Clostridium Difficile Colitis

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What is Clostridium Difficile

- Gram positive rod
- Produces spores (hang out in diverticula)
- Forms Endotoxin A + B which cause diarrhea.
  - Of interest, levels of endotoxin do not predict severity of symptoms.
Antibiotics associated with C. Diff Colitis

- Frequent- Clinda/Amp/Amox/Cephalosporins
- Intermediate- PCN/Bactrim/Erythro/Quinolones
- Rare to never- Tetracycline/Metro/Vanco/parenteral amioglycosides
Clinical Manifestations

- The typical presentation is acute watery diarrhea with lower abdominal pain, low grade fever, and leukocytosis, starting during or shortly after antibiotic administration (but cases 6 months after abx).

- Reactive arthritis is a rare complication of C. difficile infection.
<table>
<thead>
<tr>
<th>Type of infection</th>
<th>Diarrhea</th>
<th>Other symptoms</th>
<th>Physical examination</th>
<th>Sigmoidoscopic examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic carriage</td>
<td>Absent</td>
<td>Absent</td>
<td>Normal</td>
<td>Normal</td>
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<tr>
<td>Antibiotic-associated diarrhea without colitis</td>
<td>Mild to moderate</td>
<td>Crampy lower abdominal discomfort</td>
<td>Slight lower abdominal tenderness</td>
<td>Normal</td>
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<tr>
<td>Antibiotic-associated colitis without pseudomembrane formation</td>
<td>Profuse – 10 or more loose bowel movements per day; fecal leukocytes present; occult bleeding may be seen; hematochezia rare</td>
<td>Nausea, anorexia, fever, malaise, dehydration, leukocytosis with left shift</td>
<td>Abdominal distention, tenderness</td>
<td>Diffuse or patchy nonspecific colitis</td>
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<tr>
<td>Pseudomembranous colitis</td>
<td>More profuse than in colitis without pseudomembranes; fecal leukocytes present; occult bleeding may be seen; hematochezia rare</td>
<td>Nausea, anorexia, fever, malaise, dehydration, leukocytosis with left shift; symptoms may be more severe than in colitis without pseudomembranes</td>
<td>Marked abdominal tenderness, distension</td>
<td>Characteristic raised, adherent, yellow plaques, diameter 2-10 mm; rectosigmoid sparing in 10 percent of cases; pseudomembranes may not be noted unless colonoscopy performed</td>
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<tr>
<td>Fulminant colitis</td>
<td>May be severe or may decrease due to the development of paralytic ileus and colonic dilatation</td>
<td>Lethargy, fever, tachycardia, abdominal pain; dilated colon/paralytic ileus may be demonstrated on plain abdominal film</td>
<td>May present as acute abdomen; peritoneal signs suggest perforation</td>
<td>Sigmoidoscopy and colonoscopy contraindicated; flexible proctoscopy with minimal air insufflation may be diagnostic</td>
</tr>
</tbody>
</table>
When to call surgery

- 1 to 3 percent of patients develop severe signs and symptoms requiring emergency colectomy because of impending perforation, severe ileus with megacolon, or refractory septicemia.
- Risk factors for the development of severe colitis are malignancy, COPD, immunosuppressive therapy, ESRD, or exposure to antiperistaltic medications or clindamycin.
Indications for surgery

- peritoneal signs,
- bacteremia unresponsiveness to antibiotics,
- progressive fever, rigors, an elevated white blood cell count
- CT scan evidence of significant pericolonic inflammation with increasing bowel wall edema.
**Pseudomembranous colitis** Endoscopic appearance of Clostridium difficile-induced pseudomembranous colitis. Left panel: Scattered pseudomembranes are visible on top of the mucosa, being separated by areas of relatively normal mucosa. Some of the lesions have a red halo (arrows), Right panel: Yellow pseudomembrane circumferentially covering the entire colonic mucosa. Courtesy of James B McGee, MD.
Epidemiology

• C. difficile is the leading cause of nosocomial enteric infection.
• Three million new cases in United States hospitals each year, affecting as many 10 percent of patients hospitalized for more than two days.
• 20,000 outpatients acquire this infection yearly.
Who does it affect?

• Elderly, debilitated individuals, especially those who are admitted to the hospital.
• Exposure to multiple antibiotics, gastrointestinal surgery, and exposure to an infected roommate.
One report studied the incidence and transmission of C. difficile infection among 428 patients admitted to a general hospital over an 11-month period. The following findings were noted:

- 29 patients (7 percent) had positive cultures at the time of admission, most of whom were exposed to antibiotics at home or in nursing homes.
- 83 patients (19 percent) with negative cultures at the time of admission became infected during their hospital stay.
- Diarrhea developed in 35 to 40 percent of patients who were or became culture-positive; the remainder were classified as asymptomatic carriers.
Carriers

• Carriers are seldom recognized or treated
  – reservoir of infection in hospitals.
• Carriers interact in a fundamentally different way with C. difficile than do patients who develop symptoms.
• Carriers and symptomatic patients are often colonized with identical strains
Why are carriers different?

- serum IgG antibodies directed against Endotoxin A
  - those with high antibody levels directed against toxin A have very few symptoms although culture positive.
  - In contrast, those who lack sufficient immunologic response have increasing symptoms.
Relapse

- 10-25% relapse rate after standard Vancomycin/Metronidazole treatment for 10-14 days.
- Theories
  - Clostridium spores in diverticula
  - Decreased anti toxin A IgG levels (immunologic response). Don’t mount sufficient response.
Treatment in 1st time relapse

• Repeat C.Diff Cx, cytotoxin assay, colonoscopy. Look for other causes of diarrhea.
• If sx’s mild-conservative tx with no abx.
• If elderly, thin, evidence of colitis treat with 2nd course of Metronidazole/Vancomycin 10-14 days.
Use Metronidazole or Vancomycin in multiple relapse?

• Vancomycin and metronidazole were studied in 163 pts with multiple relapses.
• Vancomycin, especially in tapering or pulsed doses, was more effective than metronidazole and resulted more often in clearance of both toxin and the organism from stool at the end of therapy.
Pulse therapy with Vancomycin

• Allow time for spores to grow then “nab” with vancomycin
• To be used in pts with multiple bouts.
  – Week 1 - Vanco 125mg QID
  – Week 2 - Vanco 125mg BID
  – Week 3 - Vanco 125mg QD
  – Week 4 - Vanco 125mg QOD
  – Week 5 - Vanco 125mg Q three days.
Further treatment options if continued relapse.

- Used concomitantly with Vancomycin:
- Microorganisms such as lactobacillus/Saccharomycyes boulardii, a non-pathogenic yeast used widely in continental Europe to prevent antibiotic-associated diarrhea
Is there evidence for use of S. boulardii?

• prospective double-blind controlled study randomized hospitalized patients who were treated with antibiotics to placebo or oral capsules containing viable S. boulardii. Over 23 months, 180 patients completed the study.

• Two major advantages were noted
  – a significant reduction in the incidence of simple antibiotic-associated diarrhea (10 versus 22 percent with placebo)
  – among 48 patients who became C. difficile-positive, a trend toward a lower incidence of diarrhea (9.4 versus 31 percent, p = 0.07). C. difficile toxin was found in the stool in almost all patients with diarrhea and approximately 16 percent of those without diarrhea.
A second randomized placebo-controlled trial examined the efficacy of *S. boulardii* (1 g/day for four weeks) in combination with either vancomycin or metronidazole in 124 patients with *C. difficile* diarrhea.

- *S. boulardii* had no effect on relapse rates in 64 patients who were treated for a first episode of *C. difficile* diarrhea (19 versus 24 percent with placebo, *p* = 0.86).

- In contrast, *S. boulardii* was associated with a significant reduction in the relapse rate in the 60 patients who had a history of at least one prior episode of *C. difficile* diarrhea (35 versus 47 percent, *p* = 0.02).
Concomitant treatments continued.

- anion-binding resins (6 week course)
  - Colestipol 5mg PO Q12
  - Cholestyramine 4g TID
  - Since binding resins also bind Vancomycin, must stagger dosing 2-3hrs before or after abx administration. (uncontrolled study 11 pts)

- Immunoglobulin- less favorable.
References


• Uptodate - Treatment of recurrent C, Difficile Infections. - Kelley, LaMont 7/02