Clostridium difficile
Infectious Colitis Update

Jeffrey Kennicutt, Pharm.D.
Clinical Pharmacy Specialist Infectious Disease
Pharmacy Department
St. Peters Hospital
Albany, NY 12208
eMail: jkennicutt@sphcs.org

Objectives:

- List the risk factors for this infectious disease.
- Compare and contrast the current recommended pharmacotherapy.
- Discuss options available for recurrent infection.
- Describe reasons why treatment failure occurs frequently.
What is *Clostridium difficile*

- *Clostridium difficile* is a spore-forming gram positive bacillus, a commensal bacterium of the human intestine in 2-5% of the population.
- Clostridia are motile bacteria that are ubiquitous in nature
- Spores may persist in environment for months/years.


What is *Clostridium difficile*

- 2 pathogenic endotoxins:
  - Toxin A: Enterotoxin, causes diarrhea and colonic inflammation
  - Toxin B: Cytotoxin

- Typically both toxins are produced, however 1-2% of pathogenic strains produce only Toxin B
- Some non-pathogenic strains do not produce toxin.

Antibiotic-associated diarrhea, “clindamycin colitis”, C. Diff Infection, CDI

1950’s Antibiotic-associated diarrhea became a well-recognized complication of antibiotic use. Staphylococcus aureus was the presumed pathogen. Pseudomembranous enterocolitis was the characteristic pathologic lesion. Oral vancomycin became the standard treatment.

Bartlett, J. CID 2008:46 (15 May)

Antibiotic-associated diarrhea, “clindamycin colitis”, C. Diff Infection, CDI

During the early 1980s, there were 3 important treatment changes: Vancomycin dose was reduced from 500 mg to 125 mg po 4 times daily. Metronidazole was deemed to be effective. Both treatments have high rates of relapse after treatment post d/c.

Bartlett, J. CID 2008:46 (15 May)
Annual CDAD Rates, Hospitals with >500 Beds, Intensive Care Unit Surveillance Component, NNIS


Rates of US Short-Stay Hospital Discharges with C. difficile Listed as Any Diagnosis by Age

Rates of US Short-Stay Hospital Discharges with C. difficile Listed as Any Diagnosis by Region

Potential Reasons for Increased CDAD Incidence and Severity

- Changes in underlying host susceptibility
- Changes in antimicrobial prescribing
- New strain with increased virulence
- Changes in infection control practices
Increasing Severity of CDAD due to Hypervirulent C. difficile

- **Pittsburgh, 2000**
  - Life-threatening disease from 1.6% to 3.2%
  - 2000-2001: 26 colectomies and 18 deaths

- **Quebec, 2004**
  - 30-day attributable mortality 6.9%
  - 12-month attributable mortality 16.7%


Hypervirulent BI/NAP1/027 C. difficile

"*Restriction enzyme analysis type BI, North American PFGE type 1, and PCR ribotype 027*"

- The Quebec outbreak is the largest and most documented outbreak BI/NAP1/027 (84% of the typed isolates)
- BI/NAP1/027 was first identified in 1984. Of 6000 C. difficile isolates typed prior to 2001 the BI/NAP1 strain was found in 14 (0.23%)

Pepin et al. *CMAJ* 2005;173:1037
States with BI/NAP1/027 strain of *C. difficile* (N=40), October, 2008
Restriction enzyme analysis type BI, North American PFGE type 1, and PCR ribotype 027

Increased Toxin A Production *in vitro*

*In vitro* production of toxins A and B by *C. difficile* isolates. Median concentration and IQRs are shown. *C. difficile* strains included 25 toxinotype 0 and 15 NAP1/027 strains (toxinotype III) from various locations.

Increased Toxin B Production *in vitro*

*In vitro* production of toxins A and B by *C. difficile* isolates. Median concentration and IQRs are shown. *C. difficile* strains included 25 toxinotype 0 and 15 NAP1/027 strains (toxinotype III) from various locations.


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**What Makes BI/NAP1/027 Hypervirulent**

- It produces ~ 16 fold more toxin A
- It produces ~ 23 fold more toxin B
- It produces a novel binary toxin that is cytotoxic
- Hypersporulation character
- Resistant to quinolones
- These characteristics appear to make it well suited for:
  - Increased morbidity and mortality
  - Increased transmission
Antimicrobial MIC and CDI

<table>
<thead>
<tr>
<th>Good Activity</th>
<th>MIC 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>2.0</td>
</tr>
<tr>
<td>Doripenem</td>
<td>2.0</td>
</tr>
<tr>
<td>OPT-80</td>
<td>0.125</td>
</tr>
<tr>
<td>Linezolid</td>
<td>2.0</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>0.25</td>
</tr>
<tr>
<td>Nitazoxanide</td>
<td>0.125</td>
</tr>
<tr>
<td>Ramoplanin</td>
<td>0.5</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>0.015</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>0.25</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate Activity</th>
<th>MIC 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxifloxacin</td>
<td>16</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Poor Activity</th>
<th>MIC 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clindamycin</td>
<td>&gt;128</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>32</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>&gt;128</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>&gt;128</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>32</td>
</tr>
</tbody>
</table>


BI/NAP1/027: Resistance to Fluoroquinolones

- In the Quebec outbreak all tested BI/NAP1 isolates were resistant to fluoroquinolones (Ciprofloxacin, levofloxacin, moxifloxacin and gatifloxacin)

- Of interest, all tested BI/NAP1 isolates were susceptible to clindamycin*, metronidazole and vancomycin

Severe CDAD in Populations Previously at Low Risk—Four States, 2005 (1)

- Recent reports to the Pennsylvania Department of Health and CDC
  - Young patients without serious underlying disease
  - *C. difficile* toxin-positive by routine diagnostic testing
  - Responded to CDAD-specific therapy
- Peripartum
  - Within 4 weeks of delivery
  - Reports from PA, NJ, OH, and NH
- Community-associated
  - No hospital exposure in prior 3 months
  - Reports from Philadelphia and 4 surrounding counties


Severe CDAD in Populations Previously at Low Risk—Four States, 2005 (2)

<table>
<thead>
<tr>
<th>Characteristic, No. (%)</th>
<th>Community (N=23)</th>
<th>Peripartum (N=10)</th>
<th>Total (N=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aged &lt; 18 years</td>
<td>11 (48)</td>
<td>0 (0)</td>
<td>11 (33)</td>
</tr>
<tr>
<td>Female</td>
<td>15 (65)</td>
<td>10 (100)</td>
<td>25 (76)</td>
</tr>
<tr>
<td>Antimicrobial exposure</td>
<td>15 (65)</td>
<td>9 (90)</td>
<td>24 (73)</td>
</tr>
<tr>
<td>Bloody diarrhea</td>
<td>6 (26)</td>
<td>2 (20)</td>
<td>8 (24)</td>
</tr>
<tr>
<td>Hospitalization necessary</td>
<td>6 (26)</td>
<td>4 (40)</td>
<td>10 (24)</td>
</tr>
<tr>
<td>ER visit necessary</td>
<td>3 (13)</td>
<td>2 (20)</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Relapse</td>
<td>8 (35)</td>
<td>5 (50)</td>
<td>13 (39)</td>
</tr>
</tbody>
</table>

Severe CDAD in Populations Previously at Low Risk—Four States, 2005 (3)

- Recent onset dates
  - February 26, 2003 – June 28, 2005
  - Only 1 case in 2003
- Transmission to close contacts in 4 cases
- 8 cases without antimicrobial exposure
  - 5 children; 3 required hospitalization
  - 3 had close contact with diarrheal illness
- Another 3 cases with < 3 doses of antimicrobials
- Clindamycin most common exposure (10 cases)
- Estimated minimum annual incidence of community-associated disease
  - 7.6 cases per 100,000 population
  - 1 case per 5,000 outpatient antimicrobial prescriptions

CASE: Pt with NSTEMI develops bacteremia, then surgery repair older infected R hip arthroplasty
On Day 9: 2 “loose stools” and c/o of explosive diarrhea
Pt "feels better" c/o 2x loose stool no blood not diarrhea
Positive C diff toxin A+B DX: C Diff Colitis Dx added
Pt r/o formed stools - no patient complaints diarrhea

<table>
<thead>
<tr>
<th></th>
<th>D2</th>
<th>D5</th>
<th>D8</th>
<th>D10</th>
<th>D14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alb</td>
<td>2.7</td>
<td></td>
<td>1.4</td>
<td></td>
<td>1.5</td>
</tr>
<tr>
<td>WBC</td>
<td>12.8</td>
<td>19.2</td>
<td>22.8</td>
<td>11</td>
<td>10.1</td>
</tr>
<tr>
<td>Scr</td>
<td>1.6</td>
<td>1.4</td>
<td>1.5</td>
<td>1.2</td>
<td>1.5</td>
</tr>
</tbody>
</table>

D8 New order Lactulose 15 cc PO TID titrate to 3 soft BM

D9 2x loose stool. pt c/o explosive diarrhea; Stool Assay C Diff toxin ordered; D/C Lactulose start Flagyl 500mg po TID; Cefazolin IV d/c and Cetriaxone IV started

D10 Pt “feels better” c/o 2x loose stool no blood not diarrhea
Positive C diff toxin A+B DX: C Diff Colitis Dx added

D11 Pt r/o formed stools - no patient complaints diarrhea

Patient Medication List
Admission duration 16 days

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin 1GM IV prophylaxis OR</td>
<td>D1</td>
</tr>
<tr>
<td>Cefazolin (Ancef) 1Gm IV Q8H</td>
<td>D4 - D11 7 DAYS</td>
</tr>
<tr>
<td>Metronidazole (Flagyl) 500mg po TID</td>
<td>D9 - D16 7 DAYS</td>
</tr>
<tr>
<td>Ceftriaxone (Rocephin) 1Gm IV Q24H</td>
<td>D11 - D16</td>
</tr>
<tr>
<td>Lactulose 15 cc PO TID titrate -3 soft BM 2 doses given</td>
<td>D9</td>
</tr>
<tr>
<td>Prilosec 40mg PO QD</td>
<td>D1 - D16</td>
</tr>
<tr>
<td>Rifaximin 200mg PO TID</td>
<td>D15 d/c after 3 doses</td>
</tr>
<tr>
<td>Metronidazole 500mg PO TID x 47 days</td>
<td>D16 DISCHARGE HOME LIST</td>
</tr>
<tr>
<td>Ceftriaxone 1Gm IV Q24H x42 days</td>
<td></td>
</tr>
<tr>
<td>Prilosec 40mg QD</td>
<td></td>
</tr>
</tbody>
</table>
What caused hospital acquired C. Diff. infection (CDI)? HA-CDI

- Anaerobic spore-forming bacillus
- Fecal-oral transmission through contaminated environment and hands of healthcare personnel
- Antimicrobial exposure is major risk factor for disease
  - Acquisition and growth of \textit{C. difficile}
  - Suppression of normal flora of the colon
- Clindamycin, Penicillins, and Cephalosporins, Fluoroquinolones

What’s On That Keyboard?
\textit{C. difficile} contamination in rooms of patients NOT in isolation for CDI

<table>
<thead>
<tr>
<th>Ward</th>
<th>Non-CDI rooms</th>
<th>Physician work areas</th>
<th>Nurse work areas</th>
<th>Portable equipment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord injury</td>
<td>7/22 (32%)</td>
<td>5/11 (45%)</td>
<td>0/2 (0%)</td>
<td>5/14 (36%)</td>
</tr>
<tr>
<td>Medicine</td>
<td>4/22 (18%)</td>
<td>5/11 (45%)</td>
<td>0/2 (0%)</td>
<td>5/14 (36%)</td>
</tr>
<tr>
<td>Surgery</td>
<td>4/28 (14%)</td>
<td>3/10 (30%)</td>
<td>1/5 (20%)</td>
<td>2/15 (12%)</td>
</tr>
<tr>
<td>Telemetry</td>
<td>1/14 (7%)</td>
<td>1/6 (17%)</td>
<td>0/1 (0%)</td>
<td>2/10 (20%)</td>
</tr>
<tr>
<td>Intensive care</td>
<td>1/19 (5%)</td>
<td>0/2 (0%)</td>
<td>0/2 (0%)</td>
<td>0/4 (0%)</td>
</tr>
<tr>
<td>Total</td>
<td>17/105(16%)</td>
<td>9/29 (31%)</td>
<td>1/10 (10%)</td>
<td>9/43 (21%)</td>
</tr>
</tbody>
</table>

Cleveland Veterans Affairs medical Center, Jan 2007
Point prevalence culture survey during an outbreak

Acid Suppression and CDI

- A retrospective case-control study at the Royal Victoria Hospital (Montreal) found PPI use was associated with an increased risk of CDAD (AOR 2.7, 95% CI 1.4-5.2).
  - This translates to one additional case of CDAD for every 21 patients treated with a PPI.
  - Risk of relapse was also increased (AOR 5.1, 95% CI 1.1-24.9).
- In the Pittsburgh outbreak both PPIs and H₂ blockers were associated with increased risk (OR 2.4 and 2.0 respectively).

Diarrhea is a common adverse drug reaction (ADR)

- acarbose
- antimicrobials (25% of drug-induced cases)
- biguanides
- bile salts
- colchicine
- cytotoxics
- dipyridamole
- gold preparations
- iron preparations
- laxatives
- leflunomide
- magnesium antacids
- metoclopramide
- misoprostol
- non-steroidal anti-inflammatory agents
- orlistat
- proton pump inhibitors
- ticlopidine

Case Discussion

- DAY 10 Lab result indicated Positive C. diff toxin A+B
- What caused hospital acquired C. Diff. infection (CDI)?

Risk Factors

- Advanced age
- Debilitated
- Antimicrobial exposure
- Acquisition toxigenic C. difficile
- Low serum antibody response Toxin A
Case Discussion: Is Flagyl 500mg po TID right choice for treatment?

- Mild, Moderate
- Severe
- Recurrent

CDI Severity
**C. difficile: The Ideal Rx**

- Get effective agent to site of infection
- Kill vegetative form
- Neutralize toxin
- Spare anaerobic flora
  - *B. fragilis* vanco MIC = ~ 250 mcg/ml
- Limit spore numbers
- Augment immune response
- Limit chance of relapse
- Block or prevent mucosal adherence

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**Pharmacology**

- Site of infection colonic lumen where *C. difficile* is located and toxin is produced.

<table>
<thead>
<tr>
<th></th>
<th>pK <em>A</em></th>
<th>pK <em>D</em></th>
<th>Colon Stool Concentration</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vancomycin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>125mg PO 4x Day</td>
<td>A- 0%</td>
<td>D-100%</td>
<td>1000 mcg/G &gt;1000 MIC</td>
<td>Maintained</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Flagyl IV or PO</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>500mg Q8H</td>
<td>A- 100%</td>
<td>D- 6-15%</td>
<td>9.3 mcg/G 1.3 mcg/G 4mg/L</td>
<td>Colonic inflammation required</td>
</tr>
</tbody>
</table>
**Metronidazole**
- Cheap
- PO absorbed rapidly and almost completely
- Fecal concentrations reflect secretion into colon
  - 9.3 mcg/g watery stools, 1.2 mcg/g formed stools
  - Undetectable in stools of asymptomatic *C. difficile* carriers
    - Little to no impact on colonic flora in healthy persons
- Inactivation by gut contents?
- Prolonged duration can cause polyneuropathy
  Bartlett JG. Clin Infect Dis 2006; 43: 428-431

**Vancomycin**
- Poorly absorbed given orally
  - Fecal concentrations ~ 500-1000 mcg/g
- IV used orally tastes bad
- Recommended: pregnant /lactating women
  - Teratogenic potential of metronidazole
- More effective than metronidazole in reducing epidemic strain numbers and toxin

Bartlett JG. Clin Infect Dis 2006; 43: 428-431
Adams SD, Mercer DW. Curr Opin Crit Care 2007; 13: 450-455
Oral Vancomycin vs Metronidazole in Mild and Severe Disease

Clinical Cure in Mild Disease ($n=81$)

Clinical Cure in Severe Disease ($n=69$)

Cure = resolution of diarrhea by day 6, negative toxin assay at days 6 and 10
Failure = persistence of diarrhea and/or toxin (+) after 6 days, colectomy, death


Prospective, randomized, double-blind, placebo-controlled trial (172 patients enrolled, 150 completed)

– Patients enrolled 1994-2002
– Vancomycin 125 mg PO QID x 10 days vs
– Metronidazole 250 mg PO QID x 10 days

Stratified by disease severity

Severe disease defined as:
– Intensive care unit admission
– Pseudomembranous colitis on endoscopy
OR ≥ 2 of the following
– Age > 60 years
– Temperature > 101°F
– Albumin level < 2.5 mg/dL
– WBC > 15,000 cell/mm³

Vancomycin More Effective Than Metronidazole vs. Severe CDI

Severe Defined as ≥ 10 BM/day; WBC ≥ 20,001/mm3; severe abdominal pain due to CDI

![Clinical success bar chart]


Toleramer
Vancomycin
Metronidazole

85%
79%
80%
76%
85%
65%

Clinical success
Mild
Moderate
Severe

Treatment Failures and Recurrences

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of studies</th>
<th>Treatment failure no. / total no. (%)</th>
<th>Recurrences no. / total no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metronidazole</strong></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</td>
<td>9</td>
<td>293 / 226 (13.2)</td>
<td>380 / 1877 (20.2)</td>
</tr>
<tr>
<td><strong>Vancomycin</strong></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</td>
<td>13</td>
<td>24/708 (3.4)</td>
<td>148/805 (18.4)</td>
</tr>
</tbody>
</table>


39

40
### Other Agents

- **Rifaximin (Xilantin)**
  - Non-absorbed antibiotic similar to rifampin – limited human data shows efficacy in CDAD.
  - Dose 200 mg TID
- **Nitazoxanide (Alinia)**
  - In one comparative study nitazoxanide 500 mg twice daily x 7-10 days was as effective as metronidazole
- **IVIG**
  - Provides “passive immunity”
  - Efficacy based upon anecdotal reports and case series.
  - Majority of published use has been in recurrent CDAD
  - High dose 300-500 mg/kg

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### Conclusion: Patients with CDI
**NOT from BI/NAP1/027 or with BI/NAP1/027**

- **D/C offending agent**
- **Pending an objective validated scoring system** members of IDSA for the SHEA expert committee state:
  - **SEVERE** = Leukocyte count ≥ 15,000 or Serum creatinine level increased by 50% baseline
- **SEVERE**: If no ileus then choose Vancomycin PO
- **Mild to Moderate**: Consider Flagyl 500mg po TID or Vancomycin 125mg po 4 x day
Rifamycins

- **Rifampin**
  - High colonic levels (Enterohepatic recirculation)
  - High frequency of resistance (U Pitt MC)
    - 173 / 470 (36.8%) total
      - 167 / 205 (81.5%) epidemic clone isolates
  - Drug interactions
  - Use with vancomycin (Poutanen SM CMAJ, 2004;171:51-58)

- **Rifaximin**
  - Not absorbed: 200 mg = stool concentrations up to 8,000 ug/g
  - Used with vancomycin = shorter time to culture negativity
  - Resistance reported and predicted by rifampin
    - Bartlett JG. Curr Infect Dis Reports 2009; 11: 21-28 (Jan)

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Metronidazole and Rifampin

Prospective, randomized, single-blind
- Study halted after 6 deaths in metronidazole + rifampin arm vs one death in metronidazole arm

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Metronidazole alone (n=20)</th>
<th>Metronidazole + rifampin</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to clinical improvement median days</td>
<td>6.5</td>
<td>9.0</td>
<td>.74</td>
</tr>
<tr>
<td>Time to clinical improvement mean days</td>
<td>6.6</td>
<td>7.0</td>
<td>.73</td>
</tr>
<tr>
<td>Clinical improvement at study day 10 (%)</td>
<td>13 (65%)</td>
<td>12 (63%)</td>
<td>.91</td>
</tr>
<tr>
<td>Time to relapse, median days</td>
<td>16</td>
<td>26</td>
<td>.23</td>
</tr>
<tr>
<td>relapse by study day 40, no. (%) patients</td>
<td>5/13 (38%)</td>
<td>5/12 (42%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Laboratory confirmed relapse at study day 40</td>
<td>4</td>
<td>2</td>
<td>.66</td>
</tr>
<tr>
<td>(no. patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compliance with therapy &gt; 70%, no. (%) patients</td>
<td>18 (90%)</td>
<td>14 (74%)</td>
<td>.18</td>
</tr>
</tbody>
</table>

Serial Therapy with Vancomycin and Rifaximin

- 8 patients with 4-8 episodes of CDAD
- Rifaximin 400-800 mg /day x 14 days
  - Immediately after vancomycin therapy
  - 400 mg q12h in 6 patients
  - 200 mg q8h in one, q12h in another
- 7 of 8 no further diarrhea recurrence
- One patient developed rifaximin-resistant CDAD
- Prospective study needed.


Nitazoxanide vs Metronidazole

- Nitazoxanide 500 mg q12h x 7 or 10 days or metronidazole 250 mg q6h x 10 days
- Prospective, double-blind, randomized trial

<table>
<thead>
<tr>
<th></th>
<th>Metronidazole 10 day</th>
<th>Nitazoxanide 7 day</th>
<th>Nitazoxanide 10 day (n=36)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response at 7 days</td>
<td>28 (82.4%)</td>
<td>368 (90%)</td>
<td>32 (88.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Response at 31 days</td>
<td>19 /27 (57%)</td>
<td>25 /34 (65.8%)</td>
<td>26 /31 (74.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Recurrence by 31 days</td>
<td>8 (23.5%)</td>
<td>9 (22.5%)</td>
<td>5 (13.9%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Response = complete resolution of all symptoms and signs attributable to CDI

Nitazoxanide vs Vancomycin

- Nitazoxanide 500 mg q12h or vancomycin 125 mg q6h x 10 days
- Prospective, double-blind, randomized trial

<table>
<thead>
<tr>
<th>Therapy result</th>
<th>Severe disease</th>
<th>Not severe disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vancomycin</td>
<td>Nitazoxanide</td>
</tr>
<tr>
<td></td>
<td>(n=10)</td>
<td>(n=10)</td>
</tr>
<tr>
<td>End of treatment response</td>
<td>7 (70%)</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>Relapse</td>
<td>1 (10%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Sustained response</td>
<td>6 (60%)</td>
<td>7 (70%)</td>
</tr>
</tbody>
</table>

Response = complete resolution of all symptoms and signs attributable to CDI

Small sample size precludes conclusions about noninferiority


Important principles to be aware of

- Perform testing for C. difficile only on unformed diarrheal stools
- Do not give prophylactic antimicrobial CDI therapy to patients at high risk for CDI.
- Do not treat or attempt to decolonize asymptomatic C. difficile carriers.
- Do not conduct repeated testing for C. difficile if a patient has had a stool sample positive for C. difficile (ie, do not perform TOC)
Antimotility Agents

- 20 published reports reviewed
- 55 patients treated with antimotility agents
  - 17 (31%) deteriorated
  - 6 / 15 (40%) with known outcomes died
  - complications or death:
    - Were all in "antimotility agent alone" group
    - None of the 23 who received metronidazole or vancomycin with antimotility agent
      - All 23 from one study in the UK from early 1990s
- Loperamide worsened 6 cases of CDI


Anion Exchange Resins

- Cholestyramine
  - Binds vancomycin
    - administer at least 2h after vancomycin
  - Lack of strong clinical evidence
- Colestipol
  - Failure
- Tolevamer
  - Inferior to metronidazole or vancomycin
  - Less relapse

Weiss K. Int J Antimicrob Agents 2009; 33: 4 - 7
Probiotics

- No clear cut evidence to support use
- *Lactobacillus rhamnosus* (Culturelle)
  - Seven cases of bacteremia reported
- *Saccharomyces boulardii*
  - 40 cases of fungemia reported
- Dietary supplements do not undergo rigorous testing
- Results are species and strain specific

McFarland LV. Am J Gastroenterol 2006; 101: 812-22

IVIG

- U Pitt Med Center Presbyterian between July 2001 and July 2003
- 79 patients
  - 8 received IVIG + standard therapy
    - 200-300 mg/kg x 1
- No beneficial response with IVIG
  - All cause mortality, length of stay, colectomy

<table>
<thead>
<tr>
<th>Standard therapy</th>
<th>IVIG therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success N (%)</td>
<td>Failure N (%)</td>
</tr>
<tr>
<td>Matched n=18 pairs</td>
<td>13 5</td>
</tr>
<tr>
<td>Unmatched (n=18 cases + 61 controls)</td>
<td>42 19</td>
</tr>
</tbody>
</table>

Fecal Transplant

- To restore fecal flora
- Administered via NG tube or PR
- Minimize risk of acquiring a disease by obtaining stool from individual with close physical connection
- Giving live organisms to sick patients
- Aas et al, described 18 retrospective cases (favorable response)


Impact of Colectomy

CDAD severe enough for ICU admission

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Had a colectomy n = 38 (died/total)</th>
<th>Did not have a colectomy n = 127 (died/total)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 75 yr</td>
<td>4/14 (29%)</td>
<td>46/68 (68%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Not immunosuppressed</td>
<td>6/27 (22%)</td>
<td>45/48 (51%)</td>
<td>0.001</td>
</tr>
<tr>
<td>WBC peak 20.0-49.9 x10⁹/L</td>
<td>6/28 (21%)</td>
<td>39/71 (55%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Peak lactate 2.2-4.9(mmol/L)</td>
<td>3/18 (17%)</td>
<td>23/46 (50%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

30 day mortality

No colectomy = 58%
Colectomy = 34% (p=.02)

Colectomy for Fulminant CDI

- Mount Sinai, NY
- Survival: 30 days 21/49 (43%); 5 year 8/21 (38%)
  - 20% GI reversal
- Avg age 70.5 yr, Multiple co-morbidities

- William Beaumont Hospitals, MI
- Jan 1 2000 – December 31, 2007
  - 69 (1%) underwent surgery for fulminant CDI
    - In-hospital mortality 29 of 69 (42%)
- Strongest predictors of death
  - acute respiratory failure, acute renal failure, Age > 65 yrs


Investigational Agents

<table>
<thead>
<tr>
<th>Type of agent, product name</th>
<th>Findings in humans</th>
<th>Trial status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antimicrobial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ramoplanin</td>
<td>Equivalent to vanco</td>
<td>Phase 3</td>
</tr>
<tr>
<td>OPT-80</td>
<td>Equivalent to vanco</td>
<td>Phase 2/3</td>
</tr>
<tr>
<td>rifaximin</td>
<td>Equivalent to vanco</td>
<td>Phase 2</td>
</tr>
<tr>
<td>tinidazole</td>
<td>None to date</td>
<td>Unknown</td>
</tr>
<tr>
<td>Nitazoxanide</td>
<td>Equivalent to metro</td>
<td>Phase 2</td>
</tr>
<tr>
<td>daptomycin</td>
<td>None to date</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Toxin binder</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tolevamer</td>
<td>Inferior to vanco</td>
<td>Phase 3</td>
</tr>
<tr>
<td><strong>Immunomodulator</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>monoclonal antibodies</td>
<td>None</td>
<td>Phase 2</td>
</tr>
<tr>
<td><em>C. difficile</em> vaccine</td>
<td>Decreased relapse</td>
<td>Phase 2</td>
</tr>
<tr>
<td>hyperimmune oral colostum</td>
<td>Decreased relapse</td>
<td>Phase 1</td>
</tr>
<tr>
<td>hyperimmune oral bovine</td>
<td>Decreased relapse</td>
<td>Phase 2</td>
</tr>
<tr>
<td>whey</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clin Infect Dis 2007; 45 (Suppl 2): S122-8 (Sept 1)
## Tolevamer vs Vancomycin

<table>
<thead>
<tr>
<th>variable</th>
<th>Tolevamer 3 gm (n=72)</th>
<th>Tolevamer 6 gm (n=70)</th>
<th>Vancomycin 500 mg (n=80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with resolution of CDI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (%)</td>
<td>48 (67)</td>
<td>58 (83)</td>
<td>73 (91)</td>
</tr>
<tr>
<td>Days to resolution of diarrhea (range)</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 vanco</td>
<td>&lt; .01</td>
<td>.53</td>
<td></td>
</tr>
<tr>
<td>Recurrence during Rx period</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Phase II study  
Primary endpoint = time to resolution of diarrhea (first of 2 consecutive days with 2 or less loose or watery stools or if formed stool)

Clin Infect Dis 2006; 43: 411-420, Aug 15

---

## Difimicin (OPT-80)

<table>
<thead>
<tr>
<th>Parameter or Outcome</th>
<th>Number (%) of patients in the following treatment groups showing clinical cure, failure or recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50 mg OPT 80 bid</td>
</tr>
<tr>
<td>Total patients</td>
<td>14</td>
</tr>
<tr>
<td>Diarrhea resolved by day 10</td>
<td>10 (71%)</td>
</tr>
<tr>
<td>Median time to resolution</td>
<td>6.3±3.7 days</td>
</tr>
<tr>
<td>Clinical failure</td>
<td>2 (14%)</td>
</tr>
<tr>
<td>Clinical recurrence</td>
<td>1 (8.3%)</td>
</tr>
</tbody>
</table>

Phase 2A dose ranging clinical trial of mild to moderate CDI  
Data support use of 200 mg twice daily in future trials

### Mild CDI

<table>
<thead>
<tr>
<th>Definition</th>
<th>Does not meet criteria for severe CDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Stop antibiotics&lt;br&gt;Test for CDI&lt;br&gt;metronidazole PO or IV</td>
</tr>
<tr>
<td>Dosage</td>
<td>500 mg q 6 h for 10-14 days</td>
</tr>
<tr>
<td>Response rate</td>
<td>90%</td>
</tr>
<tr>
<td>Strength and quality of evidence</td>
<td>A-I</td>
</tr>
</tbody>
</table>

Kelly CP. JAMA 2009; 301: 954-962 (Mar 4)

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### Mild CDI

Only treatment is simple discontinuation of treatment with the implicated antibiotic. This was a common ploy when the toxin test was done with use of the cytotoxin assay, which necessitated a 24–48-h delay in reported results.

This conclusion is supported by a Cochrane Library review, which states that “current evidence leads to uncertainty if mild CDI needs to be treated”.

**Mild CDI**  
**Treatment: Do Nothing**

- *C. difficile* present in up to 30% asymptomatic hospitalized patients
  - Do not treat
- For patients toxin (+) and with diarrhea
  - Discontinuation of antibiotic may suffice
    - Use less selective agent if not able to stop
- Avoid antiperistaltic and opiate agents
- Get Rob’s protocol
  - Pharmacotherapy 2006; 26: 299-311

Adams SD, Mercer DW. Curr Opin Crit Care 2007; 13: 450-455

---

**Severe CDI**

<table>
<thead>
<tr>
<th>Definition</th>
<th>ICU admit, Pseudomembranous colitis or any 2 of the following: age &gt;60 yr, temp &gt; 101F, albumin &lt; 2.5 mg/dL, WBC &gt; 15000/uL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Vancomycin PO</td>
</tr>
<tr>
<td>Dosage</td>
<td>125 mg q 6 h x 10-24 days</td>
</tr>
<tr>
<td>Response rate</td>
<td>97%</td>
</tr>
<tr>
<td>Strength and quality of evidence</td>
<td>A-I</td>
</tr>
</tbody>
</table>

Kelly CP. JAMA 2009; 301: 954-962 (Mar 4)
### If Ileus or unable to tolerate PO

<table>
<thead>
<tr>
<th>Definition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>metronidazole</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dosage</th>
<th>500 mg - 750 mg IV q6h x 10-14 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate</td>
<td>NA</td>
</tr>
<tr>
<td>Strength and quality of evidence</td>
<td>C-III</td>
</tr>
</tbody>
</table>

If possible, supplement with NG or PR vancomycin

Kelly CP. JAMA 2009; 301: 954-962 (Mar 4)

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### Refractory CDI

<table>
<thead>
<tr>
<th>Definition</th>
<th>Unresponsive to vancomycin and/or metronidazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Dosage</td>
<td>500 mg q6h x 10-14 days PO, NG, PR</td>
</tr>
<tr>
<td>Response rate</td>
<td>NA</td>
</tr>
<tr>
<td>Strength and quality of evidence</td>
<td>C-III</td>
</tr>
</tbody>
</table>

Kelly CP. JAMA 2009; 301: 954-962 (Mar 4)
## First Recurrence

<table>
<thead>
<tr>
<th>Definition</th>
<th>Symptomatic CDI after completion of course for initial episode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Metronidazole or vancomycin depending on severity</td>
</tr>
<tr>
<td>Dosage</td>
<td>Same as mild / moderate</td>
</tr>
<tr>
<td>Response rate</td>
<td>NA</td>
</tr>
<tr>
<td>Strength and quality of evidence</td>
<td>C-III</td>
</tr>
</tbody>
</table>

Kelly CP. JAMA 2009; 301: 954-962 (Mar 4)

39% of 122 primary care physicians queried would switch these patients to vancomycin.


## Second Recurrence

<table>
<thead>
<tr>
<th>Definition</th>
<th>Symptomatic CDI after completion of Rx for first recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Vancomycin prolonged course with taper/pulse</td>
</tr>
<tr>
<td>Dosage</td>
<td>125 mg q6h x 10-14d</td>
</tr>
<tr>
<td></td>
<td>q12h x 7d, q24 x 7d, q48h x8d, q72h x 15 d</td>
</tr>
<tr>
<td>Response rate</td>
<td>86%</td>
</tr>
<tr>
<td>Strength and quality of evidence</td>
<td>B-II</td>
</tr>
</tbody>
</table>


Kelly CP. JAMA 2009; 301: 954-962 (Mar 4)
Fulminant CDI

### Definition
- Progression to toxic megacolon or systemic manifestations (marked leukocytosis, hypotension, organ failure, anasarca)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Vancomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage</td>
<td>500 mg q6h x 10-14 days PO, NG, PR</td>
</tr>
<tr>
<td>Response rate</td>
<td>NA</td>
</tr>
<tr>
<td>Strength and quality of evidence</td>
<td>C-III</td>
</tr>
</tbody>
</table>
| Other modalities | IVIG 400 mg/kg IV x 1  
Fecal transplant  
Colectomy |

Kelly CP. JAMA 2009; 301: 954-962 (Mar 4)

Infection Control Strategies

- **Hand hygiene**
  - Gloves and hand washing with soap and water
- **Isolation and contact precautions**
  - Avoid sharing common rooms and toilets
- **Environmental disinfection**
- **Antimicrobial stewardship**
  - Avoid broad cephalosporins, clindamycin, other high risk agents
  - Avoid proton pump inhibitors also?
- **Education**
- **Surveillance**
  - Should monitor rate and severity of CDI

Efficacy of Hand Hygiene Methods for Removal of *C. difficile* Contamination from Hands

<table>
<thead>
<tr>
<th>Hand hygiene method</th>
<th>Decrease in colony counts (log CFU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WWS</td>
<td>1.8</td>
</tr>
<tr>
<td>CWS</td>
<td>1.8</td>
</tr>
<tr>
<td>WWA</td>
<td>1.4</td>
</tr>
<tr>
<td>AHW</td>
<td><strong>0.6</strong></td>
</tr>
<tr>
<td>AHR</td>
<td><em>-0.1</em>*</td>
</tr>
</tbody>
</table>

- Different from AHR (P<0.05)
- **Different from AHR and AHW (P<0.05)

CFU = colony forming units
WWS = warm water and soap
CWS = cold water soap
WWA = warm water and antibacterial
AHW = alcohol hand wipe
AHR = alcohol hand rub


Skin Contamination in CDI

Figure 2. Kaplan-Meier estimation of time from resolution of diarrhea (day 0) to negative results of culture specimens of abdomen and/or chest skin of patients with *Clostridium difficile*-associated disease.

Environmental Cleaning

- 2 interventions shown to be effective at interrupting disease transmission during CDI outbreak
  - Disinfection with sodium hypochlorite to minimize environmental contamination
  - Effective barrier precautions (primarily gloves)
- Sodium hypochlorite
  - 5000 ppm or a 1:10 dilution of household bleach prepared fresh daily
  - Noxious and caustic
- High concentration, vaporized hydrogen peroxide


The “Bundle” Approach

- Pittsburgh Medical Center – Presbyterian
- The “Bundle”
  - Education
  - increased and early case finding
  - Expanded infection – control measures
  - Development of CD infection management team
  - Antimicrobial management
- Rate decreased from 10.4 to 3.0 infections per 1000 hospital days

# Summary

- Prudent antimicrobial use
- Metronidazole for mild CDI
- Vancomycin for severe or unresponsive CDI
- What to do with everything else?
  - Probiotics: probably not of value
  - Value of IVIG?
  - Timing of colectomy?
- Good infection control policies critical
- Environmental cleaning

Kelly CP. JAMA 2009; 301: 954-962 (Mar 4)

## Patient Admission

duration 16 days

<table>
<thead>
<tr>
<th>Medication</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin 1GM IV prophylaxis OR</td>
<td>D1</td>
</tr>
<tr>
<td>Cefazolin (Ancef) 1Gm IV Q8H</td>
<td>D4 - D11 7 DAYS</td>
</tr>
<tr>
<td>Metronidazole (Flagyl) 500mg po TID</td>
<td>D9 - D16 7 DAYS</td>
</tr>
<tr>
<td>Ceftriaxone (Rocephin) 1Gm IV Q24H</td>
<td>D11 - D16</td>
</tr>
<tr>
<td>Lactulose 15 cc PO TID titrate -3 soft BM 2 doses given</td>
<td>D9</td>
</tr>
<tr>
<td>Prilosec 40mg PO QD</td>
<td>D1 - D16</td>
</tr>
<tr>
<td>Rifaximin 200mg PO TID</td>
<td>D15 d/c after 3 doses</td>
</tr>
<tr>
<td>Metronidazole 500mg PO TID x 47 days</td>
<td>D16 DISCHARGE</td>
</tr>
<tr>
<td>Ceftriaxone 1Gm IV Q24H x 42 days</td>
<td>HOME LIST</td>
</tr>
<tr>
<td>Prilosec 40mg QD</td>
<td></td>
</tr>
</tbody>
</table>
Thank You!

From JAMA 2009; 301; 988 (Mar 5) patient information sheet