Novel treatment (new drug/intervention; established drug/procedure in new situation)

Successful use of nitazoxanide in the treatment of recurrent *Clostridium difficile* infection

Fnu Rafiullah,¹ Sunil Kanwal,² Usman M Majeed,³ Mark A Korsten,⁴ Faisal H Cheema,⁵ Munish Luthra,¹ Muhammad Rizwan Sohail⁶

¹Department of IM, James J Peters VA MC, Bronx, New York, United States;

²Department of Cardiology, Division of Cardiology, College of Physicians and Surgeons of Columbia University, Manhattan, New York, United States;

³Department of Cardiology, Columbia University, Manhattan, New York, United States;

⁴Department of Gastroenterology, James J Peters VAMC, Bronx, New York, United States;

⁵Department of Cardiothoracic Surgery, Manhattan, New York, United States;

⁶Department of ID, Mayo Clinic MN, Rochester, Minnesota, United States

Correspondence to Dr Fnu Rafiullah, drrafiullahkhan@yahoo.com

Summary

A 78-year-old, retired Caucasian male presented in emergency room with 3 days history of progressive watery diarrhoea. Two weeks earlier, he received intravenous levofloxacin for community acquired pneumonia. The patient was diagnosed as severe *Clostridium difficile* infection based on clinical presentation, labs and imaging studies. The patient was initially treated with intravenous metronidazole and oral vancomycin. While awaiting subacute rehabilitation placement, the patient relapsed twice. After first recurrence the patient was treated with 2 weeks of oral nitazoxanide. After second recurrence, the patient was treated 2 weeks of nitazoxanide followed by tapering dose of vancomycin. The patient was followed and no relapse was reported at 1 year follow-up visit.

BACKGROUND

Clostridium difficile infection (CDI) is a commonly encountered clinical problem and can often be a therapeutic challenge.¹ It is a leading cause of infectious diarrhoea in hospitalised patients in United States.² The incidence and case death rate of CDI doubled between year 2000 and 2005³ and according to a recent estimate 3 million cases are diagnosed every year.⁴ Although *C difficile*, a spore forming gram positive anaerobe, can colonise the healthy intestines,² the risk of colonisation linearly increases with hospitalisation and use of antimicrobials.^{5 6} Antimicrobial therapy alters the normal colonic microflora, an important defense mechanism against *C difficile*, and thus predisposes to CDI.⁷ The clinical presentation varies and ranges from mild diarrhoea to severe life threatening colitis,⁸ and the treatment can be challenging, especially in recurrent disease.¹ We describe an interesting case of recurrent CDI that was successfully treated with two courses of nitazoxanide followed by a tapering dose of oral vancomycin. This case also highlights how the limitations of available healthcare resources may possibly amplify the morbidity and therapeutic challenges associated with CDI.

CASE PRESENTATION

A 78-year-old, retired Caucasian male presented in emergency room with 3 days history of progressive watery diarrhoea. His stools frequency was 'too numerous to count', and the stool consistency was mucoid with no foul smell or blood in it. Associated symptoms were nausea, poor appetite and generalised abdominal cramps. Two weeks earlier, he had been admitted and received intravenous levofloxacin for a community acquired pneumonia exacerbating his chronic obstructive pulmonary disease

(COPD). Now he was having occasional cough with greenish phlegm. The patient was also taking omeprazole 20 mg EC besides other medications.

Pertinent medical history included chronic diarrhoea and radiation therapy for prostate cancer with most recent treatment 18 months before the current presentation. Other comorbidities included hypertension, coronary artery disease, peptic ulcer disease, gastro-oesophageal reflux disease, COPD and pulmonary tuberculosis treated in remote past.

The patient was a social drinker, exsmoker and denied recreational drugs. He was independent in terms of his daily activities. On physical examination, he was afebrile, his heart rate was normal, he looked pale, there were signs of dehydration including hypotension (78/47 mm Hg), dry mucous membranes and generalised weakness. Systemic examination revealed mild abdominal distention, tenderness in right lower abdominal quadrant, voluntary guarding and hypoactive bowel sounds. Rest of the systemic examination was normal.

In the emergency room, his blood pressure responded to intravenous fluids and he received intravenous levofloxacin 750 mg for possible recurrence of pneumonia.

INVESTIGATIONS

His complete blood count and electrolytes were normal except white cell count of 15900 with 83% neutrophils suggesting infectious aetiology. The complete metabolic profile was within normal limits except serum albumin of 3.1 gm/dl. Other baseline tests including electrocardiogram, chest roentgenogram and stool microcopy were also normal. ELISA of his stools tested positive for *C difficile* antigen and cell culture positive for toxin. The abdominal

Figure 1 CT abdomen/pelvis showing bowel wall thickening and submucosal oedema.

and pelvic CT with both per oral and intravenous contrast demonstrated mild but diffuse colonic wall thickening and mucosal enhancement. In addition, a thickened and low attenuation submucosa, most conspicuous in rectum and sigmoid colon, was reported. All these findings were considered consistent with *C difficile* colitis (figure 1).

DIFFERENTIAL DIAGNOSIS

1. *C difficile*
2. Radiation proctitis

TREATMENT

Contact precautions were instituted and treatment started with intravenous metronidazole and oral vancomycin. The patient's abdominal distention led to suspicion of intestinal obstruction. However physical examination and abdominal series ruled out this suspicion. A foley catheter was placed for possible obstruction of urine outflow by the prostate which relieved the abdominal distention. With aggressive treatment, his symptoms rapidly improved. His clinical status remained stable over the course of next several days. Although clinically well, he remained hospitalised while awaiting subacute rehabilitation placement.

One week later, while still awaiting transfer to subacute rehabilitation facility, his diarrhoea relapsed and signs and symptoms as noted on initial presentation recurred. Recurrent *C difficile* colitis was suspected. Stool microscopy was negative for ova or parasites. However, some fecal leucocytes were seen. ELISA was repeated and his stools tested positive for *C difficile* antigen and toxin. At this point, we decided to treat this episode with nitazoxanide (synthetic nitrothiazolyl-salicylamide derivative) 500 mg orally twice daily. The patient responded within 48–72 h of treatment and had reduction in his stool frequency, consistency of the stools considerably improved, abdominal distention decreased and peripheral leucocyte count dropped towards normal. The patient remained afebrile and haemodynamically stable. Two weeks course of therapy resulted in the resolution of his symptoms; however he remained hospitalised awaiting subacute rehabilitation placement.

Despite improvement in severity of illness, the patient continued to pass 2–3 soft stools a day. A gastroenterology consult was requested and a colonoscopy was advised which suggested radiation proctitis as a cause of poorly formed stools. The symptoms resolved with loperamide and hydrocortisone enema. Unfortunately, the patient could not be discharged, as he needed subacute rehabilitation placement. About one week later, he again developed bloody diarrhoea with 8–10 episodes per day. He also complained of abdominal cramps and abdominal distention recurred. Stool microscopy revealed red blood cells, few white blood cells but no ova or parasites. *C difficile* antigen and cytotoxin were again positive by ELISA. The patient stools were negative for acid fast bacilli on three separate occasions. His serum immunoglobulin level was normal and he reacted negative to HIV and celiac disease serology (antiendomysial, antitissue transglutaminase). The abdominal obstructive imaging series was also negative. The diagnosis of recurrent *C difficile* colitis was made and the patient was restarted on nitazoxanide 500 mg oral twice daily for 3 weeks. The patient improved and started having semisolid stool 3–4 times/day. *C difficile* antigen and cytotoxicity turned negative on four occasions on subsequent testing. He was discharged on 5 weeks course of oral vancomycin taper as advised by infectious disease service.

OUTCOME AND FOLLOW-UP

The patient was followed in outpatient clinic and no relapse was reported at 1 year follow-up visit.

DISCUSSION

CDI is a common clinical problem and treatment of recurrent infection can be challenging.^{1 2} We describe here a case of recurrent CDI, which highlights interesting challenges of treating such cases and brings to attention an important, limitation of available healthcare facilities. The combination of hospitalisation and use of systemic antibiotics are major risks as the use of similar antibiotics in the community settings are less likely to cause CDI.⁹ Having said that, community acquired CDI in the absence of antibiotic use

Figure 2 Treatment algorithm for *Clostridium difficile* infection.

has been reported.¹⁰ In our case, the patient was recently hospitalised and was treated with levofloxacin for pneumonia. CDI typically presents with fever, abdominal discomfort, anorexia, nausea and leukocytosis.¹¹⁻¹² Patients have watery stools without gross blood and mucus. The presentation was typical in our case and diagnosis was relatively easy based on ELISA for *C. difficile* antigen and toxin later confirmed with cytotoxicity assay in cell culture to identify the toxigenic strain of *C. difficile*. False negative rate of the commonly used *C. difficile* toxin test is 10% or higher.¹³⁻¹⁴ As such, all negative tests should be repeated, and if again negative in presence of strong clinical suspicion, more sensitive test like tissue culture, cytotoxicity assays (gold standard) can be used.¹⁵ Molecular techniques, such as PCR are also being simplified to identify *C. difficile* genetic material in the stools.¹⁵ Other tests like colonoscopy can help in detection of colitis and imaging studies like CT scan can diagnose complications like toxic megacolon, perforation and colonic wall thickening during fulminant CDI.¹¹

The standard treatment is summarised in the figure 2.¹⁶ Our patient was diagnosed with severe disease as defined by old age and high leucocyte count and hypotension.¹⁶⁻¹⁷ The treatment was started with parenteral metronidazole and oral vancomycin. Although it is not advised to treat with combination of these medications but our patient presented with severe complicated diseases and in that case the combination is recommended.¹⁶ The patient responded to 10 days of therapy.

Post treatment stools analyses are not routinely recommended, however in our particular case, analyses were performed because of severe disease¹⁸ and were found to be negative. Many patients continue to have positive *C. difficile*

toxin assay for some weeks even after successful treatment and clinical recovery.¹⁹ However, 15%–30% patients with positive stool test for toxin will suffer recurrence which is defined by symptoms after successful resolution of initial episode and other causes of diarrhoea excluded.²⁰ Recurrence usually occurs within 2 weeks of stopping the treatment, as in our case, but late recurrences up to 2 months post treatment have been reported.²¹ Recurrence may be due to relapse²² or reinfection with the same or different strain from the environment.²³ Some patients may experience 3 to 10 or even more episodes of recurrence.²⁰ In contrast, refractory CDI means that infection is unresponsive to treatment and is suspected if symptoms do not improve after 2–3 days of therapy. In our case, the patient presented with similar symptoms a week after the resolution of initial episode. The patient was, thus, diagnosed with recurrent CDI. Interestingly, it has been reported that treatment failure may not be due to the microbiologic resistance to the primary treatment drug.²⁴ It seems that a vicious circle is created when the CDI treatment (metronidazole or vancomycin) disturbs the colonic flora.²⁵ In our patient, a decision was made to treat the recurrence with nitazoxanide, which based on limited evidence published-to-date, seems effective²⁶⁻²⁷ but whose therapeutic role is not well defined for this condition. The drug was given orally in a dose of 500 mg twice daily and the patient responded in 48–72 h of therapy. A total of 2 weeks course was prescribed.

The resolution was followed by another episode of diarrhoea within a week. Based on the nature of recurrent, CDI was suspected. However, colonoscopy demonstrated the evidence of radiation proctitis. The patient had a prostate resection followed by radiation therapy in the

past with most recent treatment being dose 18 months ago. This episode was managed by loperamide and topical steroids. The symptoms resolved, however, only for a short while and third episode of diarrhoea occurred. This time the stools tested positive for *C difficile* and the patient was thus initiated on a second course of nitroxanide. The patient responded to treatment and was then discharged on a tapering dose of oral vancomycin.

Management of multiple recurrences is less clear.² Therapy of CDI with antibiotics should not be extended longer than necessary so that complications of treatment can be avoided and normal flora can re-grow.²⁵ The patient should be monitored very carefully for any potential complications and if clinical condition deteriorates, surgical intervention (colectomy) can be life saving.²⁸

Our patient suffered recurrent CDI episodes in a typical clinical scenario where use of antibiotics and hospitalisation were the most likely predisposing factors. The patient was not discharged after successful treatment of each episode because rehabilitation was needed. However, it appears that non-availability of services resulted in unnecessarily prolonged stay. As an increase in the age of hospitalised patient is expected in the coming decade, it can be assumed that prolonged admissions may increase the morbidity and the economic burden of treating CDI.

Learning points

- The treatment of recurrent CDI can be challenging.
- We described here a case of recurrent CDI which was successfully treated with nitazoxanide followed by a tapering dose of oral vancomycin. Although successful in our case, there is a need for a well-designed clinical trial to systematically explore the clinical utility of nitazoxanide in the patients with CDI.
- Another important implication is the identification and possible limitation of available healthcare resources which might increase the morbidity and overall healthcare costs associated with CDI.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. Kyne L, Kelly CP. Recurrent Clostridium difficile diarrhoea. *Gut* 2001;**49**:152–3.
2. Kelly CP. A 76-year-old man with recurrent Clostridium difficile-associated diarrhea: review of C. difficile infection. *JAMA* 2009;**301**:954–62.
3. Zilberberg MD, Shorr AF, Kollef MH. Increase in adult Clostridium difficile-related hospitalizations and case-fatality rate, United States, 2000–2005. *Emerg Infect Dis* 2008;**14**:929–31.
4. Ricciardi R, Rothenberger DA, Madoff RD, et al. Increasing prevalence and severity of Clostridium difficile colitis in hospitalized patients in the United States. *Arch Surg* 2007;**142**:624–31; discussion 631.
5. Clabots CR, Johnson S, Olson MM, et al. Acquisition of Clostridium difficile by hospitalized patients: evidence for colonized new admissions as a source of infection. *J Infect Dis* 1992;**166**:561–7.
6. Aslam S, Hamill RJ, Musher DM. Treatment of Clostridium difficile-associated disease: old therapies and new strategies. *Lancet Infect Dis* 2005;**5**:549–57.
7. Weir E, Flegel K. Protecting against Clostridium difficile illness. *CMAJ* 2005;**172**:1178.
8. Poutanen SM, Simor AE. Clostridium difficile-associated diarrhea in adults. *CMAJ* 2004;**171**:51–8.
9. Kyne L, Warny M, Qamar A, et al. Asymptomatic carriage of Clostridium difficile and serum levels of IgG antibody against toxin A. *N Engl J Med* 2000;**342**:390–7.
10. Centers for Disease Control and Prevention (CDC). Severe Clostridium difficile-associated disease in populations previously at low risk—four states, 2005. *MMWR Morb Mortal Wkly Rep* 2005;**54**:1201–5.
11. Bartlett JG, Gerding DN. Clinical recognition and diagnosis of Clostridium difficile infection. *Clin Infect Dis* 2008;**46** Suppl 1:S12–8.
12. Kelly CP, Poethoukakis C, LaMont JT. Clostridium difficile colitis. *N Engl J Med* 1994;**330**:257–62.
13. Bartlett JG. Clinical practice. Antibiotic-associated diarrhea. *N Engl J Med* 2002;**346**:334–9.
14. Dallal RM, Harbrecht BG, Boujoukas AJ, et al. Fulminant Clostridium difficile: an underappreciated and increasing cause of death and complications. *Ann Surg* 2002;**235**:363–72.
15. Stamper PD, Alcabasa R, Aird D, et al. Comparison of a commercial real-time PCR assay for tcdB detection to a cell culture cytotoxicity assay and toxigenic culture for direct detection of toxin-producing Clostridium difficile in clinical samples. *J Clin Microbiol* 2009;**47**:373–8.
16. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). *Infect Control Hosp Epidemiol* 2010;**31**:431–55.
17. Zar FA, Bakkanagari SR, Moorthi KM, et al. A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity. *Clin Infect Dis* 2007;**45**:302–7.
18. Kelly CP, LaMont JT. Clostridium difficile—more difficult than ever. *N Engl J Med* 2008;**359**:1932–40.
19. Issack MI, Elliott TS. Clostridium difficile carriage after infection. *Lancet* 1990;**335**:610–1.
20. Maroo S, Lamont JT. Recurrent clostridium difficile. *Gastroenterology* 2006;**130**:1311–6.
21. Fekety R, McFarland LV, Surawicz CM, et al. Recurrent Clostridium difficile diarrhea: characteristics of and risk factors for patients enrolled in a prospective, randomized, double-blinded trial. *Clin Infect Dis* 1997;**24**:324–33.
22. Walters BA, Roberts R, Stafford R, et al. Relapse of antibiotic associated colitis: endogenous persistence of Clostridium difficile during vancomycin therapy. *Gut* 1983;**24**:206–12.
23. Wilcox MH, Fawley WN, Settle CD, et al. Recurrence of symptoms in Clostridium difficile infection—relapse or reinfection? *J Hosp Infect* 1998;**38**:93–100.
24. Sanchez J, Fnu R, Sunil K, et al. Metronidazole susceptibility in Clostridium difficile isolates recovered from cases of C. difficile-associated disease treatment failures and successes. *Anaerobe* 1999;**5**:201–4.
25. Gerding DN, Muto CA, Owens RC Jr. Treatment of Clostridium difficile infection. *Clin Infect Dis* 2008;**46** Suppl 1:S32–42.
26. Musher DM, Logan N, Bressler AM, et al. Nitazoxanide versus vancomycin in Clostridium difficile infection: a randomized, double-blind study. *Clin Infect Dis* 2009;**48**:e41–6.
27. Musher DM, Logan N, Hamill RJ, et al. Nitazoxanide for the treatment of Clostridium difficile colitis. *Clin Infect Dis* 2006;**43**:421–7.
28. Peláez T, Alcalá L, Alonso R, et al. In vitro activity of ramoplanin against Clostridium difficile, including strains with reduced susceptibility to vancomycin or with resistance to metronidazole. *Antimicrob Agents Chemother* 2005;**49**:1157–9.

This pdf has been created automatically from the final edited text and images.

Copyright 2011 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Rafiullah F, Kanwal S, Majeed UM, Korsten MA, Cheema FH, Luthra M, Sohail MR. Successful use of nitazoxanide in the treatment of recurrent *Clostridium difficile* infection. *BMJ Case Reports* 2011;10.1136/bcr.04.2011.4123, Published XXX

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow