Pseudomembranous Colitis

Synonyms: Clostridium difficile-associated diarrhoea/disease, CD-positive diarrhoea, antibiotic-associated colitis

Pseudomembranous colitis (PMC) is an acute, exudative colitis usually caused by Clostridium difficile. PMC can rarely be caused by other bacteria - eg, Staphylococcus spp. or enterotoxigenic Clostridium perfringens, Campylobacter spp., Listeria spp. and Salmonella spp.

PMC has emerged, particularly in recent years, as a major and very expensive healthcare problem. Spores formed by the organism are implicated in spread of infection and have implications for hygiene and prevention of infection. C. difficile is an anaerobic Gram-positive rod which secretes two types of toxin (A and B), which cause disruption to the barrier function of the colonic mucosa. They are cytotoxic to cells of the intestinal tract, B being about 1,000 times more potent than A. Transmission of infection is via an indirect faeco-oral route, through spores left on surfaces. The spores can survive for months and patients can become carriers. The risk of colonisation increases with length of hospital stay.

C. difficile is classified into strains by polymerase chain reaction (PCR) ribotyping:
- Ribotype 001 is a common cause of C. difficile infection (CDI) in the UK.
- C. difficile 027 (also known as C. difficile NAP1/027 or C. difficile BI/NAP1/027) is associated with higher mortality, severity and relapse rate.
- C. difficile 078 has a higher incidence among community-acquired C. difficile infection (CA-CDI).

Epidemiology
- The incidence and severity of CDI around the world was reported in 2012 as having increased over a period of 20 years due to the emergence of hypervirulent strains, increased use and misuse of antibiotics, and the increase of susceptible at-risk populations.
- However, counts and rates for CDI are falling across the NHS. 21,695 cases of CDI were reported in patients aged 2 years and over between April 2010 and March 2011. This is a reduction of 15% on the total number of cases of CDI reported in 2009/10 and a 40% reduction on the cases reported in 2008/09.
- Associated national rates have also decreased during this period, from 72.0 cases per 100,000 population in 2008/09 to 43.0 in 2010/11.
- C. difficile is the main pathogen of antibiotic-associated colitis and accounts for up to 25% of hospital-acquired antibiotic-associated diarrhoea.
- Any antibiotic can increase the risk of CDI, including metronidazole and vancomycin, which are used in the treatment of CDI.
- Disease has been reported following as little as one dose of antibiotic.
- Although the attributable risk has varied among studies, fluoroquinolones, macrolides, clindamycin, beta-lactam/beta-lactamase inhibitors and cephalosporins have been shown to pose a significant risk for the development of CDI.
- Antineoplastic agents and proton pump inhibitors have also been associated with CDI.

Risk factors
- Prolonged courses of antibiotics.
- Multiple antibiotic usage.
- Increasing age.
- Severe comorbidity.
- Non-surgical invasive gastrointestinal procedures.
- Presence of a nasogastric tube.
- Inpatient residence on ITU.
Increasing duration of hospital stay; patients in long-term care facilities.
Immunocompromised patients.

Presentation
Colonisation with *C. difficile* can be associated with a range of possible clinical states:

- The asymptomatic carrier state.
- Mild self-limited diarrhoea.
- Pseudomembranous colitis.
- Fulminant colitis.

Generally there is a history of antibiotic exposure together with risk factors for colonisation:

- Typically, symptoms come on between 5 and 10 days after antibiotic therapy. Occasionally patients will not have had antibiotic exposure.
- Most patients become unwell during their course of antibiotics, but 25-40% may not do so for as many as 10 weeks afterwards.\(^3\)
- Most affected individuals experience watery diarrhoea (varies from self-limiting to severe and debilitating) ± blood-stained stools, abdominal cramps, fever (especially so in severe cases), rigors ± sepsis.
- Severe abdominal pain is uncommon but may mimic an acute abdomen.
- Frank rectal bleeding suggests other causes (for example, inflammatory bowel disease).

Differential diagnosis

- Crohn's disease.
- Ulcerative colitis.
- Diverticular disease.
- Other infections:
  - Gastroenteritis
  - Campylobacter
  - Salmonella
  - Shigella
  - Cholera
  - Amoebiasis

- Acute abdomen due to surgical pathology.
- Ischaemic colitis.

Investigations\(^{3,6}\)

- FBC (WCC elevated in 80%, often very high).
- Renal function tests and electrolytes.
- Hypoalbuminaemia may be present (due to a protein-losing enteropathy).
- Diagnosis in CDI and PMC focuses on detection either of *C. difficile* or of its toxins in stool samples. The particular method used will depend on the laboratory. Generally, repeat testing on three stool samples is recommended. Samples can usually be frozen or refrigerated if more than a four-hour delay in processing is expected. Liaison with the laboratory may be helpful to avoid delay. Methods of testing include:
  - The stool cytotoxin test, which has high sensitivity (94-100%) and specificity (99%) and has been the standard test (it relies on detection of cytotoxic effect on cultured fibroblasts, negated by a specific antibody).\(^{7}\)
  - Enzyme-linked immunoassay techniques. Toxin can be demonstrated in the stool but these have varying sensitivity and specificity (69-87%).\(^{7}\)
  - Culture of *C. difficile* directly from the stool is the most sensitive diagnostic test but does not differentiate between toxin-producing and non-toxin-producing bacteria.
  - PCR testing appears to be rapid, sensitive and specific but needs further evaluation before it can be recommended for routine testing.\(^{8}\)

- Testing for *C. difficile* or its toxins should be performed only on diarrhoeal (unformed) stool, unless ileus due to *C. difficile* is suspected. Testing of stool from asymptomatic patients is not clinically useful.\(^{8}\)

- Sigmoidoscopy (or colonoscopy):
  - Can show the characteristic pseudomembranous plaque appearance in about half of affected patients.
  - May require biopsy to confirm diagnosis.
  - Is not used routinely but is usually performed if rapid diagnosis is needed or in a patient who has ileus (often as part of work-up for other colonic disease).

- Imaging studies:
  - Plain X-rays and CT scanning may be helpful.
  - Useful in severe disease but not likely to be helpful in early or mild colitis.
  - Can detect complications (perforation, toxic dilatation).
  - Barium enemas can be harmful and should be avoided.
Reporting

Any of the following defines a *C. difficile* infection case in patients aged 2 years and above and must be reported to Public Health England or the equivalent agency in Northern Ireland, Scotland and Wales. [6]

- Diarrhoeal stools where the specimen is *C. difficile* toxin-positive.
- Toxic megacolon or ileotomy where the specimen is *C. difficile* toxin-positive.
- PMC revealed by lower gastrointestinal endoscopy or computed tomography.
- Colonic histopathology characteristic of CDI (with or without diarrhoea or toxin detection) on a specimen obtained during endoscopy or colectomy.
- Faecal specimens collected post-mortem where the specimen is *C. difficile* toxin-positive or tissue specimens collected post-mortem where pseudomembranous colitis is revealed or colonic histopathology is characteristic of CDI.

Management

- Correct fluid losses or electrolyte imbalance with oral or intravenous (IV) electrolyte solutions.
- Avoid antiperistaltic agents such as loperamide or opiates (codeine) because of the risk of retention of toxins in the lumen.
- Ceasing the causative antibiotic (if possible) allows resolution in ~3 days in 22%. Consider changing to an antibiotic less likely to cause PMC - aminoglycosides, macrolides, vancomycin or tetracyclines.
- Metronidazole and vancomycin have been the mainstays of therapy, with some recent data supporting the expanding role of vancomycin in the treatment of severe CDI. Adjunctive therapy with probiotics, IV immunoglobulin, or rifampin has been used in refractory or recurrent CDI. Vancomycin is the drug of choice for an initial episode of severe CDI. [8]
- Most studies have found no statistically significant difference in efficacy between vancomycin and other antibiotics, including metronidazole, fusidic acid, nitazoxanide or rifaximin. Teicoplanin may be another option. [9]
- Fidaxomicin is now available in the UK for the treatment of CDI in adults. One study found the rates of clinical cure after treatment with fidaxomicin were similar to those after treatment with vancomycin. Fidaxomicin was associated with a significantly lower rate of recurrence of CDI. [10] A further study found that early recurrence (within 14 days) was reported in 27% of patients treated with vancomycin and 8% of patients treated with fidaxomicin. In patients with a first recurrence of CDI, fidaxomicin was similar to vancomycin in achieving a clinical response at end of therapy but superior in preventing a second recurrence within 28 days. [11]
- Adherence to the recommended infection control measures and the judicious use of antibiotics should also be part of the global management of CDI in long-term care facilities. [12]

There is insufficient evidence of any benefit with probiotic therapy as an adjunct to antibiotic therapy for *C. difficile* colitis. There is no evidence to support the use of probiotics alone in the treatment of *C. difficile* colitis. [13]
Surgery\[14\]

- Surgery may be life-saving for patients with acute severe colitis.
- Referral for a surgical opinion is required if the patient fails to respond to treatment or has signs of an acute abdomen, radiological signs of acute disease, a rising white blood cell count, a rising creatinine concentration, or a rising lactate concentration.

Criteria for a diagnosis of severe colitis:

Stool frequency: >6 in 24 hours, and at least one of the following: pulse rate >90 beats/minute, temperature >37.8°C, haemoglobin <10.5 g/L, ESR >30 mm in first hour.\[14\]

Prognosis

- In healthy individuals a good response to treatment is usually expected but the illness can cause severe debility and prolonged hospital stays.
- CDI is implicated as a significant cause of morbidity and mortality among hospitalised patients.\[3\]
- Recurrent colitis and diarrhoea occur in approximately 25% of patients.\[8\]
- Early identification of CDI and prompt initiation of therapy with the most appropriate agent are critical to minimise morbidity and mortality.\[14\]

Complications

Complications of severe \textit{C. difficile} colitis include dehydration, electrolyte disturbances, hypoalbuminaemia, toxic megacolon, bowel perforation, hypotension, acute kidney injury, systemic inflammatory response syndrome, sepsis and death.\[6\] Extraintestinal manifestations are rare and include:\[9\]

- Bacteraemia.
- Splenic abscess.
- Osteomyelitis.
- Reactive arthritis or tenosynovitis.

Prevention

- Administration of currently available probiotics is not recommended to prevent primary CDI, as there are limited data to support this approach.\[8\]
- Overall preventative measures, such as strict handwashing and patient isolation policies for patients with diarrhoea, seem to be effective. There is less evidence of benefit for environmental cleansing measures.
- Handwashing should be done correctly to be effective. Alcohol gels do not kill spores and are not recommended.\[15\]
- Appropriate antibiotic prescribing; minimise the frequency and duration of antimicrobial therapy and the number of antimicrobial agents prescribed.\[8\]

Further reading & references

- Antibiotic prophylaxis in surgery; Scottish Intercollegiate Guidelines Network - SIGN (April 2014)
- Clostridium difficile: guidance, data and analysis; Public Health England
- Updated Guidance on the Diagnosis and Reporting of Clostridium Difficile; Dept of Health, March 2012

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