Psuedomembranous Colitis

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Incidence

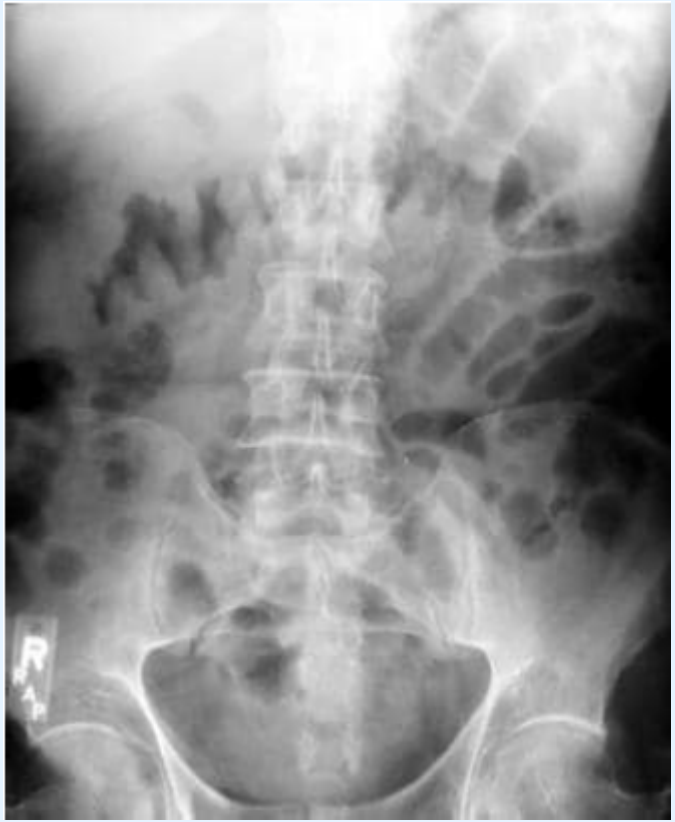
- Incidence of antibiotic-associated diarrhea varies from 5-39% depending on the antibiotic type. .
- Pseudomembranous colitis complicates 10% of the cases of antibiotic-associated diarrhea.
- C difficile is found in the stool of 15-25% of asymptomatic, antibiotic treated, hospitalized adults.
- Most cases of PMC over the last three decades have occurred in association with antimicrobial therapy. Nearly all antimicrobial agents have been implicated in causing PMC

Other risk factors

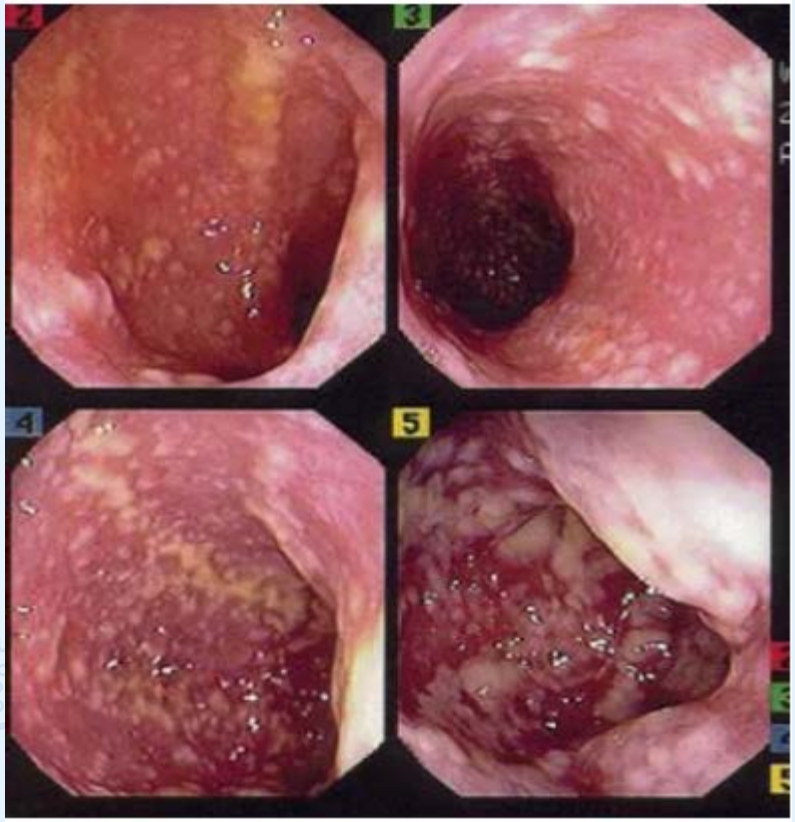
- Advanced age
- Hospitaliztion
- Inflammotry bowel disease
- Chemotherapy
- Immunosuppresion

Clinical presentation

- Watery diarrhea, with as many as 15 to 30 stools per day
- Abdominal pain or cramps (often have lower quadrant tenderness in association with fever and leukocytosis.)
- Fever – absent, low-grade, or quite high.
- Oligoarticular, asymmetric, large joint arthropathy.
- Peripheral leukocyte count (10,000 to 20,000/mm3 , but it may be much higher.)
- Hypoalbuminemia – due to loss of protein in the stool



- Frontal abdominal radiograph in a patient with proved pseudomembranous colitis. Note the nodular haustral thickening, most pronounced in the transverse colon.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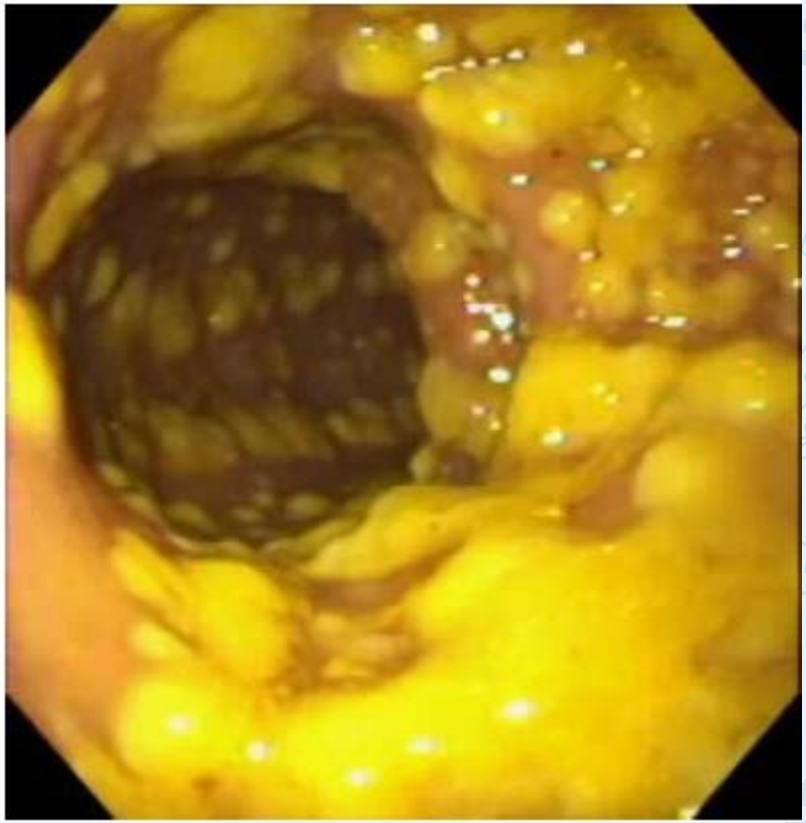

Complications

- Hypovolemic shock, dehydration, and electrolytes depletion may occur.
- Hypoproteinemia as a result of protein-losing enteropathy may occur in patients with prolonged diarrhea.
- Cecal perforation, toxic megacolon , hemorrhage, and sepsis also can occur.

Pathophysiology

- Disruption of the normal bacterial flora of the *colon*
- Colonization with *C. difficile*
- Release of toxins
- Mucosal damage and inflammation

Toxin production by pathogens

- Toxin A (or enterotoxin)
- Toxin B (or cytotoxin)
- Both are heat-labile proteins that activate the release of cytokines from human monocytes.
- Work in tandem – one disrupting the cell cytoskeleton and the other involving the activation of the signal transduction pathways of the immune system
- Toxins are released by C.difficile and internalized by endocystosis
- Inactivate rhoA, a protein responsible for the maintenance of cytoskeleton of the cells
- Widening of junctions of enterocytes leading to fluid loss and diarrhea

Attraction of cytokines

- Caused by activation of components of immune system
- Toxins A and B cause mast cell degranulation, upregulation of leukocyte adhesion and release of cytokines from granulocytes
- Toxin A attracts neutrophils and both toxins stimulate the release of cytokines, such as interleukin (IL) 1, IL-6, IL-8 and tumor necrosis factor from human monocytes
- Both toxins A and B act on mast cells to release to release histamine
- Both toxins activate phospholipase A2 leads to calcium influx and the production of arachidonic acid metabolites. The arachidonic acid cascade leads to the production of Prostaglandins and leukotrienes.
- Prostaglandins and leukotrienes produce increased blood flow in local capillary beds and an increase in capillary permeability Prostaglandins can also induce chemokinesis and cellular infiltration by Phagocytes.
- Release of leukocytes, mucin, fibrin and cellular debris results in the formation of a psuedomembrane

Medical Treatment

- In mild or moderate cases, supportive therapy alone is sufficient. This includes discontinuing or changing the offending antibiotics, avoiding narcotics and antidiarrheal agents, maintaining fluid and electrolyte intake, and enteric isolation.
- Most patients, 75% of symptomatic patients and 25% of patients with colitis, will experience complete recovery within 10 days. In fulminant or intractable cases, hospitalization for IV hydration will be necessary.
- Oral treatment with antimicrobial agents effective against C.difficle is the preferred treatment. No reliable parenteral treatment for pseudomembranous colitis exists.
- In elderly patients and in severely ill Patients empirical antibiotic treatment should be started when the diagnosis is suspected.

- In severe cases, in cases where supportive therapy fails, and in cases where the offending antibiotic cannot be discontinued, short course (7-10 d) of specific antibiotics therapy should be administered along with the Supportive therapy and the offending antibiotic should be changed to another appropriate agent when possible.
- Recurrent disease respond well to re-treatment with vancomycin.
- In cases with multiple recurrences, a few suggested therapeutic regimens exist. A long course of oral antibiotic (4-6 wk) may be administered, .followed by gradual tapering, or pulsing, of vancomycin.
- Another suggested regimen is administering 5-7 days of intermittent antibiotic treatment periods alternating with periods off antibiotics. Treatment with a combination of vancomycin and rifampin was reported to be successful in some cases.

- **Antidiarrheal agents** - Antiperistaltic drugs should be avoided. They may provide temporary symptomatic relief, but they may protract the disease by prolonging the mucosal exposure to the bacterial toxins, resulting in more severe colonic damage. Postoperative narcotics may play a similar role.
- **Restoration of normal flora** In patients with multiple relapses, attempts have been made to recolonize the colon by introducing organisms to suppress C.difficile. Oral Lactobacillus GG has been used. Enema with feces from healthy person, though it carries the risk of disease transmission, also has been used. Oral nonpathogenic yeast, such as Saccharomyces , also has been used effectively in treatment of multiple relapses.

Surgical Therapy

- Two thirds of patients with toxic megacolon require surgical intervention.
- Diverting ileostomy or resection of diseased bowel (subtotal colectomy)
- -This was necessary treatment before antibiotic therapy was available
- -This treatment currently is used only as a life-saving measure ,such as in cases of perforated cecum or toxic megacolon.
- Colostomy or ileostomy
- -This approach is used rarely for direct instillation of antibiotic into the colon lumen in patients with paralytic ileus.
- Early subtotal colectomy It is advocated by some surgeons: fulminant toxic cases that do not respond after a week of intensive medical care because the risk of perforation increase after 7 days of ineffective medical therapy.

Follow up care

- Many patients remain asymptomatic carriers for C difficile, and most of them never relapse.
- Ten percent to 20% of all treated patients will have a relapse regardless of the therapeutic agent used. This could be due either to germination of spores or reinfection. Response to re-treatment with vancomycin usually is favorable. patients with multiple symptomatic relapses, vancomycin pulsing is recommended.

Outcome and Prognosis

- The overall mortality rate is 2%.
- The mortality rate in untreated elderly or debilitated patients is 10-20%.
- Even with surgical intervention, the mortality rate in patients with toxic megacolon is 35%.

Prevention

- Passive immunization, which has been effective in animals, may be potentially useful in protecting those who are at high risk of acquiring the disease. Immunologic studies of toxin A, toxin B and other virulence actors have led to toxoids that have been used for the production of antibodies that might be used to generate a vaccine in this group of patients.


Thank you