Update on *Clostridium difficile* Colitis

*Clostridium difficile* infection has recently emerged in populations without any known risk factors. This presentation will focus on the historical background, diagnosis, and treatment of *Clostridium difficile* colitis. The discussion will also address the means for control and prevention of infection.

**Objectives:**

- Develop an understanding of the differential diagnosis of pseudomembranous colitis
- Develop an understanding of the risk factors for *Clostridium difficile* infection
- Develop a basic understanding of the diagnosis and treatment of *Clostridium difficile* infection
Update on the Newest Emerging Infection: Community-Associated *Clostridium difficile* Colitis

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**Clostridium difficile** Colitis

- Well-recognized iatrogenic complication of antibiotics use
- 15%-25% of all cases of antibiotic-associated diarrhea
- Wide spectrum of disease severity
- Likelihood increases with severity of the disease
- 95%-100% cause of antibiotic-associated pseudomembranous colitis

**Historical Background**

- 1935: *C. difficile* described
- 1943: Penicillin and typhlitis connection
- Early 1950s: Pseudomembranous colitis (PMC) & antibiotic use
  - *Staphylococcus aureus* suspected pathogen
  - Oral vancomycin standard therapy
C. difficile Era

- 1974: Reports of high rates of PMC among patients on clindamycin
- Stool cultures negative for S. aureus
- 1978: Cytopathic toxin that was neutralized with Clostridium sordellii antitoxin
- Search for the species began
- Reported in NEJM in 1978
- 2000: Emergence of a toxin hyperproducing strain (BI/NAP1/027)
  - Some with no history of antibiotic exposure

BI/NAP1/027

- More severe diseases, more refractory to therapy
- Higher rates of relapse, toxic megacolon
- Requiring colectomy, associated shock & death
- Produces more toxins A & B in vitro
- Absence of tcdC, a genetic sequence responsible for downregulation of toxin production
- Presence of binary toxin (role unclear)
- In vitro resistance to fluoroquinolones

Pseudomembranous Colitis

- Lesions nearly always limited to the colon
- S. aureus enterocolitis commonly involves small bowel
- Anatomic lesions best detected by colonoscopy
- 20%-30% of lesions limited to proximal colon
- Sigmoidoscopy may miss proximal lesions
- CT can also be helpful
Pseudomembranous Colitis
Differential Diagnosis

- Intestinal obstruction
- Colon cancer
- Leukemia
- Severe burns, shock, uremia
- Heavy metal poisoning
- Hemolytic-uremic syndrome
- Crohn’s disease
- Shigelllosis
- Neonatal necrotizing enterocolitis, ischemic colitis
- Hirschsprung disease

Risk Factors

- Hospitalization, LTCFs
  - Risk increases with duration of hospital stay
- Age > 65 years
  - Neonates: High rates of *C. difficile* colonization
- Antibiotic exposure
  - Cephalosporins, broad-spectrum penicillins
  - Fluoroquinolones
  - Less common with other classes
- Methotrexate
- Use of acid-suppressive therapy (controversial)
- GI surgery or GI procedures

Clinical Presentation

- Watery diarrhea (gross blood is rare)
- 15-30 bowel movements/day
- Abdominal cramps
- Lower quadrant abdominal pain (~22%)
- Low grade fever (~28%)
- Leukocytosis (~50%)
  - Can be in leukemoid range
- Low albumin
Diagnosis

- Cell cytotoxicity assay
  - Long turnaround time, expensive, not widely available
- Enzyme immunoassays (EIA)
  - Detects toxins A & B
  - Standard for most laboratories in the US, inexpensive, fast results (< 4 hours)
- EIA test for common antigen
- Stool culture
- Combination of tests

Treatment

- Supportive care, withdrawal of implicated antibiotic
- Avoidance of antiperistaltics
- Metronidazole (250 mg qid or 500 mg tid x 10 days)
  - Lower cost
  - Relatively high failure rates in recent reports
  - Slower clinical response compared to oral vancomycin
  - Recommended for less severe disease
- Oral vancomycin (125-250 mg qid x 10 days)
  - Only drug that is FDA approved
  - Not absorbed in colon; very high levels
  - Concern for vancomycin-resistant enterococcus (debatable)
  - Recommended for severe disease or those not responding rapidly to metronidazole

Severe Disease

- Leukocyte count $\geq 15,000$ cells/mm$^3$ or
- Creatinine increased by $\geq 50\%$ from baseline
- Requires admission to ICU
- Develops severe sepsis or septic shock
- Develops megacolon
- Requirement for colectomy
Potential Future Therapies

- Nitazoxanide, rifaximin
- Toxin-binding polymer
- Tolevamer
- Poorly absorbed antimicrobials
  - OPT-8 (Difimicin)
  - Ramoplanin
- Monoclonal antibodies
- *C. difficile* vaccine

Complications

- Recurrence following discontinuation of therapy (~20%)
- Recurrence of identical symptoms within 8 weeks after therapy is discontinued
- 50% due to infection with new strain of *C. difficile*
- Failure to mount an immune response
  - Low levels of IgG against toxin A

Control & Prevention Measures

- Multifactorial
- Isolation, contact precaution
- Environment (room cleansing with 10% bleach)
- Personnel hygiene
- Ineffective: Alcohol-based hand sanitizers
- Effective: Hand washing with chlorhexidine or with soap and water
- Antimicrobial stewardship
Recommended Readings