Preservation of the Gut Microflora Leading to Less Recurrence of \textit{Clostridium difficile}-associated Diarrhea (CDAD): Crappy Data or Solid Evidence?

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Learning Objectives:

1. Recognize the role of intestinal microflora in colonization resistance
2. Assess the risks of different antibiotic classes in promoting CDAD
3. Explain the mechanism behind CDAD recurrences
4. Evaluate fidaxomicin’s role in CDAD treatment
Introduction to *Clostridium difficile*-associated Diarrhea (CDAD)

I. *C. difficile* in Antibiotic-associated Diarrhea (AAD)
   A. Named “difficult clostridium” for its difficulty to isolate and grow on media
   B. In 1974, investigators noted 20% of patients receiving clindamycin developed diarrhea; of these, 50% had pseudomembranous colitis, prompting the search to find causative agent
      1. Isolated *C. difficile* from the ceca of hamsters with AAD
      2. *C. difficile* caused disease in antibiotic naïve hamsters, establishing it as causative agent
      3. Toxins from hamsters matched those found in stools of patient with AAD, linking it to the human disease → *Clostridium difficile*-associated diarrhea (CDAD)

II. Epidemiology
   A. Most common health care-related infectious diarrhea in developed countries
   B. National statistics of CDAD
      1. 117% increase in CDAD on hospital discharges based on diagnosis code from 2000 to 2005
      2. Mortality rates increased by 35%, from 5.7 to 23.7 deaths per million population from 1999 to 2004
   C. Well documented increase in incidence and severity of CDAD across North America
      1. Particularly attributed to the hypervirulent BI/NAP1/027 strain
         a. Associated with more frequent, more severe, and more recurrence of CDAD compared to previous observations
         b. Has been mainly prevalent in hospital-associated CDAD

![Figure 1: Total number of discharges from 1993-2009 with ICD-9 diagnosis code of CDAD](image)

D. Accounts for 20-30% of AAD, 50-70% of antibiotic-associated colitis, >90% of antibiotic-associated pseudomembranous colitis
E. Risk factors
   1. Exposure to agents known to alter the intestinal microflora
      a. Antimicrobials
      b. Chemotherapy agents
   2. Advanced age
      a. Diminished immune response
      b. Comorbidities
   3. Gastric acid suppression

III. Etiology, Microbiology and Pathogenesis
A. \textit{C. difficile}: anaerobic gram-positive, spore-forming, toxin-producing bacillus
   1. Spore form: resistant to heat, acid and antibiotics
   2. Vegetative form: produces toxin and susceptible to antibiotics
B. Virulence mainly due to toxins A and B
   1. Toxins internalized by intestinal epithelia cells
   2. Compromises cells’ ability to uptake nutrients and carry out vesicular transport
   3. Ultimately leads to cell apoptosis
C. Person-to-person transmission via fecal-oral route
D. Clinical presentation
   1. Symptoms of CDAD usually begin 2-3 days after colonization
      a. Mild to moderate diarrhea
      b. Fulminant and pseudomembranous colitis

IV. Diagnosis
A. Toxin assays: evidence of toxin
   1. Enzyme immunoassay (EIA)
      a. Used to be the preferred assay, but has since fallen out of favor
      b. Direct detection of both toxins A and B in stool filtrates
      c. 70-95% sensitivity, but 99% specificity
   2. Polymerase chain reaction (PCR): approved by FDA in 2009
      a. Real-time PCR assays for the toxin B encoding gene
      b. Rapid detection with high sensitivity and specificity (93-97%)
B. Organism detection assays: presence of the organism
   1. Anaerobic stool culture
      a. Rarely used for diagnosis
      b. Most sensitive, but slow turnaround time (three days)

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<table>
<thead>
<tr>
<th>Intestinal Microflora, Antimicrobials, and Colonization</th>
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</table>
I. Role of Intestinal Microflora and Colonization
A. Human colon contains >100 bacterial species with \( \sim 1 \times 10^{12} \) bacteria colonizing the intestine
B. Obligate anaerobes outnumber facultative organisms \( \sim 1000:1 \)
C. Indigenous bacteria provides “colonization resistance”
   1. Prevent access of adherence sites or niches in the mucosa
   2. Deplete nutrients
   3. Produce inhibitory substances or condition
D. Risk factors facilitating pathogen overgrowth

![Figure 2: Mechanisms promoting intestinal overgrowth of pathogens](image)

E. Antibiotics usage and CDAD

1. Nearly all antimicrobials have been associated with CDAD
2. Outbreaks linked antibiotic usage and their selective pressure for resistant strains
   a. Antibiotics most commonly associated with CDAD
      i. Clindamycin
         a) Widely use in 1970s – 1980s
            1) Severe CDAD outbreaks in the early 1990s
            2) Predominant C. difficile strains had clindamycin MIC ≥ 256 µg/mL
      ii. 2nd and 3rd generation cephalosporins
      iii. Fluoroquinolones
   3. Best for strategy for CDAD intervention is antibiotic stewardship

F. Not all antibiotics pose equal risk in altering intestinal microflora

1. Two categories of antibiotics against C. difficile in murine cecal models
   a. Antibiotics with anaerobic activity
      i. Clindamycin, ceftriaxone, piperacillin-tazobactam
   b. Antibiotics with facultative gram-negative but minimal anaerobic activity
      i. Levofloxacin, cefepime, aztreonam
c. After treatment with antibiotics, cecal content inoculated with *C. difficile*

![Figure 3: C. difficile growth at 2 h post antibiotic discontinuation](image1)

![Figure 4: C. difficile growth at 3 days post antibiotic discontinuation](image2)

d. Results identified three antimicrobial categories
   i. Minimal anaerobic and *C. difficile* activity
      a) Aztreonam
      b) Did not promote *C. difficile* growth during or post treatment
   ii. Anaerobic activity, but minimal *C. difficile* activity
      a) Ceftriaxone
      b) Promoted *C. difficile* growth during and post treatment
   iii. Anaerobic and *C. difficile* activity
      a) Piperacillin-tazobactam
      b) Inhibited *C. difficile* growth during therapy, but promoted growth post treatment

e. Implications
   i. Disruption of anaerobic intestinal microflora facilitates *C. difficile* growth
   ii. Extrapolate findings of piperacillin-tazobactam’s risk for promoting *C. difficile* growth to that of oral vancomycin
      a) Possible explanation for the mechanism of CDAD recurrence
Treatment of CDAD

I. Initial Episode\textsuperscript{8,9}
   A. Discontinue any concurrent systemic antibiotic if possible
   B. Mild or moderate
      a. WBC ≤ 15,000 cells/µL
      b. Serum creatinine < 1.5 times premorbid level
      c. Treatment: metronidazole 500 mg three times/day by mouth for 10-14 days
   C. Severe
      a. WBC ≥ 15,000 cells/µL
      b. Serum creatinine > 1.5 times premorbid level
      c. 2 of the following: age > 60, fever > 100.9°F, albumin < 2.5 mg/dL
      d. Pseudomembranes on colonoscopy
      e. Admission to the intensive care unit
      f. Treatment: vancomycin 125 mg four times /day by mouth for 10-14 days

<p>| Table 1: Antimicrobial Agents for Initial Episode\textsuperscript{11} |
|------------------------|------------------|------------------|------------------|</p>
<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>Spectrum of Activity</th>
<th>PK/PD</th>
</tr>
</thead>
</table>
| Metronidazole          | DNA breakage and inhibit protein synthesis | Anaerobic bacteria and protozoa | - Fecal conc. = 9.3 ± 7.5 µg/g  
  |                        |                  | - Bactericidal  
  |                        |                  | - Absorption: nearly complete |
| Vancomycin             | Inhibit cell wall synthesis | Gram-positive bacteria | - Fecal conc. = 1000 – 3000 µg/g  
  |                        |                  | - Bactericidal  
  |                        |                  | - Absorption: minimal |

II. Recurrent Episodes\textsuperscript{8,10}
   A. Similar recurrence rate for metronidazole and vancomycin: 19-20%\textsuperscript{24}
   B. Recurrent CDAD due to either relapse or reinfection\textsuperscript{22}
      1. Relapse: endogenous persistence of the same strain of \textit{C. difficile}
      2. Reinfections: acquisition of a new strain from exogenous source
      3. Mean time to relapse is 14.5 days post treatment
   C. Treatment strategies
      1. First recurrence: same agents based on severity
         a. May consider rifaximin chaser\textsuperscript{26-28}
            i. Rifaximin 400 mg orally 2 times daily for 14 days immediately following standard metronidazole or vancomycin
            ii. Successful at reducing recurrences in several case series studies
            iii. Potential for isolates to develop increased MIC during treatment
         b. May consider adding probiotics: \textit{Lactobacillus} or \textit{Saccharomyces boulardii}\textsuperscript{29-31}
            i. Evidence has been inconclusive on efficacy
            ii. Should be avoided in immunocompromised and critically ill patients
      2. Second recurrence: tapered and/or pulsed vancomycin regimen\textsuperscript{8}
         a. 125 mg 4 times/day for 10-14 days, 125 mg 2 times/day for a week, 125 mg once/day for a week, then 125 mg every other day for 2-8 weeks
         b. Inhibit \textit{C. difficile} growth while allowing intestinal microflora to be restored
      3. Other options for multiple recurrences
Tolevamer: On the Right Track

I. Tolevamer: a soluble, anionic polymer that noncovalently binds *C. difficile* toxin A and B

A. Mechanism of action: toxin neutralization rather than antibacterial activity

| Table 2: Louie et al.\(^{33}\) |
|------------------|-------------------------------------------------|
| **Objective**    | Compare the safety, tolerability, and efficacy of tolevamer and vancomycin for the treatment of mild to moderate CDAD |
| **Design**       | Phase II multicenter, prospective, randomized, double-blind, double-dummy, active-controlled |
| **Patient Population** |  \(\geq 18\) y/o with confirmed primary or recurrent (required to have a positive *C. difficile* toxin assay within 7 days before enrollment) or presumed recurrent mild to moderate CDAD (positive toxin assay within 7 days before enrollment or 24 h after enrollment); \(\geq 3\) loose or watery stools 24-h before enrollment |
|                  | Exclusions: pregnancy, severe CDAD (\(\geq 12\) stools; severe, persistent abdominal pain or distension); \(K^- < 2.5\) mEq/L; \(K^+ < 3.0\) mEq/L and history of cardiac ischemia, CHF, or LVH; and \(K^- < 3.5\) mEq/L and history of cardiac arrhythmias or taking digoxin; patients who received \(\geq 48\) h of vancomycin or metronidazole for current CDAD episode |
| **Outcomes**     | Primary: time to resolution of diarrhea (TTROD), CDAD resolution (first day of 2 consecutive days with any number of hard or formed stools or \(\leq 2\) loose or watery stools) |
|                  | Secondary: number of stools, average stool consistency (score: hard, 1; formed, 2; loose, 3; and watery, 4), abdominal discomfort, and recurrence (after resolution, \(\geq 3\) loose or watery stools in 24-h with positive toxin assay or presence of pseudomembranes and no other likely etiology) |
| **Methods**      | Randomized to oral tolevamer 3 g (1 g three times/day) or 6 g (2 g three times/day) for 14 days, or oral vancomycin 500 mg (125 mg four times/day) for 10 days |
|                  | Patients requiring continual CDAD antibiotic could be extended to additional 14 days for tolevamer, but not vancomycin; maximum therapeutic duration was 28 days |
|                  | 6-8 week follow-up period |
|                  | Study personnel recorded daily stool counts and average consistency (days 1-14) via in-patient interviews and out-patient phone interviews |
|                  | Assessed adverse event and concomitant medications daily, serum K⁺ level at least every 4 days |
| **Statistics**   | Intent-to-treat (ITT): all randomized patients who received at least 1 dose of study drug |
|                  | Per protocol (PP): patients not excluded based on prospectively defined criteria or major protocol violations |
|                  | Power analysis: 78 patients/group to detect noninferiority with 80% power based on PP |
|                  | Noninferiority: if median TTROD is statistically significantly \(< 2\) days longer in tolevamer 6 g group compared to vancomycin 500 mg group |
|                  | Chow test also used to assess noninferiority |
|                  | Baseline characteristics and demographics: 2-way analysis of variance and Cochran-Mantel-Haenszel (CMH) |
|                  | P value calculated using CMH, log-rank test compared times to event, and Wald \(x^2\) assessed |
**Conclusions**

**Implications**

**trial34,35**

**Phase**

**Unpublished**

**Authors’**

**Results**

<table>
<thead>
<tr>
<th></th>
<th>Tolevamer 3-g (n = 72)</th>
<th>Tolevamer 6 g (n = 70)</th>
<th>Vancomycin 500 mg (n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDAD resolution no. (%)</td>
<td>48 (67)</td>
<td>58 (83)</td>
<td>73 (91)</td>
</tr>
<tr>
<td>TTROD, median days [95%CI]</td>
<td>4.0 [2.0-6.0]</td>
<td>2.5 [2.0-3.0]</td>
<td>2.0 [1.0-3.0]</td>
</tr>
<tr>
<td>P value vs. vancomycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>By log-rank test in TTROD</td>
<td>&lt;0.01</td>
<td>0.53</td>
<td>–</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence proportion (%)</td>
<td>11/48 (23)</td>
<td>6/58 (10)</td>
<td>14/73 (19)</td>
</tr>
<tr>
<td>P value</td>
<td>0.61</td>
<td>0.19</td>
<td>–</td>
</tr>
<tr>
<td>Recurrence (Post-hoc adjust.)</td>
<td>7/44 (16)</td>
<td>4/56 (7)</td>
<td>14/73</td>
</tr>
<tr>
<td>P value</td>
<td>0.62</td>
<td>0.05</td>
<td>–</td>
</tr>
</tbody>
</table>

- PP: tolevamer 6 g was noninferior to vancomycin CDAD resolution (P=0.53 by log-rank test)
- ITT: noninferiority not established between tolevamer 6 g vs. vancomycin
- Post-hoc adjustment: reclassified patients with recurrence during treatment as treatment failure
- Tolevamer had significantly worse secondary outcomes vs. vancomycin except for recurrence
- Hypokalemia was more common in tolevamer 6 g vs. vancomycin (23% vs. 7%)

**Authors’ Conclusions**

- Tolevamer 6 g no less effective than vancomycin in TTROD and associated with a lower recurrence rate

**Unpublished Phase III trial34,35**

- Tolevamer was inferior to vancomycin and metronidazole in initial CDAD treatment
  - Never brought to the market

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Tolevamer (n=266)</th>
<th>Vancomycin (n=134)</th>
<th>Metronidazole (n=143)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical success (%)</td>
<td>46</td>
<td>81</td>
<td>72</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Recurrence rate (%)</td>
<td>3</td>
<td>23</td>
<td>27</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

**Implications**

- Mechanism of action causes minimal intestinal microflora alteration
  - Allows restoration of microflora during and post therapy
  - Probable mechanism for decreased recurrence rate
- No statistical significance in recurrence in phase II may be due to under power of study
- Need at least some antimicrobial activity against *C. difficile* for initial treatment, but less alteration to the intestinal microflora leads to less recurrence
Fidaxomicin: Road Towards a More Complete Management of CDAD

I. Fidaxomicin (OPT-80)
   A. 18-membered macrocyclic antibiotic
   B. Bactericidal, targets gram-positive bacteria and selected anaerobes
   C. Absorption: minimal with fecal conc. = 1225 ± 75 µg/g

II. Fidaxomicin In vitro Activities\textsuperscript{36,37}
   A. In vitro studies: fidaxomicin against indigenous bowel bacteria

<table>
<thead>
<tr>
<th>Organism</th>
<th>Drug</th>
<th>MIC\textsubscript{50} (µg/mL)</th>
<th>MIC\textsubscript{90} (µg/mL)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Clostridium difficile</em></td>
<td>Fidaxomicin</td>
<td>0.12</td>
<td>0.25</td>
<td>0.06 – 2</td>
</tr>
<tr>
<td></td>
<td>Metronidazole</td>
<td>0.25</td>
<td>0.5</td>
<td>0.25 – 1</td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
<td>1</td>
<td>2</td>
<td>0.5 – 4</td>
</tr>
<tr>
<td><em>Bacteroids</em> spp.</td>
<td>Fidaxomicin</td>
<td>256</td>
<td>&gt;1024</td>
<td>256 – &gt;1024</td>
</tr>
<tr>
<td></td>
<td>Metronidazole</td>
<td>1</td>
<td>4</td>
<td>0.25 – 16</td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
<td>64</td>
<td>128</td>
<td>16 – 256</td>
</tr>
</tbody>
</table>

B. Both vancomycin and fidaxomicin have good activity against *C. difficile*
C. Fidaxomicin is distinctly less active against *Bacteroides* group than vancomycin

III. Fidaxomicin in Fecal Studies
   A. Fecal microbiota reflects distal human colon microbiological composition\textsuperscript{38}
   B. Louie et al.\textsuperscript{39}
      1. End points measured during and after CDAD treatment
         a. Suppression of *C. difficile* quantitative counts
         b. Changes in *Bacteroides* species during treatment
         c. Reemergence of *C. difficile* vegetative and/or spore counts after therapy
         d. Re-expression of *C. difficile* cytotoxin B after treatment
   2. Patients treated for mild to moderate CDAD:
      a. Fidaxomicin: 50 mg (n=10), 100 mg (n=8), and 200 mg (n=12) orally every 12 h for 10 days
      b. Vancomycin 125 mg orally four times daily for 10 days as standard control (n=8)
      c. Serial stool samples obtained at study entry and at days 4, 10, 14, 21, 28, and 42
   3. Results
      a. Except for one patient in fidaxomicin 100 mg group, all were clinical responders with *C. difficile* counts reduced to < 10² CFU/g of stool by day 4 through day 10
Table 4: Changes in Bacteroides Group (BG) Counts Over 10-day Treatment Period

<table>
<thead>
<tr>
<th>Treatment (no. patients)</th>
<th>Mean ± SD of log₁₀ CFU of BG count/g of stool on:</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Day 10</td>
</tr>
<tr>
<td>Fidaxomicin 200 mg (n = 12)</td>
<td>6.6 ± 2.9</td>
<td>7.3 ± 3.1</td>
</tr>
<tr>
<td>Vancomycin 125 mg (n = 8)</td>
<td>7.4 ± 2.7</td>
<td>3.6 ± 1.9</td>
</tr>
</tbody>
</table>

Table 5: Reemergence of *C. difficile* Spores and toxin B in Follow-up Period (days 21 to 28)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean log₁₀ CFU spores/g of stool ± SD [95% CI]</th>
<th>P value vs. vanc</th>
<th>No. of subjects with positive toxin B</th>
<th>P value vs. vanc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fidaxomicin 200 mg</td>
<td>2.3 ± 0.9 [1.8-2.8]</td>
<td>0.04</td>
<td>0/9</td>
<td>0.03</td>
</tr>
<tr>
<td>Vancomycin 125 mg</td>
<td>3.6 ± 2.0 [2.4-4.7]</td>
<td>–</td>
<td>3/8</td>
<td>–</td>
</tr>
</tbody>
</table>

4. Implications:
   a. Both fidaxomicin and vancomycin are effective in reducing *C. difficile* count
   b. *Bacteroides spp.* as a marker for intestinal microflora
      i. Marked reduction of BG in vancomycin vs. fidaxomicin
   c. Follow-up period (days 21 to 28) in fidaxomicin
      i. Lower post treatment spore count
      ii. Infrequent re-expression of *C. difficile* toxin B
   d. Extrapolate: comparative beneficial intestinal ecology effect by fidaxomicin

C. Tannock et al.⁴⁰
1. Fidaxomicin’s impact on fecal microflora composition compared to vancomycin
2. Methods: patients treated for mild to moderate CDAD
   a. Fidaxomicin: 50 mg (n=8), 100 mg (n=7), 200 mg (n=8) orally twice daily for 10 days
   b. Vancomycin 125 mg orally four time daily for 10 days (n=8)
   c. Fecal samples from healthy subjects single sample (n=8)
   d. Fecal collections on days 0, 7, 10 and 21
   e. Fecal samples tested for the seven most commonly detect bacteria groups in human feces using oligonucleotides probes
      i. Clostridial cluster XIVa and IV, *Bacteroides-Provotella, Bifidobacterium, Atopobium*, enterobacteria, and *Enterococcaceae-Lactobacillaceae*
      ii. Groups measured as proportions to total bacterial community
3. Results:
   a. Fidaxomicin
      i. Clostridial clusters XIVa and IV increased during and after treatment
      ii. Proportion of Clostridial cluster XIVa attained similar levels as controls by day 10 (P > 0.05)
   b. Vancomycin
      i. Proportion of Clostridial clusters and *Bifidobacterium* reduced by day 10 of treatment vs. control (P < 0.05)

4. Implications
   a. Fidaxomicin minimally alters intestinal microflora relative to vancomycin
      i. Less effect on Clostridial clusters XIVa and IV and *Bifidobacteria* proportions
      ii. Gram-positive commensals are relatively unaffected
D. Phase III clinical trial: fidaxomicin vs. vancomycin

Table 6: Louie et al.\textsuperscript{41}

<table>
<thead>
<tr>
<th>Objective</th>
<th>Compare the efficacy and safety of fidaxomicin with vancomycin in CDAD treatment</th>
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</thead>
<tbody>
<tr>
<td>Design</td>
<td>Phase III multicenter, prospective, double-blind, randomized, parallel-group</td>
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<tr>
<td>Patient Population</td>
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</table>
• $>16$ y/o diagnosed with CDAD (diarrhea of $>3$ unformed stools 24-h before randomization and positive toxin A, B, or both in 48-h before randomization)  
• Exclusions: life-threatening or fulminant CDAD, toxic megacolon, previous fidaxomicin exposure, history of ulcerative colitis or Crohn’s disease, or $>1$ CDAD within 3 months prior to the study |
| Outcomes |  
• Primary: clinical cure rate  
  o Clinical cure: $\leq 3$ unformed stools for 2 consecutive days, maintenance of resolution for therapy duration and no further therapy  
  o Clinical failure: persistent diarrhea, the need for additional CDAD therapy, or both  
• Secondary: CDAD recurrence within 4 weeks after end of therapy (reappearance of $>3$ diarrhea stools/day; toxin A or B, or both; need for retreatment) and global cure (diarrhea resolution without recurrence) |
| Methods |  
• Randomized to oral fidaxomicin 200 mg every 12 h or oral vancomycin 125 mg every 6 h for 10 days  
• Stratified by 1\textsuperscript{st} episode (primary occurrence) or 2\textsuperscript{nd} episode (first recurrence)  
• Assessed patients daily for clinical cure or failure  
  o Once clinical cure met, followed for 28 days after last dose of study drug for recurrence |
| Statistics |  
• Primary: noninferiority, one-sided lower 97.5% confidence interval  
  o Demonstrated if lower boundary of confidence limit within -10% margin  
• Secondary: two-sided tests based on normal distribution, with significance level of 0.05  
• TTROD (h) analyzed with Kaplan-Meier method, Gehan-Wilcoxon test for time curves comparisons |
| Results |  
• 629 patients randomized, 596 in modified intent-to-treat (mITT), 548 in per-protocol (PP)  
• No significant differences in demographic and baseline clinical characteristics in mITT and PP: age, unformed stools/day, inpatient status, lack of response to metronidazole, treatment for CDAD in previous 24 h, previous episodes of CDAD, BI/NAP1/027 strain |

<table>
<thead>
<tr>
<th></th>
<th>mITT</th>
<th>PP</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Fidaxomicin (n=287)</td>
<td>Vancomycin (n=309)</td>
</tr>
<tr>
<td>Clinical cure [n (%)]</td>
<td>253 (88.2)</td>
<td>265 (85.8)</td>
</tr>
<tr>
<td>Secondary outcome</td>
<td>P-value</td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
<td>39/253 (15.4%)</td>
<td>67/265 (25.3%)</td>
</tr>
<tr>
<td>Global Cure [n (%)]</td>
<td>214 (74.6%)</td>
<td>198 (64.1%)</td>
</tr>
</tbody>
</table>

- Lower boundary of 97.5% CI for clinical cure rate difference was $-3.1$ in mITT and $-2.6$ in PP, showing noninferiority  
- No statistical differences in subgroup analyses of clinical cure rate  
- Subgroup analysis for rate of recurrence in fidaxomicin vs. vancomycin in PP group  
  o CA use: fidaxomicin 8/56 (14.3%) vs. vancomycin 20/65 (30.8%), $P=0.03$  
  o $>65$ y: fidaxomicin 16/85 (18.8%) vs. vancomycin 31/103 (30.1%), $P=0.08$  
  o Previous CDAD episode: fidaxomicin 6/36 (16.7%) vs. vancomycin 12/38 (31.6%), $P=0.14$  
  o Non-NAP1/BI/027: fidaxomicin 8/103 (7.8%) vs. vancomycin 27/106 (25.5%), $P < 0.001$  
- Adverse effects: no significant difference between fidaxomicin and vancomycin, no discontinuation due to intolerance to the study medications
### E. Combined data in two phase III – fidaxomicin vs. vancomycin in patients on concurrent antibiotics

Table 7: Mullane et al.42

<table>
<thead>
<tr>
<th>Objective</th>
<th>Study the effects of concomitant antibiotics (CAs) on response to fidaxomicin or vancomycin</th>
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</thead>
<tbody>
<tr>
<td>Design</td>
<td>Pooled data from 2 prospective double-blind, randomized, parallel-group, noninferiority studies</td>
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<tr>
<td><strong>Patient Population</strong></td>
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<tr>
<td>≥ 16 y/o diagnosed with first CDAD episode (see previous definition) or first CDAD recurrence within 3 months, received &lt; 24 h pretreatment with vancomycin or metronidazole, treated for at least 3 days with metronidazole without improvement</td>
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<tr>
<td>Exclusion: life-threatening or fulminant CDAD, toxic megacolon, previous fidaxomicin exposure, history of ulcerative colitis or Crohn’s disease, or &gt; 1 CDAD within 3 months before study</td>
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<tr>
<td><strong>Outcomes</strong></td>
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<tr>
<td>Primary: clinical cure defined as resolution of diarrhea (≤ 3 unformed stools for 2 consecutive days) maintained until end of therapy or for 2 days thereafter</td>
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<td>Secondary: recurrence (reappearance of CDAD symptoms within 4 weeks after completing treatment, presence of toxin A, B, or both in stool, and need for retreatment) and global cure (clinical cure with no recurrence)</td>
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<tr>
<td><strong>Methods</strong></td>
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<tr>
<td>Randomized to oral fidaxomicin 200 mg twice daily or oral vancomycin 125 mg four times daily for 10 days</td>
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<tr>
<td>CAs were considered if received ≥ 1 oral or IV antibiotic during treatment or follow-up period</td>
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<tr>
<td>Categorized by antibiotic class and risk of contributing to progression of CDAD</td>
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<tr>
<td>Evaluable population: received ≥ 3 treatment days and considered to have clinical failure, received ≥ 8 treatment days and evaluated for cure at end-of-treatment</td>
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<tr>
<td>Evaluable for recurrence: if cured at end of treatment, had recurrent symptoms within 28 days or evaluated at a follow-up visit 28 ± 2 days following last study drug dose, and received no other antibiotics for CDAD or confounding medications</td>
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<tr>
<td><strong>Statistics</strong></td>
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<tr>
<td>Response rates for clinical cure, recurrence, and global cure: 2-sided 95% confidence interval (CI) constructed around point estimates</td>
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<tr>
<td>Outcome analysis based on CA usage duration</td>
<td></td>
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<tr>
<td>Clinical cure and TTROD based on CA used during treatment (days 1-10)</td>
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<tr>
<td>Global cure based on CA used during treatment or follow-up (days 1-40)</td>
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<tr>
<td>Recurrence rate based on CA used during treatment (days 1-10), during follow-up (days 11-40), and at any time (days 1-40)</td>
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<tr>
<td>Subgroup analysis by CA exposure and CDAD treatment: 2-sided CI constructed around differences and ( \chi^2 ) test to determine significance of differences in proportions</td>
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<tr>
<td>TTROD analysis by Kaplan-Meier analysis using log rank, Wilcoxon tests to determine significance</td>
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<tr>
<td>P &lt; 0.05 is considered significant</td>
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</tbody>
</table>
• Results are for per protocol (PP) population, all outcomes similar to intent-to-treat

Results

- 1164 subjects enrolled
  - 999 evaluable for clinical and global cure (fidaxomicin n=481, vancomycin n=518)
  - 794 evaluable for recurrence (fidaxomicin n=391, vancomycin n=403)
- Baseline characteristics similar between treatment groups
- Effect of CA regardless of CDAD treatment
  - Increased TTROD (P < 0.001) and decreased clinical cure (P < 0.001) and global cure (P = 0.005)
- High risk CA category vs. low risk and ≥ 2 vs. 1 CA classes significantly reduced clinical cure
- Effect of fidaxomicin or vancomycin treatment with or without CA

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>% (proportion) of subjects</th>
<th>Differences (95% CI)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Fidaxomicin</td>
<td>Vancomycin</td>
<td></td>
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<tr>
<td>No CA</td>
<td></td>
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<tr>
<td>Clinical cure</td>
<td>92.33 (361/391)</td>
<td>92.79 (386/416)</td>
<td>-0.46 (-4.13 to 3.19)</td>
</tr>
<tr>
<td>Recurrence: lower in fidaxomicin vs. vancomycin in all study periods</td>
<td>&lt;0.001</td>
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<tr>
<td>Global cure</td>
<td>80.8 (282/349)</td>
<td>69.1 (259/375)</td>
<td>11.7 (5.43 to 17.89)</td>
</tr>
<tr>
<td>Any CA</td>
<td></td>
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</tr>
<tr>
<td>Clinical cure</td>
<td>90.0 (81/90)</td>
<td>79.41 (81/102)</td>
<td>10.6 (.23 to 20.34)</td>
</tr>
<tr>
<td>Recurrence</td>
<td></td>
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<tr>
<td>At any time</td>
<td>16.85 (15/89)</td>
<td>29.17 (28/96)</td>
<td>-12.31 (-23.9 to -0.12)</td>
</tr>
<tr>
<td>Global cure</td>
<td>72.73 (96/32)</td>
<td>59.44 (85/143)</td>
<td>13.31 (2.11 to 24.1)</td>
</tr>
<tr>
<td>No high-risk CA</td>
<td></td>
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<tr>
<td>Clinical cure</td>
<td>92.22 (403/437)</td>
<td>91.97 (424/461)</td>
<td>0.25 (-3.32 to 3.79)</td>
</tr>
<tr>
<td>Recurrence: lower in fidaxomicin vs. vancomycin in all study periods</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global cure</td>
<td>80.79 (328/406)</td>
<td>68.26 (299/438)</td>
<td>12.52 (6.66 to 18.25)</td>
</tr>
<tr>
<td>Any high-risk CA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical cure</td>
<td>88.65 (39/44)</td>
<td>75.44 (43/57)</td>
<td>13.2 (-2.25 to 27)</td>
</tr>
<tr>
<td>Recurrence: no significant different in all study periods</td>
<td>n/s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global cure</td>
<td>66.67 (50/75)</td>
<td>56.25 (45/80)</td>
<td>10.42 (-4.83 to 25.1)</td>
</tr>
</tbody>
</table>

- Fidaxomicin vs. vancomycin in patients receiving any CA
  - Clinical cure rate significantly higher in fidaxomicin (90% vs. 79%, P=0.04)
  - Lower recurrence rate in fidaxomicin patients at any time (16% vs. 29%, P=0.048)

Authors’ Conclusions

- Compared with vancomycin, treatment with fidaxomicin appears to blunt the deleterious effects of CA on initial response and the risk of recurrence

Implications

- Patients receiving any CA may achieve higher rate of clinical cure and less recurrence with fidaxomicin compared to vancomycin
- Potential weakness: categorization of CA class risk is based on expert opinion and patients not stratified by the number of CA used
I. “Colonization Resistance”
   A. Maintained by indigenous microflora
      1. Obligate anaerobes outnumber facultative organisms

II. Disruption of the Microflora
   A. Antibiotics with anaerobic activity promote *C. difficile* growth
      1. Both oral vancomycin and metronidazole have potent anaerobic activity
   B. Recurrence happens post therapy in the absence of normal gut microflora

III. Current Treatments for Multiple Recurrences
   A. Aim to restore intestinal microflora

IV. Tlevamer
   A. Non-antimicrobial is associated with lower recurrence rate
   B. Not effective for treatment

V. Fidaxomicin
   A. Narrow spectrum of anaerobic activity → less alteration to intestinal microflora
      1. Significantly lower CDAD recurrence rate and higher global cure vs. vancomycin
   B. Significantly higher clinical cure and global cure rates in patients receiving any CA
      1. Greatest difference may be seen in patients receiving high-risk CA

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**Summary**

I. Economic Data for CDAD
   A. Estimated direct hospital cost per case of CDAD
      1. $2,871 to $4,826 for primary episode
      2. $13,655 to $18,067 for recurrent episode

II. The Cost to Prevent One Recurrence
   A. Fidaxomicin: $276/day (inpatient)
   B. Vancomycin oral solution: $5/day (inpatient)
   C. Metronidazole $3/day (inpatient)
   D. NNT = 10: need to treat 10 patients with fidaxomicin to prevent 1 recurrence
      1. Fidaxomicin for 10 days = $2760/patient → $27,600 for 10 patients
      2. Vancomycin/metronidazole for 10 days = $30-50/patient → $500 for 10 patients
   E. It would cost $27,000 to prevent one recurrence using fidaxomicin
   F. Fidaxomicin may not be an affordable option for treating first episode

III. In Whom Should We Consider Using Fidaxomicin?
   A. Patients at risk for ≥ 1 recurrences
      1. No agreement has been reached on optimal treatment of a recurrence
      2. Clinical predictors and risk factors for recurrence
         a. Advance age ≥ 65 y/o: OR 1.62 [95% CI: 1.11-2.36]
         b. Concomitant antibiotics during or post *C. difficile* therapy: OR 1.71-4.73
         c. Previous CDAD relapse: OR=1.80, [95% CI 1.06-3.05]
      3. Fidaxomicin may have the most benefit in patients with these risks
   B. Patients on any CA with fidaxomicin
      1. Higher clinical cure and global cure rate, as well as lower recurrence rate
      2. Clinical cure: fidaxomicin 90% vs. vancomycin 79.4% (P < 0.001)
a. No high-risk CA
   i. Fidaxomicin 92.2% vs. vancomycin 92% (P = 0.89)
b. Any high-risk CA
   i. Fidaxomicin 88.6% vs. vancomycin 75.4% (CI -2.25 to 27), P = 0.09
c. Greater difference in clinical cure rate seen in any high-risk CA subgroup, though not significant; may be due to lack of power

C. Patients with first recurrence: pooled from two phase III trials\textsuperscript{46}
   1. 128 subjects randomized to fidaxomicin (n=66) or vancomycin (n=62)
      a. CDAD recurrence
         i. Fidaxomicin 19.7% vs. vancomycin 35.5% (P = 0.045, absolute reduction: 15.8%)

D. Patients with non-BI/NAP1/027 strain
   1. Significantly lower recurrence rate with fidaxomicin 7.8% vs. vancomycin 25.5% (P < 0.001)

IV. Future Areas of Study
   A. Pharmacoeconomic analysis on the cost of recurrent CDAD, both inpatient and outpatient
   B. Potential clinical identification of BI/NAP1/027 strain for tailoring therapy
   C. Larger studies in patients with multiple recurrences and patients ≥ 65 yr.


