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

Intravenous immunoglobulin in treatment of *Clostridium difficile* colitis

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Summary

Clostridium difficile infection is the most common infectious cause of healthcare-acquired diarrhoea. Severe infections cause therapeutic challenges for healthcare providers. Various novel treatment modalities are currently being explored for treatment of severe disease. The authors report a 70-year-old female who presented to the emergency room with 1 week history of fever, watery diarrhoea, diffuse abdominal pain and weakness. *C difficile* toxin was detected in the stool and abdominal CAT scan showed extensive colonic wall thickening. The patient was started on intravenous metronidazole along with oral vancomycin. Due to the severity of the infection the patient was given intravenous immunoglobulin for 4 consecutive days. The patient had vast improvement in her clinical symptoms with resolution of the multi-organ system failure. It is currently considered that the predominant intravenous immunoglobulin's mechanism of action is through binding and neutralisation of toxin A by IgG antitoxin A antibodies.

BACKGROUND

Clostridium difficile is a gram-positive, anaerobic, spore forming, rod-shaped bacterium and has been linked to antibiotic associated diarrhoea. *C difficile* infection is the most common infectious cause of healthcare-acquired diarrhoea.¹ The incidence of this infection has sharply increased in the previous decade and so has the associated death rate and burden on healthcare cost. *C difficile* has also become more refractory to standard therapy and more severe, as indicated by increased rates of toxic megacolon, disease requiring colectomy, associated shock, or death.^{2 3} Severe infections cause difficult management issues for patients and therapeutic challenges for their healthcare providers. Various novel treatment modalities are currently being explored for treatment of the severe disease. We discuss a case where intravenous immunoglobulin (IVIG) was used in the treatment of severe colitis.

CASE PRESENTATION

A 70-year-old female presented to the emergency room with a 1 week history of fever, watery diarrhoea, diffuse abdominal pain and weakness. The patient denied symptoms of melena or haematochezia. She denied having any associated nausea or vomiting. The patient had been successfully treated for a urinary tract infection with levofloxacin, a week prior to the onset of her symptoms. Medical history included hypertension and an episode of *C difficile* colitis 5 months prior to this presentation. The patient was staying independently and denied any recent sick contacts or contact with pets. She denies any alcohol, nicotine or illicit drug use.

Physical examination on arrival revealed a patient with marked respiratory distress. She was febrile on presentation and hypotensive with blood pressure of 84/56 mm

Hg. The patient was tachypneic with respiratory rate of 32 per min. Patient had a distended abdomen with tenderness present in the lower quadrants. She had hypoactive bowel sounds. Cardiovascular and respiratory system auscultatory findings were normal.

INVESTIGATIONS

The patient was started on intravenous fluids and dopamine to provide adequate vasopressor support. She was intubated and ventilator support was provided considering her respiratory distress. Routine laboratory investigation revealed elevated white blood cell count of 36 980 cells/mm³ with absolute neutrophil count of 34 020 cells/mm³. Patient had new onset renal insufficiency with serum creatinine of 1.9 mg/dl and glomerular filtration rate of 26 ml/min/1.73 sq.m. Considering the history of *C difficile* colitis and recent antibiotics use with the past 2 weeks, *C difficile* infection was considered. The patient was initially started on the standard regimen of metronidazole 500 mg intravenously every 8 h and oral vancomycin 500 mg every 6 h. A *C difficile* toxin PCR which detects the *C difficile* toxin B gene in the stool specimen was positive. CAT scan of the abdomen showed extensive colonic wall thickening involving the ascending colon, hepatic flexure, transverse colon and the splenic flexure.

DIFFERENTIAL DIAGNOSIS

Ischaemic, inflammatory or infectious causes of colitis were considered. With detection of *C difficile* toxin in the stool a diagnosis of *C difficile* colitis was made. Other infectious causes of colitis were ruled out as stool sample was negative for diarrhoea producing bacterial pathogens and other ova and parasites. Considering the acuity and the clinical picture, inflammatory bowel disease was excluded.

TREATMENT

Intravenous metronidazole and oral vancomycin along with vasopressor support in the form of intravenous fluids and dopamine was continued. Considering severe *C difficile* infection with multiorgan system failure surgical colectomy was discussed, however declined by the patient's family. Considering the severe clinical picture and based on previous institutional experience IVIG was initiated. The patient received four doses of 30 grams IVIG on days 2 to 6 of hospitalisation.

OUTCOME AND FOLLOW-UP

Immediate effects were seen after the second dose with improvements in the white blood cell counts and the stool output. Also the patient's renal insufficiency improved and she was tapered off dopamine drip on day 3 of hospitalisation. The patient was extubated successfully on day 5 of hospitalisation. Patient's leucocytosis and diarrhoea completely resolved within a week of hospitalisation. Metronidazole and vancomycin were continued for 14 days and the patient was discharged from the hospital.

DISCUSSION

C difficile pathogenic strains induce diarrhoea through the elaboration and secretion of two exotoxins namely, toxin A and toxin B. Toxin A is an inflammatory toxin, leading to fluid secretion, increased mucosal permeability and marked enteritis and colitis. Toxin B is cytotoxic, leading to cell injury and apoptosis.⁴ The level of immune response to *C difficile* colonisation is the major determinant of the severity of the disease. The first report describing use of IVIG for treatment of *Clostridium* infection in humans was published in 1991.⁵ IVIG was used to treat five children with recurrent disease. These children were found to have significantly lower levels of IgG antitoxin A antibody as compared to healthy children. The authors reasoned that passively immunising the experimental group by transfusing antitoxin A IgG antibodies using IVIG would help in their recovery. All children receiving IVIG had clinical resolution of diarrhoea while on therapy.

Since then various small, mostly retrospective and non-randomised reports have shown some success in using IVIG in the treatment of protracted, recurrent, or severe *C*

difficile infection.⁶ Diarrhoea resolution rates were higher; however the recurrence rates were similar. It is currently considered that the predominant mechanism of action for IVIG is through binding and neutralisation of toxin A by IgG antitoxin A antibodies. The mechanism of IgG antitoxin A antibody delivery to the lumen is unknown, however it is presumed to occur secondary to inflammation-induced mucosal damage. Further studies are needed before adopting IVIG as routine treatment for severe infection.

Learning points

- *C difficile* infection is the most common infectious cause of healthcare-acquired diarrhoea.
- *C difficile* pathogenic strains induce diarrhoea through the elaboration and secretion of two exotoxins namely, toxin A and toxin B.
- Various small, mostly retrospective and non-randomised reports have shown some success in using IVIG in the treatment of protracted, recurrent, or severe *C difficile* infection.
- The predominant mechanism of action for IVIG is through binding and neutralisation of toxin A by IgG antitoxin A antibodies.

Competing interests None.

Patient consent Obtained.

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