The Treatment of *Clostridium difficile* Infection

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Disclosures

I have received grants, and served as a consultant on Advisory Boards for:

- BD GeneOhm Diagnostics
- Merck Frosst Canada Ltd
- Optimer Pharmaceuticals Canada
Objectives

- to review evidence-based clinical practice guidelines for the management *Clostridium difficile* infection
- to consider novel approaches for the treatment of patients with *C. difficile* infection
**Clostridium difficile**

- implicated in 20%-30% of antibiotic-associated diarrhea
- major cause of nosocomial infectious diarrhea
- disease caused by production of toxin A and toxin B

C. difficile Toxins

**Toxin A**
- enterotoxin, causing intestinal mucosal injury and fluid secretion

**Toxin B**
- cytotoxin, disrupts intestinal cell tight junctions
**C. difficile** Pathogenesis

Acquisition of toxigenic *C. difficile* followed by *disruption of normal bowel flora* (eg. with use of antibiotics)

- **Toxin Ab present**
  - asymptomatic
  - *C. difficile* colonization

- **No toxin Ab**
  - *C. difficile*-associated diarrhea
C. difficile
Complications

- acute abdomen, peritonitis, toxic megacolon, colon perforation
- recurrent infection
Recurrent *C. difficile*

- occurs in 20-30%; may be relapse or re-infection
- a recurrence is associated with a higher risk of repeated recurrences
- often associated with concurrent or repeat antibiotic therapy

C. difficile Diagnosis

CDI should be suspected in any hospitalized patient with diarrhea who has received antibiotics in the previous 2 months (fever and leukocytosis are often present).
The Latest in C. difficile Diagnostics

Bomers, BMJ 2012

RESEARCH

Using a dog’s superior olfactory sensitivity to identify Clostridium difficile in stools and patients: proof of principle study

Marije K Bomers consultant1, Michiel A van Agtmael consultant2, Hotsche Luik canine trainer and psychologist3, Mark C van Veen resident4, Christina M J E Vandenbroucke-Graus professor5, Yvo M Smulders professor6

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Abstract

Objective To investigate whether a dog’s superior olfactory sensitivity can be used to detect Clostridium difficile in stool samples and hospital patients.

Design Proof of principle study, using a case control design.

Setting Two large Dutch teaching hospitals.

Participants A 2 year old beagle trained to identify the smell of C difficile and tested on 360 patients (320 with C difficile infection and 40 controls).

Intervention The dog was guided along the wards by its trainer, who was blinded to the participants’ infection status. Each detection round concerned 10 patients (one case and nine controls). The dog was trained to lie or sit down when a C difficile was detected.

Main outcomes measures Sensitivity and specificity for detection of C difficile in stool samples and in patients.

Results The dog’s sensitivity and specificity for identifying C difficile in stool samples were both 100% (95% confidence interval 91% to 100%). During the detection rounds, the dog correctly identified 25 of the 30 cases (sensitivity 83%, 85% to 94%) and 26 of the 270 controls (specificity 96%, 95% to 99%).

Conclusion A trained dog was able to detect C difficile with high estimated sensitivity and specificity, both in stool samples and in hospital patients infected with C difficile.

Introduction

Clostridium difficile infection is common, particularly in people in healthcare facilities who have received antimicrobials. C difficile causes clonorchis intestinal disease, with symptoms ranging from mild diarrhea to severe pseudomembranes, colitis and toxic megacolon. The bacterium can be transmitted through...
<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture</td>
<td>≥90</td>
<td>80-90</td>
</tr>
<tr>
<td>Cytotoxin assay</td>
<td>75-85</td>
<td>≥97</td>
</tr>
<tr>
<td>EIA toxin assay</td>
<td>70-85</td>
<td>95</td>
</tr>
<tr>
<td>GDH (common Ag)</td>
<td>85-95</td>
<td>96</td>
</tr>
<tr>
<td>PCR for toxin B</td>
<td>≥90</td>
<td>≥96</td>
</tr>
</tbody>
</table>

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

Since publication of the Society for Healthcare Epidemiology of America position paper on *Clostridium difficile* infection in 1995, significant changes have occurred in the epidemiology and treatment of this infection. *C. difficile* remains the most important cause of healthcare-associated diarrhea and is increasingly important as a community pathogen. A more virulent strain of *C. difficile* has been identified and has been responsible for more-severe cases of disease worldwide. Data reporting the decreased effectiveness of metronidazole in the treatment of severe disease have been published. Despite the increasing quantity of data available, areas of controversy still exist. This guideline updates recommendations regarding epidemiology, diagnosis, treatment, and infection control and environmental management.

*Infect Control Hosp Epidemiol* 2010; 31(5):431-455
CDI Treatment Guidelines
General Principles

• Discontinue inciting antibiotic(s) as soon as possible (A-II)
• If severe CDI is suspected, begin empiric treatment as soon as possible (C-III)
• Avoid anti-peristaltic agents (C-III)

SHEA/IDSA Guidelines, Infect Control Hosp Epidemiol 2010
Concurrent Antibiotics and Response To Treatment for *C. difficile* Infection

Table 2. Effect of Concomitant Antibiotic (CA) Therapy During Treatment and/or Follow-up Periods

<table>
<thead>
<tr>
<th>Endpoint study period</th>
<th>No CA</th>
<th>≥1 CA</th>
<th>Difference, % (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical cure (n = 999)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment (days 1–10)</td>
<td>92.57 (747/807)</td>
<td>84.38 (162/192)</td>
<td>8.19 (2.98–13.89)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Recurrence (n = 794)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment (days 1–10)</td>
<td>17.88 (113/660)</td>
<td>23.88 (32/134)</td>
<td>−6.00 (−14.04 to 1.46)</td>
<td>.11</td>
</tr>
<tr>
<td>Follow-up (days 11–40)</td>
<td>17.74 (113/665)</td>
<td>24.81 (32/129)</td>
<td>−7.06 (−15.3 to 0.60)</td>
<td>.06</td>
</tr>
<tr>
<td>At any time (days 1–40)</td>
<td>17.57 (107/609)</td>
<td>23.24 (43/185)</td>
<td>−5.67 (−12.63 to 0.92)</td>
<td>.08</td>
</tr>
<tr>
<td><strong>Global cure (n = 999)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At any time (days 1–40)</td>
<td>74.72 (541/724)</td>
<td>65.82 (181/275)</td>
<td>8.91 (2.54–15.37)</td>
<td>.005</td>
</tr>
</tbody>
</table>

**NOTE.** Data are % (proportion) of subjects unless otherwise specified.
Vancomycin or Metronidazole?
Vancomycin vs Metronidazole (early studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>Antibiotic</th>
<th>No. patients</th>
<th>Initial cure (%)</th>
<th>Recurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vanco</td>
<td>52</td>
<td>100</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Metro</td>
<td>42</td>
<td>95</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>Vanco</td>
<td>31</td>
<td>94</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Metro</td>
<td>31</td>
<td>94</td>
<td>16</td>
</tr>
</tbody>
</table>

Efficacy of Vancomycin and Metronidazole for Treatment of *C. difficile* Infection

- Zar, Clin Infect Dis 2007
- Tolevamer studies (Louie, ICAAC, Washington, 2007; Bouza, ESCMID, Barcelona, Spain, 2008)
C. difficile Treatment Response Rates

**Figure 3.** Response Rates to Vancomycin and Metronidazole Therapy, According to the Severity of C. difficile Infection.

Zar, Clin Infect Dis 2007
Criteria for Severe *C. difficile* Infection

- Pseudomembranous colitis
- Treatment in an ICU
- Any two of:
  - Age > 60 yrs
  - Temp > 38.3°C
  - WBC > 15,000
  - Albumin < 2.5 mg/dL

Zar, Clin Infect Dis 2007
C. difficile Treatment

- Treatment guidelines stratified:
  - first episode or recurrence
  - disease severity

SHEA/IDSA Guidelines, Infect Control Hosp Epidemiol 2010
C. difficile Infection (CDI) Definitions

- Mild-Moderate CDI
- Severe CDI
  - WBC $\geq 15,000$ mm$^3$ or rising
  - creatinine $> 50\%$ higher than before
- Severe complicated CDI
  - criteria as above plus hypotension, ileus, perforation, toxic megacolon

Cohen, Infect Control Hosp Epidemiol 2010
## CDI Treatment Guidelines

### First Episode

<table>
<thead>
<tr>
<th>CDI</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st episode, mild-moderate</td>
<td>metronidazole 500 mg PO tid X 10-14 days</td>
</tr>
<tr>
<td>1st episode, severe</td>
<td>vancomycin 125 mg PO qid X 10-14 days</td>
</tr>
</tbody>
</table>

Cohen, Infect Control Hosp Epidemiol 2010
<table>
<thead>
<tr>
<th>CDI</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st episode, severe, complicated</td>
<td>vancomycin 500 mg PO qid + IV metronidazole ± vancomycin rectal instillation</td>
</tr>
</tbody>
</table>

Cohen, Infect Control Hosp Epidemiol 2010
In severe CDI, addition of metronidazole to vancomycin had no benefit.
Severe, Complicated CDI

- Surgery (colectomy) may be life-saving
- Consider colectomy if toxic megacolon, colonic perforation, septic shock
- Serum lactate >5 mmol/L, postoperative mortality > 75%

Surgical Management of Severe CDI

Diverting loop ileostomy with colonic lavage may be an alternative to colectomy

Neal, Ann Surg 2011
# CDI Treatment Guidelines

## Recurrent Disease

<table>
<thead>
<tr>
<th>CDI</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; recurrence</td>
<td>same as for initial episode</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; recurrence</td>
<td>vancomycin, pulsed/tapered</td>
</tr>
</tbody>
</table>

Cohen, Infect Control Hosp Epidemiol 2010
Treatment of Recurrent CDI

- “Tapered” vancomycin: 500 mg qid X 14 days and then slowly tapered over 6-12 wks
- “Pulsed” vancomycin: 500 mg qid X 14 days and then 500 mg very 2-3 days X 6-12 wks (± subsequent taper)

McFarland, Am J Gastroenterol 2002
Other Antimicrobial Agents for the Treatment of CDI

• teicoplanin, fusidic acid, bacitracin have all had equal efficacy to Vanco/Metronidazole in small RCTs (equal response to treatment and recurrence rates)

McFarland, J Med Microbiol 2005
What’s new for the treatment of *C. difficile* infection?
New Treatment Strategies for *C. difficile*

- new drugs
- immune modulation
- non-toxigenic *C. difficile*
- restoration of fecal microbiota
Fidaxomicin (Dificid™)

- macrocyclic antibiotic
- inhibits RNA synthesis
- inhibits *C. difficile* sporulation and toxin production
- minimal absorption; fecal concentrations >MIC$_{90}$ (0.125 μg/ml)
- usual dose: 200 mg. BID
Fidaxomicin versus vancomycin for infection with 
Clostridium difficile in Europe, Canada, and the USA: 
a double-blind, non-inferiority, randomised controlled trial

Olivier A Cornely, Derek V Crook, Roberto Espósito, André Pradier, Michael S Somers, Karl Weiss, Pamela Sears, Sherwood Gorbatch, for the OPT-80-004 Clinical Study Group

Summary

Background: Infection with Clostridium difficile is the primary infective cause of antibiotic-associated diarrhoea. We aimed to compare efficacy and safety of fidaxomicin and vancomycin to treat patients with C difficile infection in Europe, Canada, and the USA.

Methods: In this multicentre, double-blind, randomised, non-inferiority trial, we enrolled patients from 45 sites in Europe and 41 sites in the USA and Canada between April 19, 2007, and Dec 11, 2009. Eligible patients were aged 16 years or older with acute, toxin-positive C difficile infection. Patients were randomly allocated (1:1) to receive oral fidaxomicin (200 mg every 12 h) or oral vancomycin (125 mg every 6 h) for 10 days. The primary endpoint was clinical cure, defined as resolution of diarrhoea and no further need for treatment. An interactive voice-response system and computer-generated randomisation scheme gave a randomisation number and medication kit for each participant. Patients and investigators were masked to treatment allocation. Non-inferiority was prespecified with a margin of 10%. Modified intention-to-treat and per-protocol populations were analysed. This study is registered with ClinicalTrials.gov, number NCT00468728.

Findings: Of 535 patients enrolled, 270 were assigned fidaxomicin and 265 vancomycin. After 26 patients were excluded, 509 were included in the modified intention-to-treat (mITT) population. 193 (91·7%) of 216 patients in the per-protocol population given fidaxomicin achieved clinical cure, compared with 213 (90·6%) of 235 given vancomycin, meeting the criterion for non-inferiority (one-sided 97·5% CI 4·3%). Non-inferiority was also shown for clinical cure in the mITT population, with 221 (87·7%) of 252 patients given fidaxomicin and 225 (86·8%) of 257 given vancomycin cured (one-sided 97·5% CI 4·3%). In most subgroup analyses of the primary endpoint in the mITT population, outcomes in the two treatment groups did not differ significantly; although patients receiving concomitant antibiotics for other infections had a higher cure rate with fidaxomicin (46 [90·2%] of 51) than with vancomycin (33 [73·9%] of 45; p=0·031). Occurrence of treatment-emergent adverse events did not differ between groups. 20 (7·6%) of 264 patients given at least one dose of fidaxomicin and 17 (6·5%) of 260 given vancomycin died.

Interpretation: Fidaxomicin could be an alternative treatment for infection with C difficile, with similar efficacy and safety to vancomycin.

From the University of Calgary, Calgary, AB, Canada (T.J.L.); McGill University (M.A.M.) and the University of Montreal (K.W.) — both in Montreal; the University of Chicago, Chicago (K.M.M.); Wellstar Infectious Disease, Marietta, GA (R.L.); Tufts Medical Center, Boston (P.C., S.C.); and Optimer Pharmaceuticals, San Diego, CA (S.C., P.S., Y.K.S.). Address reprint requests to Dr Louie at the Division of Infectious Diseases, Departments of Medicine and Microbiology and Infectious Diseases, University of Calgary, Foothills Hospital, 1403 29 St NW, Calgary, AB T2N 4N1, Canada, or at thomas_louie@albertahealthservices.ca.

**ABSTRACT**

**BACKGROUND**

Clostridium difficile infection is a serious diarrheal illness associated with substantial morbidity and mortality. Patients generally have a response to oral vancomycin or metronidazole; however, the rate of recurrence is high. This phase 3 clinical trial compared the efficacy and safety of fidaxomicin with those of vancomycin in treating C difficile infection.

**METHODS**

Adults with acute symptoms of C difficile infection and a positive result on a stool toxin test were eligible for study entry. We randomly assigned patients to receive fidaxomicin (200 mg twice daily) or vancomycin (125 mg four times daily) orally for 10 days. The primary end point was clinical cure (resolution of symptoms and no need for further therapy for C difficile infection as of the second day after the end of the course of therapy). The secondary end points were recurrence of C difficile infection (diarrhea and a positive result on a stool toxin test within 4 weeks after treatment) and global cure (i.e., cure with no recurrence).

**RESULTS**

A total of 629 patients were enrolled, of whom 548 (87.1%) could be evaluated for the per-protocol analysis. The rates of clinical cure with fidaxomicin were noninferior to those with vancomycin in both the modified intention-to-treat analysis (88.2% with fidaxomicin and 85.8% with vancomycin) and the per-protocol analysis (92.1% with fidaxomicin and 88.9% with vancomycin). Fidaxomicin and vancomycin were equally well tolerated, with no significant differences observed in the incidence of adverse events.
Fidaxomicin vs Vancomycin for *C. difficile* Infection

- 2 large international double-blind RCTs
- fidaxomicin and vancomycin had similar cure rates (88% vs 86%)
- lower recurrence rates with fidaxomicin (15% vs 25%, esp. non-NAP-1 strains; $P=0.005$)

Figure 2. Rates of Primary and Secondary End Points.
## Fidaxomicin vs Vancomycin: Sustained Clinical Response

<table>
<thead>
<tr>
<th>Drug</th>
<th>Response rates (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>End of treatment</td>
<td>25 days after end of treatment</td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>86</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Fidaxomicin</td>
<td>88</td>
<td>71*</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.001*  
Response to Therapy and Recurrence Rates in Patients with Epidemic (BI) *C. difficile*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Vancomycin (n=363)</th>
<th>Fidaxomicin (n=356)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>REA Group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BI (NAP1)</td>
<td>127 (35)</td>
<td>120 (34)</td>
</tr>
<tr>
<td>Other</td>
<td>236 (65)</td>
<td>236 (66)</td>
</tr>
<tr>
<td><strong>Cure rate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BI (NAP1)</td>
<td>109 (86)</td>
<td>105 (88)</td>
</tr>
<tr>
<td>Other</td>
<td>220 (93)*</td>
<td>225 (95)*</td>
</tr>
<tr>
<td><strong>Recurrence rate (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>99 (25)</td>
<td>51 (13)*</td>
</tr>
<tr>
<td>BI (NAP1)</td>
<td>30 (31)</td>
<td>21 (23)</td>
</tr>
<tr>
<td>Other</td>
<td>69 (25)</td>
<td>30 (13)*</td>
</tr>
</tbody>
</table>

Petrella, Clin Infect Dis 2012

* P < 0.001
Fidaxomicin vs Vancomycin for *C. difficile* Infection

- subset analysis suggests fidaxomicin more effective than vancomycin in patients taking concurrent antibiotics (Mullane, Clin Infect Dis 2011)

- subset analysis suggests in patients with a 1st recurrence, fidaxomicin had similar clinical response as vancomycin, but was superior in preventing another recurrence within 28 days (Cornely, Clin Infect Dis 2012)
Why Might Fidaxomicin Reduce Rates of Recurrent CDI?

- Fidaxomicin preserves normal intestinal bacterial flora\(^1\)
- Fidaxomicin inhibits *C. difficile* sporulation\(^2\)

\(^1\)Louie, Clin Infect Dis 2012; \(^2\)Babakhani, Clin Infect Dis 2012
Other “New” Drugs for the Treatment of CDI

• **Rifamixin**: in a series of 8 patients with recurrent CDI, Vanco followed by rifamixin effective *(Johnson, Clin Infect Dis 2007)*

• **Nitazoxanide**: in a small RCT, equivalent to metronidazole *(Musher, Clin Infect Dis 2006)*

• **Tigecycline**: effective in a small series of patients with severe refractory CDI *(Herpers, Clin Infect Dis 2009)*
Immune Modulation as Treatment for *C. difficile* Infection

- IVIG
- Anti-toxin monoclonal antibodies
- Vaccine (toxoid)
IVIG for Treatment of *C. difficile* Infection

- anecdotal reports, case series in patients with severe or recurrent CDI
- some studies show benefit, but others do not

Addition of human monoclonal antibodies against toxin A & toxin B to standard therapy reduced risk of recurrence (7% vs 25%; P<0.001) in phase II clinical trial

Lowy, N Engl J Med 2010
Other Approaches for *C. difficile* Treatment

- **CamSA**
  (bile salt analog, inhibits *C. difficile* sporulation)

- **Non-toxigenic *C. difficile***

- **Fecal transplant**
  (“the only time you should take crap from a spouse”)

Summary

• Treatment of CDI with metronidazole or vancomycin should be based on disease severity.
• Fidaxomicin has equivalent response rate to vancomycin, but is associated with fewer recurrent infections.
• Other treatment strategies are being investigated.
The End