

CLOSTRIDIUM DIFFICILE COLITIS - 2

Epidemiology

- Leading cause of nosocomial enteric infections
- Estimated 3 million new cases of C. Diff diarrhea and colitis each year
- Affecting over 10% of patients hospitalized for >2 days
- In contrast, only affects 20,000 outpatients annually

Risk factors

- Among patients treated with antibiotics; additional risk factors affect likelihood of infection
 - Elderly, debilitated
 - Multiple antibiotics
 - exposure to infected roommates
 - Tube feeds ----- may be due to handling and contamination of equipment by health care workers

Transmission

- In approximately 50% of rooms occupied by patients with C. diff infection, the organism can be cultured from various surfaces in the room
- Toilets, bedpans, floors, scales, furniture may all carry spores of C. Diff
- Transmission via hands, clothing, and stethoscopes of health care workers common
- Using exam gloves and careful hand washing reduces transmission of infection

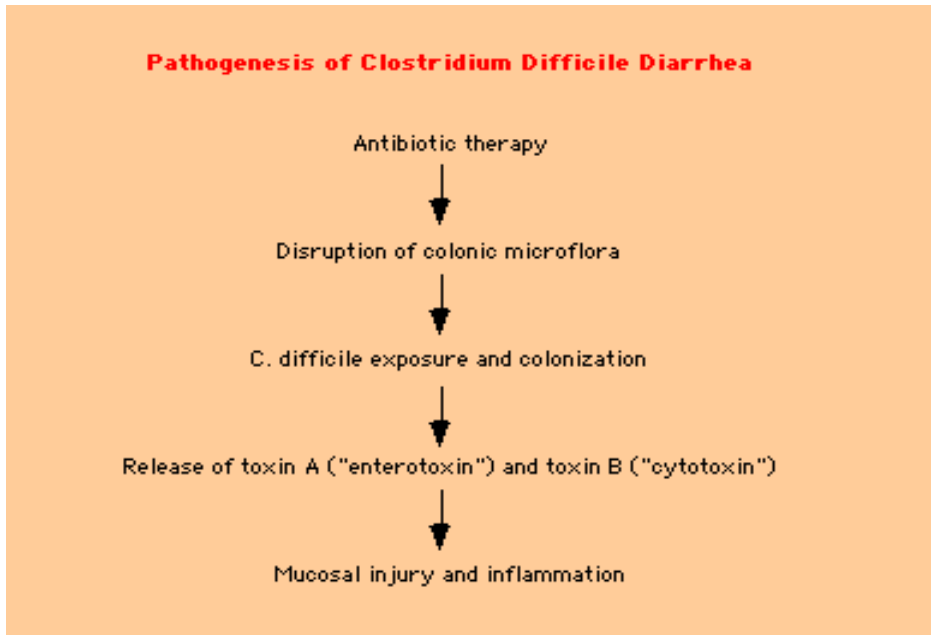
Diagnosis

- Cytotoxicity assay: gold standard;
 - sensitivity 94-100%, specificity 99%
 - disadvantage: high cost, time (2-3days for results)
- ELISA: 70-90% sensitivity, specificity 99%, based only on detection of toxin A; misses toxin B, or mutated strain
- Endoscopy: when diagnosis is in doubt: sigmoidoscopy or colonoscopy

Pathogenesis

- C. Diff strains may be either toxigenic or non-toxigenic
- Non-toxigenic are not pathogenic
- Toxin producers may be categorized as low, medium, or high toxin producers
- However, disease severity is not directly related to level of toxin production or to concentration of toxin in stool
- Infection is initiated when antibiotic alter the normal intestinal flora → colonization by C. Diff
- Pathogenic C. diff releases toxins A and B
 - Both are cytotoxic against cultures fibroblasts and other cells
 - Toxins cause inflammatory reaction, which may damage colon
 - Toxins adhere to receptors on the human colonocyte brush border, and cause necrosis and shedding of cells into the lumen

- In studies, toxin A causes an acute inflammatory diarrhea with massive infiltration of the intestinal mucosa with neutrophils and monocytes



- All antibiotics may predispose to C diff infection
- Most common to cause symptoms is clindamycin
- Unknown why only certain patients exposed to given Antibiotic become colonized with C. diff

Antimicrobial Agents that may Induce Clostridium Difficile Diarrhea and Colitis

Frequently associated	Occasionally associated	Rarely or never associated
Ampicillin	Penicillins other than ampicillin	Parenteral aminoglycosides
Amoxicillin	Sulfonamides	Tetracyclines
Cephalosporins	Erythromycin	Chloramphenicol
Clindamycin	Trimethoprim	Metronidazole
	Quinolones	Vancomycin

Pathogenesis – pseudomembranes

- C Diff toxins → loss of actin filaments in colon → shedding of cells from basement membrane into the lumen → leaves shallow ulcer on mucosal surface → serum proteins, mucus, and inflammatory cells flow out from ulcer → creates typical colonic pseudomembrane

Pathologic features of pseudomembranous colitis

- Type 1 : mild form
 - Limited to superficial epithelium and immediately adjacent lamina propria
- Type 2: more severe disruption of glands, marked mucin secretion, and more intense inflammation of basal lamina
- Type 3: severe necrosis of full thickness of mucosa with confluent pseudomembrane

Clinical Manifestations

- Variations in clinical manifestations are related to host factors not strain virulence or toxin produced
 - Presence of colonic receptors for toxin
 - Concentration of specific anti-toxin antibodies in sera and secretions
 - The carrier state
 - antibiotic associated diarrhea without colitis
 - antibiotic associated colitis without pseudomembrane formation
 - pseudomembranous colitis
 - fulminant colitis leading to toxic megacolon

Carrier State

- 70% of infected hospitalized patients remain asymptomatic
- Clinically silent but shed toxigenic organisms in feces
- Provide a reservoir for continued contamination of the hospital environment
- Thought to be due to presence of IgG antibodies against Toxin A, which protect against developing diarrhea and colitis

Antibiotic Associated Diarrhea without Colitis

- Acute Diarrhea, Lower abdominal pain, Low grade Fever and mild leukocytosis, beginning after antibiotic administration
- Most common complication of antibiotic therapy of hospitalized patients
- C. diff toxins present in stool, but sigmoidoscopy is normal
- Diarrhea will resolve with discontinuation of inciting antibiotic

Antibiotic Associated Colitis without pseudomembrane formation

- Malaise, Abdominal pain, profuse watery diarrhea, cramps relieved by diarrhea, low grade fevers, leukocytosis
- Sigmoidoscopy may reveal patchy or diffuse erythematous colitis

Pseudomembranous Colitis

- Patients have same symptoms as those without pseudomembranes
- Raised whitish-yellow plaques, 1 cm in diameter, scattered over colonic mucosa

Fulminant Colitis

- 2-3% patient with Cdiff
- c/o severe lower or diffuse abdominal pain & distension
- high fevers, chills, marked leukocytosis (40,000), metabolic acidosis

- prominent diarrhea or ileus (in those whom are pooling secretions in a dilated, atonic colon)
- Severe complication
 - Toxic megacolon: dilated colon (>7 cm in greatest diameter) with signs of severe systemic toxicity
 - Radiologically: dilation of small and large intestine, air-fluid levels(mimicking obstruction), sub-mucosal edema (“thumb- printing”)
- Some patients may present with signs of perforation

Toxic Megacolon

- Toxic megacolon is a potentially lethal complication of inflammatory bowel disease (IBD) or infectious colitis that is characterized by total or segmental nonobstructive colonic dilatation plus systemic toxicity
- Definition: segmental or total colonic distension of >7cm in presence of acute colitis and signs of systemic toxicity
- Incidence of TM is dependent on cause
 - Incidence of TM in IBD is 1-2.5%
 - Incidence of TM in PMC is .4-3%

Treatment of C diff colitis

- Most important step is cessation of inciting antibiotic
- First line medical treatment: Metronidazole 500 mg po TID (Alternative : Vancomycin 125 mg po QID)
- Both are equally effective
 - Three reasons for starting with flagyl
 - Equally effective
 - Vancomycin administration can lead to VRE
 - Flagyl is inexpensive
- Duration of therapy: 10-14 days; not necessary to repeat stool toxin assays in pts who are responding well to flagyl therapy
- Severe Infection: profuse diarrhea, leukocytosis, high fever
 - Start with metronidazole, but switch to vanco quickly if no apparent response
 - Vancomycin po- 125 mg po qid escalate upwards at 48 hr intervals to as high as 500 mg QID if symptoms fail to abate
- If do not respond to Vancomycin alone, add Flagyl 500 mg IV q8H (IV vanco not used because drug not excreted in colon)
- No strains of C. difficile isolated thus far have proven to be resistant to either Metronidazole or Vancomycin

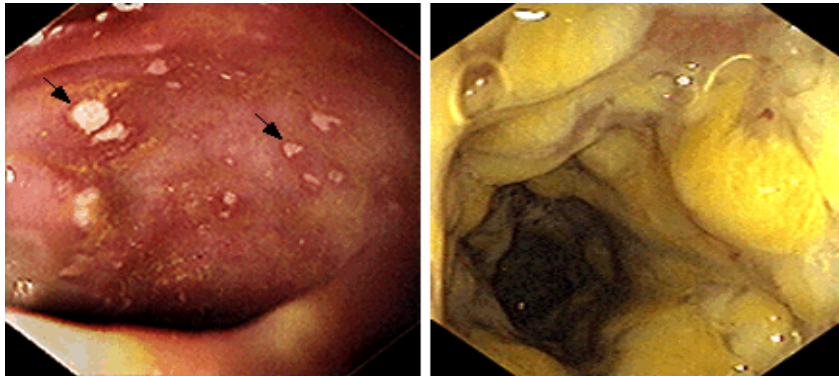
Relapsing Infection

- 10-25% of cases relapse
 - usually within first few days of completing therapy (2-30 days)
 - assumes that symptoms completely abated while on therapy (otherwise is a case of refractory illness)
 - usually is re-infection with same strain that causes initial infection

- antibiotic resistance is not a factor, since antibiotic resistance in *C. diff* has not been described
- treatment again is Flagyl 500 mg po tid
- Other options;
 - Tapering and pulsed vancomycin therapy
 - Therapy with micro-organisms to re-institute natural flora (AKA Bacteriotherapy)
 - Immunoglobulin therapy with IgG
- 60% adults have serum antibodies to *c. difficile* toxin A and B

Surgical Therapy

- Early surgery has been shown to reduce rate of perforation from 33% to 12% and mortality from 20% to 7%
- Studies have also shown that medical treatment can be continued as long as patient is clinically improving
- Patient is usually followed with serial KUBs
- 3% cases necessitate surgical therapy
- Indicators: Impending perforation, severe ileus with megacolon, refractory septicemia, peritoneal signs, bacteremia unresponsive to antibiotics
- Risk factors: malignancy, COPD, immunosuppressive therapy, renal failure, exposure to anti-peristaltic medications or therapy with Clindamycin
- Recommended surgery: STC with end ileostomy



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.



Toxic megacolon Plain film of the abdomen from a patient with toxic megacolon associated with *C. difficile* infection. The large and small intestines are grossly dilated. Dilatation of the small bowel, which has the thin transverse folds of the valvulae conniventes (short arrow), is seen best in the left lower quadrant. Large bowel dilation occupies most of the right lower quadrant and has characteristic thick haustral markings that do not extend across the entire lumen (long arrows). Courtesy of J Thomas LaMont, MD.

Michael Wolfeld M.D.
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