protective immunity

Young, healthy volunteers
90 days after first dose

Prevention & treatment approaches for C. difficile infection (CDI)

Colonization resistance impaired

C. difficile colonization

Toxin production

Diarrhea

Recurrent diarrhea

Host susceptibility

Passive: IVIG, HuMAbs, Hyperimmune globulin

Toxoid vaccine

Anti-toxin immune response

Protection

Antibiotic husbandry

Infection control

Bacteriotherapy & probiotics

Anti-colonization vaccine

CAMPs, Bacteriocins

Inhibit germination

Antibiotics

Block toxin transcription

Inhibit sporulation

Block toxin activation

Bind toxins

Surgery

Protection