

Serum-Derived Bovine Immunoglobulin as Novel Adjunct in Complicated *Clostridium difficile* Colitis Treatment

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ABSTRACT

Clostridium difficile infection (CDI) is a well-known complication of antibiotic therapy. It is associated with significant morbidity, mortality, and cost in the hospital setting. The main symptoms include watery diarrhea, abdominal pain, and distension, but CDI can also present as toxic megacolon, bowel perforation with peritonitis, sepsis and renal failure. Therapy includes metronidazole and oral vancomycin, with rectal vancomycin and fecal transplant reserved for more complicated cases. Adjunctive treatments such as probiotics have been tried with mixed results. We present a patient with complicated CDI treated with adjuvant serum-derived bovine immunoglobulin, a novel approach in this context.

INTRODUCTION

Clostridium difficile is a Gram-positive anaerobic bacterium that is known to cause colitis after normal gut flora has been altered by antibiotics. Watery diarrhea is the cardinal symptom of *C. difficile* infection (CDI) and is known as *C. difficile*-associated diarrhea (CDAD). Abdominal pain, distension, fever, lactic acidosis, and marked leukocytosis can also occur.¹ Complications of CDI include recurrent disease and fulminant colitis, which may present as toxic megacolon, bowel perforation with peritonitis, sepsis, or renal failure, or any combination thereof. Treatment is antibiotic-centered: metronidazole is used in less severe cases, while oral and rectal vancomycin are reserved for more severe or recurrent infections.²

Serum-derived bovine immunoglobulin (SBI) is a medical food prescribed under physician supervision. It has been used in gastrointestinal enteropathies such as irritable bowel syndrome with diarrhea, inflammatory bowel disease, human immunodeficiency virus enteropathy, and chemotherapy-induced mucositis.³⁻⁶ The mechanism of action of SBI occurs through the binding of endotoxins and other microbial components, promoting a healthy gut microbiota by improving immune function.⁷ To our knowledge, the use of SBI in the setting of CDI has only been documented in a case of CDI with CDAD.⁸

CASE REPORT

A 60-year-old man presented with 4 days of diarrhea. His past medical history included longstanding opioid use due to injuries sustained during a motor vehicle accident. Two weeks prior to presentation, he was treated with fluoroquinolones for dysuria and urinary frequency. Toward the end of his antibiotic course, he experienced more than 10 daily episodes of watery brown stool with associated abdominal bloating. He denied abdominal pain, nausea, fever, or chills.

At the time of presentation, the patient's vital signs were within normal limits. His physical examination was significant for dry mucous membranes, skin tenting, and mild abdominal distension. Bowel sounds were hypoactive in all four quadrants, and his abdomen was non-tender to palpation.

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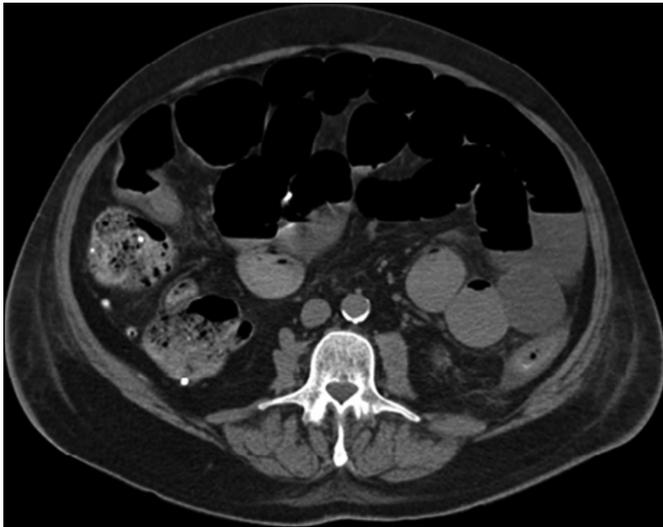


Figure 1. CT scan showing severely distended loops of the small bowel with air-fluid levels.

Laboratory studies were significant for white blood cell count 15.3 K/uL with 19% bands, sodium 129 mmol/L, anion gap 21, bicarbonate 19 mmol/L, creatinine 2.61 mg/dL, and lactate 5.9 mmol/L. Computed tomography (CT) scans of the abdomen and pelvis revealed diffuse bowel wall thickening of the descending colon, sigmoid colon, and rectum, with mesenteric stranding and paracolic fluid. The patient was given empiric intravenous levofloxacin and metronidazole for presumed infectious colitis.

On hospitalization day 2, *C. difficile* toxin polymerase chain reaction was found to be positive. Intravenous therapy was transitioned to oral vancomycin at an initial dose of 125 mg orally every 6 hours. Although repeat abdominal CT demonstrated an improvement in bowel wall thickening, distended loops of small bowel, consistent with ileus, were now noted (Figure 1). The patient required escalation of opioid medication to control severe back pain from the accident. A single dose of methylaltraxone was given to alleviate opioid-induced bowel stasis, resulting in a bowel movement with relief of abdominal distention on hospital day 5. Despite maintenance therapy with polyethylene glycol, the patient experienced recurrent distention and underwent flexible sigmoidoscopy on hospital day 9 to evaluate treatment efficacy. Pseudomembranes on the sigmoid colonic wall were noted (Figure 2), and the oral vancomycin dose was increased to 500 mg orally every 6 hours. Though the patient remained afebrile with improvement of leukocytosis and lactic acidosis, his abdominal distention and constipation persisted. An abdominal radiograph revealed persistent dilated bowel loops. Due to ongoing lower back pain, the patient refused daily rectal vancomycin enemas 4 times.

On hospital day 12, twice daily 5 g oral SBI therapy was initiated. Subsequently, the patient experienced significant, rapid



Figure 2. Pseudomembranes visible on flexible sigmoidoscopy.

improvement in symptoms. His abdominal distention improved quickly, and over the next 4 days his stool consistency and frequency returned to normal. Nearly complete resolution of abdominal symptoms was noted by hospital day 16 (Figure 3). He was discharged on hospital day 19 and followed up with gastroenterology 2 weeks later, showing continued improvement.

DISCUSSION

C. difficile is a bacterium known to cause colitis, with an estimated mortality rate of 6.5% in both non-severe and severe infections.⁹ Since 2003, CDI has increased in



Figure 3. Post-treatment improvement of bowel loop distention.

severity and has become more refractory to therapy.¹⁰ Historically, the treatment of CDI has been pharmacologically centered. However, nonantibiotic treatment for refractory, complicated cases have evolved and include fecal bacteriotherapy, probiotics, surgery, and monoclonal antibodies against *C. difficile* toxins.^{11,12}

SBI is a newer nonantibiotic therapy. This plasma protein concentrate is approved by the U.S. Food and Drug Administration and is marketed as a “medical food.”¹³ Oral preparations of SBI are safe when administered in doses up to 20 g/d and are available by prescription.¹⁴ Routine follow-up is suggested to monitor for side effects. The most common complaints include mild nausea, constipation, stomach cramps, headache, and polyuria.³

In vitro, the mechanism of action of SBI occurs through immunoglobulin binding of antigens and subsequent inhibition of antibody-antigen translocation across damaged epithelium via steric exclusion. A reduction in inflammatory cytokine production was seen in this same model, secondary to antigen binding and immune exclusion.¹⁵ Similarly, multiple murine trials show a significant reduction in proinflammatory cytokines, resulting in a decreased incidence of mucositis and colitis.^{4,16} In patients with inflammatory bowel disease who previously failed conventional therapy, co-administration of SBI contributed to symptomatic improvement.⁵ In the setting of *C. difficile*, SBI specifically binds and neutralizes endotoxins A and B, reducing their cytotoxic effects.¹⁷

In our patient, despite significant improvement after the initiation of SBI, it is probable that the clinical response was multifactorial. Resolution of opioid-induced stasis, in conjunction with improved antibiotic efficacy, could have contributed to the outcome. However, the rapid improvement after the initiation of SBI late in the course of disease should not be overlooked and prompts a more thorough study of the efficacy of SBI.

To our knowledge, this is the first reported case of adjunctive use of SBI in a patient presenting with clinically severe CDI with ileus. Although encouraging results have been demonstrated with murine models, the successful utilization of SBI in a human represents a promising addition to the armamentarium of CDI treatment.

DISCLOSURES

Author contributions: All authors approved the final version of the manuscript. S. Ferm, N. Varadi, and C. Fisher wrote and edited the manuscript. E. Gutkin supervised the manuscript process. C. Fisher is the article guarantor.

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Informed consent was obtained for this case report.

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