

CASE REPORT

Corticosteroid treatment of severe, non-responsive *Clostridium difficile* induced colitis

C Cavagnaro, S Berezin, M S Medow

Arch Dis Child 2003;88:342-344

Clostridium difficile can cause inflammatory diarrhoea and colitis by disrupting normal colonic flora. Corticosteroids are effective against diarrhoea associated with inflammatory bowel disease, but their effectiveness in treating inflammatory diarrhoea of *C difficile* has not been reported. In this preliminary report, we describe the use of corticosteroids in a child with severe *C difficile* diarrhoea and colitis refractory to standard treatments.

Clostridium difficile is a Gram positive spore forming anaerobic bacillus that can cause severe diarrhoea and colitis in both adults and children.¹ *C difficile* infection occurs primarily in hospitalised patients following antibiotic induced disruption of the normal colonic flora. This is most often caused by ampicillin, amoxicillin, cephalosporins, and clindamycin.¹ *C difficile* induced diarrhoea usually occurs within 4–9 days after initiation of antibiotic therapy; however up to one third of patients may develop diarrhoea after antibiotics have been discontinued.¹

Two toxins produced by *C difficile* are responsible for symptoms: toxin A and toxin B.² While both toxins appear to have enterotoxic and cytotoxic qualities, toxin A is generally considered more responsible for the biological expression of *C difficile* as an enteric pathogen, while toxin B appears to have greater cytopathic effects.³ The most commonly used clinical tests to diagnose *C difficile* infection are stool assays for toxins A or B, or a more rapid, less sensitive enzyme linked immunosorbent assay (ELISA) for the *C difficile* toxins.⁴

No treatment is indicated for asymptomatic carriers of *C difficile*. In diagnosed cases of mild antibiotic associated diarrhoea, it is recommended that antibiotics be discontinued, which often leads to resolution of symptoms. In mild to moderate cases of *C difficile* induced diarrhoea or colitis, oral metronidazole is considered the treatment of choice.⁴ More than 95% of patients will respond to oral metronidazole, showing improvement of diarrhoea within 2–3 days and complete resolution of symptoms within 7–10 days.⁵ Oral vancomycin is equally effective in treating *C difficile* diarrhoea; however, the only difference between the two treatments is that vancomycin is more expensive.⁵ Because of its cost and the possibility of promoting vancomycin resistant bacteria, vancomycin is only recommended for people who fail to respond to or are intolerant of metronidazole, who are pregnant, under the age of 10, or who have severe pseudomembranous colitis.⁴

Recurrent cases of *C difficile* induced diarrhoea can usually be managed with the same agent used to treat the initial episode. However, no specific treatment regimen has been proven effective to prevent multiple relapses or recurrences of *C difficile* induced diarrhoea. Some proposed treatments include oral administration of Lactobacillus GG,⁶ faecal enemas from healthy individuals,⁷ and oral administration of a live yeast, *Saccharomyces boulardii*.⁸ Intravenous immunoglobulin therapy has been shown to be useful in treating patients with severe, refractory *C difficile* colitis.⁹

Corticosteroids have been shown to be effective against the inflammatory diarrhoea associated with inflammatory bowel disease. Their effectiveness against the inflammatory diarrhoea of *C difficile*, however, has not been reported. In this case report we describe the outcome of using corticosteroids in a young boy suffering from severe *C difficile* diarrhoea and colitis that was refractory to standard treatments.

CASE REPORT

Prior to hospitalisation, the patient, a 5 year old African American boy, had been treated for a presumptive sinusitis with amoxicillin for 10 days. He had not shown any improvement after 10 days and was subsequently started on amoxicillin-clavulanate. After five days of treatment with amoxicillin-clavulanate, the patient developed a profuse diarrhoea (more than 10 loose stools per day) with tenesmus and the appearance of frank blood in his stools. He was hospitalised at a community hospital for fluids and electrolyte replacement. A stool sample taken at that time was positive for *C difficile* toxin. After 48 hours without improvement he was transferred to the Pediatric Gastroenterology Service at Westchester Medical Center for evaluation and treatment of bloody diarrhoea.

On admission he had a temperature of 102.3° F. His weight and height were 31 pounds (<5th percentile) and 42 inches (25th percentile), respectively. On examination, he had diffuse abdominal tenderness, no rebound tenderness, mild distension, and active bowel sounds. He had 1+ pitting oedema of his ankles, and periorbital and sacral regions. Rectal examination showed haem positive stool and no perianal disease. An abdominal flat plate x ray showed an ileus pattern.

Laboratory values on admission included a white blood cell count of $19 \times 10^9/l$ (80% polymorphonuclear neutrophils, 5% bands, 2% eosinophils), an erythrocyte sedimentation rate of 32mm/h, a haemoglobin of 72 g/l, a haematocrit of 21% a total protein of 43 g/l, and an albumin of 21 g/l. Liver enzymes, reticulocytes, prothrombin time, partial thromboplastin time, platelet count, blood urea nitrogen, creatinine, urinalysis, and urine culture were all within normal limits. His stool was still positive for *C difficile* toxin. Stools sent for culture, cryptosporidium, and ova and parasites were all negative.

The patient was immediately started on intravenous metronidazole (20 mg/kg/day divided into eight-hourly doses) and oral vancomycin (40 mg/kg/day divided into six-hourly doses) because of the severity of the diarrhoea and colitis. He was continued on this regimen for two weeks. During this time he was also transfused twice with 1 g/kg albumin on days 1 and 10, and with 10 ml/kg packed red blood cells on day 4. Despite this aggressive antibiotic treatment, his diarrhoea persisted over the course of these two weeks with approximately 10–15 loose bloody stools per day.

On hospital day 14 a flexible sigmoidoscopy was performed up to 30 cm. The mucosa was noted to be friable and oedematous, and studded with raised nodules that exhibited a green-yellow exudate, consistent with a pseudomembrane. During

the procedure the patient was noted to have marked abdominal distension. A biopsy was therefore not taken to avoid the possibility of bowel perforation.

After sigmoidoscopy, the patient was started on intravenous methylprednisolone (2 mg/kg/day in two divided doses). His diarrhoea resolved within 24 hours of initiating the methylprednisolone. Stool samples for *C difficile* toxin were positive three days after starting steroid therapy, but were negative after seven days. On day 17 he was switched to oral prednisone (2 mg/kg/day in two divided doses). Steroid therapy was gradually discontinued over the course of one month. A repeat colonoscopy to the level of the caecum was performed two weeks later, which showed a completely normal appearing colonic mucosa. The patient was followed for one year, and a colonoscopy was performed to the level of the terminal ileum. The colon was normal, both visually and histologically. He continued to be asymptomatic for one additional year. His weight and height were at the 25th percentile at this time. He was subsequently lost to follow up.

DISCUSSION

The patient presented with a classic history associated with *C difficile* infection, specifically, a regimen of antibiotic therapy shortly before the development of profuse diarrhoea. The diagnosis of *C difficile* infection was supported by the detection of *C difficile* toxin in the patient's stool as well as by visualising pseudomembrane structures during endoscopy. The patient's diarrhoea and abdominal discomfort continued for two weeks despite aggressive treatment for *C difficile* with metronidazole and vancomycin. Although refractory to these first treatments, this patient's infection did appear to have a favourable response to methylprednisolone.

While metronidazole and vancomycin are successful in rapidly treating *C difficile* induced diarrhoea and colitis in a majority of patients, a small percentage will have a delayed or incomplete response. The reason for this difference in responses has not been explained, but it has been shown that a low serum albumin and prolonged duration of antibiotic therapy are both strong predictors of a prolonged course of *C difficile* colitis despite treatment.¹⁰ The hypoalbuminaemia seen in these patients is likely the result of protein loss through the stool from inflammatory exudates.¹⁰

In patients with *C difficile* colitis, a serum albumin of less than 25 g/l and a fall of serum albumin of more than 11 g/l have been associated with increased mortality.¹¹ According to a prospective study by Nair *et al*, the mean serum albumin in patients who responded promptly (≤ 14 days) was 26.7 g/l versus 20.7 g/l in those who failed to respond promptly (> 14 days, if at all).¹⁰ The more severe hypoalbuminaemia, rather than being a cause of the poor prognosis, may simply be an indicator of a more severe colitis with an accompanying higher protein loss.¹⁰ In our patient a serum albumin of 21 g/l on presentation could have served as a marker for an increased refractoriness to treatment.

Corticosteroids have remained the mainstay of therapy for acute flare-ups of inflammatory bowel disease.¹² The exact mechanism of action of corticosteroids in inflammatory bowel disease is not completely understood, but is likely multifactorial. Corticosteroids inhibit phospholipase activity, thereby preventing the release of arachidonic acid from membranes and decreasing eicosanoid production.¹³ They also result in a decreased release of the inflammatory cytokines, interleukin 1 (IL-1) and IL-2.¹⁴ Corticosteroids also decrease the phagocytic function of neutrophils, as well as the adherence and chemotaxis of eosinophils, monocytes, and neutrophils.¹⁵ Steroids also decrease diarrhoea by enhancing colonic sodium and water absorption.¹⁶

C difficile diarrhoea and colitis is also partly mediated by a secondary inflammatory reaction to the *C difficile* toxins. Both toxins A and B induce the increased local production of proin-

flammatory cytokines, including IL-1 and tumour necrosis factor.¹⁷ Toxin A has also been shown to be a chemoattractant for neutrophils and an activator of macrophages and mast cells, causing them to produce various inflammatory mediators.¹⁸ Toxin A has been shown to cause a florid inflammatory reaction in animal intestinal loop assays.¹⁹

Because of the inflammatory mechanisms common to both inflammatory bowel disease and *C difficile* colitis, it seems likely that corticosteroids may also have a therapeutic effect on *C difficile* colitis. The reduction of inflammation within the colon by steroids may facilitate clearance of the *C difficile* toxins and recovery from the disease. In our patient, the initial effect of the steroids was likely anti-inflammatory, as the clinical symptoms improved while the stools remained positive for the *C difficile* toxin.

It is also possible that corticosteroids may have a direct inhibitory effect on the *C difficile* toxins. In a study by Chang *et al*, inhibition of binding of the *C difficile* toxin to human erythrocyte lysate was found with a number of sterols.²⁰ Further studies are necessary to see whether this inhibition of *C difficile* binding also occurs with human colonic epithelial cells.

Although corticosteroids are generally not utilised as therapy for *C difficile* colitis, a one month course of therapy is unlikely to result in significant side effects. The most common steroid induced side effects are acne, moon facies, hirsutism, and cutaneous striae, which are reversible following discontinuation of therapy. More serious side effects such as muscle weakness, osteoporosis, aseptic necrosis, diabetes mellitus, glaucoma, and psychosis would rarely occur as a result of one month steroid administration. High doses of corticosteroids can cause immunosuppression and compromise the ability to resist infections; however, this was not an issue for this patient. Careful monitoring of this potential problem is strongly recommended.¹²⁻¹⁶

It is possible that our patient's symptoms may have resolved despite corticosteroid treatment. However, he had failed to show improvement after 14 days of antibiotic therapy, while most patients usually exhibit some resolution of symptoms within 2-3 days.⁵ While we cannot be certain that corticosteroids were a direct cause of our patient's improvement, he did appear to have a dramatic response once methylprednisolone was started. The only steroid induced side effect exhibited by our patient was moon facies, which resolved rapidly following discontinuation of steroids. Our observations suggest that corticosteroids may be an effective therapy for cases of severe, non-responsive *C difficile* induced colitis. As this is a preliminary report, further controlled studies are necessary to confirm this observation.

Authors' affiliations

C Cavagnaro, S Berezin, M S Medow, Department of Pediatrics, Division of Pediatric Gastroenterology and Nutrition, New York Medical College, Valhalla, New York, USA

Correspondence to: Dr M S Medow, Division of Pediatric Gastroenterology and Nutrition, New York Medical College, Munger Pavilion, Room 101, Valhalla, New York 10595, USA; Marvin_Medow@nymc.edu

Accepted 20 August 2002

REFERENCES

- Kelly CP, LaMont JT. Clostridium difficile infection. *Annu Rev Med* 1998;49:375-90.
- Pathoulakis C. Pathogenesis of Clostridium difficile-associated diarrhoea. *Eur J Gastroenterol Hepatol* 1996;8:1041-7.
- Bartlett JG. Clostridium difficile infection: pathophysiology and diagnosis. *Semin Gastrointest Dis* 1997;8:12-21.
- Fekety R. Guidelines for the diagnosis and management of Clostridium difficile-associated diarrhea and colitis. *Am J Gastroenterol* 1997;92:739-50.
- Teasley DG, Gerding DN, Olson MN, *et al*. Prospective randomized trial of metronidazole vs. vancomycin for the treatment of C. difficile associated diarrhea and colitis. *Lancet* 1983;2:1043-6.
- Gorbach SL. Successful treatment of relapsing Clostridium difficile colitis with Lactobacillus GG. *Lancet* 1987;2:1519.

- 7 **Schwan A**, Sjolins, Trottestam U, *et al.* Relapsing *Clostridium difficile* enterocolitis cured by rectal infusion of normal feces. *Scand J Infect Dis* 1984;**16**:211–15.
- 8 **McFarland LV**, Surawicz CM, Greenberg RN, *et al.* A randomized placebo-controlled trial of *Saccharomyces boulardii* in combination with standard antibiotics for *Clostridium difficile* disease. *JAMA* 1994;**271**:1913–18.
- 9 **Salcedo J**, Keates S, Pothoulakis C, *et al.* Intravenous immunoglobulin therapy for severe *Clostridium difficile* colitis. *Gut* 1997;**41**:366–70.
- 10 **Nair S**, Yadav D, Corpuz M, *et al.* *Clostridium difficile* colitis: factors influencing treatment failure and relapse—a prospective evaluation. *Am J Gastroenterol* 1998;**93**:1873–6.
- 11 **Ramaswamy R**, Grover H, Corpuz M, *et al.* Prognostic criteria in *Clostridium difficile* colitis. *Am J Gastroenterol* 1996;**91**:460–4.
- 12 **Shah SA**, Peppercorn MA. Inflammatory bowel disease therapy: an update. *Compr Ther* 1995;**21**:296–302.
- 13 **Hanauer SB**, Meyers S, Sachar DB. The pharmacology of anti-inflammatory drugs in inflammatory bowel disease. In: Kirsner JB, Shorter RG, eds. *Inflammatory bowel disease*, 4th edn. Baltimore: Williams & Wilkins, 1995:643–63.
- 14 **Brattsand R**, Linden M. Cytokine modulation by glucocorticoids: mechanisms and actions in cellular studies. *Aliment Pharmacol Ther* 1996;**10**:81–92.
- 15 **Boumpas DT**, Chrousos GP, Wilder RL, *et al.* Glucocorticoid therapy for immune-mediated diseases: basic and clinical correlates. *Ann Intern Med* 1993;**119**:1198–208.
- 16 **Urayama S**, Chang EB. Mechanisms and treatment of diarrhea in inflammatory bowel diseases. *Inflamm Bowel Dis* 1997;**3**:114–31.
- 17 **Flegel WA**, Muller F, Daubener W, *et al.* Cytokine response by human monocytes to *Clostridium difficile* toxin A and toxin B. *Infect Immun* 1991;**59**:3659–66.
- 18 **Johnson S**, Gerding D. *Clostridium difficile*. In: Mayhall CG, ed. *Hospital epidemiology and infection control*. Baltimore: Williams & Wilkins, 1996:399–408.
- 19 **Lima AA**, Lysterly DM, Wilkins TD, *et al.* Effects of *Clostridium difficile* toxins A and B in rabbit small and large intestine in vivo and on cultured cells in vitro. *Infect Immun* 1988;**56**:582–8.
- 20 **Chang TW**, Gorbach SL, Bartlett JG. Inhibition of binding of *Clostridium difficile* toxin by steroids. *J Infect Dis* 1980;**142**:133.

Direct Access to Medline

Medline

Link to Medline from the homepage and get straight into the National Library of Medicine's premier bibliographic database. Medline allows you to search across 9 million records of bibliographic citations and author abstracts from approximately 3,900 current biomedical journals.

www.archdischild.com