Intravenous immunoglobulin therapy for severe Clostridium difficile colitis

J Salcedo, S Keates, C Pothoulakis, M Warny, I Castagliuolo, J T LaMont, C P Kelly

Abstract

Background—Many individuals have serum antibodies against Clostridium difficile toxins. Those with an impaired anti-toxin response may be susceptible to recurrent, prolonged, or severe C difficile diarrhea and colitis.

Aims—To examine whether treatment with intravenous immunoglobulin might be effective in patients with severe pseudomembranous colitis unresponsive to standard antimicrobial therapy.

Patients—Two patients with pseudomembranous colitis not responding to metronidazole and vancomycin were given normal pooled human immunoglobulin intravenously (200–300 mg/kg).

Methods—Antibodies against C difficile toxins were measured in nine immunoglobulin preparations by ELISA and by cytotoxin neutralisation assay.

Results—Both patients responded quickly as shown by resolution of diarrhea, abdominal tenderness, and distension. All immunoglobulin preparations tested contained IgG against C difficile toxins A and B by ELISA and neutralised the cytotoxic activity of C difficile toxins in vitro at IgG concentrations of 0·4–1·6 mg/ml.

Conclusion—Passive immunotherapy with intravenous immunoglobulin may be a useful addition to antibiotic therapy for severe, refractory C difficile colitis. IgG antitoxin is present in standard immunoglobulin preparations and C difficile toxin neutralising activity is evident at IgG concentrations which are readily achievable in the serum by intravenous immunoglobulin administration.

Methods

MEASUREMENT OF ANTI-C DIFFICILE IgG IN IMMUNOGLOBULIN PREPARATIONS

Nine human immunoglobulin preparations intended for intravenous administration were studied. Three batches of immunoglobulin were obtained from each of the following producers: Alpha Therapeutic Corporation (Los Angeles, California, USA), Armour Pharmaceutical Company (Kankakee, Illinois, USA), and Baxter Healthcare Corporation (Glendale, California, USA). All were highly purified preparations of intact unmodified IgG isolated from large pools of human plasma by cold alcohol fractionation.

Human IgG levels to C difficile antigens were measured by enzyme linked immunosorbent assay (ELISA) as previously described. Forty IgG directed against highly purified C difficile toxins A and B and against a culture filtrate of toxigenic C difficile (strain VPI 10463) were measured separately. The C difficile culture filtrate contains toxins A and B as well as non-toxin C difficile antigens. ELISA results are...
Intravenous IgG for C difficile colitis

Case reports and Results

**PATIENT 1**
A 63 year old woman developed diarrhoea, cramping abdominal pain, and abdominal distension five days after laparotomy for staging of non-Hodgkin’s lymphoma. She received intravenous ceftazidime perioperatively but had not been treated with cytotoxic chemotherapy. She had a peripheral blood leucocytosis of 22 000 cells/µl with 6% band forms. Flexible sigmoidoscopy and biopsy demonstrated pseudomembranous colitis of the rectum and sigmoid colon. Treatment was begun with both intravenous metronidazole (500 mg, six hourly) and oral vancomycin (250 mg, six hourly). After five days she continued to suffer from profuse diarrhoea and had a persistent leucocytosis of 21 000 cells/µl. The patient’s abdomen became distended and diffusely tender. A plain abdominal radiograph showed an ileus pattern with both small intestinal and colonic dilatation. A computed tomogram showed dilatation of the colon and the presence of ascites (fig 1). Intravenous immunoglobulin was administered (300 mg/kg). The diarrhoea improved rapidly. After 36 hours her abdominal pain and distension had resolved and her white blood cell count was normal at 9800 cells/µl. Treatment with metronidazole and vancomycin was continued for a further 10 days. One month later she suffered a recurrence of diarrhoea and had a positive stool cytotoxin assay. On this occasion she responded to treatment with oral metronidazole.

**PATIENT 2**
A 64 year old man underwent left upper lobectomy for large cell lung cancer. Intravenous vancomycin and ceftazidime were administered postoperatively for the treatment of pneumonia. Six days after surgery he developed diarrhoea, cramping abdominal pain, a fever of 102°F (38.9°C), diffuse abdominal tenderness, and abdominal distension. A stool test for C difficile cytotoxin was positive and he was treated with oral metronidazole (500 mg, six hourly). An abdominal radiograph showed thickening of the wall of the colon with thumbprinting (fig 2A). Flexible sigmoidoscopy was performed three days later because of increasing abdominal pain and distension, and showed pseudomembranous colitis (fig 2B). Oral vancomycin (250 mg, six hourly) was initiated. Nine days later he showed no improvement and had continuing diarrhoea, abdominal discomfort, and intermittent fevers. Intravenous immunoglobulin (200 mg/kg) was administered. Within 24 hours his diarrhoea and fever resolved and did not recur.

**C difficile ANTITOXIN ACTIVITY IN HUMAN IMMUNOGLOBULIN PREPARATIONS**

The rapid clinical response of these two patients to intravenous administration of normal pooled human serum immunoglobulin led us to test a variety of human IgG preparations for neutralising antibodies against C difficile toxins A and B. All nine of the human immunoglobulin preparations tested contained IgG against C difficile culture filtrate (fig 3A). Antibody levels varied slightly with an approximately fourfold difference in antibody titre between the preparations with the highest and lowest antibody levels. We also measured IgG levels against purified C difficile toxin A and toxin B. A representative result for an immunoglobulin preparation with mid-range anti-C difficile IgG...
levels is presented in fig 3B (this particular preparation is identified by an arrow in fig 3A).

All preparations contained IgG against both C. difficile toxin A and toxin B as measured by ELISA.

Finally, we determined whether pooled human immunoglobulin was capable of neutralising the cytotoxic effects of C. difficile toxins. All nine preparations neutralised C. difficile culture filtrate cytotoxicity at IgG concentrations of 0.4–1.6 mg/ml. Culture serum from a healthy volunteer who lacked specific antibodies against C. difficile toxin A or toxin B failed to neutralise the cytotoxicity of C. difficile culture filtrate in this assay.

Discussion

Most patients who develop C. difficile diarrhoea respond promptly to either oral metronidazole or vancomycin. Diarrhoea may recur when these agents are discontinued but even then almost always resolves quickly when antimicrobial therapy is resumed. Persisting diarrhoea despite appropriate treatment with metronidazole and vancomycin, as occurred in both patients in this report, is unusual. Both patients also had severe colitis as evidenced by pseudomembrane formation, thickening of the colonic wall, abdominal tenderness, and abdominal distension. Severe, unresponsive pseudomembranous colitis may result in colonic perforation, septicemia, and death. Colectomy may be life saving in these circumstances. However, many patients are considered unfit for colectomy because of advanced age and severe coexisting medical problems. Even those who are considered fit to undergo colectomy for severe pseudomembranous colitis have a mortality rate of approximately 50%. Thus it was felt that intravenous immunoglobulin treatment for unresponsive pseudomembranous colitis was justified for the two patients presented in this report. In both instances there was rapid clinical improvement immediately following immunoglobulin administration.

Both patients in this report had recognised risk factors for C. difficile colitis including anti-
Intravenous IgG for C difficile colitis


