Pseudomembranous Colitis: Causes and Cures

Christina M. Surawicz\textsuperscript{a} Lynne V. McFarland\textsuperscript{a,b}

\textsuperscript{a}University of Washington and \textsuperscript{b}Biocodex Inc., Seattle, Wash., USA

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 associated 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
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 rekindled 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].

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.
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 colonoscoped 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 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 induced 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].

*Clostridium 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]. *Clostridium 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 rhoA, 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 accumula-
tion 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 compo-
nents in the immune system. *C. difficile* toxins A and B
cause mast cell degranulation, upregulation of leukocyte
adhesion and release of cytokines from granulocytes. Tox-
in 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 activate phospholipase A₂ leading to calcium influx and the production of arachi-
donic 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 capil-
lary permeability. Prostaglandins can also induce chemokinesis and cellular infiltration by phagocytes. The at-
traction of immune cells is easily observed on histologic sec-
tions or scintigraphic examination of the intestinal muco-
sa 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 pseudomem-
brane. 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 nerv-
ous system. The early observations that toxins of *C. diffi-
cile* 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-spect-
trum antibiotics as these have the greatest disruptive
impact on the normal intestinal flora [61]. Cases of PMC
have reported that clindamycin, cephalosporins and am-
picillins are of the highest risk [62]. Ambulatory patients
receiving antibiotics were most frequently (83%) affected
in one study of PMC [11]. Rifampin, usually not associat-
ed 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 clinda-
mycin 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 pa-

tients 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 cis-
platin 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 surger-
ies (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
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.

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
favor the advice of Fekety and Shah [80] who recommend the use of parenteral vancomycin as well as metronidazole. These authors feel that this is such a desperate clinical situation that anything that might help should be used. Vancomycin can be given by nasogastric tube or as enemas. A colonoscope can be used to decompress the colon and medicines can be delivered through a colon decompression tube. Rarely a surgical cecostomy may be necessary to decompress the colon and deliver the vancomycin to the colon lumen.

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].

**Special Situations**

**C. difficile-Culture-Positive Toxin-Negative Diarrhea.** Some patients have culture-positive stools but without positive toxin assays and do respond to therapy for eradication of *C. difficile* disease.

**C. difficile in Patients with AIDS.** Patients with HIV infection often acquire *C. difficile* because they are on many antibiotics. They usually respond well to therapy and this is rarely a case for profuse diarrhea.

**Cancer Chemotherapy.** Many cancer chemotherapeutic agents predispose patients to PMC, but recognition may be delayed because they may not be on antibiotics. Prompt recognition and early therapy are important.

**Recurrent *C. difficile* Infection**

Most patients respond to treatment with resolution of diarrhea, but in 20% of patients it will recur; these patients are even more likely to have continued further recurrences which presents a challenging clinical problem. The pathophysiology is not known, but in some instances the recurrence is due to the same strain of *C. difficile*. Therapeutic approaches to recurrent *C. difficile* colitis have included repeating the same or an alternate antibiotic, giving vancomycin in tapered or pulsed doses for longer (several weeks) courses and adding toxin-binding resins such as cholestyramine or colestipol. *Saccharomyces boulardii* is a nonpathogenic yeast with an unusual growth optimum temperature of $37^\circ C$ (fig. 3). The yeast was originally isolated from the lychee fruit in southeast Asia in the 1920s after observations of folkloric use as an antidiarrheal. Since 1962, it has been used in Europe and many other countries as an antidiarrheal agent. Animal studies using the hamster model of clindamycin colitis showed a significant decrease in mortality when animals were treated with *S. boulardii* compared to placebo [82]. When *S. boulardii* was used to treat relapse in the same animal model, it was also highly efficacious [83]. In an open trial, 85% of 13 patients responded to combined therapy treatment with vancomycin and *S. boulardii* and reported no further recurrences [84]. A placebo-controlled trial of *S. boulardii* as an adjunct to antibiotic therapy for recurrent *C. difficile* infection showed an efficacy of *S. boulardii* of 58% [85].

Two cases of *C. difficile* disease were successfully treated with the oral administration of nontoxigenic strains of *C. difficile* [86]. This approach may be associated with a decrease in recurrent PMC, although only a small number of individuals have been treated.
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.

References

Pseudomembranous Colitis

Digestion 1999;60:91–100


