Pseudomembranous Colitis: Causes and Cures

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Key Words

Clostridium difficile · Pseudomembranous colitis · Antibiotic side effects

Abstract

Clostridium difficile is the most common nosocomial pathogen of the gastrointestinal tract and has increased in frequency over time. Typical symptoms of *C. difficile* infection include diarrhea, which is usually nonbloody, or colitis associated with severe abdominal pain, fever and/or gross or occult blood in the stools. Pseudomembranous colitis (PMC), the severest form of this disease, occurs as a result of a severe inflammatory response to the *C. difficile* toxins. This review focuses on PMC, as this severe form is associated with the greatest medical concern. Diagnosis rests on detection of *C. difficile* in the stool, either by culture, tissue culture assay for cytotoxin B or detection of antigens in the stool by rapid enzyme immunoassays. Oral therapy with metronidazole 250 mg 4 times a day for 10 days is the recommended first-line therapy. Vancomycin is also effective, but its use must be limited to decrease the development of vancomycin-resistant organisms such as enterococci. Vancomycin (125–500 mg 4 times a day for 10 days) should be limited to those who cannot tolerate or have not responded to metronidazole, or when metronidazole use is contraindicated, as in the first trimester of pregnancy. A therapeutic response within a few days is usual. Recurrence of symptoms after antibiotics occurs in 20% of cases and is asso-

ciated with persistence of *C. difficile* in the stools. Further recurrences then become more likely. Therapy with antibiotics in a pulsed or tapered regimen is often effective as are efforts to normalize the fecal flora. The yeast *Saccharomyces boulardii* has been proven in controlled trials to reduce recurrences when given as an adjunct to antibiotic therapy. Careful hand washing and environmental decontamination are necessary to prevent epidemics.

Introduction

Pseudomembranous colitis (PMC) is a serious colonic disease which can occur when antibiotics or other agents disrupt the normal colonic flora. The severity of illness ranges from benign diarrhea to PMC. Although antibiotic-associated diarrhea may be common (10–30%), PMC is far less frequent (1–5%). Consequences of PMC may include increased or lengthened hospitalization stays and increased morbidity and mortality. In this paper, we will review the causes and cures of only the severest form, PMC.

The earliest description of PMC was in 1893 when a young woman died following gastric surgery [1]. After surgery, she developed diarrhea, which became bloody, and she died shortly thereafter. Her postoperative care had included alcohol enemas. In this case, which clearly antedated the use of antibiotics, risk factors for altered colonic

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flora included the enemas as well as surgery of the gastrointestinal (GI) tract. In the preantibiotic era, PMC was associated with ischemic cardiovascular insufficiency, colonic obstructions, heavy metal intoxications, sepsis, shock and uremia [2, 3]. In the 1950s, the etiology of PMC was thought to be *Staphylococcus aureus*, but since 15–30% of normal healthy adults were also colonized, its role in PMC was disputed [4, 5]. Interest in PMC was reignited when clindamycin was introduced for anaerobic infections; one study found that 10% of patients treated with this antibiotic developed PMC [6]. In the 1970s, the connection was made between the anaerobe, *Clostridium difficile*, a toxin produced in animals and PMC found in humans [7–9]. Since that time, *C. difficile* has remained the major culprit attributable in 90–99% of PMC cases, but other etiologies may exist. As newer, broader-spectrum antibiotics have been introduced into the pharmacopoeia, PMC has been associated with nearly all types of antibiotics. PMC will remain a clinical concern due to its persistence (even though treatments do exist for *C. difficile*-associated PMC), medical complications and its close association with the frequent use of broad-spectrum antibiotics.

Symptoms and Complications

Symptoms

PMC is usually associated with watery diarrhea (99%), fever (29%), abdominal pain or cramping (33%) and leukocytosis (61%) [10]. In a study of 48 patients with endoscopic PMC, the above symptoms usually occurred after 4 days of antibiotic treatment [11], but symptoms can occur up to 6 weeks after antibiotics have been discontinued [12]. Symptoms can occur within a day or two of starting antibiotics, suggesting that alteration in the colonic flora can develop rapidly. Cases have even been documented after a single dose of cephalosporin given as preoperative prophylaxis [13, 14]. Disease can occur in association with any antibiotic; it is most common with penicillin, ampicillin, clindamycin and cephalosporins and less frequent with trimethoprim-sulfamethoxazole and metronidazole [15, 16]. In general, it is more commonly associated with oral than parenteral antibiotics and with antibiotics which suppress the anaerobic flora in the colon.

Diarrhea is the usual presenting symptom; it is usually watery but can have gross or occult blood. Occasionally patients will have an atypical presentation without diarrhea but with toxic megacolon and an acute abdomen [17, 18] or appendicitis [19].

Fig. 1. PMC, creamy white plaques coat the mucosa. This is a typical endoscopic appearance of PMC. Reprinted with permission from Surawicz and Owen *Gastrointestinal and Hepatic Infections* (Philadelphia, Saunders, 1994).

When PMC is severe or does not respond to therapy, complications can occur. In a study of 48 cases of PMC, complications included hypokalemia (37%), renal failure (27%) and hypoproteinemia (50%) [11]. Some patients will require surgery if the colitis is severe or refractory to therapy. Indications for surgery can include severe pain, development of organ failure, subserosal air in the colon wall, a worsening CT scan or signs of peritonitis. Although surgical intervention for PMC is infrequent (<1%), the mortality rate in these patients is very high (38%) [20].

Late-onset complications of PMC have been reported and include acute oligoarthritis and hemolytic-uremic syndrome [21–23]. Four cases of arthritis developing after the onset of PMC have been reported; this seems to be associated with HLA-B27 antigen type and responds to treatment with vancomycin [21].

Diagnosis

PMC is diagnosed by assessing the patient on three levels: clinical evaluation, stool assays for enteric pathogens and visualization of the colonic mucosa. The first is the medical history and clinical presentation. A history of recent antibiotic use, recent hospitalization, intestinal surgery or residence in a chronic care facility may all predispose to PMC. Symptoms of watery diarrhea, abdominal pain or cramping and fever are typical.

Fig. 2 a, b. Low-power view of a colonic mucosal biopsy of PMC shows a large pseudomembrane emanating from the surface mucosa. A higher-power view shows that the pseudomembrane consists of fibrin, polyps and debris. The higher-power view shows two points of attachment of the pseudomembrane to the surface of the mucosa. The colonic mucosa itself is relatively uninfamed.

The diagnosis of PMC includes the detection of *C. difficile* in the stool. These are the most commonly performed tests. The 'gold standard' for *C. difficile* detection is the tissue culture assay for toxin B, but this test is expensive, takes 24–48 h for results and is not available in all laboratories. Newer immunologic assays have been developed which are more rapid and easier to perform, but these are also expensive [24]. Tests for the detection of *C. difficile* toxins include enzyme immunoassays that have sensitivities ranging from 52 to 99%, the tissue culture assay with sensitivities ranging from 82 to 99% and the latex agglutination assay with sensitivities ranging from 47 to 67% [25–27]. *C. difficile* may also be detected by microbial cultures which have the ability to detect very low concentrations in the stool [28]. This test will also be positive in 5–10% of persons who are asymptomatic carriers. Olson et al. [29] found that 38% of patients with *C. difficile* disease detected during a 10-year surveillance would have been missed if culture had not been performed. A finding of negative *C. difficile* assays in a patient with PMC presents a difficult diagnostic problem as it may be due to a false-negative test result.

The third level of diagnosis is colonoscopic or sigmoidoscopic visualization of pseudomembranes. These tests are indicated when immediate diagnosis is necessary. Pseudomembranes may occur throughout the colon but are most frequent in the left colon (fig. 1). Andrejak et al. [11] studied 48 patients with PMC who had been colono-

scoped and found that all pseudomembranes were located between the left angle of the colon and the rectum, which was well within the reach of the flexible sigmoidoscope. Unlike ulcerative colitis, which extends proximally from the rectum, PMC can be patchy and the rectum may be spared [30]. Proctosigmoidoscopy may be completely negative, thus colonoscopy may be needed in some cases [31, 32]. In a study of 22 patients with PMC, flexible sigmoidoscopy detected 91% of the cases compared to rigid sigmoidoscopy, which only detected 77% of the cases [33]. Gross sigmoidoscopic findings usually reveal characteristic raised yellow-tan or green plaques which bleed when raised from the mucosa. These plaques range in size from small distinct nodules (2–10 mm) to a confluent layer of pseudomembrane overlying the mucosa. The colonic mucosa may also show erythema, friability and edema [24]. Ischemic colitis may also exhibit a yellow confluent pseudomembrane [30]. Histologic findings include epithelial necrosis, distended goblet cells, infiltration of the lamina propria with leukocytes, and plaques consisting of inflammatory cells, fibrin and mucin [10, 24, 34, 35] (fig. 2a, b). Diffuse pseudomembranes are more common in *C. difficile* PMC, whereas ischemic colitis is associated with hyalinized lamina propria, atrophic crypts, hemorrhage and full-thickness mucosal necrosis [36]. Even when there are no gross pseudomembranes, histologic examination of biopsies may show an inflammatory exudate which erupts from the surface epithelium

in a 'summit' or 'volcano' lesion, often near or overlying normal-appearing mucosa [10, 30]. Crohn's disease and ulcerative colitis rarely exhibit these summit-like lesions and the mucosa is more inflamed and necrotic.

Other diagnostic tests for PMC have not shown better sensitivities over sigmoidoscopy or colonoscopy. Abdominal radiological examinations may show an edematous or distended colon, but this finding is not specific for PMC. Positive findings can be seen in patients with severe PMC and toxic megacolon when 'thumbprinting' and mucosal thickening can be observed, but these features are also seen with ischemic colitis [30]. CT may be useful for detecting PMC in patients with right-sided disease [37].

The diagnosis of PMC may be delayed due to the lack of suspicion or patient refusal of sigmoidoscopic examination. A report of a patient who had refused a colonoscopy resulted in a delay of 6 weeks before the PMC was finally diagnosed [38]. PMC should be suspected in any patient with recent exposure to antibiotics or a recent hospitalization and symptoms of inflammatory diarrhea, abdominal pain and fever with a positive *C. difficile* test.

Differential Diagnosis

Differential diagnosis must include the exclusion of other causes of diarrhea which may mimic PMC. Colitis may be included by medications (alcohol, nonsteroidal anti-inflammatory drugs, gold, vasopressin, cyclosporine, methotrexate, etc.) or other chronic conditions (Crohn's, inflammatory bowel disease, collagenous colitis, ischemic colitis) [39]. Acute infectious colitis is usually due to bacterial pathogens (*Campylobacter*, *Salmonella*, *Shigella*) and occasionally due to cytomegalovirus, even in immunocompetent individuals. A case of PMC associated with *Escherichia coli* 0157:H7 has been reported [40]; this child with colitis had gross and microscopic pseudomembranes, indicating that pseudomembranes are not always specific for *C. difficile*. A common mechanism is likely with toxin-induced ischemic effects on the colonic mucosa as similar histologic findings have been seen in ischemic colitis [36].

Pathophysiology

The pathophysiology of PMC may involve up to four distinct pathways. The first is the disruption of the normal intestinal microflora by the inducing antibiotic or agent. The normal intestinal flora possesses 'colonization resistance' or the ability to inhibit the colonization of opportunistic pathogens through a variety of mechanisms

[41, 42]. The second mechanism is the result of toxins produced by pathogens that lead to cellular distortion and subsequent diarrhea. The third mechanism involves the excessive chemotactic response to inflammatory cells. The fourth mechanism results from inflammatory cell effects on the enteric nervous system.

Colonization Resistance

The ability of the normal intestinal microflora to resist overgrowth by pathogenic organisms is called colonization resistance. This ability operates by several mechanisms including competition for nutrients, production of bacteriocins or toxin-degrading proteases and receptor site competition [30, 43]. The disruption of this barrier effect by antibiotics or medical procedures decreases the normal colonization resistance and allows pathogens to overgrow in the colon. Broad-spectrum antibiotics that have a greater impact on normal flora populations are associated with higher rates of intestinal disease [30].

Toxin Production by Pathogens

The most extensively studied etiology of PMC is *C. difficile*, an obligate spore-forming anaerobe that produces several virulence factors including toxin A, toxin B, tissue-degradative enzymes (proteases, collagenase, hyaluronidase, heparinase and chondroitin-4-sulfatase) and fimbriae [42]. The two major virulence factors are toxin A, a potent enterotoxin and cytotoxin, and toxin B, a potent cytotoxin and a mild enterotoxin [44]. Both of these toxins are coproduced and important in pathogenesis and are usually found in patients with *C. difficile*-associated PMC [45, 46].

C. difficile toxin A, a large protein of 308,000 MW, binds to human carbohydrate antigens I, X and Y on human epithelial cell surfaces, but its exact intestinal receptor sites in humans have not been identified [47, 48]. *C. difficile* toxin B, a large protein of 270,000 MW, is heat labile, but its receptor site has not been identified in either humans or in animals [48].

The actions of *C. difficile* toxins A and B are bimodal: one disrupting the cell cytoskeleton and the other involving the activation of the signal transduction pathways of the immune system. Toxins A and B are produced by *C. difficile* in the lumen during infection and bind to receptor sites on the surface of the enterocyte. The toxins are then internalized by endocytosis. Once inside the cell, the toxins inactivate a guanine-nucleotide-binding protein called *rho A*, leading to the disaggregation of F actin [48, 49]. *Rho* is involved in maintaining the cytoskeleton structure within the cell. The consequence of cytoskeleton

disruption is cellular rounding which widens the tight junctions between enterocytes leading to fluid loss and diarrhea [50].

The tissue damage by toxin A results in a viscous hemorrhagic fluid response contrasted to the 'ricewater' fluid produced by cholera toxin [43]. Ligated ileal loops in rabbits and rats also show extensive hemorrhagic fluid accumulation and a significant increase in intestinal permeability [17]. Other effects of toxin A involve inhibition of protein synthesis but usually do not result in cellular lysis [51].

Attraction of Cytokines

A third mechanism of PMC is the activation of components in the immune system. *C. difficile* 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 [52–55]. Both toxins A and B act on mast cells to release histamine and may affect leukocyte, endothelial cell and platelet interactions through the upregulation of certain adhesion molecules [52]. Both toxins activate phospholipase A₂ leading to calcium influx and the production of arachidonic acid metabolites. The arachidonic acid cascade leads to the production of prostaglandins and leukotrienes [43]. 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. The attraction of immune cells is easily observed on histologic sections or scintigraphic examination of the intestinal mucosa and neutrophil infiltration is a prominent feature of PMC [35, 56].

The profuse release of leukocytes, mucin, fibrin and cellular debris results in the formation of a pseudomembrane. Plaques do not form in neutropenic patients [57]. The toxins are largely immune cell attractants and cellular morphology disrupters rather than being lytic, which may explain the observation that pseudomembranes often overlie normal-appearing enterocyte layers.

Neurologic Interactions

The fourth mechanism may involve the enteric nervous system. The early observations that toxins of *C. difficile* could have neurologic effects were largely ignored until recently [58, 59]. *C. difficile* toxin A has been found to increase myoelectric activity before causing mucosal damage in rabbit colonic loop models [55]. Pothoulakis et

al. [60] found that substance P antagonists are able to block the inflammation, necrosis and mast cell reactions usually induced by toxin A. The involvement with the enteric nervous system and intestinal diseases requires further study.

Risk Factors

Including Antibiotics

PMC is usually associated with the use of broad-spectrum antibiotics as these have the greatest disruptive impact on the normal intestinal flora [61]. Cases of PMC have reported that clindamycin, cephalosporins and ampicillins are of the highest risk [62]. Ambulatory patients receiving antibiotics were most frequently (83%) affected in one study of PMC [11]. Rifampin, usually not associated with PMC, has been reported in a review of 10 cases of patients with tuberculosis treated with rifampin who later developed PMC [63]. The route of antibiotics does not seem to be a significant predictor of PMC, but oral routes are more frequently reported than parenteral injections [30]. Interestingly, the route of antibiotic need not be oral, as shown by a case of fulminant PMC caused by clindamycin vaginal cream [64].

Nonantibiotic Medications

Most cases of PMC are associated with antibiotic use, although 1–7% of cases of PMC have had no documented antibiotic exposure [34]. PMC has been reported in patients without antibiotic exposure who have insulin-dependent diabetes mellitus, hepatic and renal failure, malnutrition, cystic fibrosis or have had upper GI tract surgery [61]. Chemotherapy with 5-fluorouracil and cisplatin has also been associated with PMC [65–67].

Surgery

Previous surgery has been reported as an additional predisposing factor in 29–67% of patients with PMC [10, 62].

Abdominal and vascular surgery has the highest rate of postsurgical PMC (6–9%), whereas other types of surgeries (orthopedic, cardiovascular, obstetric or plastic) are associated with PMC in less than 1% [52].

Age

PMC is most common in adults, especially in elderly patients. In a study of 39 patients with PMC, the median age was 64 years (range 33–92 years) and 38 were male, which may have been due to the study population at a

Veterans Administration Medical Center [10]. In another study of 29 patients diagnosed as having PMC at two English hospitals, the mean age was younger (51 years) with a range of 12–77 years, and 62% were female [34].

Infrequent reports of pediatric PMC have been made [12, 68, 69]. In a review of 43 children with PMC, the mortality rate was 20%, and 95% were associated with antibiotics [12]. Qualman et al. [68] reported 7 cases of fatal PMC caused by *C. difficile*. All these children (aged 9 months to 17 years) were compromised by either Hirschsprung's disease, lymphoma or leukemia. The altered host factors in these children (altered motility in Hirschsprung's disease or neutropenia in children with malignancies) may have allowed a more fulminant disease than normally seen in children.

Treatment

Antimicrobial Therapy

The initial evaluation should assess the level of hydration and severity of illness. It may be reasonable to treat for presumptive *C. difficile* infection in anyone who develops diarrhea in the hospital, in some cases of chronic diarrhea, or when symptoms worsen or progress, or in anyone who has had a prior history of *C. difficile* disease.

The two most commonly used antibiotics to treat *C. difficile* disease are metronidazole and vancomycin. The recommended dose for metronidazole is 250 mg 4 times a day for 10 days, and for vancomycin it is 125–500 mg 4 times a day for 10 days. Metronidazole is well absorbed from the GI tract. Its side effects include nausea, vomiting, peripheral neuropathy, a metallic taste in the mouth and an antabuse side effect which means that patients must avoid drinking alcohol. Although resistance of *C. difficile* to antibiotic therapy is rare, cases of pseudomembranous colitis have been reported in association with metronidazole. The low dose of vancomycin, 125 mg 4 times a day, was as effective as the higher vancomycin dose of 500 mg 4 times a day in mild to moderate disease, although this has not been tested in PMC. The lower dose of vancomycin is significantly less costly [70, 71]. In contrast to metronidazole, vancomycin is not well absorbed from the GI tract; side effects are uncommon, although rash has been reported. It is very uncommon for vancomycin to be a cause for PMC; 1 case has been reported, but the patient had chronic renal failure, was on dialysis and could easily have acquired *C. difficile* from another source.

Recent recommendations from the Centers of Disease Control strongly suggest the use of metronidazole as a first-line drug of choice for the treatment of *C. difficile* disease. The two drugs are equally efficacious in mild to moderate disease, but there are no trials comparing therapy in patients with severer disease. Vancomycin use must be restricted because of the development of vancomycin-resistant enterococcus [72]. Vancomycin can be used when there is no response to metronidazole or when a patient cannot take metronidazole because of first-trimester pregnancy or inability to tolerate the drug's side effects.

There are other antibiotics which have been used to treat *C. difficile* disease. Oral bacitracin has been given in doses of 80,000 units/day. However, this drug is very expensive and its use is limited because its taste is very poor [73]. In one study it was less effective than vancomycin. Fusidic acid has also been used to treat *C. difficile* disease [74] but is not available in the USA. Teicoplanin is a glycopeptide antibiotic given in doses of 100 mg twice a day for 10 days. It has been shown to be equivalent in efficacy to vancomycin 500 mg 4 times a day [75]. It is not currently available in the USA.

Nonantimicrobial Therapy

The bile-salt-binding resin cholestyramine has been used to treat *C. difficile* disease. The agent does cause constipation in normal individuals which might be helpful in decreasing diarrhea. There is no evidence, however, that this actually does bind the toxins of *C. difficile* and resin binding may actually bind antibiotics and thus decrease their efficacy. Thus, these authors do not recommend the use of cholestyramine or other bile-salt-binding resins in the treatment of *C. difficile* disease.

Clinical Response

The usual response to therapy is improvement in diarrhea within 1–4 days with resolution by 2 weeks. Recurrence of diarrhea is a difficult clinical problem and occurs in 10–50% of cases with an overall risk of recurrence of about 20% (see below).

Treatment of Severe PMC with Ileus or Toxic Colon

Patients with an associated ileus or toxic colon represent a major therapeutic challenge because delivery of oral antibiotics to the colon becomes quite difficult. Therapy should include intravenous metronidazole which may penetrate the intestinal tissue at doses of 500 mg every 6–8 h [76, 77]. While some authors feel that intravenous vancomycin may have no role [78, 79], other authors do

The major indications for surgery are worsening clinical condition despite adequate therapy. Such clinical clues include organ failure, peritonitis and progressive colitis. It is important to perform serial clinical evaluation in these critically ill patients to look for signs that urgent surgery may be needed. The mortality from toxic colon or perforation ranges from 2 to 8%. An abdominal CT scan showing a very thick colon wall and a presence of ascites are poor prognostic signs [81]. However, it is important to note that even if the situation looks severe on a CT scan, this should not be the sole reason to perform surgery as CT scans may not accurately correlate with the actual clinical severity. When surgery is needed, the procedure of choice is a subtotal colectomy since segmental resection often leads to reoperation to remove the remaining diseased bowel [20].

Rectal bacteriotherapy has been reported to treat relapsing PMC. Specifically, fecal enemas have been given to patients, using rectal infusion of homologous feces donated from healthy donors, such as relatives [87]. This is not advisable, however, as it is impossible to assure the safety of homologous feces, and other pathogens could be introduced inadvertently.

Somewhat more aesthetically appealing, however, is the use of a rectal installation of mixtures of anaerobes which may result in clearing of *C. difficile*. Five patients with relapsing PMC were treated with a rectal installation of 10 different facultatively aerobic and anaerobic bacteria, with prompt clearing of *C. difficile* and its toxin from the stool [88]. An additional patient in this study was treated with an enema of fresh feces from a healthy relative. This study showed that *Bacteroides* sp. had been absent during the patient's illness and was present after recovery, suggesting that colonization with *Bacteroides* sp. appears to be especially important in maintaining normal bowel function and strengthening the resistance to GI

infections. The ability of *Bacteroides* sp. to aid in the restoration of intestinal homeostasis may be related to its production of β -lactamase.

Lactobacillus GG is a species with unusual characteristics. It is resistant to gastric acid and to bile, and survives in the human GI tract for 7 days. In a published letter, 5 patients with relapsing *C. difficile* disease (2–5 prior relapses) had no further relapses after oral therapy with *Lactobacillus* GG, but successful double-blind studies have not been reported [89].

Conclusion

PMC remains a difficult clinical problem as patients are severely ill at diagnosis and may require surgery if antibiotic treatments fail. Future challenges include the search for effective treatments, especially for patients with recurrent *C. difficile*-associated PMC.

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