A Modern Plague: *Clostridium difficile* and Inflammatory Bowel Disease

David G. Binion, M.D.
Co-Director, Inflammatory Bowel Disease Center
Director, Translational Inflammatory Bowel Disease Research
Division of Gastroenterology, Hepatology and Nutrition
UPMC Presbyterian Hospital
Visiting Professor of Medicine
University of Pittsburgh School of Medicine
Pittsburgh, PA

Disclosure

- Honoraria/consulting – UCB Pharma
- Investigator initiated studies – UCB Pharma

Overview

I. Background – *C. difficile*
II. Impact of *C. difficile* on IBD
III. Diagnostic considerations *C. difficile*
IV. Treatment considerations
**Clostridium difficile – the “difficult” bacteria**

- 1930’s - Bacillus difficillis first described as part of the normal flora of neonates.
- 1974 - C. difficile recognized as complication of Clindamycin use.
- 1978 – C. difficile identified as the cause of antibiotic-associated pseudomembranous colitis in humans.
- 1984 – ELISA testing for C. difficile.
- Clinical syndrome may range from watery diarrhea, abdominal pain, pseudo-membranous colitis, toxic megacolon, sepsis, colonic perforation and death.


**C. difficile: Changing spectrum of clinical disease**

- In the past: C. difficile linked to antibiotic use. Most cases treated successfully with metronidazole.
- Diminished therapeutic response to metronidazole (50% failure rate with initial course of treatment).


**Epidemic strains of C. difficile**

700 C. difficile related deaths in Quebec, Canada in one year (2003-4)
400 C. difficile related deaths annually in Quebec at the present time
BI/NAP1 Epidemic strain \textit{C. difficile}

- Regional outbreaks - Pittsburgh, PA, Quebec, Canada and the mid-Atlantic and southeastern U.S.

- \textit{C. difficile} in low risk populations – young individuals, peripartum women, community dwelling and in individuals with no exposure to antibiotics.


\textit{BI/NAP1 Epidemic strain \textit{C. difficile}}

\textit{C. difficile Epidemic in U.S.}

\textit{BI/NAP1 \textit{C. difficile} in U.S. Nov. 2007 (n = 38)}

\textit{BI/NAP1 \textit{C. difficile} in U.S. Oct. 2008 IDSA Meetings}

\textit{Centers for Disease Control and Prevention. Data & Statistics about \textit{Clostridium difficile} infections. www.cdc.gov/ncidod/dhqp/id_cdiff_data.html}

\textit{Current burden of \textit{C. difficile} in U.S.}

- October 2008 – BI/NAP1 has been isolated in all 50 states (IDSA).
- Total number of \textit{C. difficile} cases annually in U.S. is >500,000.
- Total number of \textit{C. difficile} related deaths annually in the U.S. is >15,000.
- Epidemic is predicted to worsen.
- Cause?
Where does the majority of antibiotic use occur in the U.S.?

- Poultry industry – antibiotic use to prevent diarrheal illness
- Corn fed beef require antibiotics to prevent bacterial overgrowth

Antibiotic use in food animal industry

- Colonization and carriage with the epidemic strain *C. difficile* (B1 NAP1 strain) reported in cows.
- *C. difficile* has been isolated from retail ground meat purchased in Canada.

References:
C. difficile infectious inoculum is 10 spores

C. difficile spores may be resistant to cooking. Source of bacterial food poisoning?

Are IBD patients contracting C. difficile in our clinics?

- C difficile spores will live in the environment for up to 60 days.
- Majority of IBD patients contract C difficile as outpatients.
- IBD patients have frequent contact with the outpatient clinic environment.
- Does the clinic/physician office pose a risk for C difficile infection?

C. difficile: Pathogenic mechanisms

1) Antibiotic destroys normal bacterial flora
2) C difficile grows and secretes toxins
3) Toxins inflame and ulcerate mucosa
4) Damaged mucosa secretes fluid causing diarrhea

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II. Impact of *C. difficile* on IBD

*Clostridium difficile*

- *C. difficile* and IBD present in identical fashion ranging from mild diarrhea to fulminant colitis.
- Early studies performed 2 decades ago indicated little overlap between *C. difficile* and IBD, concluding “No need for routine screening for *C. difficile* in IBD population”.
- Recent studies: Increasing incidence and severity of *C. difficile* in IBD population
- *C. difficile* recently identified to have a significant negative impact on IBD morbidity.


Increasing impact of *C. difficile* on IBD

Increasing Impact of *Clostridium difficile* on IBD

![Graph showing increasing impact of *Clostridium difficile* on IBD over time.](image)

Increasing Proportion of *Clostridium difficile* Patients With IBD

![Graph showing increasing proportion of *Clostridium difficile* patients with IBD over time.](image)

Complications: *Clostridium difficile* Infected Patients With IBD*

![Graph showing complications in *Clostridium difficile* infected patients with IBD.](image)
Endoscopic Appearance of *C. difficile*

Endoscopic appearance of *C. difficile* in control patients

Endoscopic appearance of *C. difficile* in patients with IBD

Ulcerative Colitis

Crohn’s Disease


Histologic appearance *C. difficile*

Control patient

Crohn’s disease patient

Classic pseudomembrane on histology—mucin, fibrin, necrotic debris

Extensive cryptitis crypt abscesses in Crohn’s colitis pt with active *C. difficile*. No inflammatory pseudomembranes are identified.


Demographic Data: IBD Patients With *C. difficile*

91% Colonic IBD

61% Recent antibiotic exposure

**Clostridium difficile in IBD: Morbidity and Mortality**

IBD patients with C. difficile compared with IBD alone:
- Longer hospital stay
- Increased hospitalization costs
- Higher colectomy rates
- Increased mortality rate –
  - 118 IBD C. diff deaths in NIS 2004
  - (>500 IBD C. diff deaths in U.S. 2004)
  - UC C. diff operative mortality 25%

**Clostridium difficile in IBD: Increasing U.S. hospitalizations 2004 - 2007**

**C. difficile in IBD: Asymptomatic carriage**

*Clostridium difficile* and host immune status
- Increased asymptomatic carriage of *C. difficile* in IBD – 8%
- IgG immune response to toxin A seen in 50% of patients.
- Immune response correlates with asymptomatic carriage.
- Inability to mount immune response may result in infection and chronic, relapsing clinical course.
**C. difficile in IBD: Impact of immunosuppression**

*Clostridium difficile* and IBD treatment

- Patients with most severe colitis with worse outcomes
- Maintenance immunosuppression correlated with infection (purine analogs, methotrexate)
- No association of anti-TNF therapy with *C difficile*.
- Corticosteroids associated with 3 fold increase in developing *C difficile* – inhibition of humoral immune response to toxin A?


**C. difficile and IBD: Summary**

*Clostridium difficile* and IBD

- Patients with colitis are at increased risk
- Maintenance immunosuppression correlated with infection (purine analogs, methotrexate)
- 10% of cases were new IBD presentations
- Contributes to flare in setting of new and longstanding disease in remission
- Recommend multiple stool samples for ELISA toxin A, B analysis. 54% of patients detected on first stool sample.
- No prompt response to metronidazole, consider vancomycin p.o.


**III. Diagnostic considerations: C. difficile in IBD**

- Laboratory
  - Leukocytosis
  - Hypoalbuminemia
- Radiographic
- Endoscopy - Pseudomembranes in 50% of patients with CDAD – rare in IBD patients.
- Leukocytosis, hypoalbuminemia, pseudomembranes are markers of severity
**Diagnosis of Clostridium difficile**

- Cell culture toxin assay (cytotoxicity) is the gold standard.
  - Excellent sensitivity.
  - Requires 24 – 48 hrs; labor intensive and expensive.
  - Performed in 15 hospitals in U.S. (total of 6,000 hospitals).
- ELISA for toxin A and/or B.
  - More rapid, less expensive and requires less expertise.
  - Sensitivity varies from 79% to 97%.
  - Performed in >90% of US hospitals at this time.
- PCR analysis of stool samples.
  - Sensitivity in IBD population?
- Stool culture.
  - Important for strain identification.
  - Too slow for routine clinical use.

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**C difficile cytotoxicity assay**

(A) Negative cell culture cytotoxicity assay.
- Human fibroblasts remain spindle-shaped and in contact with each other

(B) Positive cell culture cytotoxicity assay revealing cytopathic effects of C. difficile toxin B causing cell rounding and separation. (Courtesy of Ray Hariri, PhD)

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**Stool ELISA testing in IBD patients for C. Difficile toxins A and B**

![Stool ELISA testing chart](chart.png)

- A stool sample to reach 90% detection with ELISA
- Positive C. difficile ELISA

PCR assays for detection of *C. difficile* toxin genes in stool samples

<table>
<thead>
<tr>
<th>Gene Target</th>
<th>Chemistry/Manufacturer</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Gold standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>tcdB</td>
<td>Prodesse (Gen-Probe, Waukesha, WI, USA)</td>
<td>77.3</td>
<td>98.2</td>
<td>98.4</td>
<td>TC</td>
<td></td>
</tr>
<tr>
<td>tcdB</td>
<td>BD GeneOhm (BD Diagnostics, LaJolla, CA, USA)</td>
<td>96.4</td>
<td>99.1</td>
<td>94.9</td>
<td>Composite</td>
<td></td>
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<tr>
<td>tcdB</td>
<td>Cepheid (Sunnyvale, CA, USA)</td>
<td>97.1</td>
<td>93.0</td>
<td>72.3</td>
<td>99.4</td>
<td>Composite</td>
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<tr>
<td>tcdB</td>
<td>BD GeneOhm</td>
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<td>95.4</td>
<td>88.5</td>
<td>95.4</td>
<td>TC</td>
</tr>
<tr>
<td>tcdB</td>
<td>BD GeneOhm</td>
<td>83.6</td>
<td>98.2</td>
<td>89.5</td>
<td>97.1</td>
<td>Composite</td>
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<tr>
<td>tcdC</td>
<td>FRET</td>
<td>86.5</td>
<td>97.6</td>
<td>73.7</td>
<td>99.4</td>
<td>Composite</td>
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<tr>
<td>tcdB</td>
<td>SYBR green</td>
<td>93.3</td>
<td>97.4</td>
<td>78.6</td>
<td>99.4</td>
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<tr>
<td>tcdB</td>
<td>Taqman-FAM</td>
<td>87.1</td>
<td>96.5</td>
<td>78.0</td>
<td>99.2</td>
<td>Composite</td>
</tr>
</tbody>
</table>

Special IBD scenarios with *C. difficile*

*C. difficile* in ileo-anal Pouchitis
- Chronic refractory pouchitis
- Unresponsive to broad spectrum antibiotics
- *C. difficile* developed while patients were on metronidazole therapy
- 19% of pouch patients with *C. difficile*

*C. difficile* in segments of diverted bowel
- One case report of *C. difficile* in UC pt following subtotal colectomy with end-ileostomy.
- Treated successfully with 10 day course of metronidazole suppositories.

*C. difficile* enteritis: An early complication in IBD patients following colectomy
- Rare but associated with significant morbidity with mortality rates ranging from 60-83%
IV. Therapeutic considerations: 
*C. difficile* in IBD

- *C. difficile* isolation and contact precautions.
- Daily stool testing for *C. difficile* (until positive sample). Possibility for in-hospital acquisition.
- Empiric oral vancomycin from day 1, alone or in combination with metronidazole (IV or po).
- Maintain oral diet!
- Decrease corticosteroid dosing – steroids blunt humoral immunity and IgG response to toxin A is necessary to resolve CDAD.

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Approach for hospitalized IBD patients with 
Suspected/confirmed *C. difficile*

- *C. difficile* isolation and contact precautions.
- Daily stool testing for *C. difficile* (until positive sample). Possibility for in-hospital acquisition.
- Empiric oral vancomycin from day 1, alone or in combination with metronidazole (IV or po).
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Oral vancomycin vs metronidazole for *C. difficile*

<table>
<thead>
<tr>
<th></th>
<th>VANCOMYCIN</th>
<th>METRONIDAZOLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA-approved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Colonic levels</td>
<td>&gt; 500 mg/ml</td>
<td>0 - 10 mg/ml</td>
</tr>
<tr>
<td>Effectivity</td>
<td>++++</td>
<td>+++</td>
</tr>
<tr>
<td>Dosage</td>
<td>1g/6h</td>
<td>500mg/8h</td>
</tr>
<tr>
<td>Treatment</td>
<td>10 days</td>
<td>10 days</td>
</tr>
<tr>
<td>Failure rate</td>
<td>4%</td>
<td>13-14%</td>
</tr>
<tr>
<td>Relapse rate</td>
<td>10-25%</td>
<td>10-25%</td>
</tr>
<tr>
<td>Side effects</td>
<td>Limited</td>
<td>Significant</td>
</tr>
<tr>
<td>Response time (days)</td>
<td>3 days</td>
<td>4.6 days</td>
</tr>
<tr>
<td>Cost</td>
<td>4+++</td>
<td>+</td>
</tr>
</tbody>
</table>


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Oral vancomycin for *C. difficile*

- Only FDA approved drug for the treatment of *C. difficile*
- Tablets of vancomycin – shortages in past, high cost
- Patent for vancomycin tablets will expire at the end of 2010
- Parenteral (intravenous formulation) vancomycin for oral use
- Decreased cost – involves hospital pharmacy formulation
- Palatability can be improved
  - mouthwash “chaser”
  - Apple juice “chaser”
- Parenteral vancomycin for enema formulation

Decreasing colectomy rate among hospitalized IBD patients with *C. difficile*

Number of infections and rate of hospitalization remained constant, but significant decrease in colectomy rate.
- High index of suspicion
- Use of oral vancomycin
- Decreased corticosteroid dosing


![Graph showing changing outcomes over time](image)
Preventive strategies - *C. difficile*

- **Prophylaxis**
  - Limit exposure to antibiotics
  - MacFarland *et al.* Probiotics (*Saccharomyces boulardii*, *Lactobacillus rhamnosus GG*, and probiotic mixtures) effective for the prevention of CDAD (OR 0.59). Data was strongest with *S. boulardii*.
  - Environmental decontamination requires 10% sodium hypochlorite solutions.
  - Alcohol based hand gels are ineffective against spore-forming organisms. Soap and water dislodges spores from skin.

  Leischner, J., et al., American Society for Microbiology, 2005. ((abstract # LB 29)).

Refractory and recurrent *C. difficile* - I

**Refractory *C. difficile***:
- Intravenous immunoglobulin was used in a series of 14 patients (200 mg/kg). 64% responded. One patient required 2nd dose.
- Consideration for hypogammaglobulinemia associated IBD.

**Recurrent *C. difficile***:
- 59% of IBD patients (27 out of 46) had a recurrence.
  Of the recurring patients, one-quarter required colectomy.

*C. difficile* treatment regimens used:
1. Prolonged courses of vancomycin with or without pulse dosing (2 months)
2. Initial course of vancomycin followed by rifaximin maintenance course.


**C. difficile** Experimental Therapies

**Stool transplantation**:
- Following vancomycin course, PEG colonic prep, blended and filtered donor stool is introduced via naso-duodenal tube or via colonoscopy.

**Loop ileostomy – vancomycin flush (UPMC Protocol)**:
- Loop ileostomy is created in severely ill patients facing colectomy and vancomycin is perfused into the efferent limb.

**Monoclonal antibodies against *C. difficile* toxin A and B**:
- 200 non-IBD patients randomized to receive either monoclonal antibody against CDA and CDAB or placebo.
  Recurrence rates of *C. difficile* were 7% vs 25% (p<0.001).

**C. difficile toxin vaccine**:
- Inactivated *C. difficile* toxoids A and B were administered to 3 patients with recurrent disease, with no relapse.
### Summary and Conclusions - I

- *C. difficile* has doubled in North American Medical Centers in the past 5 years.
- IBD colitis patients have been affected at highest rate.
- *C. difficile* in IBD is associated with high rates of hospitalization and colectomy and increased mortality.
- Antibiotic use may not be required to precipitate infection.
- Endoscopic and Histologic appearance is frequently not classical – pseudomembranes not always present.
- Multiple stool ELISA samples for toxin analysis are required to make a diagnosis.

### Summary and Conclusions - II

- Metronidazole failure rate is 50%; Oral vancomycin may be superior in hospitalized patients.
- *C. difficile* enteritis may occur in post-colectomy patients and patients with ileoanal reconstruction.
- *C. difficile* recurrence rates are high.
- Early surgical consultation for patients developing severe disease (>10 BM/day, WBC>20K, severe abdominal pain, ileus).
- Hand washing with soap and water is essential to prevent nosocomial transmission.