**Clostridium difficile** infection in cystic fibrosis: an uncommon but life-threatening complication

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**Abstract**

Adults with cystic fibrosis (CF) have significant rates of asymptomatic *Clostridium difficile* carriage and are frequently exposed to risk factors for *C. difficile* infection (CDI). Despite this, the rate of reported CDI in CF is low. We describe three cases of near fatal CDI in adults with CF and review the literature regarding presentation, management, and recurrence prevention. Early recognition is important as the clinical presentation may be atypical and the illness can be severe and even life-threatening. Management can be complicated by respiratory and nutritional failure. CF-related gastrointestinal dysfunction may alter the typical host–pathogen interaction between patient and *C. difficile*, potentially explaining the low rates of CDI and atypical presentation.

**Introduction**

*Clostridium difficile* is a spore forming Gram-positive organism responsible for antibiotic associated colitis. In cystic fibrosis (CF) patients, the prevalence of asymptomatic gastrointestinal colonization by *C. difficile* (22–46%) is higher than in healthy (3%) and hospitalized (20%) adults. Despite these relatively high carriage rates and frequent exposure to known risk factors, *C. difficile* infection (CDI) appears infrequent in CF.

**Case Report**

This case report comprises three cases of near fatal CDI in pre-transplantation adults with CF (Table 1). All three patients had recently received intravenous antibiotics for respiratory exacerbations within 7–21 days prior to their presentation. All patients presented with severe abdominal pain, fever, and tachycardia. Of note, none had diarrhoea. Blood test showed leucocytosis and hypoalbuminaemia. All patients were stool positive for *C. difficile* toxin. All three patients had severe pancolitis on abdominal CT (Fig. 1). Two patients underwent sigmoidoscopy, which confirmed pseudomembranous colitis (Fig. 2). Antibiotic treatment for *C. difficile* was commenced between 24 and 120 hours after symptom onset. The clinical course was complicated by severe abdominal pain and distension, along with respiratory and nutritional failure in all three patients. All three patients required parenteral antipseudomonal antibiotics for the treatment of concurrent respiratory exacerbation precipitated by the severe colitis, and also total parenteral nutrition. No surgical intervention was required by any of these patients, and all of them survived. The length of hospitalization ranged from 28 to 38 days. At 12 months follow-up, none of these patients experienced recurrent CDI despite having been exposed to further courses of antipseudomonal antibiotics.

**Discussion**

A literature search on Medline, EMBASE, and PubMed databases identified several reports of severe CDI in adults.
| Patient characteristics | Case 1 | Case 2 | Case 3 |
|--------------------------|-------|-------|-------|
| Age, gender              | 32, male | 24, male | 23, female |
| Genotype                 | F508del/3659delC | F508del/1154insTC | Homozygous F508del |
| FEV₁ (% predicted)       | 74 | 48 | 45 |
| GORD                     | Yes | Yes | Yes |
| Recent antibiotics       | IV tazocin | IV meropenem | IV ceftazidime |
|                         | IV tobramycin | IV ceftazidime | IV tazocin |
|                         | PO ciprofloxacin | PO ciprofloxacin | PO ciprofloxacin |
| Days from end of the last antibiotic course to CDI presentation | 21 | 7 | 14 |
| Antacid therapy          | Pantoprazole | Pantoprazole | Ranitidine |
| Clinical presentation    |       |       |       |
| Diarrhoea                | Absent | Absent | Absent |
| Vomiting                 | No | Yes | Yes |
| Abdominal pain           | Severe—generalized | Severe—right iliac fossa | Severe—generalized |
| Temperature (°C)         | 38.7 | 38.2 | 38.6 |
| HR (/min)                | 110 | 130 | 125 |
| BP (mmHg)                | 135/75 | 115/70 | 115/80 |
| WCC (×10⁹ L)             | 17.7 | 65.7 | 16 |
| CRP (mg/L)               | 54 | — | 248 |
| Lactate (mmol/L)         | 2.1 | 2.5 | — |
| Albumin (g/L)            | 26 | 24 | 16 |
| Cr (µmol/L)              | 75 | 155 | 70 |
| Diagnostic testing       |       |       |       |
| C. difficile toxin A + B  | Positive on day 3 | Positive on day 2 | Positive on day 2 |
| Abdominal CT             | Proximal/transverse colitis | Pancolitis (Fig. 1) | Pancolitis |
| Limited sigmoidoscopy    | Pseudomembranes | Pseudomembranes (Fig. 2) | — |
| Pathology                | Pseudomembranous colitis | Pseudomembranous colitis | — |
| Complications            | Respiratory failure & ascites | Respiratory failure & ascites | Respiratory failure & Re-feeding syndrome |
|                         | Acute renal failure | | Chest sepsis and haemoptysis |
| Specific CDI treatment    | PO metronidazole | IV/PO/PR metronidazole | PO metronidazole |
|                         | PO vancomycin | PO vancomycin | PO vancomycin |
| Duration of CDI therapy  | 2 weeks of vancomycin and metronidazole | 4 weeks of inpatient vancomycin and metronidazole | 6 weeks of vancomycin |
|                         | | 6 months of outpatient oral vancomycin | |
|                         | | 3 weeks of metronidazole | |
| Length of admission (days) | 38 | 35 | 28 |
| FEV₁ (% predicted) on discharge | 59 | 45 | 42 |
with CF including those who had received lung transplant [1,2]. Many patients with CF, including the three patients highlighted in this case report, did not have diarrhoea at their initial presentation with severe CDI. The atypical presentation has contributed to potential delays in presentation, diagnosis, and treatment of severe CDI in CF. Severe CDI is associated with significant morbidity and mortality in post-transplantation patients with CF [1,2].

The rates of asymptomatic *Clostridium difficile* carriage are high in CF [3]. Therefore, it is surprising that severe CDI is not more frequently observed [3]. There are several possible explanations for this observation, including: (1) prolonged gastrointestinal transit time in CF facilitates bacterial overgrowth which may increase the number of intestinal species with inhibitory effects on *C. difficile* [3]; (2) reduced intestinal pH in CF [3] may be protective against CDI; (3) immunological response to previous *C. difficile* toxin exposure may reduce the risk of clinical disease; and (4) patients with new *C. difficile* acquisition are more likely to develop CDI than those chronically colonized with *C. difficile*. Therefore, the higher *C. difficile* colonization rate may be protective against CDI. The reduced frequency of diarrhoea in CDI may be due to CFTR dysfunction-

| Table 1. Continued |
|-------------------|
| Case 1 | Case 2 | Case 3 |
| **12-Month follow-up** | No further Ab courses | No further Ab courses | No further recurrence of CDI despite further Ab courses |
| Prophylaxis during subsequent Ab therapy | NA | NA | PO vancomycin |

*Ab*, antibiotic; *BP*, blood pressure; *Cr*, creatinine; *CRP*, C-reactive protein; *CT*, computed tomography; *FEV₁*, forced expiratory volume in the first second; *HR*, heart rate; *GORD*, gastro-oesophageal reflux disease; *IV*, intravenous; *PO*, per oral; *PR*, per rectum; *WCC*, white cell count.

Figure 1. CT of the abdomen (Case 2) demonstrated marked, diffuse generalized oedema and thickening of the colon. The colonic wall thickness measures up to 22 mm. The accordion sign* is present with mucosal thickening, producing alternating oedematous haustral folds separated by transverse mucosal ridges (arrow).

Figure 2. Endoscopic photograph (Case 2) of the transverse colon showing oedematous mucosa with thick overlying pseudomembrane (arrowhead), without overt necrosis.
1. Abdominal pain can be due to many factors in people with CF [3] and diarrhoea is not a cardinal feature of CDI in CF. Therefore, a healthy level of suspicion for CDI is required when patients with CF present with abdominal symptoms. Vigilant C. difficile toxin testing and early abdominal imaging should be considered if a patient has significant abdominal pain or distension. Abdominal CT scan often reveals large intestine distension, colonic wall thickening, fat stranding, and unexplained ascites (Fig. 1).

2. Therapy should be initiated for suspected CDI with oral or intravenous metronidazole for mild to moderate presentations. Oral vancomycin should be initiated for severe cases for 10–14 days [4]. In severe CDI cases where oral vancomycin is poorly tolerated, current guideline recommends nasogastric and rectal administration of vancomycin in combination with intravenous metronidazole [4].

3. For refractory CDI, combination antimicrobials (vancomycin and metronidazole) or alternative antimicrobial agents (e.g. tigecycline) are recommended [4]. Bowel perforation, toxic megacolon and clinical deterioration despite antibiotic therapy are indications for surgery, most commonly, subtotal colectomy with an end ileostomy [4].

4. In recurrent CDI, oral vancomycin is recommended as first-line treatment. Alternative therapies such as oral fidaxomicin, rifampicin, nitazoxanide, or faecal microbiota transplantation are potential options in selected patients with recurrent CDI who are not amenable to first-line treatment [4].

5. Early nutritional support is necessary in severe CDI in patients with CF. If enteral nutrition is not feasible total parenteral nutrition may be required.

6. Regular airway clearance should be maintained throughout the acute illness. Whilst avoidance of intravenous antibiotics is advised, this is not always practical in patients with concurrent exacerbations of their CF airways disease.

7. The role of secondary prophylaxis in a patient who has previously had CDI is unknown. There are no guidelines to support this decision. However, concurrent oral metronidazole or vancomycin appears reasonable during antibiotic treatment in patients with CF who had experienced a recent episode of CDI within the last few months. Moderate evidence exists on the efficacy of probiotics in reducing the risk of primary CDI [5]; however, its efficacy in preventing recurrent CDI remains unclear.

8. Patient education on symptom recognition of CDI is important in facilitating early presentation and treatment in CF.

Disclosure Statements
No conflict of interest declared.
Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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