

Pseudomembranous colitis in four patients with cystic fibrosis following lung transplantation

B. Yates, DM. Murphy, AJ Fisher, FK. Gould, JL. Lordan, JH. Dark and PA. Corris.

Applied Immunobiology and Transplantation Research Group. University of Newcastle and The Freeman Hospital, High Heaton, Newcastle upon Tyne, NE7 7DN, United Kingdom.

Corresponding author: Professor Paul A Corris,  
The William Leech Centre for Lung Research,  
The Freeman Hospital,  
High Heaton,  
Newcastle upon Tyne,  
NE7 7DN  
United Kingdom,  
e-mail: [Paul.Corris@ncl.ac.uk](mailto:Paul.Corris@ncl.ac.uk)

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## Abstract

Pseudomembranous colitis is an uncommon complication in cystic fibrosis patients despite the use of multiple, high-dose antibiotic regimens and the frequency of hospital admissions. In this report, we describe a series of four patients from a total of 137 patients with cystic fibrosis undergoing lung transplantation who developed fulminant pseudomembranous colitis. Initial presentation was variable and the mortality rate was 50% despite urgent colectomy. In one case the presenting abdominal distension was thought to be due to meconium ileus equivalent. We conclude that *Clostridium difficile* colitis may be a difficult diagnosis in patients with cystic fibrosis and follow a fulminant course after lung transplantation.

## Introduction

*Clostridium difficile* colitis is rare in patients with cystic fibrosis (CF) although asymptomatic carriage has been reported to occur in up to 50% [1] [2]. We describe four patients following lung transplantation with variable presentation who developed severe pseudomembranous colitis with significant morbidity and mortality. The role of computed tomography (CT) scanning in diagnosis is discussed.

### Case 1

Two months following lung transplantation, a 22 year old man with CF was treated for acute allograft rejection and pulmonary infection with steroids and antibiotics. He initially received piperacillin-tazobactam which was subsequently changed to flucloxacillin after 48 hours following culture of *Staphylococcus aureus* from bronchoalveolar lavage. Whilst his respiratory status improved over the following days, he developed abdominal pain, constipation and a palpable mass in the right iliac fossa. A clinical diagnosis of meconium ileus equivalent was made, a condition he had experienced previously. He was treated with gastrograffin and had a good bowel movement later that day. Although his symptoms initially settled, he developed further pain three days later with associated diarrhoea and a neutrophil leucocytosis. An abdominal radiograph showed thickened large bowel with very little luminal gas. Computed tomography of his abdomen confirmed gross thickening of the entire colon consistent with severe pseudomembranous colitis (figure 1). Stool analysis confirmed *Clostridium difficile* toxin. Metronidazole was commenced but due to the high risk of perforation a subtotal colectomy was performed. Severe pseudomembranous colitis was confirmed on histopathological examination. He made an uneventful recovery.

### Case 2

A 32-year-old lady, 10 years post lung transplantation for CF, developed neutropenic sepsis and renal failure. She was commenced on intra-venous piperacillin-tazobactam and continuous veno-venous haemofiltration. Although she had diarrhoea, stool was negative for *Clostridium difficile* toxin. A CT scan of her abdomen showed thickening of her colon. Flexible sigmoidoscopy with biopsies failed to show any evidence of infection or colitis. She improved over the next three days but then developed profuse diarrhoea and a neutrophil leucocytosis. A presumptive diagnosis of pseudomembranous colitis was made and metronidazole commenced. Stool analysis subsequently confirmed *Clostridium difficile* and she gradually improved.

### Case 3

A 28-year-old man with CF underwent lung transplantation and received aztreonam and clindamycin. His initial postoperative course was complicated by reperfusion injury requiring re-intubation and renal failure. He developed abdominal distension and initially a clinical diagnosis of meconium ileus equivalent was made. Abdominal radiography showed grossly dilated large bowel and a manual evacuation was performed. The following day he became septic and hypotensive, antimicrobial treatment was changed to piperacillin-tazobactam and fluconazole in light of bronchoalveolar lavage culture. A laparotomy was performed on the suspicion of perforation. No perforation was found but a caecostomy was fashioned to decompress his bowel. At 37 days post transplant he remained ventilator and dialysis dependant but without further bowel problems and off antibiotics. He developed right upper abdominal pain; ultra-sonography revealed gallbladder sludge but also a thickened

colon suggestive of colitis. A CT scan confirmed grossly thickened large bowel at risk of perforation despite minimal diarrhoea rectally and only soft stool from his stoma. Piperacillin-tazobactam, metronidazole and caspofungin were commenced. Colectomy was delayed as he initially refused consent but by this time he was deteriorating rapidly with sepsis. He died one week following colectomy from multiple organ failure. Histological examination of the resected colon showed severe pseudomembranous colitis.

#### **Case 4**

A 38-year-old lady with CF underwent lung transplantation, complicated by early haemodynamic instability followed by renal failure and failed extubation. She then developed abdominal distension and diarrhoea, negative for *Clostridium difficile* toxin. Despite continuing episodes of diarrhoea and distension, stool toxin remained persistently negative. Bronchoalveolar lavage isolated *Pseudomonas spp.* and she was commenced on ciprofloxacin and aztreonam. Diarrhoea, abdominal pain and distension remained problematic, and a CT showed thickened large bowel consistent with pseudomembranous colitis. A further stool specimen now tested positive for *Clostridium difficile*. Metronidazole was commenced with resolution of diarrhoea and negative stool toxin after five days. However her clinical condition remained critical and she died 42 days post transplantation from multi organ failure.

## Discussion

*Clostridium difficile* is a spore forming Gram positive bacillus. It is a well recognized cause of antibiotic associated diarrhoea[3]. Asymptomatic carriage is rare in healthy adults though more frequent during hospitalization occurring in up to 25% of inpatients [2] [4]. *Clostridium difficile* colitis results from a chain of events: firstly a disruption of bowel flora followed by colonisation and finally toxin mediated mucosal damage and inflammation [4]. The clinical symptoms may vary from a mild diarrhoea to fulminant colitis with severe septic shock (seen in 1 - 3%) [5]. Diagnosis is made by the detection of toxins within the stool. Pseudomembranous colitis, the most severe manifestation of the disease, presents with diarrhoea, abdominal cramping and tenderness, with systemic symptoms that may lead to haemodynamic collapse. Treatment with metronidazole or vancomycin should be promptly initiated and improvement is generally seen within 48 - 72 hours [4]. Surgical intervention is mandatory in perforation and may be required, either in severe cases where medical treatment is not sufficient, or where improvement is not seen.

Carriage rates of *Clostridium difficile* in patients with CF have been reported to be up to 50%, yet despite this and the numerous courses of antibiotics and hospital admissions these patients undergo, pseudomembranous colitis remains rare [1] [2] [6]. The first case was described in 1992 with only a few subsequent reports [2] [6] [7]. A genotype link (N1303K mutation) has been described between CF and *Clostridium difficile* [7] though none of our patients possessed this genotype. To date, although various hypotheses have been suggested there is no conclusive reason to explain the low rates of *Clostridium difficile* in CF [7],[9]. Pseudomembranous colitis has been described with a high incidence in post lung transplant patients by Dallal *et al* [3]. Their series of 2334 patients with *Clostridium difficile* over an 11 year period included 78 of 250 lung transplants causing significant morbidity and mortality. We describe four cases of severe *Clostridium difficile* colitis in patients with CF post lung transplantation and illustrate a number of important points in the diagnosis and management of these patients. Firstly the presentation was varied and particularly in the first case associated initially with absence of diarrhoea and signs far more in keeping with meconium ileus equivalent. Patient three underwent caecostomy and despite grossly abnormal CT appearances of his large bowel he did not exhibit significant diarrhoea. Both of these patients went on to have a subtotal colectomy, early in the course of the first patient's illness and delayed following failed medical therapy in the third patient. The two other cases with diarrhoea responded rapidly to metronidazole. Computed tomography played an important role in the management of these patients, in terms of assisting with diagnosis, in excluding meconium ileus equivalent, and giving prognostic information regarding the severity of disease. The importance of toxin negative stool analysis despite obvious symptoms and extensive radiographic abnormality is highlighted with cases two and four. Indeed in patient two even sigmoidoscopy after CT scanning revealed negative findings. A high index of clinical suspicion with close monitoring of patients condition is required as symptoms and signs may be misleading and deterioration with haemodynamic collapse sudden.

Immunosuppression may have played a role in the variable presentation of disease and is likely to be important in the pathogenesis of disease in our cases by increasing the risk of colonisation as highlighted by Dallal's series[3], however the low overall rate of *Clostridium difficile* in our institution mitigates against this being the sole reason.

Diagnosis is often made difficult in the intubated ventilated patient due to communication difficulty. The two patients on a ventilator both had early tracheostomy performed with a speaking valve.

Enteral nutritional support is of great importance in any critically ill patient for energy provision and maintenance of enterocyte integrity. All four of our patients received enteral feeding throughout their illness with either nasogastric feeding or oral supplementation.

Antibiotics had been administered in the preceding days to weeks in all patients. Three of the four patients had been treated with piperacillin-tazobactam shortly before presentation. Piperacillin-tazobactam is not listed as a common cause of *Clostridium difficile* colonisation, and in fact its use in the treatment of hospital-acquired infections is credited with lowering the incidence of *Clostridium difficile* [8].

In conclusion, we present a series of four patients with cystic fibrosis following lung transplantation who developed severe *Clostridium difficile* colitis. Mortality was 50%, two patients required colectomy and disease was certainly a significant event in the decline of a further patient. Presentation of disease was in one case mistaken for meconium ileus equivalent, and in a further case a diagnosis took several days to secure highlighting the need for high clinical suspicion. Computed tomography revealed colitis in all patients and not only suggested the diagnosis but gave an important indicator as to the severity of disease. *Clostridium difficile* colitis is an uncommon but important diagnosis in patients with CF following lung transplantation. The persistent carriage of *Clostridium difficile* in the bowel of prospective transplant recipients with CF may represent a relative contraindication, particularly patients with a prior history of pseudomembranous colitis and we recommend all lung transplant centres to be vigilant for this problem.

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There are no conflicts of interest

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## Figure 1

CT abdomen showing gross thickening of large bowel wall and luminal obliteration.

