UPDATE ON CLOSTRIDIUM DIFFICILE DISEASE
Richard A. Jacobs, M.D.,PhD

Case
MQ is a 44 year old woman that I first saw in Sept 2006
In MVA in Jan 2003 requiring spinal surgery
Subsequently developed fecal incontinence unresponsive to conservative therapy
June 2003 underwent sphincteroplasty with perioperative antibiotics
2 weeks later developed diarrhea with positive C. difficile toxin assay
Treated with metronidazole for 2 weeks; relapse treated with vancomycin

In the subsequent 3 years she had been treated with:
Several courses of metronidazole, including one of six months resulting in peripheral neuropathy
Multiple courses of oral vancomycin
Saccharomyces boulardii
Nitazoxanide (Alinia®)
Cholestyramine
IVIG
Every attempt at stopping medication resulted in a relapse

A PROCEDURE WAS PERFORMED
Rates of C. difficile by Age

- Spores
  - Persist in the environment for extended periods
  - Are resistant to alcohol and acid
  - Under appropriate conditions of pH, O₂ tension and exposure to bile can convert to the vegetative form
- Vegetative (replicative) form
  - Can produce toxin
  - Are sensitive to acid

C. difficile—Reservoirs and Acquisition

- 3%-5% of healthy adults are colonized
- Higher in other populations
  - 8% nursing home residents
  - 7-14% of elderly hospitalized adults
  - 13% of patients admitted to an ID ward (most HIV +ve)
  - 14% in H SCT recipients
- MAJORITY OF DISEASE-CAUSING ORGANISMS ARE HOSPITAL-ACQUIRED
Hospital Acquisition of C. difficile

- Prospective study of 428 patients admitted to a medical ward over an 11 month period
- 7% (29) +ve on admission
- Of the initially 399 -ve patients, 83 or 21% acquired C. difficile
  - 63% (52) remained asymptomatic
  - 37% (31) developed C. difficile diarrhea
- Median time to acquisition—12 days (range 3-98 days)

Hospital Acquisition of C. difficile

- Patient-to-patient transmission of C. difficile was evidenced by:
  - time-space clustering of cases
  - Identical immunoblot types
  - More frequent and earlier acquisition of C. difficile among patients exposed to roommates with +ve cultures

| Culture Source | Rooms w/ culture +ve pts | Rooms w/ asymptomatic carriers | Rooms w/ pts w/ C.difficile diarrhea | Total +ve/Total tested (%)
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Bedrail</td>
<td>0</td>
<td>2</td>
<td>10</td>
<td>12/31 (39%)</td>
</tr>
<tr>
<td>Commode</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>5/13 (38%)</td>
</tr>
<tr>
<td>Floor</td>
<td>5</td>
<td>3</td>
<td>18</td>
<td>26/72 (36%)</td>
</tr>
<tr>
<td>Call button</td>
<td>1</td>
<td>2</td>
<td>6</td>
<td>9/32 (28%)</td>
</tr>
<tr>
<td>Windowsill</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>3/30 (10%)</td>
</tr>
</tbody>
</table>

- Hand carriage among hospital personnel
  - Cultures before and after contact
  - Fecal contact, examining pt, feeding the pt, taking temperature
  - Nurses, physicians, students, housekeepers, physical therapists, etc

- 57% (20/35) acquired C. difficile after contact
Clinical Implications of Epidemiology

- Hand hygiene
- Soap & water (spores resistant to alcohol)
- Infection Control
  - Single rooms
  - Contact precautions (gowns and gloves)
  - Terminal cleaning
  - Bleach (to kill spores)

Clinical Implications—Unsettled Issues

- Recent description of airborne dispersal of C. difficile (CID 2010;50(11):1450-57)
- Spores isolated from air of 70% of patients
- “Fecal Cloud” surrounding symptomatic patients
- Lidless-toilets and airborne dispersal of C. difficile (J Hosp Inf; 2012:1-5)
- ??? Airborne Precautions

C. difficile Toxins

- Toxin A is a potent enterotoxin (causes fluid loss) and a very active WBC attractant (causes inflammation)
- Toxin B is a potent cell cytotoxin (kills cells)
- All disease causing strains produce either Toxin A & B or Toxin B alone

Hypervirulent C. difficile

Severe Clostridium difficile--Associated Disease in Populations Previously at Low Risk --- Four States, 2005

CDC

Weekly, December 2, 2005 / 54(47):1231-1236

Severe C. difficile disease in four states: A review of recent outbreaks and their implications for outbreak response and control.

FDA

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Hypervirulent C. difficile

CDC

Weekly, December 2, 2005 / 54(47):1231-1236

Severe C. difficile disease in four states: A review of recent outbreaks and their implications for outbreak response and control.

FDA
Toxin Gene-Variant Strain

1. Binary toxin genes
2. Ciprofloxacin resistant
3. 18 bp tcdC deletion (inactivates negative regulator of Toxin A&B genes and allows for hyperproduction of toxins A&B)

Increased Toxin A Production In Vitro

Increased Toxin B Production In Vitro
Risk Factors

- Antibiotics
  - Usually develops after 5-10 days of antibiotics, but can occur after one dose or as late as 4-6 weeks after discontinuation
  - Antineoplastic drugs with antibacterial activity
  - Doxorubicin
  - Cetuximab
  - Cyclophosphamide
  - Sulfonamide
  - Chlorambucil
  - Methotrexate

Antibiotics Associated With C. Difficile

<table>
<thead>
<tr>
<th>Frequent</th>
<th>Infrequent</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporins (especially 2nd &amp; 3rd gen agents)</td>
<td>Tetracyclines</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>Ampicillin &amp; amoxicillin</td>
<td>Trimethoprim-sulfamethoxazole</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Macrolides</td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Vancomycin</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Vancomycin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Additional Risk Factors

- Age > 64
- Co-morbid conditions, especially IBD
- Use of PPI
  - Allows more vegetative organisms to bypass acidity of stomach
- “LOW RISK” individuals can develop C. diff
  - Community
  - Without exposure to antibiotics

C. diff in “Low Risk” Individuals

- Organism contaminates the environment
- Being around someone with C. diff
- Foodborne transmission (CID 2010;51:577-582)
  - 20% of ground beef and 14% of veal in Canada
  - Up to 42% of retail beef, turkey and pork in the US
- C. diff carriage in healthy infants (CID 2012;55:1209)
  - Point prevalence study in 2 French daycares
  - 14% carried toxin-producing strains
Pathogenesis

- Colonization resistance
- Normal microbiota of the GI tract constitutes a complex and poorly understood host defense system that prevents colonization with C. difficile
- When this ecosystem is disrupted by antibiotics, colonization can occur
- Symptomatic disease occurs in those with low antibody titers to toxin A & B

Clinical Manifestations

- Range from asymptomatic to severe disease
- 90-95% have watery diarrhea; 5-10% have bloody diarrhea
- 80% have abdominal pain, fever and leukocytosis
- 50% have +ve fecal WBC’s
  - Not a useful test
- May progress to toxic megacolon

Normal Colon vs. Pseudomembranous Colitis (PMC) on Colonoscopy

Normal Colon

Colon with PMC due to Clostridium difficile Infection

Pseudomembranous Colitis

Yellow lesion against hyperemic bowel

Mushroom-shaped pseudomembrane

H & E, optical magnification 400x
Pseudomembranous Colitis

Laboratory Diagnosis of C. diff

Laboratory Diagnosis

- Cytotoxin assay
  - Sensitive and specific
  - 48-72 hours to complete
- Enzyme immunoassay (EIA) for toxin
  - Rapid
  - Sensitivity only 75-80%
- 2-stage testing
  - Very sensitive and specific
  - Same day results
2-Stage Testing

- Screening test for bacterial glutamate dehydrogenase (GDH), a metabolic enzyme produced almost exclusively by C. difficile
- Very sensitive (>95%) with a negative predictive value of 99%
- Rapid test—hours
- PCR for toxin B gene
- Sensitivity = 95%
- Rapid test with same day reporting

New Testing Method

Cliff the C. diff sniffing Beagle
100% accurate in detecting C. diff stool
83% accurate in detecting C. diff in patients
98% accurate in detecting negative controls

Therapy of C. difficile Disease

- Three first line drugs
  - Metronidazole (Flagyl®)
  - Oral vancomycin (Vancocin®)
  - Fidaxomicin (Dificid®)
- FDA approved in 1978
- FDA approved in 1978
- FDA approved in 2011

C. difficile-Associated Diarrhea (CDAD)

A Comparison of Vancomycin and Metronidazole for the Treatment of Clostridium difficile-Associated Diarrhea, Stratified by Disease Severity

Fred A. Zen, Broslavo R. Sekasaveli, E. M. Li, S. T. Mutho, and Melanie D. Cook
University of Idaho at Coeur, Spokane, and Saint Louis Hospitals, Coeur, Idaho
Clin Infect Dis 2007;45:502
C. difficile-Associated Diarrhea (CDAD)

- 172 CDAD patients enrolled, 150 completed study
- Metronidazole 250 mg PO QID X 10 days
- Vancomycin 125 mg PO QID X 10 days
- Disease severity:
  - Age > 60
  - Temp > 38.3°C
  - WBC > 15,000 cells/mm³
  - Albumin < 2.5 mg/dL
  - Endoscopic evidence of pseudomembranes (2 pts)

Results:
- Mild CDAD cure:
  - Metronidazole 90%
  - Vancomycin 98% (p = .36)
- Severe CDAD (> 2 points) cure:
  - Metronidazole 76%
  - Vancomycin 97% (p = .02)

Clinical Practice Guidelines
Infect Cont Hosp Epidemiol 2010;31(5)

<table>
<thead>
<tr>
<th>Clinical definition</th>
<th>Suspected clinical data</th>
<th>Recommended treatment</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial episode, mild or moderate</td>
<td>leukocytosis or a white blood cell count of &lt;12,000 cells/mm³ and fever or a severe condition and an age &gt; 70 years</td>
<td>Metronidazole, 500 mg 3 times per day for 10-14 days</td>
<td>B-1</td>
</tr>
<tr>
<td>Initial episode, severe</td>
<td>leukocytosis or a white blood cell count of &gt;12,000 cells/mm³, or higher or a severe condition and age &gt; 70 years or an age &gt; 70 years with a white blood cell count of &gt;15,000 cells/mm³</td>
<td>Vancomycin, 250 mg 4 times per day for 10-14 days</td>
<td>B-1</td>
</tr>
<tr>
<td>Initial episode, severe, complicated</td>
<td></td>
<td>Vancomycin, 380 mg every 4 hours for 7-10 days, plus metronidazole, 380 mg every 8 hours, or, if metronidazole is contraindicated, Vancomycin, 500 mg every 4 hours for 7-10 days, plus clindamycin, 900 mg every 8 hours</td>
<td>C-III</td>
</tr>
</tbody>
</table>

Fidaxomicin versus Vancomycin for Clostridium difficile Infection

Thomas J. Louis, M.D., Mark A. Miller, M.D., Kathleen M. Murase, D.O., Karl Weiss, M.D., Arnold Lentnek, M.D., Yousun Golin, M.D., Sherwood Gorbach, M.D., Pamela Sears, Ph.D., and Yousuf Shau, Ph.D., for the OPT-80001 Clinical Study Group

Fidaxomicin v Vancomycin

- Prospective, randomized, double-blind, controlled study
- Compare fidaxomicin 200 mg orally twice daily (287 patients) and vancomycin 125 mg orally four times daily (309 patients)
- Exclusions
  - Severe disease (megacolon)
  - IBD
  - More than one recurrence

One caveat—reduces recurrences for non NAP1 strains; recurrence rate the same for epidemic NAP1 strains

<table>
<thead>
<tr>
<th>Strain Type</th>
<th>Fidaxomicin mITT</th>
<th>Vancomycin mITT</th>
<th>Fidaxomicin PP</th>
<th>Vancomycin PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAP1(0/027)</td>
<td>16/29 (57.1)</td>
<td>14/47 (30.0)</td>
<td>4/41 (10.4)</td>
<td>0/30 (0.0)</td>
</tr>
<tr>
<td>Non-NAP1(0/027)</td>
<td>12/17 (70.6)</td>
<td>14/30 (46.7)</td>
<td>4/13 (4.8)</td>
<td>0/24 (0.0)</td>
</tr>
</tbody>
</table>

Why is Fidaxomicin So Effective?

- Bactericidal
- PAE (postantibiotic effect)
- Narrow spectrum
  - No activity against Bacteroides spp
  - Maintains "colonization resistance"
- No PAE
- Broader spectrum
  - Activity against Bacteroides spp as well as other anaerobes
Potential Uses of Fidaxomycin

- **Post-Hoc Analysis of 2 randomized trials**
  - **FIRST RECURRENCE (128 patients)**
    - Fidaxomycin = vancomycin for clinical response
    - Fidaxomycin superior to vancomycin in preventing 2nd recurrence (20% v 36%)
  - **CONTINUED ANTIBIOTIC USE**
    - Fidaxomycin associated with higher cure rate (90% v 80%) and fewer recurrences (17% v 29%)
  - **PATIENTS WITH CANCER (153 patients/30 with hematologic malignancies)**
    - Fidaxomycin associated with higher cure rates (97% v 88%) and fewer recurrences (14% v 30%)

Role of Fidaxomicin in Therapy

- Based on the study it should be used as first line therapy for all patients with new onset C. difficile disease and possibly those with 1st recurrence, malignancy and continued antibiotic use
- **COST IS AN ISSUE**
  - Fidaxomycin $135/200mg tab ($2,700 for 10 days)
  - Vancomycin $32/125 mg tab ($1,280 for 10 days)
  - Metronidazole $0.72/500mg tab ($21.60 for 10 days)

Other (Second-Line) Therapies for C. difficile

- Nitazoxanide (Alinia®)—500 mg BID X 7-10 days (Clin Infect Dis 2006;43:421)
- Rifaximin—400 mg QID X 10-14 days
  - Used as a “chaser” for therapy of recurrent disease (Clin Infect Dis 2007;44:846)
- Toxin binding agents—cholestyramine/Tolevamer 2 gm TID X 14 days (Clin Infect Dis 2006;43:411)
- Probiotics

Probiotics for C. difficile

- Evolving area of study
- Difficult to generalize because of different products/doses/durations used in studies
- Best data is for PROPHYLAXIS
  - May decrease risk of C. diff in high-risk patients taking antibiotics (elderly/IBD/PPI)
- Little data to support adjunctive administration of probiotics for routine use in treatment of C. difficile
- May be efficacious in recurrent disease—data not robust
Recurrent C. difficile Disease

- 20% of patients relapse after appropriate therapy
- Some, like the patient presented, can have multiple relapses
- THIS IS WHAT MAKES C. DIFFICILE "CLOSTRIDIUM DIFFICULT"

Recurrent CDAD

- The best approach would be to decrease the risk of recurrent disease

The NEW ENGLAND JOURNAL of MEDICINE

Treatment with Monoclonal Antibodies against Clostridium difficile Toxins

Israel Levy, M.D., Ph.D., Deborah C. Moore, M.D., M.P.H., Brett A. Levy, M.D., Barbara M. Blair, M.D., Roger Bartor, M.D., Deke N. Gerdung, M.D., Geoffrey Norton, M.B., Ch.B., William D. Thomas, Jr., Ph.D., Mark Levy, Ph.D., Susan Sloan, Ph.D., Catherine A. Hal, Ph.D., and Donna M. Ambrosino, M.D.

N Engl J Med
2010;362:197

Monoclonal Antibodies To Prevent Recurrent Disease

- Randomized, double-blind, placebo-controlled study of two monoclonal antibodies against Toxins A & B
- 10 mg/kg of each antibody given as single infusion to patients with C. difficile disease treated with either metronidazole or vancomycin
- Outcome—recurrent disease at 84 days
Monoclonal Antibodies To Prevent Recurrent Disease

- Effective in subgroups with
  - Epidemic toxin—8% vs 32% (p = 0.06)
  - Previous recurrences—7% vs 38% (p = 0.006)

Recurrent CDAD

- Several approaches to therapy
  - Longer courses
  - Tapering courses
  - Tapering course with "rifaximin chaser"
  - Tigecycline
  - Addition of probiotics (Saccharomyces boulardii)
  - IVIG
  - FECAL Microbiota Transplantation

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Table 1: Suggested Approaches to Therapy

<table>
<thead>
<tr>
<th>Initial episode</th>
<th>Second recurrence</th>
<th>Other options for recurrent infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole at a dose of 500 mg three times daily for 10 to 14 days</td>
<td>Vancocin at a dose of 125 mg every 6 hours for 14 to 21 days, followed by maintenance at a dose of 625 mg every 12 hours for 7 days</td>
<td>Vancomycin at a dose of 400 mg per kilogram of body weight once every 6 weeks for a total of 2 to 3 doses</td>
</tr>
<tr>
<td>Metronidazole at a dose of 400 mg three times daily for 10 to 14 days</td>
<td>Rifaximin at a dose of 400 mg per kilogram of body weight once every 6 hours for a total of 2 to 3 doses</td>
<td>Vancomycin at a dose of 125 mg every 4 hours daily for 14 days, followed by - Maintenance at a dose of 625 mg every 12 hours for 7 days</td>
</tr>
<tr>
<td>Tigecycline</td>
<td></td>
<td>- Tigecycline</td>
</tr>
</tbody>
</table>
Recurrent CDAD

- Several approaches to therapy
  - Longer courses
  - Tapering courses
  - Tapering course with "rifaximin chaser"
  - Tigecycline
  - Addition of probiotics (Saccharomyces boulardii)
  - IVIG
  - FECAI Microbiota Transplantation

Fecal Microbiota Transplantation (FMT) for Recurrent C. difficile

<table>
<thead>
<tr>
<th>Author</th>
<th># of Patients</th>
<th>Route</th>
<th>Success</th>
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<tbody>
<tr>
<td>Gastroenterol 2013;42:490</td>
<td>70</td>
<td>Colonoscopy</td>
<td>100% non-NAP1 89% NAP1</td>
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<tr>
<td>Am J Gastroenterol 2012;107:1079</td>
<td>33</td>
<td>Colonoscopy</td>
<td>91% Vanco/2nd FMT 96%</td>
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<tr>
<td>Am J Gastroenterol 2012;107:764</td>
<td>43</td>
<td>Colonoscopy</td>
<td>90% 2nd FMT 99%</td>
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<td>Anaerobe 2012, EPUB</td>
<td>75</td>
<td>NG Tube</td>
<td>79% Vanco 96%</td>
</tr>
<tr>
<td>NEJM 2012;366:407</td>
<td>36</td>
<td>ND Tube</td>
<td>81% 2nd FMT 94%</td>
</tr>
</tbody>
</table>

Back To The Patient

- Had fecal biotherapy via the NG route
- Spoke to her several weeks ago
- Major complaint was constipation