Recent PHE Guidance on C. difficile infection (CDI) treatment

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Updated guidance on the management and treatment of *Clostridium difficile* infection

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**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; and Mark H. Wilcox, MD


Cohen S *et al.* ICHE 2010.


Date of preparation: November 2013     DIF13049UKg
Unmet CDI treatment needs

- Reduced recurrence
- Improved sustained cure rate
- Time to resolution of symptoms
- Severe CDI
- Prediction tools to optimise treatment options
- Reduced mortality
How is CDI currently managed?

- Until now treatments have included metronidazole and vancomycin but these are sub-optimal
  - Failure in ~10-20% of cases\(^1\)
  - According to severity of infection
  - Recurrence occurs in ~20% of cases
  & ~45% subsequently recur again\(^1\)
- Death
  - 17% 30-day mortality (~7% attributable)\(^2\)
  - 24-48% mortality rate from severe CDI\(^3\)

‘We recommend using any of the following to indicate severe CDI and so to use oral vancomycin (or fidaxomicin) in preference to metronidazole.’

- WCC >15 109/L
- Acutely rising blood creatinine (>50% increase above baseline)
- Temperature >38.5°C;
- Evidence of severe colitis (abdominal signs, radiology)
Rates of clinical success for metronidazole and vancomycin

Clinical success was defined as diarrhoea resolution and absence of severe abdominal discomfort due to CDI on Day 10; NS, not significant.

Two identical multicentre, randomised, double-blind, parallel-group clinical trials

Johnson et al. Poster presented at ID Week 2012, San Diego, USA; 818.

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Poor efficacy of metronidazole
S. Johnson et al., IDWeek 2012; tolevamer studies

- Overall, vancomycin significantly enhanced clinical success in comparison with metronidazole
  - 81.1% vs. 72.7%; OR [95% CI]: 1.681 [1.114, 2.537], P>0.05)
- Median time to resolution of diarrhoea =5 days for each group
- Recurrence was seen in 20.6% of vancomycin-treated subjects and 23% of metronidazole-treated subjects.
- Frequency of treatment-emergent AEs similar between groups
- Discontinuation due to adverse events was more frequent with metronidazole (11.2%) than vancomycin (6.5%)
- More subjects experienced nephrotoxicity-related AEs with vancomycin (12 subjects [4.6%]) than metronidazole (3 subjects [1%])

https://idsa.confex.com/idsa/2012/webprogram/Paper35060.html
Concentration of *Clostridium difficile* in stool of 10 patients whose therapy was changed from metronidazole to vancomycin
Activity of metronidazole against *C. difficile* ribotype 027 in gut infection model


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Determinants of recurrence risk

- Flora inhibition (antibiotics)
- Spore persistence
- Antibody deficit
- Previous recurrence
- Strain type
- Host biomarkers e.g. albumin
- Age
- Co-morbidities
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Effect of CA on outcome after treatment of CDI with fidaxomicin or vancomycin

<table>
<thead>
<tr>
<th></th>
<th>No CA</th>
<th>CA</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical cure (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA during treatment*</td>
<td>93%</td>
<td>84%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Recurrence (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA during treatment*</td>
<td>18%</td>
<td>24%</td>
<td>0.11</td>
</tr>
<tr>
<td>CA during follow-up†</td>
<td>18%</td>
<td>25%</td>
<td>0.06</td>
</tr>
<tr>
<td>CA at any time‡</td>
<td>18%</td>
<td>23%</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Sustained response (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA at any time‡</td>
<td>75%</td>
<td>66%</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Median time to resolution of diarrhoea (h)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CA during treatment*</td>
<td>54</td>
<td>97</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


Fidaxomicin

- Reduced recurrence by ~50%
- Less effective against CD 027 (but same true for vancomycin)
- Some resistance emergence in VRE (not in CD)
- No fidaxomicin resistance in CD, but one isolate (cure patient) MIC = 16 mg/L
- Concomitant antibiotics
- Cost

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# Fidaxomicin vs Vancomycin Phase 3 CDI Studies

<table>
<thead>
<tr>
<th>Per protocol, microbiologically evaluable</th>
<th>Fidaxomicin 200 mg bd</th>
<th>Vancomycin 125 mg qds</th>
<th>P value</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Cure</strong></td>
<td>92.1% (244/265 pts) 91.7%</td>
<td>89.8% (254/283 pts) 90.6%</td>
<td>NA</td>
<td>(-2.6, )*</td>
</tr>
<tr>
<td><strong>Recurrence</strong></td>
<td>13.3% (28/211) 12.8%</td>
<td>24.0% (53/221) 25.3%</td>
<td>0.004</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Sustained Cure</strong></td>
<td>77.7% (206/265) 79.6%</td>
<td>67.1% (190/283) 65.5%</td>
<td>0.006</td>
<td>0.001</td>
</tr>
</tbody>
</table>

* one-sided 97.5% CI  
NA = Not Applicable (trial met non-inferiority endpoint)  

http://www.optimerpharma.com/pipeline.asp?pipeline=1  

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Fidaxomicin pivotal phase 3 trials:
time to recurrence

Early recurrence (relapse):
Fidaxomicin: 7.4%  p<0.001
Vancomycin: 19.3%

Late recurrence (relapse/reinfection):
Fidaxomicin: 7.3%  p=0.560
Vancomycin: 8.4%


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Fidaxomicin prevents CDI relapse & re-infection
whole genome sequencing data

Treating other recurrences and death without recurrence as a competing risk

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Persistence of fidaxomicin

Date of preparation: November 2013     DIF13049UKg
Chilton C et al. ECCMID 2013. LB-2817.
‘Fidaxomicin should be considered for patients with severe CDI who are considered at high risk for recurrence; these include elderly patients with multiple co-morbidities who are receiving concomitant antibiotics.’
‘Fidaxomicin should be preferred for patients with recurrent CDI, whether mild, moderate or severe, because of their increased risk of further recurrences.’

‘The efficacy of fidaxomicin in patients with multiple CDI recurrences is unclear. Depending on local cost-effectiveness based decision making, oral vancomycin is an alternative.’
Weak evidence base for probiotics
Cochrane Review 2013

Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Joshua Z Goldenberg¹, Stephanie SY Ma², Jane D Saxton¹, Mark R Martzen³, Per O Vandvik⁴, Kristian Thorlund⁵, Gordon H Guyatt⁵, Bradley C Johnston⁶,⁷

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Contact address: Bradley C Johnston, bradley.johnston@sickkids.ca. bjohnst@mcmaster.ca.

Editorial group: Cochrane Inflammatory Bowel Disease and Functional Bowel Disorders Group.


Review content assessed as up-to-date: 21 February 2013.
C. difficile associated diarrhoea (CDAD)

Diarrhoea and positive stool cytotoxin/culture for C. difficile

C. difficile infection (CDI)

Positive stool cytotoxin/culture for C. difficile
Cochrane Review 2013 probiotics & ‘CDAD’
Of the 1120 patients who were eligible to participate in the study, 865 were excluded from participation. The remaining 255 patients were enrolled in the trial between January 2009 and March 2009.

Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhoea and *Clostridium difficile* diarrhoea in older inpatients (PLACIDE): a randomised, double-blind, placebo-controlled, multicentre trial

Stephen J Allen, Kathie Wareham, Duolao Wang, Caroline Bradley, Hayley Hutchings, Wyn Harris, Anjan Dhar, Helga Brown, Alwyn Foden, Michael B Gravenor, Dietrich Mack

**Summary**

**Background** Antibiotic-associated diarrhoea (AAD) occurs most frequently in older (≥65 years) inpatients exposed to broad-spectrum antibiotics. When caused by *Clostridium difficile*, AAD can result in life-threatening illness. Although underlying disease mechanisms are not well understood, microbial preparations have been assessed in the prevention of AAD. However, studies have been mostly small single-centre trials with varying quality, providing insufficient data to reliably assess effectiveness. We aimed to do a pragmatic efficacy trial in older inpatients who would be representative of those admitted to National Health Service (NHS) and similar secondary care institutions and to recruit a sufficient number of patients to generate a definitive result.

**Interpretation** We identified no evidence that a multistrain preparation of lactobacilli and bifidobacteria was effective in prevention of AAD or CDD. An improved understanding of the pathophysiology of AAD is needed to guide future studies.
‘We cannot at present recommend the use of probiotics for the prevention of AAD or CDI.’
Cloaca
Wim Delvoye
Faecal transplantation

- the ultimate probiotic?

- Eiseman et al 1958, pts with severe AAD
- 160 cases (largest n=18), 15 failures i.e. 90% success
- Randomised, sham-procedure-controlled clinical trial in the Netherlands
Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent Clostridium difficile infection.

Gough E, Shaikh H, Manges AR.

Department of Epidemiology Biostatistics and Occupational Health, McGill University, 1020 Pine Avenue West, Montreal, Quebec, Canada.

Abstract
Clostridium difficile infection (CDI) is a gastrointestinal disease believed to be causally related to perturbations to the intestinal microbiota. When standard treatment has failed, intestinal microbiota transplantation (IMT) is an alternative therapy for patients with CDI. IMT involves infusing intestinal microorganisms (in a suspension of healthy donor stool) into the intestine of a sick patient to restore the microbiota. However, protocols and reported efficacy for IMT vary. We conducted a systematic literature review of IMT treatment for recurrent CDI and pseudomembranous colitis. In 317 patients treated across 27 case series and reports, IMT was highly effective, showing disease resolution in 92% of cases. Effectiveness varied by route of instillation, relationship to stool donor, volume of IMT given, and treatment before infusion. Death and adverse events were uncommon. These findings can guide physicians interested in implementing the procedure until better designed studies are conducted to confirm best practices.
Rates of cure without relapse for recurrent CDI

Extremely labour intensive

Nasoduodenal tube endoscopy

Screening for what?

There must be an easier way!

Cost

FDA letter requirement for IND/NDA

Fecal transplants may stall as FDA cracks down on docs

*By JoNel Aleccia, Senior Writer, NBC News*

Potentially life-saving fecal transplants that use poop to cure nasty gut infections may become harder to get now that government health officials are getting serious about regulating the procedures.

Food and Drug Administration officials say they have started requiring doctors and clinics that perform fecal transplants to apply for investigational new drug applications, known as INDs, in order to continue their work.

The federal officials say that will boost “regulatory clarity” about the procedures. But doctors say that, for now, the time-consuming INDs could bring poop transplants to a virtual standstill.

“I’m already seeing that because of this requirement, a lot of doctors that were doing fecal transplants have either shut down or put their patients on hold,” said Dr. Colleen Kelly, a gastroenterologist with...

http://vitals.nbcnews.com/_news/2013/06/04/18659576-fecal-transplants-may-stall-as-fda-cracks-down-on-docs

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‘A cost-effectiveness evaluation of donor faeces transplantation has not been performed, which is notable considering the complexity of the procedure (donor testing, consenting, sample processing and endoscopy). antibiotics.’
Algorithm 1. 1st episode of *Clostridium difficile* infection (CDI)

Diarrhoea **AND** one of the following:
Positive *C. difficile* toxin test **OR** Results of *C. difficile* toxin test pending **AND** clinical suspicion of CDI

If clinically appropriate discontinue non-*C. difficile* antibiotics to allow normal intestinal flora to be re-established
Suspected cases must be isolated

**Symptoms/signs: not severe CDI**

_None of:_ WCC >15, acute rising creatinine and/or colitis
Oral metronidazole 400mg 8-hourly 10-14 days

**Symptoms/signs: severe CDI**
WCC >15, acute rising creatinine and/or colitis
Oral vancomycin 125 mg 6-hourly 10-14 days.
Consider oral fidaxomicin 200 mg 12-hourly 10-14 days in patients with multiple co-morbidities who are receiving concomitant antibiotics

**DAILY ASSESSMENT**

Symptoms improving
Diarrhoea should resolve in 1-2 weeks
Recurrence occurs in ~20% after 1st episode; 50-

Symptoms not improving or worsening
Should not normally be deemed a treatment failure until day 7 of treatment.

http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317138914904
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Algorithm 2 Recurrent *Clostridium difficile* infection (CDI)

Recurrent CDI occurs in ~15-30% of patients treated with metronidazole or vancomycin

Recurrence of diarrhoea (at least 3 consecutive type 5-7 stools) within ~30 days of a previous CDI episode AND positive *C. difficile* toxin test

Must discontinue non- *C. difficile* antibiotics if at all possible to allow normal intestinal flora to be re-established
Review all drugs with gastrointestinal activity or side effects (stop PPIs unless required acutely)
Suspected cases must be isolated

Symptoms/signs: **not life-threatening CDI**
Oral fidaxomicin 200 mg 12-hourly for 10-14 days
(efficacy of fidaxomicin in patients with multiple recurrences is unclear)
Depending on local cost-effectiveness decision making,
Oral vancomycin 125 mg 6-hourly 10-14 days is an alternative

Daily Assessment
(include review of severity markers, fluid/electrolytes)
Investigational therapeutic approaches for CDI

- Ramoplanin
- Anti-toxin monoclonal antibodies (Merck)
- Lipopeptide CB-183,315 (Cubist)
- LFF571 (Novartis)
- Vaccine – primary/secondary prevention (San-Pasteur)
- Cadazolid (Actelion)
- Non-Toxigenic CD strain (Viropharma)
- Novacta (lantibiotic), Summit, Oritavancin
- ‘Tailored bacteritherapy’

Date of preparation: November 2013
Summary CDI treatment issues

- Need to identify patients with severe infection at risk of recurrence
- Detrimental effect of concomitant antibiotics
- Use accordingly metro’, vancomycin or fidaxomicin
- Multiple new drugs / interventions under investigation
- Need to improve evidence base for when to use different CDI treatment options
- Future role of metronidazole in CDI
- Can new treatment options reduce mortality?