We report three cases of *Clostridium difficile* pancolitis in adults with cystic fibrosis (CF) in whom the presenting symptoms were atypical. All three required treatment with systemic steroids, in addition to oral vancomycin and metronidazole to achieve resolution of the colitis. This experience suggests that *C. difficile* colitis should be considered in individuals with CF presenting with non-specific abdominal symptoms.

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1. Case 1

A 20-year-old pancreatic insufficient CF male, FEV₁ 60% predicted, presented with a one week history of fever and vomiting. He had not opened his bowels for 4 days. He was dehydrated, hypotensive, tachycardic and had a temperature of 39 °C. His abdomen was soft, the lower quadrants were mildly tender and his bowel sounds were quiet. Abdominal X-ray was not suggestive of distal intestinal obstruction syndrome (DIOS) and the erect chest X-ray showed no free air under the diaphragm. His WBC was 67 × 10⁹/L (normal range 4–11 × 10⁹) and CRP 305 mg/L (normal range 0–10).

Prior to this episode he had required frequent intravenous anti-pseudomonal antibiotics and a two month course of oral steroids for treatment of recurrent right upper lobe consolidation. He had a past history of gastro oesophageal reflux, liver disease and CF related diabetes. His maintenance treatment included omeprazole, and azithromycin had recently been discontinued due to diarrhoea.

An abdominal CT (Fig. 1) showed pancolitis and an enlarged appendix. He was transferred to the intensive therapy unit, fluid resuscitated and given intravenous cefuroxime and metronidazole before undergoing a laparoscopic appendicectomy. The appendix was inflamed but had not ruptured and there was no evidence of an intra-peritoneal collection. Flexible sigmoidoscopy showed pseudomembranous colitis and stool tissue-culture cytotoxicity assay was positive for *C. difficile* toxin. Intravenous cefuroxime was stopped and he was commenced on oral vancomycin and oral prednisolone 40 mg od. He made a rapid clinical improvement and 6 days later his CRP and WBC had reduced to 12 and 13 respectively. Vancomycin was prescribed for 10 days in total and the prednisolone was weaned gradually to zero. Stool samples were negative for *C. difficile* toxin on subsequent testing.

Two months later, during a further course of intravenous anti-pseudomonal antibiotics stool samples were *C. difficile* toxin positive again. Oral metronidazole was started and continued for the duration of the intravenous antibiotics. Subsequent stool samples were negative and on this occasion he remained clinically well.

To date, 1 year later, he has experienced no further bowel problems despite two further courses of intravenous antibiotics.
antibiotics, with oral metronidazole cover, to treat pulmonary exacerbations.

2. Case 2

A 34 year-old pancreatic insufficient CF male, FEV\textsubscript{1} 45% predicted, presented with a 4 day history of colicky abdominal pain and nausea. He had experienced one episode of diarrhoea but otherwise reported normal stools. He had a history of gastro oesophageal reflux which was treated with omeprazole. He was chronically infected with \textit{Pseudomonas aeruginosa} and \textit{Mycobacterium abscessus} and was treated with long term minocycline, clarithromycin, nebulised TOBI and subcutaneous interferon gamma. In the previous year he had required one 14-day course of intravenous meropenem and colomycin, which he completed three weeks prior to this admission.

On examination he was dehydrated, tachycardic, hypotensive and had a temperature of 39 °C. There was no evidence of pulmonary exacerbation. His abdomen was soft, moderately distended and tender in the lower quadrants with quiet bowel sounds. His CRP was 161 and WBC 12.1. Abdominal X-ray suggested faecal loading in the large bowel with no small bowel obstruction. An abdominal CT scan showed severe pancolitis, flexible sigmoidoscopy confirmed pseudomembranous colitis and his stool sample was positive for \textit{C. difficile} cytotoxin. He was treated with intravenous metronidazole, oral vancomycin and intravenous fluids. However, his pain, fevers and nausea failed to resolve and his CRP rose to 356. Intravenous hydrocortisone 100 mg bd was added, following which his clinical condition rapidly improved. His CRP reduced to 72 within 2 days of starting steroid treatment and his stool became \textit{C. difficile} cytotoxin negative after 5 days of antibiotic treatment. He completed three weeks treatment with oral vancomycin and metronidazole and weaned the oral prednisolone to zero. He discontinued minocycline and clarithromycin while an inpatient and these were recommenced following completion of colitis treatment. To date he has remained symptom free from a bowel perspective for eight months despite requiring two further courses of intravenous antibiotics to manage pulmonary exacerbations. During these he was prescribed oral metronidazole cover and no \textit{C. difficile} toxin was detected.

3. Case 3

A 24-year-old CF male, FEV\textsubscript{1} 21% predicted, presented with a 3 day history of severe abdominal pain. He had not opened his bowels for 4 days. He had a past history of gastro oesophageal reflux and type 2 respiratory failure requiring nasal ventilation. His medications included azithromycin and esomeprazole.

He was haemodynamically stable and well hydrated but his temperature was 39.4 °C. There was no evidence of pulmonary exacerbation. His abdomen was soft but slightly distended with moderate tenderness in the lower quadrants. Bowel sounds were normal. His abdominal X-ray was suggestive of DIOS (Fig. 2), however his CRP was 191 and WBC 25. An abdominal CT was requested which showed pancolitis. He was treated empirically with intravenous metronidazole and oral vancomycin. The

![Fig. 1. Case 1 (C. difficile pancolitis).](image1)

![Fig. 2. Case 3. Abdominal X-ray with small gas collections throughout the large bowel suggestive of faecal loading and a degree of small bowel obstruction consistent with distal intestinal obstruction syndrome.](image2)
azithromycin was stopped. Stool samples were negative for *C. difficile* cytoxin but a flexible sigmoidoscopy showed pseudomembranous colitis (Fig. 3). Despite 2 days of intravenous antibiotics his CRP rose to 310. Intravenous hydrocortisone was started and 5 days later his CRP fell to 25. He completed 7 days of intravenous metronidazole and 28 days of oral vancomycin. The intravenous hydrocortisone was converted to prednisolone and gradually weaned to zero.

Eight months later, having had two uneventful courses of intravenous antibiotics for pulmonary exacerbations, he presented again with constipation, vomiting, high fevers and abdominal pain. Immediately prior to this he had taken a two week course of azithromycin 500 mg daily to treat a pulmonary exacerbation. CT confirmed pancolitis with proximal small bowel obstruction. This was resolved after 4 days of treatment with intravenous metronidazole, oral vancomycin and intravenous hydrocortisone. TOBI nebs were started as prophylaxis in preference to oral agents and he was encouraged to take probiotics.

4. Discussion

Positive stool cultures for *C. difficile* have been reported in up to 43% of individuals with CF but patients with toxin producing strains were asymptomatic [1] and overall the reported incidence of symptomatic *C. difficile* infection is low [2]. No individuals attending our CF centre had been diagnosed with *C. difficile* colitis until 2006 and the cause of this apparent cluster remains unclear. Following contact with the organism, treatment with antibiotics is the major risk factor for the development of *C. difficile* colonisation. Impaired immunity and reduction of gastric acidity are also associated factors [3,4]. While none of the three patients had been in contact at any time, all three had recently been prescribed intravenous anti-pseudomonal antibiotics, intermittent courses of oral ciprofloxacin, macrolides long term and proton pump inhibitors. Fluoroquinolone resistant *C. difficile* strains have been implicated in severe nosocomial outbreaks of *C. difficile* diarrhoea [5] and studies in the non-CF population suggest that macrolides are a significant risk factor [6]. Genes encoding fluoroquinolone and macrolide resistance in *C. difficile* have been identified and may be becoming more prevalent [7]. As a consequence, we have tended to stop macrolide prophylaxis in individuals that have developed *C. difficile* colitis, unless the potential benefit of continuation outweighs the theoretical risk, as in Case 2 where clarithromycin was prescribed in the context of *M. abscessus* infection.

The cases described are notable for the insidious onset of symptoms, with little or no diarrhoea, culminating in the development of fulminant *C. difficile* pancolitis. The absence of diarrhoea is perhaps unsurprising given the pivotal role of CFTR in chloride secretion into the intestinal lumen. The symptoms and abdominal X-ray may, in fact, be suggestive of DIOS, as in Case 3. It is therefore important to consider *C. difficile* colitis in CF patients presenting with fevers and vague gastrointestinal symptoms.

The recent report of four CF patients with fulminant *C. difficile* colitis following lung transplantation with 50% mortality highlights the importance of vigilance for the presence of this pathogen [8]. A prior history of *C. difficile* colitis may now need to be considered when assessing the suitability of individuals for lung transplant listing.

While identification of *C. difficile* toxin in stool may indicate the presence of disease, no test is 100% sensitive and sigmoidoscopy may be required to confirm the diagnosis, as in Case 3. This test is safe in patients with severe colonic inflammation when performed by experienced operators [9]. Abdominal CT scanning made a major contribution in securing the diagnosis in our series and suggests that cross sectional imaging is useful in narrowing the differential diagnosis in patients presenting with non-specific abdominal pain in the context of fevers and high inflammatory markers.

Oral metronidazole is the first line treatment for *C. difficile* and intravenous metronidazole is also efficacious. If there is no improvement in symptoms after 3 days, oral or rectal vancomycin or oral teicoplanin may be added [10]. There is some evidence to support the use of probiotics to promote recolonisation with normal bowel flora [11]. Although there is little evidence for the use of systemic steroids in patients with pseudomembranous colitis, the close temporal relationship between the prescription of systemic steroids and clinical improvement, particularly in Cases 2 and 3 in our series, suggests that they were beneficial.

Inability to mount an adequate specific antibody response to *C. difficile* toxins predisposes patients to more severe disease [3] and could predict those patients most at risk. Case series report success in using *C. difficile* toxoid vaccine or intravenous immunoglobulin for recurrent or refractory cases [12,13]. If symptoms were to recur despite cessation of oral antibiotic prophylaxis and use of probiotics, one could consider prophylactic immunoglobulin as in other forms of specific antibody deficiency.

In summary, *C. difficile* colitis should be considered in CF individuals presenting with non-specific abdominal symptoms. Systemic steroids may be beneficial in patients with pancolitis not responding to conventional antibiotic treatment.

Fig. 3. Flexible sigmoidoscopy showing yellow adherent plaques (white arrows) typical of pseudomembranous colitis.
References


