Clostridium difficile Infection (CDI):
Discovering the need for new treatment algorithms and care pathways

APRIL 4, 2013
Overview of Potential Treatment Options for CDI
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George G. Zhanel, PhD, FCCP

Professor - Department of Medical Microbiology and Infectious Diseases, Faculty of Medicine, University of Manitoba

Director, Canadian Antimicrobial Resistance Alliance (CARA, www.can-r.ca), Winnipeg, MB
Overview of Potential Treatment Options for CDI

George G. Zhanel
(Microbiologist/Pharmacologist)

Professor: Department of Medical Microbiology/Infectious Diseases
Faculty of Medicine, University of Manitoba and
Research Director: Canadian Antimicrobial Resistance Alliance (CARA),
www.can-r.ca, Winnipeg, Canada
<table>
<thead>
<tr>
<th><strong>In the past 2 years I have been an employee of:</strong></th>
<th>University of Manitoba/Health Sciences Center</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In the past 2 years I have been a consultant of:</strong></td>
<td>NA</td>
</tr>
<tr>
<td><strong>In the past 2 years I have held investments in the following pharmaceutical organizations, medical devices companies or communications firms:</strong></td>
<td>NA</td>
</tr>
<tr>
<td><strong>In the past 2 years I have been a member of the Scientific advisory board of:</strong></td>
<td>NA</td>
</tr>
<tr>
<td><strong>In the past 2 years I have been a speaker for:</strong></td>
<td>Astellas, Cubist, Merck, Optimer, Pfizer</td>
</tr>
<tr>
<td><strong>In the past 2 years I have received research support (grants) from:</strong></td>
<td>Abbott, Achaogen, Affinimum, Astellas, AstraZeneca, Bayer, Cerexa, Cubist, Forest, Merck, Optimer, Pfizer, Sunovion, The Medicines Company, Theravance, Triton, Trius</td>
</tr>
<tr>
<td><strong>In the past 2 years I have received honoraria from:</strong></td>
<td>Astellas, Cubist, Merck, Optimer, Pfizer</td>
</tr>
<tr>
<td><strong>I agree to disclose approved and non-approved indications for medications in this presentation:</strong></td>
<td>YES / NO…YES</td>
</tr>
<tr>
<td><strong>I agree to use generic names of medications in this presentation:</strong></td>
<td>YES / NO…YES</td>
</tr>
</tbody>
</table>

There are no relationships to disclose ☑️
Objectives

1. Compare the current treatment recommendations for CDI
2. Contrast vancomycin with fidaxomicin for the treatment of CDI
3. List the advantages and disadvantages of fidaxomicin in the treatment of CDI
Canadian Antimicrobial Resistance Alliance (CARA)

Antimicrobial Resistant Infections

- Surveillance/epidemiology
- Rapid Diagnostics
- Mechanisms
- Treatment/Prevention

Patient outcomes
# SHEA Clostridium difficile Guidelines 2010: IDSA

<table>
<thead>
<tr>
<th>Clinical Definition</th>
<th>Clinical Data</th>
<th>Rec Treatment</th>
<th>Rec Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial episode (mild-mod)</td>
<td>Leukocytosis (WBC ≤15,000) Scr &lt; 1.5x baseline</td>
<td>Metronidazole 500mg TID PO 10-14days</td>
<td>A-I</td>
</tr>
<tr>
<td>Initial episode (severe)</td>
<td>Leukocytosis (WBC ≥15,000) Scr ≥ 1.5x baseline</td>
<td>Vancomycin 125mg QID PO 10-14days</td>
<td>B-I</td>
</tr>
</tbody>
</table>

# SHEA *Clostridium difficile* Guidelines 2010: IDSA

<table>
<thead>
<tr>
<th>Clinical Definition</th>
<th>Clinical Data</th>
<th>Rec Treatment</th>
<th>Rec Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial episode (severe, complicated)</td>
<td>Hypotension or shock, ileus, megacolon</td>
<td>Vancomycin 500mg QID PO/NG +/- Metronidazole 500mg Q8H IV</td>
<td>C-III</td>
</tr>
<tr>
<td>First recurrence</td>
<td></td>
<td>Same as initial episode (ie. metronidazole)</td>
<td>A-II</td>
</tr>
<tr>
<td>Second recurrence</td>
<td></td>
<td>Vancomycin taper or pulsed regimen</td>
<td>B-III</td>
</tr>
</tbody>
</table>

Potential *Clostridium difficile* Treatments

**Metronidazole**

- effective in mild-mod CDI
- very low fecal concentrations
- reports of increased failure rates and slow response
- inferior to vancomycin in severe CDI

Venugopal and Johnson CID 2012;55 (Suppl 2):71-76.
Potential *Clostridium difficile* Treatments

**Vancomycin**

- the gold standard comparator in clinical trials
- for multiple recurrences used as taper/pulsed regimen
- many limitations (effects on flora, VRE selection, dosing etc)

Venugopal and Johnson CID 2012;55 (Suppl 2):71-76.
Potential *Clostridium difficile* Treatments

- Metronidazole
- Vancomycin

- Nitazoxanide (not approved for CDI, * special access)
- Rifaximin (not approved for CDI, * special access)
- Tigecycline (not approved for CDI)
- Bacitracin (not approved for CDI, use the IV)
- Fusidic acid (not approved for CDI, *special access)
- Teicoplanin (not approved for CDI, *special access)
- Probiotics
- Resins (not approved for CDI)
- IVIG (not approved for CDI)
- Fecal transplant
- Fidaxomicin

Venugopal and Johnson CID 2012;55 (Suppl 2):71-76.
Fidaxomicin Review

1. Review non-Clinical Trial and Clinical Trial data with fidaxomicin
   - Chemistry
   - Mechanism of action/resistance
   - Microbiology
   - PK/PD
   - Data on:
     - impact on normal flora
     - Inhibiting spore formation
     - Inhibiting toxin expression
     - selection of VRE and Candida spp.

2. Clinical trial data
Fidaxomicin: a new macrocyclic antibacterial

• First in a new class of antibiotics called “macrocycles”
  • Fermentation product of *Dactylosporangium aurantiacum*
  • 18 membered ring

• Health Canada approval
  June 07, 2012

Johnson and Wilcox. JAC 2012;67:2788-2792.
Fidaxomicin Mechanism of Action

- Inhibits transcription by bacterial RNA polymerase
- MOA distinct from rifamycins
- Not cross-resistant with rifamycins
- Rapid resistance should not occur

## Activity versus *Clostridium difficile* (MIC ug/ml, n= 208)

<table>
<thead>
<tr>
<th></th>
<th>≤ 0.06</th>
<th>0.12</th>
<th>0.25</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fidaxomicin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>73</td>
<td>65</td>
<td>51</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vancomycin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>120</td>
<td>81</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td><strong>Metronidazole</strong></td>
<td>25</td>
<td>102</td>
<td>67</td>
<td>13</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Karłowsky and Zhanel. AAC 2008;52:4163-4165.
Fidaxomicin is Bactericidal in Vitro

- Bactericidal against *C. difficile* in vitro
  - NAP1/027/BI (4x MIC ≥ 3 log_{10} in 48hrs)
  - Killing > vancomycin
  - Bactericidal vs. lab generated mutant with reduced susceptibility
- Long post-antibiotic effect vs *C. difficile*


Johnson and Wilcox. JAC 2012;67:2788-2792.
Fidaxomicin is Bactericidal in Vivo

Fidaxomicin 200 mg bid vs Vanco 125 mg QID

Louie et al. AAC 2009;53:261-263.
Fidaxomicin-Microbiology

- Very active versus most Clostridia spp (not C. coccoides or C. leptum), including C. difficile
- Poor activity (MIC > 64ug/ml) versus Gram-negative bacilli
  - aerobes/anaerobes
  - Enterobacteriaceae
  - Bacteroides spp., Bifidobacterium spp., Prevotella spp., Veillonella spp., Fusobacterium spp.)

Johnson and Wilcox. JAC 2012;67:2788-2792.
Fidaxomicin Pharmacokinetics and Pharmacodynamics

Pharmacokinetics:
- Minimal systemic absorption
  - 18.0-56.4 ng/mL plasma (36.2-108ng/ml OP-1118)
  - High fecal concentrations (~400-4000 ug/g range)
  - 92% of dose recovered in stool
  - <1% of dose recovered in urine as OP-1118

Pharmacodynamics:
- Acts locally in the GI tract on *C. difficile*
- Time dependent killing
- Fecal conc / MIC ~3000

Sears et al. CID 2012;55 (Suppl 2):116-120.
# Pharmacokinetics of Fidaxomicin and OP-1118 (Patients with CDI)

<table>
<thead>
<tr>
<th>Fidaxomicin Dosage (mg/day)</th>
<th>No. subjects</th>
<th>Fidaxomicin Mean Fecal Conc (ug/g)</th>
<th>OPT-118 Mean Fecal Conc (ug/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>11</td>
<td>256 +/- 136</td>
<td>393 +/- 260</td>
</tr>
<tr>
<td>200</td>
<td>9</td>
<td>442 +/- 238</td>
<td>430 +/- 263</td>
</tr>
<tr>
<td>400</td>
<td>13</td>
<td>1433 +/- 975</td>
<td>760 +/- 373</td>
</tr>
</tbody>
</table>

Fidaxomicin and OP-1118 Activity (MIC ug/ml) versus Clostridium difficile (n=135)

Resolution of diarrhea by Day 10 was achieved in 71%, 80%, and 94% of patients in the 100 mg/day, 200 mg/day, and 400 mg/day dosing groups.

There were no treatment failures in the 400 mg/day dosing group.

Clinical recurrence within 6 weeks after treatment occurred in only 2 patients: 1 in the 100 mg/day group and 1 in the 400 mg/day group.

**TABLE 3. Rates of clinical cure and recurrence in the population treated per protocol**

<table>
<thead>
<tr>
<th>Parameter of outcome</th>
<th>100 mg of OPT-80/day</th>
<th>200 mg of OPT-80/day</th>
<th>400 mg of OPT-80/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>14 (100)</td>
<td>15 (100)</td>
<td>16 (100)</td>
</tr>
<tr>
<td>Clinical cure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea resolution by day 10</td>
<td>10 (71)</td>
<td>12 (80)</td>
<td>15 (94)</td>
</tr>
<tr>
<td>Diarrhea resolves after day 10 with no additional treatment</td>
<td>2 (14)</td>
<td>1 (7)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Clinical failure (requiring change of therapy)</td>
<td>2 (14)</td>
<td>2 (13)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Clinical recurrence</td>
<td>1 (8.3)</td>
<td>0 (0)</td>
<td>1 (6.3)</td>
</tr>
</tbody>
</table>

*Recurrence of toxin-positive diarrhea within 6 weeks after treatment, evaluated in patients who were clinical successes.
Fidaxomicin Phase 3 Clinical Trials: (vs. Vancomycin for C. difficile)

TWO PHASE 3, RANDOMIZED, DOUBLE-BLIND, NON-INFERIORITY STUDIES OF DIFICID® (fidaxomicin) (N=542) VERSUS VANCOMYCIN (N=563)¹

**ENROLLED PATIENTS¹**
- CII defined by >3 unformed bowel movements (UBM) in the 24 hours before randomization and presence of either C. difficile toxin A or B in the stool within 48 hours of randomization
- Aged ≥ 18 years
- No more than 24 hours of pretreatment with vancomycin or metronidazole
- No prior CII history or only one prior CII episode in the past 3 months

**EXCLUDED PATIENTS¹**
- Subjects with life-threatening/fulminant infection, hypotension, septic shock, peritoneal signs, significant dehydration, or toxic megacolon

**RANDOMIZATION**
- DIFICID 200 mg twice daily¹
- vancomycin 125 mg four times daily¹

**END OF TREATMENT**
- CLINICAL RESPONSE at the end of 10-day treatment
  - Primary endpoint; Non-Inferiority analysis

**END OF FOLLOW-UP**
- SUSTAINED CLINICAL RESPONSE at 30-day follow-up
  - Secondary endpoint; Superiority analysis

Renal impairment was defined as estimated creatinine clearance of <79 ml/min.¹⁹

CDI severity was defined as: mild (4 to 5 UBM per day or white blood cell [WBC] < 12,000/mm³), moderate (6 to 9 UBM per day or WBC of 12,001-15,000/mm³), or severe (≥ 10 UBM per day or WBC > 15,001/mm³).¹⁵

- 16% WERE PRESENTING WITH FIRST CDI RECURRENCE
- 33% MODERATE CDI
- 50% ≥ 65 YEARS
- 48% RENAL IMPAIRMENT
- 29% CONCOMITANT SYSTEMIC ANTIBIOTIC THERAPY
- 36% BI ISOLATES
Significant Canadian participation in Fidaxomicin clinical trial program

- 406 Canadians enrolled in trial [54% QC]
- Canadian patients represented 37% of trial population
- 20 unique Canadian sites [9 QC sites]
Fidaxomicin versus Vancomycin for Clostridium difficile Infection

Thomas J. Louie, M.D., Mark A. Miller, M.D., Kathleen M. Mullane, D.O., Karl Weiss, M.D., Arnold Lentnek, M.D., Yoav Golan, M.D., Sherwood Gorbach, M.D., Pamela Sears, Ph.D., and Youe-Kong Shue, Ph.D., for the OPT-80-003 Clinical Study Group*

Fidaxomicin versus vancomycin for infection with Clostridium difficile in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial

Prof Oliver A Cornely MD, Prof Derrick W Crook MD, Prof Roberto Esposito MD, André Poirier MD, Michael S Somero MD, Prof Karl Weiss MD, Pamela Sears PhD, Prof Sherwood Gorbach MD, for the OPT-80-004 Clinical Study Group
Fidaxomicin Achieved a Comparable Clinical Response Rate at the End of a 10-Day Treatment Versus Vancomycin

Response Rate

- Trial 1: DIFICID 88.2% vs. Vancomycin 85.7%
  - Difference (95% CI): 2.6% (-2.9%, 8.0%)
  - P = NS

- Trial 2: DIFICID 87.7% vs. Vancomycin 86.7%
  - Difference (95% CI): 1.0% (-4.8%, 6.8%)
  - P = NS

* Confidence interval was using a 2-sided method recommended by Agresti and Caffo (2000) and p-value using Pearson’s chi-square test.

## Efficacy outcomes for clinical cure and recurrence rate endpoints in subpopulations at risk

<table>
<thead>
<tr>
<th>Recurrence Risk Factor</th>
<th>% Clinical Cure</th>
<th></th>
<th>% Recurrence</th>
<th></th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vanco</td>
<td>Fidaxo</td>
<td>Vanco</td>
<td>Fidaxo</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>90.1</td>
<td>91.9</td>
<td>NI</td>
<td>24.6</td>
<td>13.0</td>
</tr>
<tr>
<td>Concomitant antibiotics</td>
<td>79.4</td>
<td>90.0</td>
<td>p&lt;.05</td>
<td>29.0</td>
<td>17.0</td>
</tr>
<tr>
<td>Cancer</td>
<td>87.5</td>
<td>97.3</td>
<td>p=.06</td>
<td>30.0</td>
<td>14.1</td>
</tr>
<tr>
<td>Renal failure (CrCl&lt;30)</td>
<td>72.0</td>
<td>74.0</td>
<td>NI</td>
<td>33.0</td>
<td>15.0</td>
</tr>
<tr>
<td>Prior CDI</td>
<td>92.0</td>
<td>94.0</td>
<td>NI</td>
<td>35.5</td>
<td>19.7</td>
</tr>
<tr>
<td>Age&gt;65</td>
<td>93.0</td>
<td>94.0</td>
<td>NI</td>
<td>32.0</td>
<td>14.0</td>
</tr>
</tbody>
</table>

NI = Non-inferior
CAs were categorized by risk of contributing to the incidence or progression of CDI.

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Medium Risk</th>
<th>Low Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbapenems</td>
<td>Penicillin (β-lactamase sensitive)</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>2nd generation cephalosporin</td>
<td>Penicillin (β-lactamase resistant)</td>
<td>Cell wall synthesis inhibitor</td>
</tr>
<tr>
<td>3rd generation cephalosporin</td>
<td>Penicillin (extended spectrum, combination)</td>
<td>Glycopeptide</td>
</tr>
<tr>
<td>4th generation cephalosporin</td>
<td>1st generation cephalosporin</td>
<td>Imidazole</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>Macrolide</td>
<td>Lipopeptides</td>
</tr>
<tr>
<td>Clindamycin)</td>
<td>Monobactam</td>
<td>Nitrofuran</td>
</tr>
<tr>
<td>Penicillin</td>
<td>Streptogramin</td>
<td>Oxolidinone</td>
</tr>
<tr>
<td>(extended spectrum)</td>
<td></td>
<td>Polymyxin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rifamycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antifolate and/or sulfonamide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tetracycline</td>
</tr>
</tbody>
</table>

Vancomycin kills major components of the normal flora thought to prevent C. difficile disease.

Vancomycin
125mg QID in 10 CDI pts

Fidaxomicin
200mg BID in 10 CDI pts

Fidaxomicin Inhibits Sporulation – Comparator Drugs Do Not

- Sporulation
  - Responsible for transmission of \textit{C. difficile}, reinfection and relapse
  - Suppression may play a role in preventing disease occurrence and recurrence

- Fidaxomicin, its metabolite OP-1118 and comparator drugs vancomycin and metronidazole assessed for impact on new spore formation

Fidaxomicin Inhibits Sporulation

• Conclusion
  – Fidaxomicin and its metabolite strongly suppress spore formation
  – Fecal spore counts (CFU count/g) in patients who had received fidaxomicin were $2.3 \log_{10}$ lower at 21 to 28 days post-therapy than in those patients who had received vancomycin
  – Inhibition of sporulation may provide, in part, a mechanism by which fidaxomicin improves sustained clinical response (prevents recurrence)

Vancomycin vs. Fidaxomicin: Fecal *C. difficile* CFUs and [Toxin] in 89 pts

<table>
<thead>
<tr>
<th>Organism</th>
<th>Day 0</th>
<th>Day 4</th>
<th>Day 10</th>
<th>Day 14</th>
<th>Day 21</th>
<th>Day 28</th>
<th>Day 42</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VAN</strong></td>
<td>6.2 ± 2.6</td>
<td>2.2 ± 0.9</td>
<td>2.0 ± 0.0</td>
<td>3.1 ± 2.2</td>
<td>4.4 ± 2.6</td>
<td>3.9 ± 2.2</td>
<td>4.5 ± 2.4</td>
</tr>
<tr>
<td><strong>FDX</strong></td>
<td>5.8 ± 2.8</td>
<td>2.1 ± 0.9</td>
<td>2.6 ± 3.1</td>
<td>2.8 ± 3.1</td>
<td>4.4 ± 2.4</td>
<td>3.8 ± 2.1</td>
<td>3.1 ± 2.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Toxin B titer</th>
<th>Day 0</th>
<th>Day 4</th>
<th>Day 10</th>
<th>Day 14</th>
<th>Day 21</th>
<th>Day 28</th>
<th>Day 42</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VAN</strong></td>
<td>2800 ± 1250</td>
<td>neg</td>
<td>neg</td>
<td>(7/30)</td>
<td>(15/30)</td>
<td>(3/22)</td>
<td>(1/12)</td>
</tr>
<tr>
<td><strong>FDX</strong></td>
<td>2250 ± 600</td>
<td>neg</td>
<td>neg</td>
<td>(1/23)</td>
<td>(6/27)</td>
<td>(5/20)</td>
<td>(1/21)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>[Toxin] and (### pos/total)</th>
<th>Day 0</th>
<th>Day 4</th>
<th>Day 10</th>
<th>Day 14</th>
<th>Day 21</th>
<th>Day 28</th>
<th>Day 42</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VAN</strong></td>
<td>28% (26/94)</td>
<td>1260 ± 350</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FDX</strong></td>
<td>14% (13/91)</td>
<td>2400 ± 1400 [1 pt 16000]</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

No difference in CFUs over time, but toxin expression reduced 50%

Acquisition of VRE or Candida spp. colonization during CDI treatment (Vancomycin versus Fidaxomicin)

Candida species: vancomycin 29% (40/136) vs. fidaxomicin 19% (12/116) (p=0.03).

Conclusions - Fidaxomicin

- Novel chemistry
- Inhibits RNA polymerase (unique site)
- Bactericidal vs. *C. difficile* (including resistant strains)
- Selective activity versus *C. difficile*
- PK/PD: Very high fecal concentrations/MIC
- Versus vancomycin:
  - Minimal impact on normal flora
  - Inhibits spore formation
  - Inhibits toxin expression
  - Minimal selection of VRE and *Candida* spp.
  - Better overall sustained response
## Cost ($CDN)

<table>
<thead>
<tr>
<th></th>
<th>Vancomycin IV Slurry</th>
<th>Vancomycin Oral Tablet</th>
<th>Fidaxomicin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>125mg</td>
<td>500mg</td>
<td>125 mg</td>
</tr>
<tr>
<td></td>
<td>QID</td>
<td>QID</td>
<td>QID</td>
</tr>
<tr>
<td>10 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BC</td>
<td>$ 30.00</td>
<td>$ 196.00</td>
<td>$ 368.60</td>
</tr>
<tr>
<td>ON</td>
<td>$ 30.00</td>
<td>$ 196.00</td>
<td>$ 351.96</td>
</tr>
<tr>
<td>QC</td>
<td>$ 30.00</td>
<td>$ 196.00</td>
<td>$ 207.20</td>
</tr>
</tbody>
</table>

Based on Vancocin PM, and IDSA Guidelines

Update in Mar 2013

**Cost for Managing CDI ranges from $6176 to $15,397 per patient**