# Pseudomembranous Colitis – a review

# Colite Pseudomembranosa - uma revisão

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## ABSTRACT

Pseudomembranous colitis is a disease caused by Clostridium difficile that predominantly affects the lower gastrointestinal tract. Its main risk factors are antibiotic use, advanced age and hospitalization. We used the keywords Pseudomembranous colitis, Clostridium difficile, Antibiotics, Pseudomembranous, Fulminant colitis, and the search was performed in PubMed, Virtual Health Library-Brazil, Embase and Scopus. Pathogenesis is not fully understood. The most frequent clinical presentation occurs with typical symptoms. Laboratory identification of C. difficile toxin in the stool sample and / or viewing pseudomembranes in endoscopy are essential for a definitive diagnosis. The initial drug treatment is available, however many complications can occur, and surgery may be performed for the most severe cases. The current available technologies are not yet able to resolve all cases. So many other challenges must be overcome regarding the treatment and its pathogenesis, especially in refractory and recurrent disease.

**Keywords**: *Pseudomebranous colitis. Clostridium difficile. Antibiotics. Pseudomembranes. Fulminant colitis*.

**RESUMO**

A colite pseudomembranosa é uma enfermidade causada pelo Clostridium difficile que acomete principalmente o trato gastrointestinal inferior. Possui como principais fatores de risco o uso de antibióticos, a idade avançada e a hospitalização. A fisiopatogênese não está completamente esclarecida. Foram usadas as palavras-chave pseudomembranous colitis, Clostridium difficile, antibiotics, fulminant colitis, e a pesquisa foi realizada nas bases de dados PubMed, Virtual Health Library-Brazil, Embase e Scopus. A apresentação mais frequente ocorre com sinais e sintomas típicos e a Identificação laboratorial da toxina do C. difficile na amostra de fezes e/ou a visualização de pseudomembranas no exame endoscópico são imprescindíveis para o diagnóstico definitivo. O tratamento medicamentoso inicial é acessível, entretanto inúmeras complicações podem ocorrer, podendo haver necessidade até mesmo de cirurgia para resolução dos casos mais graves. As tecnologias disponíveis até o momento ainda não são capazes de solucionar todos os casos. Assim, muitos outros desafios necessitam ser superados quanto ao tratamento e à sua fisiopatogênese, especialmente na doença refratária e recorrente.

Descritores: Colite pseudomebranosa. Clostridium difficile. Antibióticos. Pseudomembranas. Colite fulminante.

## INTRODUCTION

Before 1978, there was no relationship between Clostridium difficile and pseudomembranous colitis. From the discovery of this association occurred an increase in the number of infections associated with C. difficile. The recognition of this condition brings more than three decades, new challenges for health professionals. The C. difficile infection (CDI) is commonly associated with the indiscriminate use of antibiotics, antineoplastic and immunosuppressive drugs[1]. Emergency surgery is indicated for a small minority of patients with the severe form. However, the mortality rate after surgery is high. Thus, this review aims to summarize recent findings regarding the epidemiology, pathophysiology, risk factors, clinical presentation, diagnosis, prevention, prognosis and treatment of this infection.

## METHODS

This is a literature review of pseudomembranous colitis, which was drawn from other studies on the topic, using the keywords Pseudomembranous colitis, Clostridium difficile, Antibiotics, Pseudomembranous, Fulminant colitis. The search was performed in PubMed, Virtual Health Library-Brazil, Embase and Scopus databases from the descriptive analysis of articles published from 2005 to 2012.

## EPIDEMIOLOY AND ETHIOLOGY

In 1978 it was identified that C. difficile, an anaerobic gram-positive bacteria, was the major cause of pseudomembranous colitis associated with the use of clindamicin3, one of the most common hospital infectious diarrhea in adults4,5. However, all cases associated with antibiotics possess etiology related to C. difficile, as the majority of colitis cases.

The incidence is increasing in North America. Recent studies estimate that there are about 500 thousand cases of C. difficile infection (CDI) per year and the impact on mortality is significant, estimating that about 15,000 to 20,000 patients die annually in the United States[5].

## RISC FACTORS

The three more important risk factors for pseudomembranous colitis are antibiotic use, advanced age and hospitalization. Among them, exposure to antibiotics is the most significant, observed in 96% of patients who develop the disease during their hospital stay. The most frequently associated antibiotics with CDI are clindamycin, broad-spectrum cephalosporins, and fluoroquinolones. However, almost all, including vancomycin and metronidazole, have been implicated in DCI. Even a single dose in a pre-operative prophylaxis can lead to the development of DCI[1-6].

Age is also a major risk factor for pseudomembranous colitis, increasing the number of complications and recurrences, being up to 10 times higher. This is shown as a result of senescence of the immune system against *C. difficile* toxins. The risk for acquiring the infection is also directly proportional to the length of hospital stay; patients hospitalized for one to three weeks are 15%-45% susceptible to bacterial colonization[6]. Surgery or gastrointestinal procedures have been described as risk factors[6].

## PHYSIOPATHOGENESIS

For colonization with *C. difficile* a change is required in the normal colonic flora, because when the colonic flora is normal there is resistance to colonization by pathogenic species. However, the use of antibiotics, procedures or diseases can change it. The main drugs are the antibiotics, but antineoplastic or immunosuppressive drugs may also cause DCI[2,6].

*C. difficile* exerts its pathogenic effect through the production of toxins, and the most virulent are toxins A and B. The mechanisms occur by inactivation of the Ras superfamily of GTPasis, that are vital for intracellular signaling and cytoskeletal regulation of epithelial cells of the lower gastrointestinal tract. The inactivation of these proteins results in apoptotic cell death and increased permeability of the epithelium, leading to profuse diarrhea[6,8].

The BI/NAP1/027 strain, related to a more severe disease, is responsible for most of the current outbreaks and has characteristics that differentiate it from others. First, it is able to produce 23 fold more toxins A and B than the others. It is also responsible for producing a binary toxin, which promotes a redistribution of microtubules of cells in the colonic epithelium, increasing the adherence of *C. difficile* and its pathogenicity. Finally, the high degree of strain acquired resistance to all fluoroquinolones, further inflating the rate of intra-hospital infection[3,6].

Once colonized, most patients become asymptomatic, especially in childhood, which is justified by a possible absence of receptors in the colonic epithelium to action of enterotoxins A and B[2-9].

Histologically, the disease is characterized by an inflammatory exudate associated with focal ulceration, which characterizes the pseudomembrane in endoscopic examination[1].

## SYMPTOMS

Infected patients usually have symptoms after 4-9 days of antibiotic use, but they can still occur during antibiotic therapy or within up to 8 weeks after completion. The most common symptoms are diarrhea, cramping, abdominal pain, fever and leukocytosis, but other systemic symptoms may also be present. However, in 20% of patients diarrhea may be absent, especially in those with fulminant colitis or paralytic ileus[4,9].

The clinical spectrum is highly variable, going from a self-limiting diarrhea to a pseudomembranous colitis associated with high risk. Thus *C. difficile* infection can be classified into spectra such as soft diarrhea when it occurs within 5 days, with three or more episodes per day; as moderate when the diarrhea has 5-10 days duration; and severe, when diarrhea or other symptoms are present for more than 10 days[2,9]. Most patients are classified as mild or moderate disease[9].

The stool can be characterized as poorly formed, aqueous or mucoid appearance, with characteristic odor, but rarely have traces of visible blood. The frequency can exceed 10 episodes a day[2,3]. Fever can reach temperatures of 40°C and leukocytosis up to 50,000 cells/mm³. Abdominal pain is usually located in the lower quadrants. Hypoalbuminemia, diffuse abdominal distention and tenderness, and the presence of fecal leukocytes and pseudomembranes on endoscopy may be found[4,6,7].

Patients with severe colitis have increased risk of developing toxic megacolon and paralytic ileus. Severe cases can also present fulminant colitis, acute abdomen and systemic symptoms. These may require surgery[2,4]. Complicated *C difficile* infection is defined by the presence of more than one of the following criteria: shock, megacolon, perforation, need for intensive care unit, emergency colectomy or death within 30 days after diagnosis. Studies show that 53% of these patients die in 30 days after hospitalar admission[1,6].

## DIAGNOSIS

The few and unspecific symptoms of the disease hinder their differential diagnosis, leaving considerable scope for investigation of ulcerative colitis, a chronic inflammatory bowel disease, intra-abdominal sepsis, ischemic colitis, medication use and Crohn's disease. Thus, laboratory identification of *C difficile* toxin in the stool sample and/or viewing pseudomembranes in endoscopy are necessary for the definitive diagnosis[2,3,4,9,10]. The gold standard laboratory test is the cytotoxin cell test, able to detect toxin B in stool culture. It has a sensitivity of 94 to 100% and specificity of 99%.

The enzyme-linked immunosorbent assay (ELISA) aims to detect toxins A and B of *C. difficile* in feces samples within 2 to 6 hours, having a sensitivity of 70 to 90%, requiring repeats, for 2 to 3 days in order to reduce the rate of false negatives[9,10]. Anaerobic cultures are difficult to implement and carry 2 to 5 days to grow and are not specific for toxigenic strains, but provide greater ability to determine the strain and its antimicrobial susceptibilities.

Absence of diarrhea and stool in fulminant colitis is a challenge to achieve the above tests. As the probability of a successful outcome depends on the number of bacteria and the concentration of toxin in fecal sample, the false negative rate is around 8 to 12%.

Thus, abdominal computed tomography is an excellent diagnostic option to rule out other causes of abdominal pain. The result is made available to the doctor much earlier than any laboratory test, besides being a noninvasive technique. Fast results can be duplicated and used as a method of monitoring disease progression. Suggestive findings involve thickening greater than 4 mm edema of colon wall, the sign of accordion, ascites, colonic distension and changing of the pericolic fat[9,10].

Endoscopy rule out other causes of diarrhea and evaluates the colonic mucosa in search of pseudomembranes, pathognomonic of *C. difficile* colitis, besides enabling the collection of stool samples for testing in patients without diarrhea. The classical pseudomembranes appear as white or yellowish plates, losing adhesion to mucosal surface and containing immune cells, mucus and sloughed epithelial cells. Their absence does not exclude colitis, since the sensitivity of the test is 50%. A small number of patients may also have more proximal disease, undetected by endoscopy. A smaller number of pseudomebranes occurs in immunosuppressed patients. Other findings include erythema, edema, friability and non-specific colitis with small ulcerations[2,3,9].

## TREATMENT

After the diagnosis was confirmed in the symptomatic patient, curative therapy should begin immediately. The first line of treatment consists of oral metronidazole, 500 mg, 8/8 hours or 250 mg 6/6 hours for 10 days. It can be administered intravenously in case of intolerance to oral 500mg, 6/6 hours for 10 days.

Considering the teratogenicity of metronidazole, the alternative for pregnant women and patients who fail to respond within 3-5 days after starting this medication, is vancomycin, 125 to 250mg orally, 6/6 hours for 10 days. In cases of oral intolerance, studies observed effectiveness of applying intracolonic vancomycin. It is essential care with resistant enterococci to Vancomycin[9].

Studies show that there is no difference in efficacy between these two medications, however metronidazole is preferable due to its lower cost compared to vancomycin, besides not having risk of resistance. In 2007, a randomized trial was performed comparing the effectiveness of metronidazole and oral vancomycin in 172 patients. There was similar efficacy in mild disease, but in severe disease vancomycin was significantly more efficient[10]. Absorption of Metronidazole as it moves through the intestine, bowel wall edema and absence of diarrhea may be influencing factors in the results.

Usually one week after cessation of treatment, 10-20% of patients have a relapse or recurrence, mostly by residual spores, reinfection with a new strain or inability of the host to respond appropriately with effective antibodies to toxins. Recurrences are treated equally to the initial episode, with age, abdominal surgery, hypoalbuminemia, continuous use of other antibiotics and number of episodes of C. difficile infection, risk factors. In case of failure, it is appropriate to choosing pulse therapy with vancomycin or metronidazole, combined with anion-binding resins such as cholestyramine and colestipol.

The Bacitracin is the last treatment option, because studies with stool cultures and toxin assays have demonstrated lower efficacy. Antiperistaltics are contraindicated because they lead to accumulation of toxins inside the intestinal lumen. Importantly, independent of drug choice, the suspension of other systemic antibiotics in use is recommended.

The surveys have been seeking to develop alternative due to the relative failure rate of metronidazole for the increased incidence and severity of disease, besides the possibility of resistance of enterococci to vancomycin. Studies have tested the effectiveness of Nitazoxanide, already successfully used in the treatment of intestinal parasitic and fungal infections[9]. Probiotic therapy has also been tested with *Saccharomyces boulardii* and *Lactobacillus rhamnosus* aiming recolonization of previously assaulted intestinal microflora, significantly reducing diarrhea associated with antibiotic use. Only *S. boulardii* has been successful. The use of intravenous immunoglobulin as an attempt to increase the serum antibodies against *C. difficile* toxins, besides being an expensive therapy, is relatively scarce.

Surgical treatment is required in 0.4 and 3.5% of patients, and has been done with total or subtotal colectomy with end ileostomy for fecal diversion. Although there was a reduction in mortality, its rate in the post-operative is high, 34-57%. There are three critical factors: a frequently delayed surgical intervention, incorrect selection of patients due to lack of clearly defined criteria and a disease with unpredictable clinical course[10]. There are conflicting opinions among the authors, as well as absence of guidelines, but the common surgical indications are peritonitis, ileus with toxic megacolon, perforation, refractory peritonitis, sepsis, need for vasopressor, presence of shock or organ dysfunction and colitis refractory to medical treatment.

The groups of patients most likely to require surgical treatment are those with malignancy, advanced age, immunosuppressed, renal failure, use of antiperistaltic, fulminant colitis or severe disease[9]. In an attempt to improve surgical outcomes, several studies have investigated the clinical factors that may predict which patients will develop shock if colectomy is not performed. The increase in the count of white blood cells or elevated lactate level are parameters with strong indication for surgical need.

Early colectomy should still go through the acceptance of patient, family and physician. A less invasive surgical alternative strategy would be to create a laparoscopic ileostomy for washing the distal colon. It is a minimally invasive procedure and has the possibility of reversal the ileostomy approach[10].

## PREVENSION

Prevention of pseudomembranous colitis by *C. difficile* consists both in reducing exposure to the bacteria, especially in hospitals, and in limiting the use of antibiotics. Hand hygiene, administration of antimicrobials and environmental decontamination are the main measures to control the spread of *C. difficile*. The spores of this bacterium are alcohol resistant. Therefore, handwashing should occur with soap and water before and after contact with suspected patients. Antiseptic containing chlorhexidine and the use of personal protective equipments are reasonable alternatives. The combination of hand hygiene and contact precautions showed 60-80% reduction in horizontal transmission[3].

Furthermore, decontamination with antiseptics is especially important in shared hospital equipment, such as thermometers, blood pressure devices and dressers. A 60% reduction of CDI was observed when one Antimicrobial Protection Program was implemented for a nosocomial outbreak in Quebec[11].

In addition to the transmission, administration of antimicrobial programs aims at reducing the selection of resistant strains. Several studies show that policies that limit the

broad spectrum antimicrobials reduce the incidence of transmission, especially in cases of cephalosporins and clindamicin use[12].

## CONCLUSION

Pseudomembranous colitis is an important health problem with high morbidity and mortality. However, in Brazil available epidemiological data are scarce. So, we do not know exactly how *C. difficile* behaves in our hospitals.

There are many challenges for the treatment of patients with *C. difficile*, especially those with refractory recurrent disease. Diagnostic tests are inaccurate. For severe disease, medical and surgical treatment need new therapeutic studies. Current efforts are focused on the preservation of the intestinal microbiota and immune response optimization against toxins. Improved surveillance, judicious use of antibiotics and the universal implementation of preventive measures, represent a challenge in medical practice.

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