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Pseudomembranous Colitis: Insights into Causes, Diagnostic Methods, and Treatment Approaches

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ABSTRACT

Pseudomembranous colitis (PMC) is a severe inflammatory condition of the colon most commonly associated with Clostridioides difficile infection (CDI), typically occurring after disruption of normal gut microbiota due to antibiotic exposure. The condition is characterized by profuse watery diarrhea, abdominal pain, fever, and marked leukocytosis, with severe cases progressing to toxic megacolon, sepsis, or death. Although CDI accounts for the majority of cases, pseudomembranous colitis may also arise from non-clostridial infectious agents, inflammatory bowel disease, ischemia, and drug-induced mucosal injury. Diagnosis relies on a combination of clinical assessment and laboratory testing, including glutamate dehydrogenase antigen detection, toxin A/B assays, and nucleic acid amplification tests, with endoscopic evaluation reserved for selected cases. Current treatment strategies emphasize oral vancomycin or fidaxomicin as first-line therapy, while metronidazole is reserved for limited situations. Recurrent and severe disease remains a significant clinical challenge, particularly with the emergence of hypervirulent strains such as NAP1/027. Preventive strategies focusing on antibiotic stewardship and early recognition are essential to reduce disease burden. This review provides an updated overview of the etiological factors, diagnostic modalities, and evidence-based management approaches for pseudomembranous colitis, highlighting recent advances and ongoing challenges in clinical practice.

INTRODUCTION

The human gastrointestinal tract harbors a complex and diverse microbial ecosystem, commonly referred to as the gut microbiota, comprising approximately 10^{11} microorganisms per gram of intestinal content. This microbial community plays a fundamental role in maintaining intestinal homeostasis, immune modulation, and metabolic processes such as short-chain fatty acid production and bile acid metabolism [1]. Disruption of this finely balanced ecosystem, particularly through antibiotic exposure, can lead to significant alterations in microbial diversity and function, predisposing individuals to gastrointestinal disorders.

Antibiotic-associated diarrhea (AAD) represents one of the most common clinical consequences of gut microbiota dysbiosis. Among its severe manifestations, pseudomembranous colitis (PMC) is a distinct clinicopathological entity characterized by inflammatory exudates forming pseudomembranes on the colonic mucosa. While PMC is now predominantly associated with Clostridioides difficile infection (CDI), its etiological spectrum is broader and includes other infectious, inflammatory, ischemic, and drug-induced causes.

Historically, pseudomembranous colitis was described long before the identification of C. difficile. The first documented case was reported in 1893 by Finney in association with postoperative colonic pathology [3]. Prior to the widespread use of broad-spectrum antibiotics, PMC was more frequently linked to conditions such as ischemia, sepsis, intestinal obstruction, uremia, and heavy metal toxicity [2]. However, with the extensive and often inappropriate use of antibiotics in modern clinical

practice, CDI has emerged as the leading cause of PMC worldwide.

Clostridioides difficile is an anaerobic, spore-forming, gram-positive bacillus capable of producing potent exotoxins—namely toxin A (enterotoxin) and toxin B (cytotoxin)—which mediate colonic epithelial injury and intense inflammatory responses. Despite CDI accounting for the majority of cases, an increasing body of literature highlights non-clostridial causes of PMC, emphasizing the importance of comprehensive diagnostic evaluation [4].

Given the rising incidence, recurrence rates, and emergence of hypervirulent C. difficile strains, pseudomembranous colitis continues to pose a significant clinical and public health challenge. This review aims to provide a comprehensive and updated overview of the causes, clinical manifestations, diagnostic strategies, and evidence-based treatment approaches for PMC, with particular emphasis on recent advances and guideline-driven management.

Causes of Pseudomembranous Colitis

Clostridium difficile infection (CDI): Clostridium difficile was first identified as the primary etiological agent of pseudomembranous colitis in the 1970s, coinciding with the widespread use of broad-spectrum antibiotics [5]. It is a Gram-positive, spore-forming, obligate anaerobic bacterium that produces two major exotoxins, toxin A and toxin B, which are responsible for colonic epithelial injury and inflammation [6]. The organism's ability to form spores contributes to its persistence in healthcare settings and its high recurrence rates.

Staphylococcus aureus Colitis: Before the recognition of C. difficile as the dominant cause, methicillin-resistant Staphylococcus aureus (MRSA) was considered a common pathogen responsible for both hemorrhagic and non-hemorrhagic colitis [7]. Staphylococcus aureus–associated colitis has been reported most frequently following antibiotic exposure (74%), gastrointestinal procedures (18%), and in patients with inflammatory bowel disease (2%) [8].

Klebsiella oxytoca: Klebsiella oxytoca has been identified as a causative agent in antibiotic-associated diarrhea, accounting for approximately 27% of cases among hospitalized patients [9]. Several cases reported in the literature describe the development of colitis following antibiotic use, with clinical improvement observed after withdrawal of the offending antibiotic and initiation of conservative management [10].

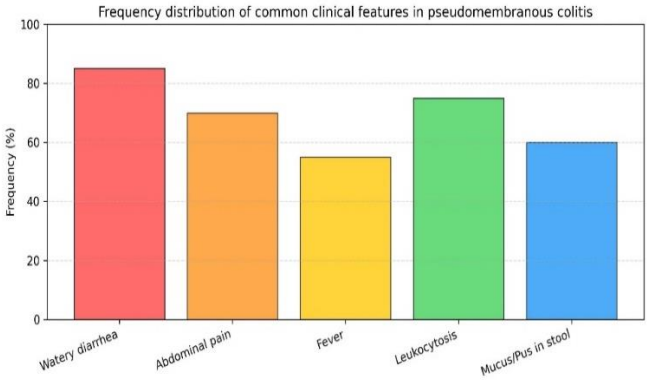
Miscellaneous agents: Other infectious agents implicated in the development of pseudomembranous colitis include Escherichia coli [11], cytomegalovirus (CMV) [12], coronavirus [13], Strongyloides stercoralis [14], and Entamoeba histolytica [15].

Inflammatory Bowel Disease: Pseudomembranous colitis may also occur in patients with inflammatory bowel disease, particularly during disease flares. This condition may present with or without additional contributing factors such as concurrent infections, medication exposure, or other drug-related effects [16].

Drug-Induced Colitis: A pseudomembranous pattern of colitis has been associated with several medications and substances, including non-steroidal anti-inflammatory drugs (NSAIDs) [17], dextroamphetamine [18], alosetron [19], voriconazole [20], and illicit substances such as cocaine [21].

Figure 1

Frequency Distribution of Common Clinical Features in Pseudomembranous Colitis



Antibiotics Associated with Pseudomembranous Colitis

Penicillins, cephalosporins, clindamycin, non-steroidal anti-inflammatory drugs (NSAIDs), trimethoprim–sulfamethoxazole, and fluoroquinolones are among the most commonly implicated medications associated with pseudomembranous colitis. The pathogenic mechanism is primarily mediated by Clostridium difficile through the production of two potent toxins: enterotoxin A and cytotoxin B. These toxins activate the host immune response, resulting in mucosal inflammation, epithelial damage, and disruption of colonic integrity [22].

Symptoms

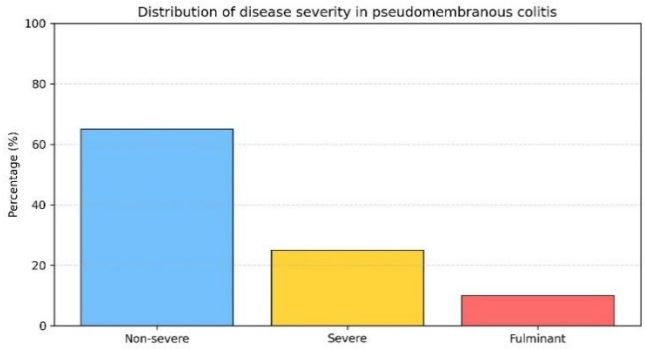
Watery diarrhea is the hallmark and most frequently reported symptom of pseudomembranous colitis, often accompanied by mucus or pus in the stool. Additional clinical manifestations include abdominal cramps, abdominal pain, and fever. Leukocytosis is one of the most commonly observed laboratory findings in affected patients. Due to antibiotic-induced alterations in the normal gut microbiota, symptoms may develop within a few days of antibiotic initiation and can persist for up to six weeks following exposure [2].

Diagnosis

As Clostridium difficile accounts for the majority of pseudomembranous colitis cases, diagnostic evaluation should initially focus on identifying C. difficile infection. The recommended first step involves enzyme immunoassay testing for glutamate dehydrogenase (GDH) antigen along with detection of toxins A and B. A positive GDH and toxin assay confirms active infection. In cases with indeterminate results, nucleic acid amplification tests may be utilized to enhance diagnostic accuracy. If clinical suspicion remains high and the patient is hemodynamically unstable, treatment should be initiated promptly without awaiting confirmatory results. When CDI therapy fails or toxin assays and cultures are negative, alternative etiologies of pseudomembranous colitis should be explored. A comprehensive clinical history plays a crucial role in identifying potential causative factors and guiding diagnosis [4].

Figure 2

Distribution of disease severity among patients with pseudomembranous colitis, showing the relative proportion of non-severe, severe, and fulminant cases.



Treatment and management

Until recently, metronidazole and vancomycin were the mainstay pharmacological treatments for Clostridium difficile infection (CDI). Metronidazole may be administered orally or intravenously, whereas vancomycin is used exclusively via the oral route for CDI management. Due to its minimal systemic absorption and poor penetration into the colonic mucosa when administered intravenously, vancomycin is not recommended for IV use in the treatment of CDI. In severe cases, intravenous immunoglobulin (IVIg) has been utilized as adjunctive therapy, while surgical intervention, such as colectomy, is reserved for a small proportion of patients with fulminant disease who fail to respond to medical management [23].

However, CDI has become increasingly difficult to treat with conventional therapies. Treatment failure rates with metronidazole have risen, with non-response reported in more than 20% of cases. Consequently, vancomycin is now preferred over metronidazole for the management of CDI. In addition, recurrence rates of CDI are steadily increasing [24]. The emergence of hypervirulent strains, particularly the NAP1/027 strain, has further complicated disease management. This strain is characterized by excessive toxin production and reduced responsiveness to standard antimicrobial therapies [25]. These challenges highlight the urgent need for more effective treatment strategies.

Fidaxomicin is a newer orally administered macrocyclic antibiotic with a narrow antimicrobial spectrum. Clinical trials have demonstrated its efficacy in the management of recurrent CDI; however, several concerns limit its widespread use. These include its relatively low activity against the NAP1/027 strain, limited evidence supporting its effectiveness in severe or fulminant colitis, and its high cost [26].

In cases where there is a diagnostic delay exceeding two days and the patient presents with severe or fulminant CDI, empiric antimicrobial therapy should be initiated promptly [27]. For all other patients, antibiotic therapy should be started only after diagnostic confirmation to minimize inappropriate antibiotic exposure and reduce the risk of adverse effects, including the overgrowth of multidrug-resistant microorganisms [28].

CONCLUSION

Pseudomembranous colitis is antibiotic-induced diarrhea that is initiated by Clostridium difficile infection along with other causes. It is diagnosed clinically and different laboratory tests help in confirmation of diagnosis. Symptoms include watery diarrhea with pus in the stool after recent antibiotic use. Inflammatory conditions of the bowel and some medicines such as NSAID are also causative factors for PMC. Treatment options include oral vancomycin, metronidazole, and a novel macrolide agent Fidaxomicin. Surgery is also performed in some severe cases. The best prevention for pseudomembranous colitis is creating awareness and avoiding the misuse of antibiotics.

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