

81299\_Auto\_Edited.docx

**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 81299

**Manuscript Type:** MINIREVIEWS

### **Non-clostridium difficile induced pseudomembranous colitis**

Gowthami Sai Kogilathota Jagirdhar, Salim Surani

#### **Abstract**

Pseudomembranous colitis is severe inflammation of the inner lining of the colon due to anoxia, ischemia, endothelial damage, and toxin production. The majority of cases of pseudomembranous colitis are due to *Clostridium difficile*. However, other causative pathogens and agents have been responsible for causing a similar pattern of injury to the bowel with the endoscopic appearance of yellow-white plaques and membranes on the mucosal surface of the colon. Common presenting symptoms and signs include crampy abdominal pain, nausea, watery diarrhea that can progress to bloody diarrhea, fever, leukocytosis, and dehydration. Negative testing for *Clostridium difficile* or failure to improve on treatment should prompt evaluation for other causes of pseudomembranous colitis. Bacterial infections other than *Clostridium difficile*, Viruses such as cytomegalovirus, parasitic infections, medications, drugs, chemicals, inflammatory diseases, and ischemia are other differential diagnoses to look out for in pseudomembranous colitis. Complications of pseudomembranous colitis include toxic megacolon, hypotension, colonic perforation with peritonitis, and septic shock with organ failure. Early diagnosis and treatment to prevent progression are important. The central perspective of this paper is to provide a concise review of the various etiologies for pseudomembranous colitis and management per prior literature.

#### **INTRODUCTION**

Pseudomembranous colitis is an acute inflammation of the colon. It is primarily due to the overgrowth of the bacterium *Clostridium difficile* and the production of toxins that damage the colonic mucosa. Prior antibiotic usage causes an imbalance in gut bacteria and predisposes to *Clostridium difficile* infection (CDI). Common medications associated with it include Penicillin, clindamycin, cephalosporins, trimethoprim-Sulphamethoxazole, Non-steroidal anti-inflammatory drugs, and fluoroquinolones. Toxin A (Enterotoxin) and Toxin B (Cytotoxin) are the causative agents for triggering the immune system and leading to inflammation in the colon<sup>1</sup>. Over the years, other causes of pseudomembranous colitis have been increasingly identified. Pseudomembranous colitis is named due to ulceration and inflammation of the colonic mucosa with the formation of pseudomembranes. The absence of *Clostridium Difficile* on testing or failure of response to *Clostridium difficile* treatment in a patient with pseudomembranes on colonoscopy should encourage physicians to evaluate for other causes of colitis. Prior literature provides evidence of pseudomembranous colitis from inflammatory causes, non-clostridial infections, chemical agents, drugs, and ischemia. It is important to evaluate these causes after the failure of antibiotic therapy to avoid prolonged, unnecessary *Clostridium difficile* treatment. Symptoms of pseudomembranous colitis include watery diarrhea with pus or mucus in stool. This is the commonest symptom in the majority of patients, followed by abdominal pain/cramps and fever. Leukocytosis is the commonest sign in these patients. Symptoms can start as early as a few days and up to 6 wk after starting antibiotics due to alteration in the gut flora<sup>2</sup>.

Pseudomembranes are composed of mucus, fibrinous material, inflammatory cells (neutrophils), and cellular debris over the colonic mucosa with mucosal damage of varying degrees. CT imaging in these patients shows diffuse mucosal wall thickening. In this brief review, we highlight various agents from previous literature which cause pseudomembranous colitis and present their management options.

## **Methods and materials**

A literature review was conducted in PubMed and Google Scholar to identify articles discussing Pseudomembranous colitis from inception till December 2022. We searched using a combination of free text words, including pseudomembranous colitis, non-clostridium, parasitic, ischemic, Chemical, strongyloidiasis, IBD, Microscopic, MRSA, Amoeba, CMV, Cocaine, chemical, and glutaraldehyde. We reviewed studies published in the English language. Relevant articles were analyzed and presented in the review.

### **Non- *Clostridium difficile* colitis**

#### **Infections**

Other than *Clostridium difficile* other bacterial infections, Viral, parasitic and fungal infections (*Aspergillus*<sup>3</sup>) have been implicated in antibiotic-associated colitis.

#### **Bacterial infections**

##### ***Staphylococcus aureus* colitis**

Before *Clostridium difficile* emerged as the commonest cause of antibiotic-associated colitis in the 1970s, staphylococcus was implicated as the commonest cause after antibiotic usage or abdominal surgery. The author describes a patient who developed MRSA proctocolitis with profuse diarrhea after Whipple's procedure that improved on oral and IV vancomycin for 14 days. C diff testing was negative twice in this patient<sup>4</sup>. The prior literature describes antibiotic-associated hemorrhagic and non-hemorrhagic colitis from *Methicillin-resistant staphylococcus aureus*<sup>5-7</sup>. Pressly *et al* describe a 37-year-old female with Crohn's disease who developed hemorrhagic colitis after staphylococcal food poisoning and subsequent use of antibiotics<sup>8</sup>. Flexible sigmoidoscopy showed segmental pseudomembranes from the rectum to the sigmoid colon, and CDI infection was negative on testing twice. Similar pseudomembranous colitis with non-bloody diarrhea has been described by Kalakonda *et al*<sup>9</sup>. Patients recovered on oral vancomycin for 7-14 days<sup>5,8,9</sup>. In a systematic review conducted by Gururangan *et al*<sup>4</sup>, on staphylococcal enterocolitis, antibiotics (74%) were the most common cause of *Staphylococcus aureus* colitis, followed by recent gastrointestinal surgeries (18%) and inflammatory bowel disease (2%)<sup>4</sup>. Forberg *et al* reported antibiotic-

associated pseudomembranous colitis from simultaneous infection with CDI and MRSA<sup>10</sup>. An autopsy after the patient's death revealed two distinct patterns of pseudomembranes from both organisms observed in the ileum and cecum. *Clostridium difficile* lesions were confined to the cecum and colon and showed 1-4 mm-sized yellow-colored, well-defined, tightly attached pseudomembranous lesions. The lesions from *Staphylococcus aureus* were located in the small intestine. They were yellowish-green, patches that covered the circumference of the mucosa and were loosely adherent. The mucosa was edematous and erythematous. Histopathology in Staphylococcal colitis showed extensive pseudomembranous consisting of necrosis, fibrin deposition, predominant polymorphonuclear cells containing phagocytes with bacteria, and clusters of gram-positive cocci on the luminal surface. *Clostridium difficile* colitis histopathology showed clearly defined pseudomembranous with necrosis, fibrin, mucin deposition and mixed inflammatory cell infiltrates with normal adjacent mucosa. Enterotoxins are responsible for staphylococcal pseudomembranous colitis. Toxic shock syndrome toxins (TSST-1) are less commonly responsible from prior literature. In a systematic review by Iwata *et al* enterotoxins, TSST-1, Protease B, and Leucotoxins were identified in 18 studies in the literature.<sup>11</sup> Another differentiating feature of *Staphylococcus aureus* colitis is the presence of bacteremia. Bacteremia in *Clostridium difficile* colitis is rare and usually follows a gastrointestinal infection or surgery. Death from staphylococcal enterocolitis has declined over the years due to accessibility to vancomycin approved by the US Food and drug administration for Staphylococcal enterocolitis<sup>4</sup>.

### ***Klebsiella Oxytoca***

In a systematic review by Motamedi *et al* *Klebsiella, oxytoca* was the most common cause of antibiotic-associated diarrhea in hospitalized patients, with a prevalence of 27%.<sup>12</sup> Akanbi *et al* describe a patient who presented with hemorrhagic colitis after taking amoxiclav for 5 days a week before the presentation. Cultures were positive only for *Klebsiella Oxytoca*<sup>13</sup>. The patient improved symptomatically after the withdrawal of antibiotics and supportive management. Few other cases are described in the literature

that resulted after the use of antibiotics and recovered after discontinuation and with conservative treatment<sup>14,15</sup>. Few deaths with colitis from *Klebsiella oxytoca* are reported. Nagamura *et al* described a patient who died of *Klebsiella Oxytoca* pseudomembranous colitis<sup>16</sup>. *Klebsiella Oxytoca* does not have an enterotoxin like CDI but secretes cytotoxins that may play a role in pseudomembranous colitis<sup>17</sup>.

### ***Escherichia Coli***

Kendrick *et al* describe a 59-year-old man who developed pseudomembranous colitis during the national outbreak of *Escherichia coli* O157: H7 from ingesting contaminated food during an outbreak<sup>18</sup>. The patient required colectomy due to worsening infection. Pathology identified fibrinous and inflammatory pseudo membranes from the cecum to the proximal rectum. Another case report by Kennedy *et al* describes a patient who developed hemolytic uremic syndrome and neurological sequelae<sup>19</sup>. The pseudomembranous extended from the mid-transverse colon to the rectum, and the biopsy revealed fibrinous exudates and polymorphonuclear cells. The intervening intact mucosa showed crypt inflammation and abscesses. Both patients recovered from the infection with supportive management. *Escherichia coli* produces Shiga-like toxins that can cause pseudomembranous types of colitis. Patients recovered off antibiotics<sup>18-20</sup> in most of the cases presented in the literature.

## **Viruses**

### **Cytomegalovirus (CMV)**

Multiple cases of pseudomembranous colitis from CMV have been described in the literature<sup>21,22 23,24</sup>. Colitis refractory to CDI treatment leads to the authors testing for other causes of pseudomembranous colitis. Positive CMV Immunohistochemical staining or the presence of inclusion bodies on colonic mucosal biopsy specimens establishes the diagnosis. The pseudomembranous is described as similar to *Clostridium difficile* colitis.<sup>25,26</sup> Chan *et al* Described 8/18 patients with colitis that were refractory to oral metronidazole and diagnosed as CMV colitis on colonic mucosal biopsy<sup>27</sup>. Four of these patients had pseudomembranes on colonoscopy. Three of the patients with pseudomembranes also had concurrent CDI with toxin positive on testing. The authors

recommend initiating early antiviral therapy before definitive diagnosis by biopsy in patients with a high risk of suspicion and stool or blood-positive CMV PCR. This is due to the high risk of rapid progress and the development of complications in untreated patients<sup>28</sup>. Factors associated with poor prognosis include older age, surgical requirement, male gender, late presentation, ulcerative colitis, and immune status. Galiatsatos *et al* report a mortality rate of >30% in patients aged >55 years with CMV colitis.<sup>29</sup> In a study by Le *et al* on CMV, colitis mortality was 26% in patients and did not differ based on immune status.<sup>30</sup> Treatment includes ganciclovir or Foscarnet and is necessary, particularly in older patients or those with immune compromise.

### **Coronavirus**

Timerbulatov *et al* described 19 cases of pseudomembranous colitis that occurred after COVID-19 infection<sup>31</sup>. The average time to development of colitis after a COVID-19 infection was 19 days. Histology of the lesions revealed necrosis extending up to the entire thickness of the colon in some cases. Histopathology revealed crypt destruction, fibrinoid deposition, and polymorphonuclear cell infiltration. Additional findings included necrosis of the neural plexus and vascular walls with hyaline deposition, probably from ischemia due to COVID-19. All patients underwent subtotal colectomy with ileostomy. Jabbar *et al* described pseudomembranous colitis in a patient with COVID-19. Histology showed inflammatory cells, fibrin, and mucin deposits along with necrotic epithelial cells.<sup>32</sup> The authors hypothesize that the prothrombotic nature of COVID-19 can predispose to intestinal ischemia complicated by pseudomembranous colitis.

### **Parasitic infections**

Parasitic infections are common in patients living or traveling to endemic regions or immunocompromised.

#### ***Strongyloides stercoralis***

*Strongyloides stercoralis* causing eosinophilic granulomatous enterocolitis with colonic ulcerations was described by Yezid *et al* in 6 patients<sup>33</sup>. Symptoms are similar to ulcerative colitis and Crohn's disease, with abdominal pain, anorexia, nausea, and

vomiting<sup>33,34</sup>. Immunosuppression from HIV and treatment with steroids for other conditions predispose to hyperinflation with *Strongyloides*. Patients recovered on a course of Thiabendazole. The presence of dead larvae in the colonic mucosal biopsy with intense surrounding inflammatory reaction is a characteristic finding<sup>33,34</sup>.

### ***Entamoeba Histolytica***

In a retrospective study conducted by Roure *et al* on 50 patients with amoebic colitis, international travel, immigrants, and immunosuppression were common risk factors for acquiring infection<sup>35</sup>. Diarrhea and abdominal pain were the commonest presenting symptoms. Pathology showed exudates containing amoeba and mucosal thickening with ulcerations which can be classic geographic, flask-shaped, and deep ulcers leading to necrosis and perforation of the intestinal wall. Chaturvedi *et al* described 30 cases of fulminant amoebic colitis with pathology showing pseudomembranes, geographical colonic ulcers, and lesions mimicking inflammatory bowel disease<sup>36</sup>. 17 patients died due to septicemia and shock due to perforation despite surgical intervention. Colonic mucosal biopsies in these studies revealed trophozoites on histology<sup>35-37</sup>. Treatment with metronidazole or tinidazole was curative. Some patients required treatment with luminal anti-parasitic medications. Tomino *et al* described a patient with colonic perforation and fulminant necrotizing amoebic colitis requiring emergency subtotal colectomy and enterectomy. The patient died from sepsis and disseminated intravascular coagulation, and multiple organ failure ten days post-procedure<sup>37</sup>.

## **Inflammatory conditions**

### **Collagenous colitis**

Yuan *et al* described 10 female patients with clinical and histological collagenous colitis who presented with chronic watery diarrhea<sup>38</sup>. Prior usage of NSAIDs and estrogen was identified. Pseudomembranes and ulcerations were identified in these patients on endoscopy. This establishes that pseudomembranous colitis is a pattern of injury that occurs due to toxic and ischemic processes and is not a separate diagnosis in itself. These patients recovered after stopping NSAIDs on conventional treatment with anti-inflammatory and anti-diarrheal agents<sup>38-40</sup>.



### **Inflammatory bowel disease (IBD)**

Pseudomembranous colitis can occur in patients with IBD during a flare with or without superimposed causative factors such as infections, medication, and drug usage<sup>41</sup>.

Kilincalp and Berdichevski reported pseudomembranous colitis in patients with a history of inflammatory bowel disease (IBD) and a lack of exposure to antibiotics. The patient had a positive CDI on testing<sup>42,43</sup>. Another report of pseudomembranous colitis in a patient with ulcerative colitis and CMV-superimposed infection is described<sup>44</sup>. A prior study by Horin *et al* describes that 13% of hospitalized IBD patients with CDI infection have pseudomembranes on endoscopy, and outcomes in these patients are not different from others<sup>45</sup>. This further establishes that pseudomembranes are an endoscopic and pathological entity that can occur due to various underlying causes.

### **Medications, Illicit drugs, and Chemicals**

Non-steroid anti-inflammatory drugs (NSAIDs)<sup>46,47</sup>, dextroamphetamine<sup>48,49</sup>, Alosetron<sup>50</sup>, Voriconazole<sup>51</sup>, and drugs such as cocaine are responsible for a pseudomembranous type of colitis.

#### **Cocaine**

Non-occlusive ischemia of the bowel in patients with no cardiac risk factors should guide clinicians to suspect cocaine-induced colitis<sup>52,53 54,55</sup>. Ellis *et al* identified 18 patients with cocaine colitis who presented within three days of cocaine use<sup>56</sup>. The proximal colon was predominantly involved, and the majority of the patients recovered with supportive management. 2 out of 4 patients who underwent laparotomy died due to peritonitis. Fishel *et al* and Leth *et al* described patients' superficial ulcerations, edema, and yellow fibrinous material<sup>54,57</sup>. Histopathology revealed findings consistent with ischemic pseudomembranous colitis.

#### **Chemicals**

Chemicals like glutaraldehyde and hydrogen peroxide can cause acute retro colitis after endoscopy procedures. Patients present with acute onset of abdominal pain, fever, and rectal bleeding after the procedure. Deficiencies in endoscopy equipment disinfection

procedures should be looked into if outbreaks occur after endoscopy in patients<sup>58,59 60,61</sup>. Endoscopic examination shows fibrin and inflammatory cell exudate with ischemic injury. Conservative treatment with bowel rest and hydration results in the improvement of symptoms<sup>60,62,63</sup>. Ensuring adequate cleaning of the channels of the endoscopy before drying prevents this condition. The colitis appearance is similar to ischemic colitis.

### **Ischemia**

Refractory CDI treatment, particularly for those with a history of vascular diseases, should raise suspicion of ischemic colitis. Ischemic colitis is commonly seen in patients >60 years of age due to predisposing risk factors such as atherosclerosis, small vessel disease, and vascular occlusion. Prolonged hypotension resulting in ischemia can also cause pseudomembranous colitis. Right-sided colon supplied by the superior mesenteric artery is prone to transient non-occlusive ischemia during episodes of hypotension or low flow states. Early ischemic changes in the colonic mucosal include punctate hemorrhages and pseudomembranes. With the progression to severe ischemic injury, the pseudomembranes become confluent, and during resolution, they resemble inflammatory bowel disease with patchy ulcerations<sup>64,65</sup>. Management includes bowel rest, intravenous fluids, gastric decompression, and antibiotics to prevent bacterial translocation. Discontinuation of any precipitating agents such as NSAIDs

### **Diagnosis and Treatment**

Since CDI causes the majority of the cases of pseudomembranous colitis, Initial management includes workup for Clostridial infections. Enzyme immune assay for Glutamate dehydrogenase antigen (GDH) test and Toxin A and B testing is the first step to identifying colonization Vs. Infection. The presence of positive GDH and Toxin testing indicates infection. Indeterminate results can be followed by nucleic acid amplification testing. Early treatment if suspicion for infection is high and in hemodynamically unstable patients while waiting for workup results should be done. Failure of treatment for CDI or negative cultures and toxin testing should be followed by exploration for other causes of colitis. Detailed history taking in patients can provide

clues to causative factors and aid in diagnosis. Stool testing to identify causes other than CDI can be done in patients with signs and symptoms of infection. Treatment varies depending on the cause of colitis. Table 1 shows the management for pseudomembranous colitis based on etiology per prior literature and evidence. 30-day All-cause Mortality in CDI is around 9-38%. Mortality in the various causes of non-*Clostridium colitis* depends on the cause, age, the extent of involvement of the colon, and progression to complications such as perforation, toxic megacolon, bacteremia, and shock. Patients requiring surgery generally had poorer prognoses. Poor prognosis in older patients could be due to a decline in humoral and cellular immunity and the existence of co-morbidities. Further research on the various causes and pathogenesis of pseudomembranous colitis, along with active reporting, is necessary to understand the true incidence of this condition and its management.

## **CONCLUSION**

Pseudomembranous colitis is a pathological finding on endoscopy and is not only due to CDI. Infectious, inflammatory, Drug, and Ischemic causes should be investigated in a patient with endoscopic findings of pseudomembranous colitis and negative CDI testing or refractory CDI treatment. Initiating early targeted treatment based on diagnosis results in the resolution of symptoms in most patients.

ORIGINALITY REPORT

0%

SIMILARITY INDEX

PRIMARY SOURCES

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	OFF
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS