Clostridium difficile and Inflammatory Bowel Disease

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Overview

I. Background – *C. difficile*

II. Impact of *C. difficile* on IBD

III. Diagnostic considerations *C. difficile*

IV. Treatment considerations
I. Clostridium difficile

- 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.
- 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 *C. difficile*

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

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

C. difficile Epidemic in U.S.

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

BI/NAP1 C. difficile in U.S. Oct. 2008 IDSA Meetings

Current burden of *C. difficile* in U.S.

- October 2008 – BI/NAP1 has been isolated in all 50 states (IDSA).
- Total number of *C. difficile* cases annually in U.S. is >500,000.
- Total number of *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.?
Antibiotic use in food animal industry

- Poultry industry – antibiotic use to prevent diarrheal illness
- Corn fed beef require antibiotics to prevent bacterial overgrowth
BI/NAP1 Epidemic strain *C. difficile* and food animals

- 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.

C. difficile infectious inoculum is 10 spores

Poutanen SM et al. CMAJ. July 6, 2004;171(1).
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 *C. difficile*: Pathogenic mechanisms

**Gut Lumen**

Colonic Mucosa

Fluid secretion

- Normal flora
- *C. difficile*
- Antibiotic
- Toxin
- PMN

Poutanen SM et al. CMAJ. July 6, 2004;171(1).
II. Impact of *C. difficile* on IBD

*Clostridium difficile*
**Clostridium difficile** and IBD

- *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. It concluded “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 *Clostridium difficile* on IBD

![Graph showing increasing number of patients affected by *Clostridium difficile* over years: 2001-2005.

Legend: P≤.01

Increasing Proportion of *Clostridium difficile* Patients With IBD

- **2000:** 4% C. diff patients
- **2001:** 7% C. diff patients
- **2002:** 16% C. diff patients

*p* <= 0.01

**Number of Patients**

- **Total C. diff patients**
- **IBD patients with C. diff**

Complications: *Clostridium difficile*
Infected Patients With IBD*

Hospitalizations

Colectomies

Endoscopic Appearance of *C. difficile*

Endoscopic appearance of *C. diff* in control patients

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

Ulcerative Colitis  Crohn’s Disease

Histologic appearance *C. difficile*

Control patient

Classical pseudomembrane on histology—mucin, fibrin, necrotic debris

Crohn’s disease patient

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. difficile* deaths in NIS 2004
  - (>500 IBD *C. difficile* deaths in U.S. 2004)

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.
Diagnosis of *Clostridium difficile*

- Cell culture toxin assay is the gold standard
  - excellent sensitivity
  - requires 24 – 48 hrs; labor intensive and expensive

- ELISA for toxin A and B
  - More rapid, less expensive and requires less expertise
  - Sensitivity varies from 79% to 97%.
Stool ELISA testing in IBD patients for *C. Difficile* toxins A and B

Special IBD scenarios with *C. difficile*

**C. difficile** in ileo-anal Pouchitis

- Two case reports
  - Chronic refractory pouchitis
  - Unresponsive to broad spectrum antibiotics
  - In both cases *C. difficile* developed while patients were on metronidazole therapy

**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.

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C. difficile enteritis: An early postoperative 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
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).
- Maintain oral diet!
- Decrease corticosteroid dosing – steroids blunt humoral immunity and IgG response to toxin A is necessary to resolve CDAD.
Oral vancomycin vs metronidazole for *C. difficile*

<table>
<thead>
<tr>
<th></th>
<th>VANCOMYCIN</th>
<th>METRONIDAZOLE</th>
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</thead>
<tbody>
<tr>
<td>FDA-approved</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Colonic levels</td>
<td>&gt; 500 mcg/ml</td>
<td>0 -10 mcg/ml</td>
</tr>
<tr>
<td>Effectivity</td>
<td>++++ Superior</td>
<td>++++ Inferior</td>
</tr>
<tr>
<td>Mild</td>
<td></td>
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<tr>
<td>Severe</td>
<td></td>
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<tr>
<td>Promotion of VRE</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Failure rate</td>
<td>4%</td>
<td>13-16%*</td>
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<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>
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<tr>
<td>Response (median time)</td>
<td>3 days</td>
<td>4.6 days</td>
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**Cost**
- **Vancomycin**: ++++
- **Metronidazole**: +

References:
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

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 in S. boulardii
- Environmental decontamination requires 10% sodium hypochlorite solutions.
- Alcohol based hand gels are in-effective against spore-forming organisms. Soap and water dislodges spores from skin.

Refractory and recurrent *C. difficile*

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

**Recurrent C. difficile:**
- 27 out of 46 IBD patients (59%) 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.
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 a 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.
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.

Hand washing with soap and water is essential to prevent nosocomial transmission.