

Intravenous Immunoglobulin for Recurrent *Clostridioides difficile* Infection

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Abstract

Introduction

Clostridioides difficile infection (CDI) imposes a substantial burden on patients, especially in cases of recurrence, leading to severe complications and prolonged hospitalisation. Recurrence complicates 8% of CDI cases in Ireland with an increased prevalence among elderly, multimorbid patients.

Cases

This series documents three cases of recurrent CDI managed with adjunctive intravenous immunoglobulin (IVIG) therapy in combination with standard antibiotics. The patients were males aged 50-87 with multiple co-morbidities and high clinical frailty scores.

Outcome

All three patients experienced successful resolution of symptoms and remained recurrence-free during follow-ups of 16–23 weeks.

Discussion

These cases highlight the potential for IVIG to reduce CDI recurrence, providing an alternative in settings where therapies like bezlotoxumab and faecal microbiota transplant are unavailable. Although limitations, including the small sample size and lack of controlled comparisons, preclude definitive conclusions, the findings underscore the need for further investigation into IVIG's role in managing recurrent CDI. This report aims to enhance the evidence base, advocating for expanded studies to evaluate the clinical and economic implications of IVIG for recurrent CDI.

Introduction

Clostridioides Difficile Infection (CDI) has a major impact on the quality of life of affected patients. In severe or complicated cases, it can result in life-threatening complications such as septic shock, acute renal injury and colonic perforation. Even in non-severe cases CDI causes a significant symptomatic burden resulting in prolonged hospitalisation and loss of independence¹. This effect is multiplied in the case of recurrent CDI (rCDI) whereby re-infection occurs within eight weeks of a previous episode². rCDI makes up 8% of CDI cases in Ireland³ and the risk of recurrence increases with each subsequent episode⁴.

Intravenous immunoglobulins (IVIG) have been utilised as a therapy for treatment of rCDI and severe CDI. There are a small number of case reports documenting its use in recurrent, severe and refractory cases⁵⁻¹¹ and one randomised control trial assessing the efficacy of IVIG in cases of severe CDI¹². There have been no controlled trials or meta-analyses to assess whether IVIG reduces the rate of recurrence of CDI or time to recurrence.

Here, three case reports of rCDI treated with IVIG are presented along with a review of current medical literature on the topic.

Case One

An 87 year old male presented with four days of diarrhoea, bowel incontinence, abdominal pain, rigors and delirium following a recent course of oral cephalixin for a urinary tract infection. He had a background of Lewy body dementia, Crohn's disease, ischaemic heart disease, prostate cancer and a long-term urinary catheter. His medical history included multiple hospital admissions that year for CDI and urosepsis. He had a clinical frailty score of seven. On presentation to hospital, he was febrile to 38.1°C, hypotensive with a blood pressure of 85/55, tachycardic with a heart rate of 116 and tachypnoeic with a respiratory rate of 22 and oxygen saturations of 95% on room air. On examination of his abdomen there was noted to be guarding. Investigations showed a white cell count of $6.6 \times 10^9/L$ and a creatinine of 62mmol/L. Computerised tomography (CT) of the abdomen and pelvis demonstrated evidence of distal colitis. He was admitted to hospital with sepsis, delirium and dehydration. A stool sample confirmed the presence of *C. difficile* toxins by enzyme immunoassay and a diagnosis of CDI was made. This was his third recurrence of CDI over the course of three months and his fifth recurrence overall. Whole genome sequencing was performed on the stool samples collected (see table 1). The strain of *C. difficile* isolated on this occasion was different from that isolated on previous episodes, suggesting re-infection with a new strain. He was treated with oral fidaxomicin 200mg twice daily (BD). His vital signs normalised however his diarrhoea and incontinence persisted. Eight days into this treatment regimen IVIG was administered at a dose of 0.4g/kg. His diarrhoea resolved within one day and a second dose of IVIG was given 72 hours later. He subsequently developed constipation,

and laxatives were required to ensure regular bowel motions. He has had no further recurrences of CDI in the 18 weeks since treatment with IVIG.

Case Two

A 50 year old male nursing-home-resident presented with diarrhoea and sepsis. He had a background of Huntington's disease, autism spectrum disorder, recurrent aspiration pneumonia and benign prostatic hypertrophy. His clinical frailty score was seven. On presentation to hospital, he was hypotensive with a blood pressure of 97/68, tachycardic with a heart rate of 99 and tachypnoeic with a respiratory rate of 22. His oxygen saturations were 98% on room air and he was afebrile (temperature 36.9°C). Hypotension resolved after receiving 2L of intravenous fluids. Investigations revealed a white cell count of $20 \times 10^9/L$, a C-reactive protein of 289mg/L, creatinine of 89mmol/L and a lactate of 2.3mmol/L. A diagnosis of severe CDI was made following the detection of *C. difficile* toxins on stool sample testing. This was the third recurrence of CDI in this patient within a three-month period. Whole genome sequencing revealed a strain of *C. difficile* that was genetically indistinguishable from both previous episodes. Fidaxomicin 200mg BD was commenced and IVIG (0.4g/kg) was administered on the same day. An additional dose of IVIG was administered 72 hours later. Diarrhoea resolved 6 days after the initiation of treatment. There have been no recurrences of CDI in the 23 weeks of follow up, however, there have been two hospital admissions for aspiration pneumonia in this timeframe.

Case three

An 83 year old male presented with one week of diarrhoea with 10-12 episodes daily. He had a background history of right hemicolectomy for adenocarcinoma, deep vein thrombosis, type two diabetes, ischaemic heart disease, chronic obstructive pulmonary disease, prostate cancer treated with radiotherapy and hormonal therapy, long term urinary catheter, pancreatitis and cholecystitis. He had a clinical frailty score of seven. On presentation to hospital his vital signs were within normal limits. His initial investigations revealed a white cell count of $8.7 \times 10^9/L$, urea of 16mmol/L, creatinine of 126mmol/L (a rise from a baseline of 85mmol/L), a lactate of 4.1mmol/L, and a pH of 7.31. Following stool sample testing a diagnosis of severe CDI with acute kidney injury (AKI) and lactic acidosis was made. This was his third episode of CDI in the space of five months. Whole genome sequencing of the *C. difficile* sample demonstrated a strain that was genetically indistinguishable from that isolated on both previous episodes. He was commenced on fidaxomicin 200mg BD. IVIG (0.4g/kg) was administered one day after commencement of antibiotic therapy with an additional dose 72 hours later. The patient subsequently started passing bloody diarrhoea with clots. CT of the abdomen and pelvis and sigmoidoscopy demonstrated findings consistent with radiation colitis. The patient had received radiotherapy for management of prostate cancer two years prior. Anticoagulation was held and the diarrhoea and bleeding

resolved four days after the first dose of IVIG. He has had no recurrences of CDI in the follow up period of 16 weeks.

Discussion

Recurrent CDI can have a significant impact on the quality of life of affected patients. Healthcare-associated CDI has the fourth greatest impact on disability-adjusted life years of any single infectious disease in the European Union¹³. One study looking at an elderly population showed a 40% one year mortality rate following CDI and a seven-fold increased risk of need for transition to a long term care facility within one year¹. All three patients in this case series experienced multiple prolonged hospital admissions as a direct result of this infection with a total of 157 bed days in a 6-month period. Between them they suffered from septic shock, haemorrhage, AKI, delirium and incontinence secondary to CDI.

The patients described here are reflective of the typical cohort affected by rCDI. All three patients had multiple co-morbidities and suffered from frailty. The majority of patients in Ireland with CDI are aged 65 years or older¹⁴ with increasing age considered the greatest risk factor for recurrence¹⁵. Other risk factors include prior hospitalisation, prior CDI episodes and recent antibiotic use^{4, 14, 16}. The risk of recurrence after initial CDI is estimated to be 20-25% with this rate rising with subsequent re-infections^{4, 14}. These cases highlight the potential benefit to both patients and healthcare services of finding therapies to reduce CDI recurrence among a frail patient cohort.

Whole genome sequencing was performed retrospectively on the *C. difficile* samples isolated from each of these patients. This enabled cases of true relapse to be differentiated from cases of re-infection. All three cases had their first two episodes caused by a genetically indistinguishable strain, indicating relapse rather than reinfection (see table 1). Case One's third episode was caused by a different ST type indicating a re-infection. We did not have WGS information for the isolate that caused Case Two's third episode, therefore, could not be sure whether this was a re-infection or relapse.

The current ESCMID guidelines outline recommendations for rCDI management¹⁶. Fidaxomicin is considered first line therapy for initial infection, with oral vancomycin as second line. For the first recurrence ESCMID recommends the use of bezlotoxumab, in addition to these antibiotics. Fidaxomicin therapy alone is second line for a first recurrence. Bezlotoxumab is a human monoclonal antibody against *C. difficile* toxin B¹⁷. Its use can be considered at the first recurrence or in index cases at high risk of recurrence. Faecal microbiota transplant (FMT) is suggested by ESCMID after a 2nd recurrence of CDI. However, FMT is not currently available in Ireland and Bezlotoxumab is not approved for reimbursement by the HSE¹⁸. This leaves clinicians in this country with the challenge of sourcing alternative treatment modalities for patients affected by rCDI.

IVIG is produced from pooled human immunoglobulins. It has been demonstrated to contain antibodies against *C. difficile* toxin A and B which mediate the enterotoxic effects of CDI⁹. Kyne et al. (2000) demonstrated that low serum levels of IgG antibodies against toxin A were associated with an increased risk of progression to infection among patients colonised with *C.difficile*¹⁹. Both Kyne et al. (2001)²⁰ and Warny et al.¹¹ have shown that development of higher antibody levels to *C. difficile* toxin A during an initial CDI conferred protection against future recurrence. These findings provide the theoretical basis for the administration of IVIG to boost antibody levels in an attempt to both treat CDI and to prevent recurrence.

Most literature regarding the use of IVIG to treat rCDI comprises of case reports and case series without any randomised controlled trials or meta-analyses. There is only one published study to date utilising control matching to assess IVIG efficacy in CDI. This study was performed by Juang et al. in 2007¹². A retrospective analysis of 18 patients with control matching was performed to assess the efficacy of IVIG in reducing mortality, length of stay and colectomy rates in severe CDI. No significant difference in clinical outcome was found. However, Juang et al. did not assess whether IVIG reduced the rates of recurrence, or time to recurrence, of CDI, nor indeed has there been any published data to specifically address this question.

IVIG is not without limitations. It can cause side effects such as headache, fever and arthralgia. However, more serious adverse events such as hypersensitivity, acute kidney injury and haemolytic anaemia are rare. A significant constraint to its use is that IVIG is typically derived from a pool of 1,000 human donations. This makes it an inherently limited resource²¹.

In all three cases presented in this report, symptom resolution following IVIG was quick, occurring within 1-6 days. The only complication noted was constipation in one case. Prior to IVIG administration, the three patients had experienced multiple recurrences, five, three and three, respectively. These recurrences occurred despite appropriate antibiotic treatment as per ESCMID guidelines. Table 1 details the timelines and treatment regimens for the previous episodes of CDI in these patients. Some experienced recurrences within 8 weeks, which may suggest treatment failure from vancomycin or fidaxomicin. After receiving IVIG, no further episodes of CDI occurred in the follow up periods of 18, 23 and 16 weeks. Prior to IVIG administration, the mean interval between recurrences had been just 44 days. On this basis we propose that the follow up period was long enough to support a true reduction in rates of CDI in these patients.

Table 1

Details of previous CDI episodes for the three cases described

		First Episode CDI			Second Episode CDI		Third Episode CDI		
Case One	Treatment	10 days	oral	fidaxomicin	14 days	oral	10 days	oral	fidaxomicin
	Time since previous episode				55 days				IVIG two doses
	Sequence type	ST11			ST11		ST5		
	Cluster code	CD 22 009c			CD 22 009c				
Case two	Treatment	14 days	oral	vancomycin	14 days	IV	5 days	oral	fidaxomicin then
	Time since previous episode				23 days				alternative days
	Sequence type	ST5			ST5				for 21 days
	Cluster code	CD 24 076			CD 24 076				IVIG two doses
Case Three	Treatment	10 days	oral	vancomycin	10 days	oral	10 days	oral	fidaxomicin
	Time since previous episode				85 days				IVIG two doses
	Sequence type	ST9			ST9		ST9		
	Cluster code	CD 24 097			CD 24 097		CD 24 097		

IVIG demonstrates potential as an effective adjunctive therapy for rCDI in patients with limited treatment options, especially in settings where other modalities, such as bezlotoxumab or faecal microbiota transplant, are unavailable. Although the sample size is small and lacks a control group, these findings support the need for larger, controlled studies to validate IVIG's clinical and economic benefits in managing rCDI.

Declarations of Conflicts of Interest:

None declared.

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