Treatment of *Clostridium difficile*: Is metronidazole good enough for your mother?

Daniel M. Rackham, PharmD, BCPS
Clinical Assistant Professor
Oregon State University College of Pharmacy
Clinical Pharmacist
Good Samaritan Regional Medical Center
October 25, 2014
Objectives

Understand the pathophysiology of *Clostridium difficile* Infection (CDI)

Recognize the clinical features and risk factors for CDI

Compare treatment regimens for CDI and their place in therapy
My name is...but I go by...

*Clostridium difficile*

*C. difficile*

**CDI – Clostridium difficile infection**

**CDC - Clostridium difficile colitis**

**CDD - Clostridium difficile disease**

**CDAD - Clostridium difficile associated disease or diarrhea**

C. *diff*
Background on *C. difficile*
Background on *C. difficile*

First described as “the difficult clostridium” *Bacillus difficilis* in 1935 by Hall and O’Toole

- Isolated in the stool of a healthy neonate and described as part of the normal intestinal flora of infants

Identified as primary etiology for pseudomembranous colitis in 1978

Background on *C. difficile*

**Clostridium**
- Spindle-shaped bacterial cell often swollen at the center by an endospore

**Clostridium difficile**
- Gram-positive, anaerobic, spore-forming rod (bacillus)

Endotoxin producing
- Endotoxins A and B

JAMA 2011;306(17):1849-50
Background on *C. difficile*

Fecal-oral transmission

*C. difficile* Infection (CDI) - Acute diarrhea w/
- Documented *C. diff* or its toxin
- No other documented cause for diarrhea

CDI complications
- Pseudomembranous colitis
- Toxic megacolon
- Sepsis and death

Community associated

Not just a hospital problem

- 20-40% of CDI cases are community associated
C. Difficile risk factors

Exposure to antibiotics is the greatest risk factor for CDI

• Also need exposure to organism (C. difficile)

Other risk factors

• Hospitalization
• Advanced age
• Exposure to acid suppressive medications

Clin Infect Dis 2008;46:S12-18
Risk of CDI with antibiotics

Pathogenesis

• Overgrowth of native or newly acquired *Clostridium difficile* after other bacteria have been killed

Nearly all antibiotics are associated with CDI

• Broad-spectrum
• Clindamycin
• Fluoroquinolones
• Beta-lactam/beta-lactamase inhibitors
• Cephalosporins

Antibiotics associated with CDI

Odds ratios for antibiotic classes

- Cephs: 4.47
- Clinda: 20.43
- FQNs: 5.65
- Macrolides: 2.55
- Pens: 3.25
- SMP/TMX: 1.84
- TCNs: 0.91

Pathogenesis of *C. difficile*

Toxin A and B production leads to:
- Inflammation
- Fluid
- Mucous secretion
- Mucosal damage

1. Ingestion of spores transmitted from other patients via the hands of healthcare workers and environment

2. Germination into growing (vegetative) form

3. Altered lower intestine flora (due to antimicrobial use) allows proliferation of *C. difficile* in colon

4. Toxin A & B production leads to colon damage +/- pseudomembrane

“More difficult than ever”
Importance of CDI

Rising incidence and virulence

Incidence

Virulence

Gastroenterology 2009;136:1913–1924
Increasing severity

Deaths caused by *C. difficile* infections *

*Age-adjusted rate of *C. difficile* as the primary (underlying) cause of death.*

SOURCE: CDC National Center for Health Statistics, 2012
C. difficile is #1

_**C. difficile** has surpassed MRSA as the leading cause of nosocomial infections in community hospitals

Infect Control and Hosp Epidemiol 2011;32(4):387-390
Bad Bugs, No Drugs: No ESCAPE

Enterococcus faecium
Staphylococcus aureus
Clostridium difficile
Acinetobacter baumannii
Pseudomonas aeruginosa
Enterobacteriaceae

Klebsiella pneumoniae

Clin Infect Dis 2009;48:1-12
Clin Infect Dis 2009;49:992-93
C. difficile virulence

BI/NAP1/027 strain

- Higher virulence-associated characteristics
  - increased toxin production
  - additional “binary” toxin
  - hypersporulation capacity
  - high-level resistance to fluoroquinolone antibiotics

- Produce higher in vitro levels of clostridial toxins A and B
  16–23 times the levels produced by toxinotype 0 strains

- “Quebec outbreak” – 37% mortality rate

Clin Infect Dis 2008;46:S12-8
States with BI/NAP1/027 C. difficile

(N=40) October, 2008

http://www.cdc.gov/ncidod/dhqp/id_Cdiff_data.html
What can be done?
Infection control measures

- Healthcare workers and visitors: use gloves (A-I)
- Emphasize compliance to hand hygiene (A-II)
- Implement an antimicrobial stewardship program (A-II)
- Don’t screen for asymptomatic carriers (A-III) or treat (B-I)
- Use sporicidal agents to clean room (B-II)
- Handwashing with soap and water (B-III)
- Healthcare workers and visitors: use gowns (B-III)
- Use private rooms with contact precautions (B-III)
- Maintain contact precautions the duration of diarrhea (C-III)
- Provide a dedicated commode for each patient (C-III)

Infect Control Hosp Epidemiol 2010; 31(5):431-455
## Hand hygiene

<table>
<thead>
<tr>
<th>Interventions compared</th>
<th>Mean log reduction (95% CI), log$_{10}$ CFU/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention 1</strong></td>
<td><strong>Intervention 2</strong></td>
</tr>
<tr>
<td>Warm water and plain soap</td>
<td>No hand hygiene</td>
</tr>
<tr>
<td>Warm water and plain soap</td>
<td>Alcohol-based handrub</td>
</tr>
<tr>
<td>Cold water and plain soap</td>
<td>No hand hygiene</td>
</tr>
<tr>
<td>Cold water and plain soap</td>
<td>Alcohol-based handrub</td>
</tr>
<tr>
<td>Warm water and plain soap</td>
<td>Antiseptic hand wipe</td>
</tr>
<tr>
<td>Warm water and plain soap</td>
<td>No hand hygiene</td>
</tr>
<tr>
<td>Warm water and antibacterial soap</td>
<td>Alcohol-based handrub</td>
</tr>
<tr>
<td>Cold water and plain soap</td>
<td>Antiseptic hand wipe</td>
</tr>
<tr>
<td>Warm water and antibacterial soap</td>
<td>Antiseptic hand wipe</td>
</tr>
<tr>
<td>Warm water and plain soap</td>
<td>Warm water and antibacterial soap</td>
</tr>
<tr>
<td>Antiseptic hand wipe</td>
<td>No hand hygiene</td>
</tr>
<tr>
<td>Antiseptic hand wipe</td>
<td>Alcohol-based handrub</td>
</tr>
<tr>
<td>Cold water and plain soap</td>
<td>Warm water and antibacterial soap</td>
</tr>
<tr>
<td>Warm water and plain soap</td>
<td>Cold water and plain soap</td>
</tr>
<tr>
<td>Alcohol-based handrub</td>
<td>No hand hygiene</td>
</tr>
</tbody>
</table>

Probiotics?

PLACIDE – no difference between probiotic and placebo in prevention of CDI (increased flatulence in probiotic arm)

Cochrane Review – no difference in incidence of CDI

Guidelines

• Administration of currently available probiotics is not recommended to prevent primary CDI, as there are limited data to support this approach and there is a potential risk of bloodstream infection (IDSA/SHEA)

• Insufficient evidence to support the routine use of probiotics to prevent CDI (American College of Gastroenterology)

Lancet 2013; 382: 1249–57
Cochrane Database of Systematic Reviews 2013, Issue 5
Does my patient have *C. diff*?
Clinical presentation of CDI

CDI defined

- Presence of diarrhea (>3 unformed stools in 24h)
- Stool tests positive for toxins from *C. difficile*

Or

- Findings consistent with pseudomembranous colitis

Clinical Features

- Watery diarrhea
- Fever
- Abdominal cramps
- Leukocytosis
- Hypoalbuminemia

Risk factors

- Use of antibiotics
- Hospitalization
- Advanced age
- Use of PPIs

Infect Control Hosp Epidemiol 2010; 31(5):431-455
NEJM 2011;365:1693-703
Diagnosis of CDI

• Only test unformed stool (unless ileus)
• Enzyme immunoassay (EIA) testing for detection of glutamate dehydrogenase (GDH) as initial screening then confirmatory testing for GDH-positive specimens using toxin EIA is recommended
• Polymerase chain reaction (PCR) is rapid, sensitive and specific, but costly

Infect Control Hosp Epidemiol 2010; 31(5):431-455
Sensitivity

90% sensitive

• If 100 people who HAVE DISEASE are tested
  90 correctly identified as having disease
  10 false negatives, who have disease

More sensitive = fewer false negatives

SNout = sensitivity = ability correctly to rule out
Specificity

90% specific

- If 100 people who **DO NOT HAVE** disease are tested

  90 correctly identified as disease free
  10 false positives, who **DO NOT HAVE** disease

More specific = fewer false positives

SPin = specificity = ability to correctly rule in
Diagnosis of CDI

GDH EIA – detects enzyme (GDH) produced by all *C. diff* isolates

- Highly sensitive (>90%), cannot differentiate between toxigenic and nontoxigenic strains

Toxin EIA – detects toxins A and B produced by most isolates

- Sensitivity 63-94%, specificity 75-100%
- High false negative since large amounts of toxin must be present

PCR – detects genes from toxin A and B

- Highly sensitive (94%) and specific (96%)

Practical approach to diagnosis of CDI

Step 1: EIA for GDH and toxins A/B
- GDH negative and toxins negative
  - Report negative
- GDH positive and toxins positive
  - Report positive

Discordant results – GDH positive and Toxins negative
- PCR test negative
  - Report negative
- PCR test positive
  - Report positive

Step 2: PCR or Cytotoxicity Assay
Meet Cliff: The dog who can smell C. diff

Cliff has been trained to sniff out the bacteria Clostridium difficile
Treatment of *C. difficile*
Treatment of *C. difficile*

Discontinue treatment with offending antibiotic if possible

Replace fluids and electrolytes

Avoid antimitotility agents

Initiate antibiotics to treat

*C. difficile*
C. difficile treatments

Traditional therapies
• Metronidazole
• Vancomycin

Newest FDA Approval
• Fidaxomicin

Alternative agents
• Rifaximin
• Nitazoxanide
• Tigecycline

“Outside the box” – currently available
• Toxin neutralizers
• Fecal transplant
• Intravenous Immune Globulin

“Outside the box” – in development
• Nontoxigenic C. difficile
• Monoclonal antibodies
• Vaccines

Clin Infect Dis 2010;51(11):1306-1313
Treatment of CDI – fecal transplant

Recurrent *Clostridium difficile* Colitis: Case Series Involving 18 Patients Treated with Donor Stool Administered via a Nasogastric Tube

Johannes Aas,¹ Charles E. Gessert,² and Johan S. Bakken³

¹Department of Gastroenterology, ²Division of Education and Research, and ³Department of Infectious Diseases, St. Mary’s/Duluth Clinic Health System, Duluth, Minnesota

Clin Infect Dis 2003;36:580-85
Aas J, et al.

18 subjects who received a total of 64 courses of antimicrobials prior to nasogastric stool

Results

- One of 16 survivors experienced a single recurrence of CDI during 90 day follow-up
  - 15/16 successfully treated
- 2 patients died from unrelated illness
- No adverse effects associated with stool treatment were observed
Fecal transplant

Systematic review reported a 92% success rate in 317 patients treated with fecal transplant

Donors needed!

The ultimate probiotic

Clin Infect Dis 2011;53(10):994-1002
Is metronidazole good enough for your mother?
## Ideal qualities of a *C. difficile* drug

<table>
<thead>
<tr>
<th></th>
<th>Active against <em>C. Difficile</em></th>
<th>Poor oral absorption</th>
<th>High fecal concentration</th>
<th>Well tolerated</th>
<th>Spares enteric flora</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole</td>
<td>❑</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>❑</td>
<td>❑</td>
<td>❑</td>
<td>❑</td>
<td></td>
</tr>
<tr>
<td>Fidaxomicin</td>
<td>❑</td>
<td>❑</td>
<td>❑</td>
<td>❑</td>
<td>❑</td>
</tr>
</tbody>
</table>
Traditional treatments

Oral metronidazole dosing
• 250 mg PO QID or 500 mg PO TID x 10 – 14 days

IV vancomycin is not an option
• Oral, nasogastric tube or via retention enema

Oral vancomycin dosing
• 125 to 500 mg PO QID x 10 – 14 days
• Until May 2011, only FDA approved treatment for C. difficile
Therapeutic controversy

Vancomycin for your mother, metronidazole for your mother-in-law, 1992

• Sherwood L. Gorbach, MD
  Tufts University, Infectious Disease

C. Diff guidelines, SHEA 1995

• “Metronidazole or vancomycin for 10 days; metronidazole is less expensive and may be preferable to avoid vancomycin resistance and other nosocomial bacterial species.”
Therapeutic controversy

ASHP Therapeutic Position Statement on preferential use of metronidazole, 1998

• “Oral vancomycin should be reserved for severe, potentially life-threatening cases or when oral metronidazole cannot be used.”

Historical recommendations

Metronidazole preferred over vancomycin

• Comparable effectiveness

• Minimize emergence of vancomycin-resistant Enterococcus (VRE) and vancomycin-resistant Staphylococcus aureus (VRSA)

• Cost

Infect Control Hosp Epidemiol 1995; 16:459-477
C. Difficile guidelines

1995 – Society for Healthcare Epidemiology of America (SHEA)

2010 – Update: SHEA and the Infectious Diseases Society of America (IDSA)
  • Infect Control Hosp Epidemiol 2010; 31(5):431-455

2013 - American College of Gastroenterology
  • Am J Gastroenterol 2013; 108:478–498
Metronidazole or vancomycin

Metronidazole may not be as effective as once thought

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Studies</th>
<th>Treatment Failure no./total no. (%)</th>
<th>Recurrence no./total no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 2000 or before</td>
<td>4</td>
<td>18/718 (2.5)</td>
<td>48/715 (6.7)</td>
</tr>
<tr>
<td>After 2000</td>
<td>5</td>
<td>275/1508 (18.2)</td>
<td>332/1162 (28.6)</td>
</tr>
<tr>
<td>Combined periods</td>
<td>9</td>
<td>293/2226 (13.2)</td>
<td>380/1877 (20.2)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 2000 or before</td>
<td>11</td>
<td>22/637 (3.5)</td>
<td>112/624 (17.9)</td>
</tr>
<tr>
<td>After 2000</td>
<td>2</td>
<td>2/71 (2.8)</td>
<td>36/181 (19.9)</td>
</tr>
<tr>
<td>Combined periods</td>
<td>13</td>
<td>24/708 (3.4)</td>
<td>148/805 (18.4)</td>
</tr>
</tbody>
</table>

Table 1. Treatment Failures and Recurrences of *C. difficile* Infection with Metronidazole and Vancomycin Therapy.*

NEJM 2008;359:1932-40
Musher DM, et al.

Relatively Poor Outcome after Treatment of *Clostridium difficile* Colitis with Metronidazole

Daniel M. Musher,¹,²,³ Saima Aslam,² Nancy Logan,¹ Srikanth Nallacheru,¹ Imran Bhaila,⁴ Franziska Borchert,¹ and Richard J. Hamill¹,²

Prospective, observational study of 207 patients treated with metronidazole

All patients received > 1.5 gm metronidazole daily for at least 7 days

Clin Infect Dis 2005;40:1586-90
Musher DM, et al.

207 CDAD patients treated with metronidazole

- 50% complete response (n=103)
- 22% refractory (n=46)
- 28% recurrence (n=58)

Refractory = signs/symptoms persist > 10 days post metronidazole initiation
Recurrence = successful treatment followed by C. diff return

Clin Infect Dis 2005;40:1586-90
A Comparison of Vancomycin and Metronidazole for the Treatment of Clostridium difficile–Associated Diarrhea, Stratified by Disease Severity

Fred A. Zar,¹ Srinivasa R. Bakkanagari,² K. M. L. S. T. Moorthi,² and Melinda B. Davis¹

¹University of Illinois at Chicago, Chicago, and ²Saint Francis Hospital, Evanston, Illinois

Clinical Infectious Diseases 2007; 45:302–7

Prospective, randomized, double-blind, placebo-controlled, trial conducted from 1994 – 2002

150 patients stratified according to disease severity

Clin Infect Dis 2007;45:302-7
Zar FA, et al. study design

Patients followed for 21 days to assess cure, relapse or intolerance

CDAD patients

Mild disease
- Vancomycin (n=40)
- Metronidazole (n=41)

Severe disease
- Vancomycin (n=31)
- Metronidazole (n=38)

Clin Infect Dis 2007;45:302-7
Zar FA, et al.

Inclusion criteria for severe disease

Any 2:

• Age > 60 yrs
• Tmax > 38.3 C (101 F)
• Albumin < 2.5 mg/dL
• WBC > 15,000 cells/µL

Or

• ICU admission
• Endoscopic evidence of pseudomembranous colitis

Clin Infect Dis 2007;45:302-7
Table 2. Rate of cure of *Clostridium difficile*-associated diarrhea by disease severity and treatment.

<table>
<thead>
<tr>
<th>Disease severity</th>
<th>No. of patients cured/ no. of patients treated (%)</th>
<th>Mtz group</th>
<th>Vm group</th>
<th>Total</th>
<th>$P^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td></td>
<td>37/41 (90)</td>
<td>39/40 (98)</td>
<td>76/81 (94)</td>
<td>.36</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td>29/38 (76)</td>
<td>30/31 (97)</td>
<td>59/69 (86)</td>
<td>.02</td>
</tr>
<tr>
<td>All</td>
<td></td>
<td>66/79 (84)</td>
<td>69/71 (97)</td>
<td>135/150 (90)</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** Mtz, metronidazole; Vm, vancomycin.

$^a$ $P$ values were calculated using Fisher’s exact test.
Zar FA, et al.

Conclusion

- “Our findings suggest that metronidazole and vancomycin are equally effective for the treatment of mild CDI, but vancomycin is superior for treating patients with severe CDI.”

Additional unpublished study confirmed superiority of vancomycin over metronidazole for treatment of severe CDI (Louie et al. ICAAC 2007 paper 3826)

Practice changing?

### 2010 guideline recommendations

<table>
<thead>
<tr>
<th>Classification</th>
<th>Clinical Criteria</th>
<th>Treatment Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial episode – Mild to moderate</td>
<td>WBC &lt; 15,000 cells/µL AND SCr &lt; 1.5x baseline</td>
<td>Metronidazole 500 mg PO TID x 10-14 days</td>
</tr>
<tr>
<td>Initial episode – Severe</td>
<td>WBC &gt; 15,000 cells/µL OR SCr &gt; 1.5x baseline</td>
<td>Vancomycin 125 mg PO QID x 10-14 days</td>
</tr>
<tr>
<td>Initial episode – Severe, complicated</td>
<td>hypotension/shock, ileus, megacolon</td>
<td>Vancomycin 500 mg PO/NG QID + metronidazole 500 mg IV Q8h, If ileus, consider rectal vancomycin</td>
</tr>
</tbody>
</table>

*Infect Control Hosp Epidemiol 2010; 31(5):431-455*
## Disease severity

Zar et al. criteria for severe disease

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60 years</td>
<td>1</td>
</tr>
<tr>
<td>Temperature &gt; 38.3 degrees C</td>
<td>1</td>
</tr>
<tr>
<td>Albumin level &lt; 2.5 mg/dL</td>
<td>1</td>
</tr>
<tr>
<td>WBC count &gt; 15,000 cells/µL</td>
<td>1</td>
</tr>
<tr>
<td>evidence of pseudomembranous colitis</td>
<td>2</td>
</tr>
<tr>
<td>ICU Hospitalization</td>
<td>2</td>
</tr>
</tbody>
</table>

≥ 2 points = severe disease

Clin Infect Dis 2007;45:302-7
# Disease severity

Severe disease indicators (expert opinion)

<table>
<thead>
<tr>
<th>Classification</th>
<th>IDSA/SHEA</th>
<th>American College of Gastroenterology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial episode – Mild to moderate</td>
<td>WBC &lt; 15,000 cells/µL AND SCr &lt; 1.5x baseline</td>
<td>Diarrhea with additional s/sx not meeting severe or complicated criteria</td>
</tr>
<tr>
<td>Initial episode – Severe</td>
<td>WBC &gt; 15,000 cells/µL OR SCr &gt; 1.5x baseline</td>
<td>Serum albumin &lt; 3 g/dL + WBC &gt; 15,000 cells/µL OR Abdominal tenderness</td>
</tr>
<tr>
<td>Initial episode – Severe, complicated</td>
<td>hypotension/shock, ileus, megacolon</td>
<td>Any: ICU, hypotension, fever &gt; 38.5 C, ileus, AMS, WBC &gt; 35,000, lactate &gt; 2.2, organ failure</td>
</tr>
</tbody>
</table>

## Recurrence recommendations

<table>
<thead>
<tr>
<th>Classification</th>
<th>Clinical Criteria</th>
<th>Treatment Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial episode – Mild to moderate</td>
<td>WBC &lt; 15,000 cells/µL AND SCr &lt; 1.5x baseline</td>
<td>Metronidazole 500 mg PO TID x 10-14 days</td>
</tr>
<tr>
<td>Initial episode – Severe</td>
<td>WBC &gt; 15,000 cells/µL OR SCr &gt; 1.5x baseline</td>
<td>Vancomycin 125 mg PO QID x 10-14 days</td>
</tr>
<tr>
<td>First recurrence</td>
<td>--</td>
<td>Same as initial episode</td>
</tr>
<tr>
<td>Second recurrence</td>
<td>--</td>
<td>Vancomycin in a tapered and/or pulsed regimen</td>
</tr>
</tbody>
</table>
Metronidazole (Flagyl™)

Drug of choice for initial episode of mild-to-moderate CDI
  • 500 mg PO TID x 10-14 days

Do not use beyond first recurrence of CDI or long-term chronic therapy because of neurotoxicity

Inexpensive generic
  • ~$12 for a 10-day course

Infect Control Hosp Epidemiol 2010; 31(5):431-455
Oral vancomycin

Drug of choice for initial episode of severe CDI
- 125 mg PO QID x 10-14 days

Regimen of choice for severe, complicated CDI
- 500 mg PO QID +/- 500 mg in 100 mL normal saline per rectum Q6h +/- metronidazole IV 500 mg Q8h

Preferred treatment of the second or later recurrence of CDI using a tapered and/or pulse regimen
- 125 mg PO QID x 10-14 days, then 125 mg BID x 1 week, then 125 mg QDAY x 1 week, then 125 mg Q2-3days for 2 – 8 weeks

Infect Control Hosp Epidemiol 2010; 31(5):431-455
Oral vancomycin

Vancomycin oral capsules (Vancocin™)
  • ~$1,200 for a 10-day course

Vancomycin oral solution
  • The parenteral form of vancomycin may be administered orally for treatment of *C. difficile*
  • Dilute in water and give to the patient to drink
    Often considered unpalatable by patients

Mix in 1:1 solution with sweetener to make more palatable

Cost ~ $50 for a 10-day course

*Vancomycin hydrochloride [package insert]. Pfizer Injectables. 2010*
* CJHP 2010;63(5):366-372*
Vancomycin 125 mg po qid x 10 days
May compound oral solution qs

Jean Salishan, PA-C
Fidaxomicin (Dificid™)

After 25+ years of metronidazole or vancomycin

Efficacy

• Fidaxomicin 200 mg PO Q12h vs. vancomycin 125 mg PO QID (n = 629)
• Non-inferior clinical cure rate
  92.1% vs. 89.8%
• Less recurrence in fidaxomicin treated patients with non-NAP1 strain
  13.3% vs. 24%, p = 0.004

Cost

• $2000 for a 10-day course

NEJM 2011;364:422-431
Fidaxomicin (Dificid™)

“Further data assessing the cost-effectiveness of fidaxomicin are needed.”

“Currently, it cannot be recommended over vancomycin for treatment of CDI. However, it may be considered for treatment of recurrent infections.”

Place in therapy

• Alternative for those intolerant of metronidazole or vancomycin
• Alternative to vancomycin for management of second or greater recurrence

Ann Pharmacother 2012;46(2):219-228
## Institutional antibiotic costs

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Cost/day</th>
<th>Cost/10d</th>
<th>Cost/14d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole</td>
<td>$1.23</td>
<td>$12.30</td>
<td>$17.22</td>
</tr>
<tr>
<td>Vancomycin capsules</td>
<td>$120</td>
<td>$1200</td>
<td>$1680</td>
</tr>
<tr>
<td>Vancomycin oral solution</td>
<td>$5</td>
<td>$50</td>
<td>$70</td>
</tr>
<tr>
<td>Fidaxomicin</td>
<td>$198.54</td>
<td>$1985.40</td>
<td>$2779.56</td>
</tr>
</tbody>
</table>
Conclusion

Is metronidazole good enough?

For **mild-moderate disease**, metronidazole is good enough for your mother.

For **severe disease**, metronidazole is **NOT good** enough for your mother or mother-in-law.

Fidaxomicin is an important advance in the treatment of *C. difficile*. 
Treatment of *Clostridium difficile*: Is metronidazole good enough for your mother?

Daniel M. Rackham, PharmD, BCPS
Clinical Assistant Professor
Oregon State University College of Pharmacy
Clinical Pharmacist
Good Samaritan Regional Medical Center
October 25, 2014