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Review Article

Pseudomembranous Colitis: Current Scenario in Paediatric Practice

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Abstract

The paper aims at providing a state-of-the-art review of the English medical literature punctuated by our own experience spread over 2 decades on pseudomembranous colitis (PMC) as a result of proliferation of the pathogen, *Clostridium difficile,* in the gut in children on antibiotics.

Though antibiotic-associated colitis from *C. difficile* (the classical form) accounts for most cases of pseudomembranous colitis (inflammatory plaques on colonic mucosa) in practice, non-*C. difficile* PMC is also known. Over the recent decades, incidence of classical PMC has been showing increasing incidence because of massive overuse, nay abuse, of antibiotics.

Usual manifestations include diarrhoea (often "bloody"), abdominal discomfort/pain/tenderness, fever, diarrhoeal dehydration and generalised weakness

Confirmation of the clinical diagnosis is by demonstration of *C. difficile* in stools, lower endoscopy, procto-sigmoidoscopy, and imaging studies..

Treatment comprises withdrawal of the offending antibiotic, drug therapy with metronidazole (or its prototypes), vancomycin, or fidaxomicin, or their varying combinations. In severe and recurrent cases, faecal transplantation may prove life-saving.

Prophylaxis is in the form of hygienic measures and rational use of antibiotics and its propagation via antibiotic stewardship program. An cost-effective vaccine remains to be available for clinical use.

Keywords: Antibiotic-Associated Diarrhea; Bloody Diarrhoea; *Clostridium difficile*; Diarrhoea; Fidaxomicin Metronidazole; Pseudomembranous Colitis; Vaccine; Vancomycin

Introduction

Incidence of pseudomembranous colitis (PMC), once infrequent in children, has been on the increase in the past few decades [1-8] because of the antibiotic abuse that is known to cause proliferation of *Clostridium difficile*, the bacterial pathogen that is usually responsible for it [9-12].

This update aims at providing a state-of-the -art review punctuated by our own experience during the past over two decades on the different aspects of this entity.

What is PMC?

By definition. PMC is a fulminant condition characterized by the development of inflammatory plaques over the luminal surface of the large gut, usually rectosigmoid colon, and, unless proved otherwise, secondary to overgrowth and proliferation of *C. difficile* following antibiotic use [1-3,6-12].

Pathological aspects

The pseudomembrane in PMC is a layer of fibro-purulent exudate. The exudate is composed of acute inflammatory cells and mucus produced by the inflamed and erupting crypts [3].

Factors such as poor oxygenation, endothelial damage, and impaired blood flow to the mucosa are responsible for pathological changes.

In appearance, the pseudomembranes are seen as the raised whitish or yellowish plaques (2–10 mm in diameter). These are scattered or confluent in distribution and are best seen in the rectosigmoid colon (Figure 1).

Peudomembrane formation may also be triggered by a number of disease states other than *C. difficile* infection.

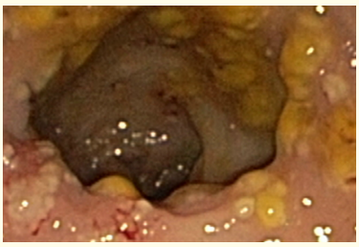

Figure 1: Pseudomembranous colitis. Note the yellowish plaques (pseudomembranes) on the luminal aspect of the sigmoid colon.

Aetiological considerations

In an overwhelming proportion of cases, *C. difficile*, a spore-forming bacteria, is the causative agent [1-3].

C. difficile infection is spread by bacterial spores found within faeces. Surfaces may become contaminated with the spores. Further spread occurs through the hands of healthcare functionaries.

Box 1 lists the risk factors for PMC.

- Antibiotics
- Hospitalisation.
- Increasing age (pre-adolescents and adolescents in paediatric practice)
- Compromised immunity.
- Pre-existing colon disease, such as inflammatory bowel disease
- Intestinal surgery.

Box 1: Risk factors for classical PMC.

Clinical manifestations

C. difficile infection does not always cause pseudomembranous colitis. In fact, most cases are asymptomatic. Others may have only antibiotic-associated colitis manifesting with diarrhoea with or without blood. Only a small proportion may progress to life-threatening fulminant colitis. Some of these fulminant colitis cases develop pseudomembrane (plaques) with potentials for such complications as toxic megacolon, peritonitis, colonic perforation, etc.

Clinical features of PMC include [3]

Usual

- Diarrhoea which may become bloody in a proportion of cases
- Abdominal discomfort/pain/tenderness
- Fever
- Dehydration as such or with dyselectrolytemia
- Weight loss
- Remarkable weakness.

Infrequent

- Acute abdomen
- Peritonitis
- Toxic megacolon
- Colonic perforation

Table 1 lists the clinical manifestations experienced by us in our 52 paediatric patients of PMC during the time span of two decades (1996-2016).

Clinical Manifestation	Number (%)
Diarrhea	26 (52)
Dysentry	24 (58)
Abdominal discomfort/pain	42 (84)
Fever	43 (86)
Dehydration	45 (90)
Generalized weakness	38 (76)
Weight loss	33 (66)
Toxic Megacolon	4 (8)

Table 1: Clinical manifestations in author's 52 paediatric subjects with classical PMC seen during 1996-2016.

Amongst the infrequent manifestations, which may well be considered complications, we have seen acute abdomen and toxic megacolon only. There was no patient of peritonitis and colonic perforation. The 4 cases of toxic megacolon were in the age group 10-15 years.

Differential diagnosis

Classical PMC (due to *C. difficile*) has a wide differential diagnosis [2-4], especially

- Infectious agents: *Staphylococcal aureus, E. coli* 0157:H7, cytomegalovirus (CMV), *Entamoeba histolytica, Strongyloides stercoralis.*
- Chemical injury
- Drugs: Nonsteroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs).

Diagnosis

High index of suspicion is the gateway to diagnosis. The confirmation of PMC is by the following investigations [13-18]:

- Stool culture
- Test for the *C. difficile* DNA or toxins.
- Complete blood count (CBC), especially for abnormally high TLC.
- Lower endoscopy and proctosigmoidoscopy for characteristic adherent raised yellow plaques.
- Abdominal X-ray and CT scan.

Therapeutic considerations

The following approach [19-24] is the current recommendation

Treatment strategies in an acute case

- **Step 1:** Withdrawal of the causative antibiotic along with rehydration therapy reduces the magnitude of manifestation in many cases.

- **Step 2:** Use of drug(s) likely to be effective against *C. difficile*, i.e. metronidazole, vancomycin, fidaxomicin or combinations of these 3 drugs.
- **Step 3:** Faecal microbial transplantation (FMT) in an extremely severe state may come in handy. This is in the form of a transplant of stool from a healthy donor. The aim is to restore the balance of bacteria in the ecosystem of the colon. The donor stool may be
  - Delivered through a nasogastric tube,
  - inserted into the colon, or
  - placed in a capsule that is to be swallowed.

Several studies have reported favourable (60-90%} therapeutic efficacy of FMT for the treatment of refractory *C. difficile* infection (CD) as in the case of PMC. The use of FMT in our 4 cases of toxic megacolon (who did not survive) may have resulted in a positive outcome as pointed out in some documentations.

Therapy in recurring PMS

- **Repeat course(s) of useful drugs: A** second or third round of metronidazole, vancomycin or fidaxomicin or combinations to resolve the problem should always be the approach in the first instance.
- **Fecal microbial transplantation (FMT):** FMT, as described earlier, is used to treat recurrent PMC.
- **Surgery:** Surgery may be an option in people who have progressive organ failure, rupture of the colon or peritonitis. Typically, surgery involves removing all or part of the colon (total or subtotal colectomy). A newer surgery that involves laparoscopically creating a loop of colon and cleaning it (diverting loop ileostomy and colonic lavage) is less invasive and gives better results.

Surgery is indicated in the following situations

- Progressive organ failure,
- Rupture of the colon
- Inflammation of the lining of the abdominal wall (peritonitis).

Role of probiotics

The efficacy of probiotics in PMC remains to be confirmed in view of the conflicting report so far [20-25].

Prognosis

Timely appropriate therapy leads to good prognosis. An occasional patient may develop such fulminant complication as toxic megacolon, sepsis (peritonitis), colonic perforation or acute abdomen. Presentation with acute abdomen may erroneously lead to unnecessary laparotomy. Outcome in these complicated cases is poor with high mortality and morbidity. None of the 4 children with toxic megacolon in our series could be saved.

Prophylaxis

Hygienic Measures: The following basic sanitation practices are helpful:

- Hand hygiene
  - Washing of hands often with soap and water.
  - Wash hands after visiting anyone in a nursing home or hospital.
- Disinfection of surfaces with chlorine bleach-based cleaning products.
- Rational use of antibiotics and promotion of antibiotic.
- Use of disposable gloves while caring for someone with *C. difficile*
- Washing clothing with soap and chlorine bleach if these become soiled with faecal matter from someone infected with *C. difficile*.

Vaccine

The potential use and efficacy of the vaccine against C. difficile depends on the development of a cost-effective vaccine. Hopefully, such a vaccine is around the corner [26-28].

Future research

Researchers need to

- Explore simple, acceptable and affordable treatment modalities for PMC (in other words, refractory and fulminant CDI}, including alternative drugs to reduce recurrence, and
- An appropriate cost-effective vaccine against *C. difficile.*

Summary and Conclusion

PMC is a serious stage of antibiotic-associated diarrhoea in which large gut mucosal inflammation with plaque formation occurs. Its incidence is on an increase with the massive use/abuse of antibiotics. Usual manifestations include diarrhoea with or without blood, abdominal pain, dehydration, weight loss and generalized weakness. Differential diagnosis includes other conditions that cause pseudomembrane in the colon. Diagnosis is by high index of suspicion with support from endoscopy, proctosigmoidoscopy and imaging studies. Treatment essentially consists in withdrawal of the offending antibiotic, control of dehydration and electrolyte disturbances, and metronidazole, vancomycin, fidaxomicin or combinations of these 3 drugs. In severe and recurrent PMC, fecal microbial transplant may be employed. An effective vaccine against *C. difficile* is yet to come of age.

Take-Home Messages

- Incidence of PMC is on an increase with the massive use/abuse of antibiotics.
- PMC is a serious stage of antibiotic-associasted diarrhea in which large gut mucosal inflammation with plaque formation occurs.
- Usual manifestations include diarrhea with or without blood, abdominal pain, dehydration, generalized weakness.
- Differential diagnosis includes other conditions that cause pseudomembranous colitis, e.g. *E. coli*, shigella, chemical injury.

- Diagnosis by high index of suspicion with support from endoscopy and imaging studies.
- Treatment essentially consists in withdrawal of the offending antibiotic, control of dehydration and electrolyte disturbances, and metronidazole, vancomycin, fidaxomicin or combinations of these 3 drugs.
- In recurrent PMC, fecal microbial transplant may be employed.
- Since an acceptable vaccine is yet available, prophylaxis is through conservative means, including good hand hygiene and rational use of antibiotics.

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