Local application of fidaxomicin in a patient with subtotal colectomy following recurring *Clostridium difficile* infection

Pavel Longin,1 Marie Valeckova,1 Ales Bilek2 and Antonin Melichar3

1Department of Anaesthesiology and Intensive Care, Regional Hospital, Havlickuv Brod, Czech Republic
2Department of Internal Medicine, Regional Hospital, Havlickuv Brod, Czech Republic
3Department of Clinical Microbiology, Regional Hospital, Havlickuv Brod, Czech Republic

**Introduction:** *Clostridium difficile* is the leading cause of antibiotic-associated diarrhoea and is a major burden to healthcare services worldwide. Fidaxomicin is a first-in-class macrocyclic antibiotic that was approved for the treatment of *C. difficile* infection (CDI) in 2011, demonstrating a narrow spectrum of activity and comparable efficacy to vancomycin in clinical trials.

**Case presentation:** We present the case of a patient with recurrent CDI who was non-responsive to standard treatment with metronidazole and vancomycin. The patient subsequently developed toxic megacolon, which had to be treated surgically by subtotal colectomy. Fidaxomicin at 200 mg twice daily was delivered in small-volume enemas directly to the oral part of the sigmoid colon to preserve the remaining rectosigmoid colon and improve the chances of restoring gastrointestinal tract continuity. After 11 days of local fidaxomicin therapy, diagnostic tests revealed that the patient was *C. difficile* negative and no recurrence of CDI was observed. Restoration of the gastrointestinal tract was successfully completed 5 months after hospital discharge.

**Conclusion:** This report describes a novel concept of local fidaxomicin delivery to the rectosigmoid colon, with an improved clinical outcome compared with metronidazole and vancomycin treatment. The study suggests that topical application of fidaxomicin may be beneficial in some CDI patients following surgical treatment for toxic megacolon.

**Keywords:** *Clostridium difficile*; colectomy; fidaxomicin; rectosigmoid colon; recurring.

**Abbreviations:** CDI, *Clostridium difficile* infection; GDH, glutamate dehydrogenase; ICU, intensive care unit.

© 2014 The Authors. Published by SGM

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0/).
On the second post-operative day, the patient developed diarrhoea, and a stool analysis (C. Diff Quik Chek Complete; Techlab) was found to be positive for *C. difficile* glutamate dehydrogenase (GDH), toxin A and toxin B. By day 4, her clinical state had worsened with a progressive rise of infectious markers (C-reactive protein, 525 mg l⁻¹; procalcitonin, 10.54 µg l⁻¹) and decreased kidney function (urea, 23.7 mmol l⁻¹; creatinin, 370.8 µmol l⁻¹). Lactate levels were normal and the patient was afebrile.

The patient was transferred to an intensive care unit (ICU) and a bowel ultrasound revealed a thickened bowel wall to 10 mm with a collapsed colon lumen (known as ‘pancolitis’). A colonoscopy (up to hepatic flexure) was performed and indicated severe colitis. Upon carrying out a biopsy, non-specific inflammatory changes were observed without cryptic formed abscesses. Noradrenalin treatment was commenced at a dose of 0.15 µg kg⁻¹ min⁻¹ to treat the further progression of septic shock and antibiotic treatment was administered to treat CDI (oral vancomycin 125 mg four times daily and intravenous metronidazole 500 mg three times daily). On day 4 post-admission, leucocyte counts peaked at 23.4 × 10⁹ l⁻¹ before gradually normalizing by day 11, as did the C-reactive protein levels (day 2, 186 mg l⁻¹; day 8, 33 mg l⁻¹). Serum creatinine levels normalized by day 8 post-admission, but diarrhoea continued at the rate of 6–10 stools day⁻¹. On days 11, 20 and 22, *C. difficile* GDH and toxin tests were negative and antibiotic therapy was discontinued on day 15. However, 8 days following ICU admission, heparin-induced thrombocytopenia was diagnosed. As a result, fondaparinux was started, and amikacin was administered 2 days later, for 4 days, to treat a urinary tract infection.

On day 27, sepsis again developed and a urinary tract infection was confirmed. A CT scan of the thorax and abdomen was performed and pneumonia was discounted, but bowel thickening was again observed. Due to the urinary tract infection and a suspicion of knee endoprosthesis infection, piperacillin/tazobactam treatment was started. Vancomycin and metronidazole were restarted due to suspicion of CDI recurrence. On day 29, toxic megacolon was confirmed by a further colonoscopy (Fig. 1a) and subsequent surgery was indicated. A subtotal colectomy with terminal ileostomy and sigmoideostomy was carried out, and the abdominal cavity was left open. A cholecystectomy was performed due to phlegmonous gall bladder observed during the operation. Recurrence of CDI was confirmed through *C. difficile* antigen and toxin tests. On completion of a biopptic sample of colon tissue, pseudomembranous colitis was revealed with reactive fibrin plaques and incipient necrosis of the colon. Piperacillin/tazobactam was continued and vancomycin at 500 mg four times daily was added via a nasogastric tube. Vancomycin (500 mg diluted in 100 ml normal saline) was also added internally through the sigmoideostomy and rectum. Intravenous fluconazole at 400 mg was added to therapy following positive identification of *Candida albicans* in a stool sample.

On day 31, closure of the abdominal cavity was performed, and on day 33 a second-look colonoscopy showed continuous circular pseudomembranous colitis (Fig. 1b). Intravenous antibiotics and antifungals were discontinued on day 36 due to elevated liver enzyme levels. On day 39, the colonoscopy was repeated and indicated that only 30 % of the mucosa had healed. Diagnostic tests revealed the presence of *C. difficile* GDH and toxin in the rectosigmoid colon and PCR-ribotyping identified a *C. difficile* stem subtype ‘like 027’ (a PCR-ribotype 176 *C. difficile* strain was confirmed in other patients who were in contact with our patient). At this phase of treatment, the patient was showing signs of malnutrition and weak muscular strength and was unable to rehabilitate following knee replacement. Consequently, resection of the remaining colon was considered; however, this solution would have removed the possibility of restoring gastrointestinal continuity. Therefore, on day 39, fidaxomicin therapy was administered locally as a final solution. Fidaxomicin at 200 mg twice daily was delivered in small-volume enemas.

![Fig. 1. Colonoscopy performed up to hepatic flexure showing toxic megacolon at day 29 post-admission (a), continuous circular pseudomembranous colitis at day 33 post-admission (b) and revitalized mucosa of the rectosigmoid colon without any signs of inflammation following local fidaxomicin application at day 50 post-admission (c).](image-url)
Discussion

In this case, locally applied fidaxomicin was used successfully to treat a 74-year-old patient with recurrent CDI and subtotal colectomy following a total knee replacement. Initially, CDI was adequately treated with a combination of metronidazole and vancomycin for 15 days. However, 11 days after discontinuation of antibiotics, CDI recurrence was noted and a colonoscopy indicated toxic megacolon that required subtotal colectomy. After 11 days of local fidaxomicin therapy, the patient was C. difficile negative and there was no recurrence of CDI. A recent systematic review concluded that total colectomy with end ileostomy (subtotal or total colectomy without primary anastomosis) is the preferred surgical procedure in patients with severe CDI (Bhangu et al., 2012). Clinical cure of the rectosigmoid stump is essential for facilitating gastrointestinal tract restoration post-colectomy. This study describes a new concept of local fidaxomicin delivery to the rectosigmoid colon, with an improved clinical outcome compared with combined metronidazole and vancomycin treatment. The study indicates that topical application of fidaxomicin may be beneficial in some CDI patients following surgical treatment for toxic megacolon. Furthermore, because the rectosigmoid stump is safely accessible through colonoscopy, the progress of treatment can easily be monitored.

However, fidaxomicin is not currently licensed for topical administration. Therefore, further studies are necessary to demonstrate the efficacy and safety of this method of administration.

Acknowledgements

Medical writing services were provided by David Burns on behalf of Astellas Pharma Europe Ltd to assist with grammar and English translations. Astellas Pharma Europe Ltd had no role in data collection or the decision to publish this manuscript.

References