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Colectomy averted: A successful case report of Fidaxomicin administration through a loop ileostomy for fulminant, *Clostridioides difficile* infection

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ABSTRACT

Clostridioides difficile infection is considered an urgent public health threat by the Centers for Disease Control and Prevention. Recent practice guidelines recommend either vancomycin or fidaxomicin for an initial episode of *Clostridioides difficile* infection and further recommend a subtotal colectomy in severe cases. There is limited data discussing novel approaches for fidaxomicin administration in severe *Clostridioides difficile* infection to avert colectomy. We describe an off-label route of fidaxomicin administration through a loop ileostomy twice daily with successful outcome.

Key Words *Clostridioides difficile*, *Clostridium difficile*, Fidaxomicin, loop ileostomy, colonic lavage

BACKGROUND

Clostridioides difficile infection (CDI) is increasing in health-care settings and is associated with substantial morbidity and mortality. Mortality rates of 15-25% have been reported within 30 days of CDI diagnosis.¹ Direct costs for acute care of CDI in the U.S. were estimated to be \$4.8 billion; and is likely substantially higher due to indirect cost management of the disease.¹ Fulminant disease is characterized by hypotension or shock, ileus, or megacolon based on the Infectious Disease Society of America (IDSA) 2018 clinical practice guidelines for CDI.² Pharmacologic treatment options for initial and recurrent episodes of CDI include vancomycin or

fidaxomicin rather than metronidazole.² Oral fidaxomicin 200mg twice daily for ten days was approved by the FDA in 2011 for the treatment of *Clostridioides difficile* associated diarrhea. Fidaxomicin effectively reduced recurrence of CDI and neutralize species of CDI, yielding symptomatic cure by targeting ‘switch regions’ within bacterial RNA polymerases.^{3,4}

When treating fulminant CDI, the IDSA guidelines recommend oral vancomycin (500mg four times daily), intravenous metronidazole (500mg three times daily) and, if ileus is present, vancomycin may also be administered per rectum (500 mg in approximately 100 mL normal saline per rectum every six hours as a retention enema).^{2,5} If surgical management is necessary, a subtotal colectomy is recommended.² However, complete removal of the large bowel has been associated with a 30-day mortality of 20- 71%.⁵ Performing a diverting loop ileostomy with colonic lavage, referred to as the ‘Pittsburgh Protocol,’ can be utilized as an alternative surgical option for fulminant disease. This procedure is associated with decreased morbidity; defined as patients requiring fewer vasoactive agents or development of shock, in addition to a significant reduction in mortality.⁵ The Pittsburgh protocol includes colonic lavage with eight liters of polyethylene glycol intraoperatively after formation of loop ileostomy, proceeded by antegrade vancomycin flushes (500mg in 500mL Ringer’s lactate every eight hours) and intravenous metronidazole (500 mg every eight hours) for ten days.^{5,6}

We present a case of fulminant CDI surgically managed with loop ileostomy, administration of the Pittsburgh protocol and the addition of fidaxomicin ileostomy administration. Following the procedure, addition of antegrade fidaxomicin ileostomy administration demonstrated marked clinical improvement, avoidance of bowel resection and clinical cure with ileostomy reversal at thirty days. This case describes the off-label administration route of fidaxomicin, in conjunction with intravenous metronidazole and vancomycin bowel irrigation.

CASE REPORT

A 75-year-old woman with a history of oxygen dependent COPD, hyperlipidemia, chronic kidney disease, hypertension and bipolar disorder presented to the emergency department for complaints of weakness, loss of appetite, diffuse abdominal pain and diarrhea 4-5 times a day, beginning five days prior to admission. The first incident of diarrhea was associated with a small amount of observed blood which had stopped spontaneously. Five days prior to admission, the patient completed a ten-day course of oral clindamycin for a foot infection. On admission she was afebrile and hemodynamically stable. Physical examination of the abdomen revealed diffuse rebound tenderness. Initial laboratory data revealed leukocytosis ($17.8 \times 10^9/L$) and elevated serum creatinine 1.8 mg/dL (baseline 1.2mg/dL). A computed tomography (CT) of the abdomen and pelvis without contrast revealed diffuse colonic wall thickening from cecum to rectum with peri-colonic fat stranding consistent with colitis, and mild ascites.

Initial pharmacotherapy for presumed CDI consisted of vancomycin (125mg orally every six hours) and metronidazole (500mg intravenously every eight hours). On day 2 of admission, stool PCR testing was positive for *C. difficile* and the medication regimen was modified to vancomycin (500mg orally every six hours) for three days and continuation of intravenous metronidazole for eighteen days. The patient refused rectal vancomycin administration. On day five of admission, despite receiving maximal pharmacologic support, the patient's disease progressed, as evidenced by new onset hypotension (systolic blood pressure < 90 mmHg), worsening leukocytosis ($30 \times 10^9/L$), the inability to tolerate enteral feeding and medication administration and subsequently was transferred to the medical/surgical intensive care unit. A repeat CT of the abdomen and pelvis without contrast revealed worsening, severe diffuse colitis, moderate ascites and new bowel wall edema. Due to the lack of clinical improvement, the patient

was brought to the operating room for laparotomy, loop ileostomy, placement of a Malecot® tube and a Jackson-Pratt drain with antegrade lavage of the colon utilizing the University of Pittsburgh protocol ⁶ (**Appendix 1**).

Post-operative day one, fidaxomicin (200mg crushed tablet mixed in 100ml 0.9% normal saline twice daily) was added to the University of Pittsburgh protocol and administered through the loop ileostomy. After five days of fidaxomicin ileostomy therapy, the medication was discontinued and within twenty-four hours the patient's condition began to deteriorate, noted by complaints of diffuse abdominal pain and an abdominal X-ray revealing a small bowel obstruction. (**Figure 1.**) Fidaxomicin ileostomy therapy was reinitiated in conjunction with the Pittsburgh protocol and continued for a total of fourteen days while the patient's clinical status improved markedly; averting the need for a total colectomy. The patient returned to the hospital after thirty days from discharge for reversal of the ileostomy without complication or recurrence. Stability data available regarding crushed alternative routes of administration of fidaxomicin are limited. Currently, one study demonstrated two-hour stability while ensuring adequate bioavailability when dispersed into water and the other study utilized 0.9% normal saline as the diluent solution.^{7,8}

DISCUSSION

This case demonstrates the successful use of fidaxomicin administration via diverting ileostomy. Our patient failed to improve adequately following the standard Pittsburgh protocol, oral vancomycin and intravenous metronidazole. However, with the addition of fidaxomicin ileostomy administration, our patient responded. Of interest, when fidaxomicin was discontinued after five days of administration, our patient's clinical condition worsened. Upon

reinitiation of fidaxomicin, she again improved, substantiating fidaxomicin efficacy on rechallenge.

Only two other published cases describe the use of fidaxomicin administered by an alternative route. One case describes a subtotal colectomy in a patient with recurrent CDI.⁷ Separately, a similar case to our report, denotes successful treatment of a patient with fulminant CDI where fidaxomicin was administered via mucous fistula.³ In this case, the patient underwent a partial colectomy where an external mucous fistula was created after failing to respond to oral and rectal vancomycin and intravenous metronidazole. Post-operatively pseudomembranes developed on the mucous fistula, prompting the addition of crushed fidaxomicin. The authors reported reduction in clinical burden of pseudomembranous disease after ten days of treatment with fidaxomicin. Unlike our case, this administration was in a mucous fistula with visible pseudomembranes.

While the 2018 IDSA guidelines recommend subtotal colectomy in severe CDI,² newer surgical literature support colon-sparing ileostomy intervention to decrease morbidity and mortality. Unfortunately, retrospective cohort studies indicate that failure in these severe cases remains high (19%).⁶ Although the addition of fidaxomicin ileostomy administration was effective in this patient, a single case report is inadequate to make recommendations for use in patients. Additional studies to determine the safety and efficacy of fidaxomicin via ileostomy should be conducted before this can be recommended treatment in refractory CDI.

CONCLUSION

Addition of antegrade administration of fidaxomicin via loop ileostomy in patients who are failing standard therapy may be an option that warrants further investigation in the treatment of fulminant *Clostridioides difficile* infection (CDI).

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Potential Conflicts of Interest. All authors: no conflicts.

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