The role of immunoglobulin for the treatment of Clostridium difficile infection: a systematic review

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Introduction

Clostridium difficile is the most common infectious cause of nosocomial healthcare-associated diarrhea. The increasing prevalence of C difficile, spread in the community, virulence and frequent relapse has created an urgent need to identify new effective treatments for C difficile infection. Among these, intravenous immunoglobulin (IVIG) is used for cases of severe C difficile infection. We undertook a systematic review to examine the published literature pertaining to the use of immunoglobulin for C difficile infection. Four retrospective studies and five case reports that addressed the use of IVIG for the treatment of C difficile infection were identified. One study on the use of oral immunoglobulin was identified. Although overall there appear to be benefits to using IVIG in recurrent severe disease, the small sample sizes and lack of control groups in three of the four studies do not allow recommendations to be made regarding the use of immunoglobulin in C difficile infection. Further research is urgently needed to clarify the role of immunoglobulin — intravenous or oral — for the treatment of C difficile infection.

KEYWORDS

Clostridium difficile; CDAD; IVIG; Immunoglobulin; Hypogammaglobulinemia

Summary

Clostridium difficile is the most common infectious cause of nosocomial healthcare-associated diarrhea. The increasing prevalence of C difficile, spread in the community, virulence and frequent relapse has created an urgent need to identify new effective treatments for C difficile infection. Among these, intravenous immunoglobulin (IVIG) is used for cases of severe C difficile infection. We undertook a systematic review to examine the published literature pertaining to the use of immunoglobulin for C difficile infection. Four retrospective studies and five case reports that addressed the use of IVIG for the treatment of C difficile infection were identified. One study on the use of oral immunoglobulin was identified. Although overall there appear to be benefits to using IVIG in recurrent severe disease, the small sample sizes and lack of control groups in three of the four studies do not allow recommendations to be made regarding the use of immunoglobulin in C difficile infection. Further research is urgently needed to clarify the role of immunoglobulin — intravenous or oral — for the treatment of C difficile infection.

The incidence and severity of CDI have been increasing in the past decade, and a highly virulent epidemic strain, producing a binary toxin, associated with considerable morbidity and mortality has been reported.12,13

The treatment of CDI is challenging. Metronidazole remains the first-line therapy, with oral metronidazole and vancomycin reserved for severe cases. However, up to 30% of patients with an initial episode of CDI will experience one or more recurrences following cessation of the medication.14

A recently recognized major risk factor for developing CDI is the presence of low serum antibody levels to C difficile toxin A.14,15 In a prospective cohort study of 271 hospitalized patients, Kyne et al. found that patients who had serum IgG antibody of 3.00 ELISA units or less were 48 times more likely to get CDI.15 This observation provides the rationale for studying immunoglobulin as a means of boosting humoral

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immunity, thus preventing or ameliorating CDI. In recent years, a handful of case reports and series have suggested that intravenous immunoglobulin (IVIG) may be beneficial in patients with severe CDI.\textsuperscript{16–25} We undertook a systematic review to examine the available evidence regarding the role of oral or intravenous immunoglobulin for the treatment of CDI.

**Methods**

Articles were identified by PubMed searches performed on April 2–5, 2008 and October 28–29, 2008 for the time period 1970–2008. Search terms were 'CDAD' (Clostridium difficile-associated disease), 'immunoglobulin', 'IVIG', and 'Clostridium difficile'. Articles that investigated immunoglobulin therapy for CDI in humans were included. No language restrictions were applied. The references of relevant articles were manually examined to identify additional studies.

**Results**

Three case series, one retrospective case–control study, and five case reports were identified that examined IVIG therapy for CDI (Tables 1 and 2). One study of oral immunoglobulin therapy was identified.

In a case series of five pediatric hypogammaglobulinemic patients with recurrent CDI, Leung et al. found that all five treated with IVIG 400 mg/kg given once every three weeks had complete resolution of symptoms. Patients required a mean of two cycles of therapy before resolution of symptoms.\textsuperscript{21}

Wilcox et al. performed a retrospective analysis of patients treated with IVIG for CDI. Of 580 patients with recurrent CDAD, five received immunoglobulin therapy. Dosing ranged from 300 to 500 mg/kg and patients were given from one to six doses. One patient had a complete response; three patients had partial resolution of symptoms with IVIG therapy, and one patient died without an apparent therapeutic response. Resolution typically occurred within 11 days of the initiation of treatment.\textsuperscript{25}

McPherson et al. conducted a retrospective analysis of 264 patients diagnosed with CDI. The study included 14 patients receiving IVIG for recurrent CDI. Nine patients had a full response, one had a partial response, and four patients continued to worsen despite therapy. No patients experienced complications attributable to IVIG therapy.\textsuperscript{22}

Juang et al. conducted a retrospective analysis of 79 patients with severe CDI, comparing 18 patients who received IVIG to a control group of 61 who did not. There were no significant differences in the demographics or CDAD severity scores in the patient groups. No significant differences were identified in terms of outcomes or severity of symptoms after treatment.\textsuperscript{20}

Hassett et al. reported a 49-year-old female with IgG1 deficiency with nine episodes of CDI associated with colitis in a two-year period, successfully treated with IVIG in combination with a probiotic agent. The patient had received unsatisfactory treatment with various doses and combinations of oral vancomycin, metronidazole, and rifampin. The patient was given 1 g daily *Saccharomyces boulardii* for probiotic therapy in combination with 30 grams every 2 weeks IVIG to treat the immune deficiency. The patient had a symptom-free interval of 24 months despite continued antibiotic pressure from treatment for sinopulmonary infections. The authors concluded that in this immune deficient patient, combining standard therapy with immunoglobulin

### Table 1: Studies examining the use of intravenous immunoglobulin for the treatment of *Clostridium difficile* infection

<table>
<thead>
<tr>
<th>Study</th>
<th>Population size</th>
<th>Controls</th>
<th>Major comorbidities</th>
<th>Dosage IVIG</th>
<th>Study time frame</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leung et al., 1991</td>
<td>5</td>
<td>None</td>
<td>Hypogammaglobulinemia</td>
<td>400 mg/kg every three weeks</td>
<td>6 months</td>
<td>All patients had full resolution of symptoms</td>
</tr>
<tr>
<td>Wilcox et al., 2004</td>
<td>5</td>
<td>None</td>
<td>Comorbidities included subarachnoid hemorrhage, femoral neck fracture, depression, CVA, and COPD</td>
<td>Ranged from 300 to 500 mg/kg given as 1 to 6 doses</td>
<td>Retrospective analysis from 2000 to 2002; resolution occurred within 11 days of initiation of therapy</td>
<td>Nine patients had full resolution of symptoms, one had a partial response, and four did not respond to therapy</td>
</tr>
<tr>
<td>McPherson et al., 2006</td>
<td>14</td>
<td>None</td>
<td>Comorbidities included pneumonia, stroke, subarachnoid hemorrhage, cellulitis, appendicitis, diabetes, UTI, ARF, AML, COPD, IHD, AF, lymphoma, bladder cancer, parotitis, sepsis, and pyelonephritis</td>
<td>Ranged from 150 to 400 mg/kg</td>
<td>Retrospective analysis from 2003 to 2005</td>
<td>No significant differences in outcome were noted between groups</td>
</tr>
<tr>
<td>Juang et al., 2007</td>
<td>61</td>
<td>Not reported</td>
<td></td>
<td>400 mg/kg</td>
<td>Retrospective analysis from 2001 to 2003</td>
<td>No significant differences in outcome were noted between groups</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; AML, acute myeloblastic leukemia; ARF, acute renal failure; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease; IVIG, intravenous immunoglobulin; UTI, urinary tract infection.
<table>
<thead>
<tr>
<th>Study</th>
<th>Patient age/gender</th>
<th>Major comorbidities</th>
<th>Failed treatment regimens</th>
<th>IVIG treatment regimen</th>
<th>Follow-up</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hassett et al., 1995</td>
<td>49 years/female</td>
<td>IgG1 deficiency; recurrent sinopulmonary infections</td>
<td>Metronidazole; vancomycin; rifampin</td>
<td>30 g every two weeks, 1 gram <em>Saccharomyces boulardii</em> daily</td>
<td>24 months</td>
<td>Patient remained asymptomatic for 2 years</td>
</tr>
<tr>
<td>Salcedo et al., 1997</td>
<td>63 years/female</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>Metronidazole; vancomycin</td>
<td>300 mg/kg IVIG once, metronidazole, vancomycin 10 days further</td>
<td>Not stated</td>
<td>Patient had recurrence 1 month later; successfully treated with 10 days metronidazole</td>
</tr>
<tr>
<td></td>
<td>64 years/male</td>
<td>Large cell lung cancer</td>
<td>Metronidazole; vancomycin</td>
<td>200 mg/kg IVIG once</td>
<td>Not stated</td>
<td>Patient improved within 24 hours; no recurrence</td>
</tr>
<tr>
<td>Beales, 2002</td>
<td>77 years/female</td>
<td>COPD; NIDDM; pneumonia</td>
<td>Metronidazole; vancomycin</td>
<td>400 mg/kg IVIG twice 21 days apart, vancomycin taper</td>
<td>10 months</td>
<td>'Quick' resolution followed by patient remaining symptom free throughout follow-up</td>
</tr>
<tr>
<td></td>
<td>75 years/female</td>
<td>COPD; NIDDM; pneumonia</td>
<td>Metronidazole; vancomycin</td>
<td>400 mg/kg IVIG twice 21 days apart, vancomycin taper</td>
<td>8 months</td>
<td>'Successful treatment', no recurrence in follow-up</td>
</tr>
<tr>
<td></td>
<td>69 years/male</td>
<td>AAA</td>
<td>Metronidazole; vancomycin</td>
<td>400 mg/kg IVIG twice 21 days apart, vancomycin taper</td>
<td>7 months</td>
<td>'Resolved', no recurrence</td>
</tr>
<tr>
<td></td>
<td>82 years/female</td>
<td>CVA; pneumonia; PEG site infection</td>
<td>Metronidazole; vancomycin</td>
<td>400 mg/kg IVIG twice 21 days apart, vancomycin taper</td>
<td>5 months</td>
<td>'Resolved', no recurrence</td>
</tr>
<tr>
<td>Murphy et al., 2006</td>
<td>57 years/female</td>
<td>CHF; Barrett’s esophagus; UTI</td>
<td>Metronidazole; vancomycin, <em>Saccharomyces boulardii</em>; rifampin</td>
<td>400 mg/kg IVIG every day for three days</td>
<td>4 months</td>
<td>Patient remains toxin positive but asymptomatic</td>
</tr>
<tr>
<td>Hassoun and Ibrahim, 2007</td>
<td>72 years/male</td>
<td>Hypothyroidism; Merkel cell carcinoma; Non-Hodgkin’s lymphoma, in remission</td>
<td>Metronidazole; vancomycin, <em>Saccharomyces boulardii</em>; rifampin</td>
<td>400 mg/kg once with vancomycin taper for 6 weeks</td>
<td>Not stated</td>
<td>Improvement after 2 days; full resolution by day 7</td>
</tr>
</tbody>
</table>

AAA, abdominal aortic aneurysm; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; IVIG, intravenous immunoglobulin; NIDDM, non-insulin dependent diabetes mellitus; PEG, percutaneous endoscopic gastrostomy; UTI, urinary tract infection.
and probiotics appeared to be more effective than standard treatment alone. 17
Salcedo et al. reported two patients with pseudomembranous colitis unresponsive to standard antibiotic therapy with metronidazole and vancomycin. Patients were treated with 200—300 mg/kg IVIG; both experienced resolution of symptoms within 24—36 hours. Salcedo et al. tested nine commonly used IVIG preparations for in vitro activity against C. difficile toxin. All nine had toxin-neutralizing activity, though the concentration varied by four-fold from the least to the most active preparation. 24
Beales published a reply to Kyne and Kelly’s therapeutics update, 26 which reported four cases of recurrent CDI successfully treated with IVIG. Patients ranged in age from 69 to 82 years, and all had recurrence after two courses of metronidazole and a vancomycin taper. IVIG 400 mg/kg was administered twice, 21 days apart, while on a second vancomycin taper. None of the patients had any further recurrences in the 5—10 months of follow-up. The author concluded that IVIG appears to be a useful adjunct to vancomycin tapers in refractory CDI. 16
Murphy et al. offered the case report of a 57-year-old female who developed recurrent CDI despite metronidazole and vancomycin therapy. The patient was first given probiotic therapy with S. boulardii; diarrhea briefly resolved, but recurred a month later. Treatment was attempted with anion exchange resins with minimal improvement. The patient was given three treatments of IVIG 400 mg/kg, and had resolution of diarrhea. The patient remained toxin-positive, but asymptomatic through four months of follow-up. 21
Hassoun and Ibrahim published a case report of a 72-year-old male receiving chemotherapy who developed severe CDI. After failing metronidazole/vancomycin treatment, the patient was given a single dose of IVIG therapy 400 mg/kg as well as a vancomycin taper. The patient improved by day 2, resolving completely by day 7, with no further recurrence. 18
Mattila et al. reported the first, and to-date, only, study comparing orally administered immunoglobulin to standard therapy. Thirty-eight patients with recurrent mild to moderate recurrent CDI were randomized to receive C. difficile immune whey (CDIW) or metronidazole. The study was stopped prematurely due to the bankruptcy of the sponsor, but preliminary results showed a comparable response between the two therapies, with 100% response with metronidazole compared to 89% in the CDIW group. After two months of follow-up, 55% of patients in the metronidazole arm had no recurrence compared to 56% in the CDIW arm. 27

Discussion
Clostridium difficile infection is a growing public health problem. 28 There is an urgent need to develop new therapeutic approaches to treating CDI, including antibiotic, 29 and non-antibiotic-based therapies, such as probiotics, 30 vaccines, 31,32 and passive immunotherapy. 33 In this review, we have focused on examining the existing evidence for the use of immunoglobulin for CDI. In our analysis we found that there is a paucity of evidence to support the use of IVIG for CDI. The preliminary studies that we identified suggest that IVIG may be beneficial in cases of recurrent CDI, but definitive recommendations are not possible with the currently available literature. The only controlled study to-date showed no benefit of IVIG compared to the standard treatment in patients with severe CDI; however, it should be noted that this is the only study that aimed to use IVIG for ‘severe’ CDI; all other reports were treating ‘recurrent’ CDI. Current treatment guidelines, which are several years old and under revision, state that IVIG may be considered to prevent multiple recurrences in patients severely affected with CDI. 14
There are currently eight FDA approved IVIG products. The products all vary slightly in method of preparation and final IgA content. The FDA has approved IVIG for six clinical indications, but over half of all IVIG prescribed is off-label. 34 Antibodies against C. difficile toxin were detected in nine commercial immunoglobulin preparations in an older study. Titers of toxin-neutralizing antibody varied by a maximum of a factor of four. 24 In the studies we included in our analysis, data on the levels of IgG to C. difficile toxin A in the blood following IVIG treatment were not reported. Finally, it is unclear how and if the IVIG enters the colon to exert its toxin binding effect. Possibly, the active inflammation seen in severe CDI allows for the exudation of some immune globulins across the colonic mucosa. 24
IVIG is prohibitively expensive and thus exploration of other ways of providing passive immunotherapy is essential. A promising area in immunoglobulin therapy for CDI is the use of oral immunoglobulins. In an animal study, oral immunoglobulin derived from eggs of immunized leghorn hens effectively neutralized toxins A and B in a hamster model. 35 A human study using bovine immunoglobulin concentrate prepared from Colostral milk of cows immunized against toxin A demonstrated that the antibody preparation retains the ability to neutralize C. difficile toxin A after transit through the stomach and small intestine. 36 A safety study of immunoglobulin-containing whey protein concentrate prepared from centrifuged milk of cows immunized against toxin A showed no significant side effects from oral treatment in severely ill patients with CDAD. 37 At this time, there has been only one study to test oral immunoglobulin therapy in humans for efficacy. The study was prematurely terminated, but the available data showed oral immunoglobulin therapy to be well tolerated and approximately as effective as metronidazole. Research on oral immunoglobulin therapy is needed to determine if it represents a viable treatment option for recurrent CDAD.
In conclusion, further studies are urgently needed to clarify the role of immunoglobulin treatment for CDI. Future studies should measure IgG levels to toxin A and adjust dosing accordingly with oral or intravenous immunoglobulin treatment.

Conflict of interest: No conflict of interest to declare.

References
Immunoglobulin for the treatment of C. difficile infection


