Descriptive study of intravenous immunoglobulin for the treatment of recurrent Clostridium difficile diarrhoea

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Objectives: Clostridium difficile diarrhoea (CDD) cases treated with intravenous immunoglobulin during a 2 year period were reviewed to determine disease severity and response to treatment.

Patients and methods: Of 580 CD cytotoxin-positive patients, five received intravenous immunoglobulin because of protracted and/or recurrent CDD (median duration 50 days, range 45–64); two had biopsy-proven pseudomembranous colitis. The five patients received a median three non-CDD antibiotic courses (range 2–8). Indices of CDD severity included hypoalbuminaemia (n = 5, median 27 g/L, range 11–29), marked hypokalaemia (n = 3, range 1.9–2.7 mM), markedly raised peripheral white cell count (n = 3, 18–34 × 10⁹ cells/L), abdominal signs (n = 3) and pyrexia (n = 1). The five cases received metronidazole for median 17 days (range 0–63) plus vancomycin for median 14 days (range 10–42) before intravenous immunoglobulin. One also received rifampicin plus vancomycin and one was given Saccharomyces boulardii.

Results: Intravenous immunoglobulin was given at a dosage of 300–500 mg/kg (most commonly 400 mg/kg) for one dose (two patients), two doses (two patients) and in one case for six doses. The latter patient died of intractable CDD, three had a good therapeutic response to intravenous immunoglobulin and CDD recurred within 6 weeks in one case. In the three successfully treated cases, CDD resolved within 11 days.

Conclusions: Intravenous immunoglobulin is useful for the treatment of intractable and severe CDD. Controlled studies are needed to assess the true value of this and other forms of passive immunotherapy.

Keywords: pseudomembranous colitis, antibiotics, immunotherapy

Introduction

Despite the causal role of antibiotics in inducing Clostridium difficile diarrhoea (CDD), recommended treatment of such cases currently consists of antimicrobial therapy. The high response rates that are achieved with both metronidazole and vancomycin in CDD do not differ significantly. However, up to 37–50% of patients with CDD treated with either metronidazole or vancomycin have a recurrence of symptoms.¹² The majority of these recurrences are due to re-infection as opposed to relapse.²³ Also, Kyne et al.² found significantly higher concentrations of both serum IgM and IgG antitoxin A in patients who had one, as opposed to multiple, episodes of CDD. Thus, there is good evidence that increased risk of CDD recurrence is associated with poor host humoral response.

There have been several case reports of patients with recurrent CDD who were successfully treated with intravenous immunoglobulin.²⁰,²¹ Reports of the effectiveness of this approach may, however, be biased towards successfully treated cases. All CDD cases treated with intravenous immunoglobulin at the study hospital in the past 2 years were therefore reviewed to determine disease severity and response to treatment.

Materials and methods

All patients at the General Infirmary, Leeds (a university teaching hospital) who received intravenous immunoglobulin for the treatment of recurrent CDD during the 2 years 2000–2 were identified by review of Pharmacy and Microbiology databases. Patients’ records were then reviewed and the following data were recorded: patient demographics and underlying diseases, previous antibiotic exposure, diarrhoea history, antibiotic treatment for CDD, outcome of antibiotic and immunoglobulin treatment of CDD including speed of response, and assessment of CDD severity as evidenced by haematology and biochemistry measurements, abdominal signs, systemic temperature and sigmoidoscopy findings. CDD cases were defined as patients with diarrhoea (at least three loose stools per day) for at least 2 days who had cytotoxin-positive faeces.

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882

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Recurrent CDD is common and difficult to manage particularly as repeated antibiotic exposure may exacerbate gut flora disturbance.1,2 There is no consensus and no data from controlled studies to inform about how to manage patients with multiple recurrences of CDD. Non-CDD specific underlying illnesses can also add to the complexity of CDD diagnostics and management.3,4 1.9 Recurrent CDD is common and difficult to manage particularly as repeated antibiotic exposure may exacerbate gut flora disturbance.1,2 There is no consensus and no data from controlled studies to inform about how to manage patients with multiple recurrences of CDD. Non-CDD specific underlying illnesses can also add to the complexity of CDD diagnostics and management.3,4

Discussion

Recurrent CDD is common and difficult to manage particularly as repeated antibiotic exposure may exacerbate gut flora disturbance.1,2 There is no consensus and no data from controlled studies to inform about how to manage patients with multiple recurrences of CDD. It was noticeable that each case received non-specific antibiotic therapy before and after the initial diagnosis of CDD. Non-CDD specific underlying illnesses can also add to the complexity of CDD diagnostics and management.3,4

Results

Of 580 C. difficile cytotoxin-positive patients, five (0.9%) received intravenous immunoglobulin (Viagam S, Bio Products Laboratory, UK; Octagam, Octapharma, UK) because of protracted and/or recurrent CDD. The five cases had diarrhoea for a median duration of 50 days (range 45–64) before treatment with intravenous immunoglobulin, and two patients had biopsy-proven pseudomembranous colitis (see Table 1). There was no evidence of toxic megacolon in any of the cases, although none had CT examination. The five cases had received a median three antibiotic courses (range 2–8) excluding specific treatment administered for CDD. Each case received non-specific antibiotic therapy before and after the initial diagnosis of CDD. Four of the five cases initially received oral metronidazole for the treatment of CDD. The fifth case received either oral vancomycin or an investigational treatment for CDD (GT160-246) as part of a randomized, double-blind controlled trial. The cases received a median three courses (range 1–4) of therapeutic antibiotics for CDD, consisting of metronidazole for a median 17 days (range 0–63) and vancomycin for a median 14 days (range 10–42), before intravenous immunoglobulin. One patient received a combination of rifampicin plus vancomycin and one was given Saccharomyces boulardii. Thus no patient received contemporaneous conventional CDD treatment and immunoglobulin therapy. Further indices of CDD severity were that all five patients became hypoalbuminaemic (median 27 g/L, range 11–29; normal 37–49), three had marked hypokalaemia (range 1.9–2.7 mmol/L; normal 3.6–5.0 mEq/L), three had a markedly raised peripheral white cell count (18–34; normal 4–11 × 10^9 cells/L), three had abdominal signs and one was pyrexial, before commencement of intravenous immunoglobulin.

Intravenous immunoglobulin was given at a dosage of 300–500 mg/kg (most commonly 400 mg/kg) for one dose (in two patients), two doses (in two patients) and in one case for six doses. Three of the five patients had a good therapeutic response to intravenous immunoglobulin. In these three successfully treated cases, CDD resolved within 11 days. CDD did not abate fully in patient 4 and then recurred 6 weeks after administration of intravenous immunoglobulin. One patient died of intractable CDD (patient 1), despite receiving six doses of intravenous immunoglobulin, and previously a total of 27 days of metronidazole and vancomycin in three separate courses.

Table 1. Patient and treatment details

<table>
<thead>
<tr>
<th>Patient</th>
<th>Demographics, underlying illnesses</th>
<th>CDD details</th>
<th>Severity indices*</th>
<th>CDD treatment history before iv Ig (days)*</th>
<th>iv Ig</th>
<th>Response</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66-year-old female, subarachnoid haemorrhage</td>
<td>two episodes, 21 and 24 days, colonoscopy showed severe PMC</td>
<td>ALB ↓11, WCC ↑34 &amp; 29, K⁺ ↓1.9, abdo tender, pyrexial</td>
<td>Metro 7, 10, Vanc 10</td>
<td>3 × 400 mg/kg, 3 × 300 mg/kg, on consecutive days</td>
<td>no therapeutic response</td>
<td>died 7 days after starting iv Ig (1 day after last dose)</td>
</tr>
<tr>
<td>2</td>
<td>97-year-old female, fractured neck of femur</td>
<td>two episodes, 20 and 29 days, flexible sigmoidoscopy showed severe PMC</td>
<td>ALB →, WCC ↑32 &amp; 22, K⁺ →, abdo tender ++</td>
<td>Metro 7, 25, 20, Vanc 40, Rif 3</td>
<td>2 × 400 mg/kg, 2 days apart</td>
<td>partial response 5 days after iv Ig; diarrhoea ceased at day 8</td>
<td>died 1 week after cessation of symptoms (unrelated to CDD)</td>
</tr>
<tr>
<td>3</td>
<td>86-year-old female, depression</td>
<td>three episodes, 36, 19 and 9 days</td>
<td>ALB ↓27, WCC ↓→, K⁺ ↓2.5</td>
<td>Metro 12, Vanc 21, 9</td>
<td>1 × 400 mg/kg</td>
<td>no further diarrhoea after iv Ig</td>
<td>9 months—no recurrence</td>
</tr>
<tr>
<td>4</td>
<td>72-year-old female, depression, cerebrovascular accident</td>
<td>three episodes, 37, 7 and 12 days</td>
<td>ALB ↓25, WCC →, K⁺</td>
<td>Metro 21, 42, Vanc 42, S. boulardii 14</td>
<td>2 × 500 mg/kg on consecutive days</td>
<td>partial response but still loose stools</td>
<td>recurrence of diarrhoea after 6 weeks</td>
</tr>
<tr>
<td>5</td>
<td>73-year-old male, chronic obstructive pulmonary disease</td>
<td>two episodes, 35 and 15 days</td>
<td>ALB ↓29, WCC ↑18 &amp; 16, K⁺ ↓3.1, Wt ↓6 kg (15% of body wt), abdo pain</td>
<td>Vanc or GT160-246 14×</td>
<td>1 × 400 mg/kg</td>
<td>partial response 4 days after iv Ig; diarrhoea ceased at day 11</td>
<td>3 months—no recurrence</td>
</tr>
</tbody>
</table>

PMC, pseudomembranous colitis.
*ALB, serum albumin, normal range 37–49 g/L; WCC, white cell count, normal range 4–11 × 10^9 cells/L; K⁺, serum potassium, normal range 3.6–5.0 mEq/L.
*Days of oral metronidazole 400 mg three times daily (Metro), vancomycin 125 mg four times daily (Vanc) or rifampicin 600 mg twice daily (Rif).
*GT160-246 is an investigational treatment for CDD and was administered as part of a randomized double-blind controlled trial.
antibiotic therapy must be avoided to prevent CDD recurrence. The elderly patients in the present case series had recurrent CDD that was refractory to conventional antibiotic therapy, and furthermore refractory, prolonged diarrhoea was associated with significant biochemical disturbances. Despite this difficult-to-treat scenario, three of five cases responded to intravenous immunoglobulin therapy. In these three successfully treated cases, CDD resolved within 11 days, and thus immediate response should not be expected. One of the cases in whom response was seen died (of an unrelated cause—bronchopneumonia) 1 week after diarrhoea stopped (15 days after immunoglobulin administration), and thus it cannot be certain that relapse would not have occurred. However, the temporal relationship of intravenous immunoglobulin administration to diarrhoea cessation, and the fact that the patient had had only one other symptom-free period in 3 months gives credibility to a claim for therapeutic response.

Although the present case series is small, it is the largest number of adults treated with intravenous immunoglobulin for CDD reported to date. Of the 11 cases published previously,3,5 five were children with a median age of 18 months.4 The aetiological role of C. difficile in this age group is uncertain, particularly as cross infection in neonates can lead to very high carriage rates. It is possible that published cases of the successful use of intravenous immunoglobulin in CDD are subject to reporting bias. All 11 previously reported CDD cases treated with intravenous immunoglobulin therapy responded favourably. It is clear from the present case series, however, that response to intravenous immunoglobulin in CDD is not universal. Four recent cases reported by Beales3 were all given intravenous immunoglobulin with a tapering course of vancomycin. There is no sound reason for using this combination. There are no controlled studies of tapering course vancomycin therapy in CDD, and it is likely that success of this approach may be due to the prolonged (4–6 week) antibiotic course, which prevents reacquisition of C. difficile while colonization resistance by bowel flora remains ineffectual against opportunistic bacterial colonization.

Population prevalence studies have detected antibodies against toxin A and/or B in the serum of ~70% of individuals.5 It is therefore not surprising that C. difficile toxin-neutralizing antibodies were found to be present in nine batches from three commercial (US) immunoglobulin suppliers in the mid-1990s.6 High concentrations of antitoxin IgG were also found in products tested in the early 1990s.6 It is notable that the titre of IgG against C. difficile culture filtrate varied by ~4-fold.7 Leung et al.8 found that the titres of serum IgG but not IgA antitoxin-A antibodies increased in children with CDD given intravenous immunoglobulin every 3 weeks. C. difficile antitoxin antibodies were not measured in the present study, and patients were treated with intravenous immunoglobulin from different batches from two different producers (with immunoglobulin sourced from outside the UK). It would have been useful to measure antitoxin concentrations, although no standard assay exists. It is possible nevertheless that the actual amount of anti-C. difficile toxin antibody administered to our patients varied markedly. The dose, duration and timing of intravenous immunoglobulin used to treat CDD have not been determined, and indeed no comparative studies of immunoglobulin therapy in patients with C. difficile infection have been performed. There are data to show that patients with low antitoxin concentrations are more likely to become symptomatic and also to experience recurrent CDD.9 However, as yet there are no data to correlate high antitoxin concentrations with treatment success. These issues should be addressed in future studies. In general, the dosage of intravenous immunoglobulin used to treat CDD in this case series and elsewhere are relatively modest compared with those used in other conditions. For example, in Guillain–Barré syndrome intravenous immunoglobulin 400 mg/kg is given daily for 5 days.

Despite the recognition that a high antibody response to C. difficile toxin A is associated with a reduced risk of infection and recurrence, little is known about the mode of action of antibodies in C. difficile infection. C. difficile neutralization, or prevention of bacterial adhesion or toxin binding to gut mucosa and receptor sites, are possible modes of antibody action. It is not known why some individuals do not mount a protective humoral response against C. difficile. Also, the relative importance of initiating antibiotic, gut flora disturbance, strain type and host antibody response in determining the risk of C. difficile infection have not been elucidated.9 A vaccine containing both C. difficile A and B toxoids has been shown to be safe and immunogenic in healthy volunteers, producing increased serum IgG and fecal IgA antitoxin concentrations in excess of those associated with protection in clinical studies.10 It remains unclear, however, whether this approach will be effective in the main target population, particularly as CDD in the elderly appears to be partly attributable to a compromised immune response.

Intravenous immunoglobulin is currently in short supply and therapy is relatively expensive. Nevertheless, CDD and especially recurrent infection consumes considerable medical resources.1 Intravenous immunoglobulin may thus still be a cost-effective treatment option for intractable cases, particularly given the absence of proven therapeutic alternatives. The prospects for controlled studies of iv immunoglobulin therapy are not good. Notably, every immunoglobulin manufacturer in the UK was contacted in writing to ask whether they were willing to support a comparative study, but all declined. However, other forms of passive immunotherapy should be explored, and controlled studies are indicated, preferably using C. difficile-specific immunoglobulin. In conclusion, intravenous immunoglobulin may be useful for the treatment of intractable, moderate–severe CDD.

References