Severe and Complicated *Clostridium difficile* Colitis

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Disease Demographics

- C. *difficile* is an anaerobic, Gram-positive, spore-forming rod that can produce exotoxins that are damaging to the colonic mucosa.
- The bacterial toxin is capable of causing significant systemic inflammation.
- Colonization with the inactive spore occurs in 2-3% of healthy adults and 20-50% of hospitalized patients.
- Although many strains have been identified, only strains that produce toxins A and B cause symptomatic disease.
- Since 2000, there has been a significant rise in incidence and severity of C. *difficile* infection (CDI).
- C. *difficile* is the primary pathogen responsible for antibiotic-associated colitis.
- Death as a direct result of infection occurs in up to 6.9% of cases.
- An estimate of the additional hospital costs due to CDI in the U.S. is $3.2 billion per year (2000-2002).
- The period between exposure to C. *difficile* and the occurrence of CDI has been estimated to be a median of 2-3 days.
- Transmission is via the fecal-oral route.

Risk Factors for Disease

- Advanced age > 64 years
- Hospitalization
- Exposure to antimicrobial agents (most important modifiable risk factor)
- Cancer chemotherapy
- GI surgery or manipulation of the GI tract
- Inflammatory bowel disease
- Proton Pump Inhibitors
- Immunosuppression
- BMI $\geq$ 35

Clinical Presentation

- Clinical manifestations range from symptomless carriage to mild or moderate diarrhea, to fulminant and sometimes fatal pseudomembranous colitis.
- Patients generally present with diarrhea, however, those with severe disease may develop a colonic ileus or toxic dilatation and present with abdominal pain and distention but with minimal or no diarrhea.

Evaluation/Diagnostics/Imaging

- Evaluation: Screen for all risk factors (see above).
- Diagnosis:
  - Presence of diarrhea AND stool positive for:
    - Cytotoxin A or B via culture OR
    - PCR for the gene responsible for toxin production
  - OR Endoscopic or histopathologic findings demonstrating pseudomembranes
- Imaging:
  - Abdominal radiographs are insensitive but may show free air, colonic dilation, mucosal edema, haustral thickening or thumb-printing.
  - Computed tomography may demonstrate continuous or segmental colonic thickening, peri-colonic stranding, severe colonic distention, free air, pneumatosis, ascites or portal-venous gas.
- Additional data:
  - CBC, serum electrolytes, lactate and arterial blood gas
  - Send stool for ova and parasites and culture.
  - Endoscopy: Not mandatory, but is diagnostic of CDI if pseudomembranes are present. Minimize insufflation. Do not biopsy.

Classification

Several scoring systems have been described to aid in classifying the severity of CDI

- SHEA/IDSA Guidelines:
  - Mild to moderate disease: WBC < 15,000 and Cr < 1.5x baseline
  - Severe disease: WBC ≥ 15,000 and Cr > 1.5x baseline

- Zar Criteria

Parameter	Finding	Points
Age (years)	≤ 60 years	0
	> 60 years	1
Temperature (˚C)	≤ 38.3 ˚C	0
	> 38 ˚C	1
Albumin	≥ 2.5 g/dL	0
	< 2.5 g/dL	1
WBC Count	≤ 15,000	0
	> 15,000	1
Pseudomembranes	No	0
	Yes	2
ICU Admission	No	0
	Yes	2

  - A score of 0 or 1 indicates mild disease. A score of ≥ 2 is severe disease

- Dallal et al. 2002

Severity	HR	% Bands	RR	Oliguria	Hypotension
Mild	Normal	Normal	Normal	None	Absent
Moderate	> 90	>10%	Mild tachypnea	Volume responsive	>100 systolic
Fulminant	> 120	>30%	Mech ventilation	Severe	Vasopressors

- Neal et al. 2011

Criteria	Points
Immunosuppression and/or chronic medical condition	1
Abdominal pain and/o distention	1
Hypoalbuminemia (<3 g/dL)	1
Fever > 38.3 ˚C	1
ICU admission	1
CT scan with findings of pancolitis, ascites, and/or bowel wall thickening	2
WBC count >15,000 or < 1,500 and/or bands > 10%	2
Creatinine 1.5x > baseline	2
Abdominal peritoneal signs	3
Vasopressors required	5
Mechanical ventilation required and attributed to CDAD	5
Disorientation, confustion, or decreased consciousness	5

  - 1-3 points “mild-moderate” disease
  - 4-6 points “severe” disease
  - ≥ 7 points “severe/complicated” disease

- The term “Complicated/Fulminant CDI” has been used to describe cases with shock, megacolon, perforation, need for ICU admission, emergency colectomy or death within 30 days of diagnosis.

Role of Non-operative Management and Associated Considerations

- Discontinue inciting antibiotics if possible
- Avoid anti-peristalstic agents as they may precipitate toxic megacolon (opiods and anticholinergics).
- Institute hospital infection control and environmental management measures.
- Healthcare workers must use gowns and gloves and practice hand hygiene with soap and water.
- Patients with mild to moderate disease should be given a trial of antibiotics and clinically observed for signs of improvement/deterioration.
- Mild to moderate: Metronidazole 500 mg P.O. TID x 10-14 days
- Severe: Vancomycin 125 mg P.O. QID x 10-14 days. Consider surgical consultation.

- Severe complicated:
    - Vancomycin 500 mg P.O. QID and Metronidazole 500 mg IV Q 8 hours.
    - If ileus add Vancomycin 500mg in 100mL normal saline per rectum Q 6 hours. P.R. QID x 10-14 days (retention enema).
    - Obtain a Surgical consultation. Strongly consider surgical management.
- Fidaxomicin (recently approved by FDA in U.S.). Reported to perform similarly to oral Vancomycin.
- Although rare, the small bowel can be infected with C. *difficile*. This should be treated with antibiotics.

Indications for Operative Intervention

- Peritonitis, worsening abdominal distention/pain, sepsis, new onset ventilatory failure, new or increasing vasopressor requirement, mental status changes, unexplained clinical deterioration, nonimproving or worsening WBC count >20K or < 3K despite appropriate antibiotics for 96 hours, nonimproving and worsening bandemia (>10%) despite appropriate antibiotic therapy for 96 hours.

Pre-operative Preparation

- Adequate I.V. access, intraoperative monitoring and pre-operative volume resuscitation
- Antibiotics dosed as scheduled

Operative Techniques/ Intra-operative Considerations

Options for surgical management:

1. Total abdominal colectomy (TAC) with end ileostomy
    - Indications: CDI with colon perforation or bowel ischemia
    - More often than not, the serosal surface of the colon will appear "uninvolved" intraoperatively as C. *diff* colitis is a mucosal disease. Do not let this affect your decision to perform a TAC with end ileostomy.
    - The rectum is generally spared in CDI and can therefore remain in situ
    - If the rectum is diseased on endoscopic evaluation, the colon should be removed and the rectum treated with systemic antibiotics.
    - Studies have shown that even in patients with only segmental disease, segmental resection results in a higher overall mortality. Therefore, should the plan be for a resection, the accepted approach is a TAC with end ileostomy.
2. Laparoscopic/open ileostomy with lavage
    - Indications: CDI with any indication for surgical management (excluding colon perforation or ischemia)
    - Technique/Protocol (Neal et al. 2011):
        - Open or laparoscopic evaluation of the colon to determine viability (only contraindication to laparoscopy is abdominal compartment syndrome). In such a case, ileostomy should be performed after an open decompressive laparotomy.
        - Creation of a loop ileostomy
        - Intraoperative antegrade lavage of the colon with instillation of 8 liters warmed polyethylene glycol and collected via rectal tube.

    - Postoperative Vancomycin irrigation (500mg in 500mL LR) every 8 hours for 10 days via Malecot catheter left in the efferent limb of the ileostomy
    - Metronidazole I.V. every 8 hours for 10 days
  - A recent multi-center EAST trial retrospectively evaluated the previously described loop ileostomy protocol (LI) with total abdominal colectomy (TC) for management of severe complicated C. difficile-associated disease (CDAD). Results showed no statistically significant difference between the groups with respect to ventilator days, ICU LOS, hospital LOS, complication rate or overall reoperation rates. The authors did report a statistically significant difference in adjusted mortality between the two groups (LI 17.2% vs. TC 39.7%; p=0.002).

Post-operative Management/ Complications

- Monitor end organ perfusion
- Continue antibiotics as directed and while signs of sepsis are present
- Optimize pre-existing medical conditions
- Optimize nutritional status

Suggested Readings

- Clinical Practice Guidelines for Clostridium *difficile* Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA).
- Steele et al. Practice Parameters for the Management of Clostridium *difficile* Infection. Dis Colon Rectum 2015; 58: 10-24.
- Seltman Ann. Surgical Management of Clostridium difficile Colitis. Clin Colon Rectal Surg. 2012 Dec; 25(4): 204-209.
- Ferrada et al. Loop ileostomy versus total colectomy as surgical treatment for Clostridium *difficile*-associated disease: An Eastern Association for the Surgery of Trauma multicenter trial. J Trauma Acute Care Surg 2017 July; 83(1): 36-40.
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- Dallal et al. Fulminant Clostridium difficile: an underappreciated and increasing cause of death and complications. Ann Surg. 2002 Mar; 235(3):363-372.
- Neal et al. Diverting loop ileostomy and colonic lavage: An alternative to total abdominal colectomy for the treatment of severe, complicated clostridium difficile associated disease. Ann Surg. 2011 Sept; 254(3):423-429.