



C. difficile Infection (CDI) Unresponsive to Antibiotics Resolved by Co-Administration of Serum-Derived Bovine Immunoglobulin/protein Isolate, a Nutritional Support Product: A Case Study



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Abstract

A patient was admitted to the hospital with her first episode of pseudomembranous colitis (PMC) and *C. difficile* infection (CDI). She was unresponsive to standard antibiotics until co-administration of serum-derived bovine immunoglobulin/protein isolate (SBI). This case suggests nutritional therapeutics, such as SBI, can be useful and safely administered with antibiotics for CDI.

Abbreviations: CDI: *C. difficile* Infections; PMC: Pseudomembranous Colitis; SBI: Serum-Derived Bovine Immunoglobulin/Protein Isolate; IVIG: Intravenous Immunoglobulin; PO: By Mouth; BID: Two Times Per Day; PRN: As Necessary; FBD: Fecal Bacteriotherapy

Introduction

Clostridium difficile infections (CDI) arise primarily from the widespread administration of antibiotics, resulting in short and long-term shifts in gut microbiota structure and metabolic function, which leads to a loss in colonization resistance [1-4]. Antibiotics disrupt the commensal colonic flora, providing a niche for *C. difficile* to multiply and exude toxins which bind to receptors on intestinal epithelial cells leading to inflammation and diarrhea [5]. Thus, the humoral immune system is also implicated in a patient's susceptibility to CDI [6-9].

This case reports a patient who was admitted to the hospital and presented with multiple, mucoid bloody stools. A colonoscopy revealed pseudomembranous colitis and stool samples confirmed strong presence of *C. difficile* toxins. The patient was unresponsive to standard antibiotics alone and she did not have improved symptoms until orally-administered immunoglobulins were added to her therapeutic arsenal. The oral immunoglobulin, serum-derived bovine immunoglobulin/protein isolate (SBI), is a prescription medical food product intended for use to manage chronic diarrhea and loose stools under medical supervision. Enteropathies, like *C. difficile* infection, result in

a distinctive nutritional requirement for SBI which cannot be met by other dietary means [10]. This case exemplifies how oral immunoglobulins are promising nutritional therapeutics for use in enteric infection due to their multifaceted mechanism which includes binding to microbial components, maintaining proper immune balance in the digestive tract, managing gut barrier function and increasing nutrient utilization [11]. Recent *in vitro* evidence demonstrates that SBI binds and neutralizes toxins A and B including hypervirulent strains of *C. difficile* (027, 078 and 087) [12]. SBI may also provide nutritional support for deficient metabolites that have occurred during CDI infection [11-14]. SBI may also aid in the restoration of colonization resistance by microbiota reconstitution, since there is preliminary evidence in other patient groups but which still needs to be shown in CDI [15]. Hence, SBI therapy may represent a safe and effective addition nutritional support product in combination with antibiotics for enteric infections.

Case, Diagnosis, Outcome and Follow-Up

A 77-year-old female was admitted to the hospital presenting with explosive watery mucoid and bloody diarrhea. A colonoscopy

the following day revealed severe pseudomembranous colitis, from the rectum to the cecum, and the stool assay was strongly positive for *C. difficile* toxin indicative of CDI. The patient was initially placed on metronidazole 500mg P.O. QID, but failed to show any clinical improvement after 4-5 days. Colesevelam was added to her medical regimen and her antibiotic switched to vancomycin 250mg P.O. QID in place of the metronidazole. After approximately 3-4 days, the patient was still having as many as 10-12 mucoid diarrhea episodes with smaller amounts of blood. Serum-derived bovine immunoglobulin/protein isolate (SBI), 5g BID (equivalent to two packets per day) was added to the medical regimen and within 48 hours she had formed stools, there was no further mucus, and the malodor experienced with her CDI vastly improved. The patient was then discharged home within 48 h to complete her course of vancomycin, 14 days total, while continuing on SBI. The patient was seen 3 days after completing her vancomycin and was still using SBI (5g BID) and cortisone (PRN) suppositories. Patient reported soft formed stools with occasional loose mucoid stools, but no bleeding. Additionally, patient reported no further cramps and no malodor to her stool. Patient was advised to continue SBI (5g BID), probiotics (*L. acidophilus*, BID) and cortisone (PRN) suppositories for a minimum of four additional weeks, with a follow-up visit scheduled for six weeks. Medical history included: paraesophageal hernia repair, right knee arthroscopy and hysterectomy. At the time of hospitalization, reported comorbidities were: hypertension, osteoarthritis, thyroid disease and depression. The patient reported taking the following medications: acetaminophen q6h PRN, clonidine 0.1mg BID, gabapentin 200 mg BID, pantoprazole 40mg BID, levothyroxine 75mcg QD, metoprolol succinate 25mg QD, trazodone 50mg QHS and venlafaxine 75mg QD.

At a second follow-up visit, patient was still using SBI (5g BID), probiotics *L. acidophilus* (BID) and cortisone (PRN) suppositories. Patient stated that she has only occasional semi-formed bowel movements, but without increased frequency on the average of once every two weeks. When asked, patient reported that her bowel movements range between a Bristol Scale Stool score of 1 to 3 (separate hard lumps to like a sausage but with cracks on its surface), occasionally a type 4 (like a sausage, smooth and soft), indicating formed to loosely formed stools [16,17]. Patient also reported passage of some mucus "once a week or so" -but according to the patient the malodor she experienced previously with *C. difficile* infection had completely resolved. Patient was advised to continue SBI (5g BID) for an additional three weeks and a final 6-week follow-up visit was scheduled. At this last visit, patient reported complete resolution of any diarrhea with no bleeding. She reports soft, formed stools daily, still taking SBI (5g BID), probiotics *L. acidophilus* (BID) and cortisone (PRN) suppositories. Patient completed the last 3-4 days of her SBI (5g, BID) regimen and is not currently scheduled for any follow-up visits.

Discussion

The use of nutritional intervention to aid in the management of chronic loose and frequent stools which arise from CDI infection has been used as an intervention previously with bovine-derived whey protein containing anti-*C. difficile* immunoglobulins [18,19]. Human IVIG administered intravenously has also been used for CDI providing positive patient outcomes, but remains too expensive to become routine practice [20]. This case presents the use of a medical food product, SBI, which is intended for use to manage chronic loose and frequent stools under physician supervision.

In this case history, within 48 hours of adding nutritional, oral immunoglobulin therapy (SBI 5g BID) to the regime of vancomycin 250mg P.O. QID and colesevelam, the patient had formed stools, decreased malodor and mucus. This patient had already been in the hospital for approximately nine days, with no improvement during the first 4-5 days on metronidazole 500mg P.O. QID and no improvement 3-4 days after switching to vancomycin 250mg P.O. QID and inclusion of colesevelam. The addition of SBI resulted in improved stool consistency, and decreased frequency as well as mucus and malodor over 48 hours that ultimately resulted in patient discharge from the hospital. The patient continued vancomycin for 14-days and SBI for approximately 14 weeks. During routine follow-up visits, she continued to report improvement in stool consistency, decreased frequency, and decreased mucus and complete resolution of malodor and bloody stools. This may be due to the immunoglobulins present in SBI binding to *C. diff* toxins A and B, thereby blocking damage to enterocytes as well as its effect on diarrheal symptoms which have been found in irritable bowel syndrome with diarrhea and HIV-associated enteropathy [14,21]. It is known that SBI binds to and neutralizes *C. difficile* toxins A and B from hypervirulent ribotypes 078, 027 and 087 *in vitro* and protects vero cells from the cytotoxic effect of these toxins A and B [12]. In particular, strain 027 has been shown to have increased toxin production and is associated with mortality in a recent meta-analysis [22,23]. Finally, *in vivo* mouse models have illustrated that SBI reduced the CDI mortality in states of malnutrition [24].

Various studies have illustrated that lost colonization resistance can be restored by reintroducing non-toxicogenic *C. difficile* (NTCD) strains at a level sufficient to outnumber the toxigenic strains [25,26]. This therapy is currently in phase 2 clinical trials (VP20621) to prevent recurrence of CDIs [27]. Unfortunately, it was recently illustrated that NTCD can become toxin producers through horizontal gene transfer of toxins A and B [28]. Over time, the re-introduced non-toxic strains could become toxigenic; therefore, this treatment method has long-term downstream caveats that might not be realized during standard clinical trial timelines. A meta-analysis of 23 randomized controlled trials deemed that there was moderate quality evidence to use probiotics as prophylactic against CDI

or recurrent CDIs [29] and the use of *S. boulardii* adjunctively to treat recurrent CDIs also has moderate evidence [30].

Another way to restore colonization resistance is by repopulating the gut microbiota through fecal transplants, or fecal bacteriotherapy (FBT). This is primarily used in recurrent CDIs, when other options have been exhausted. FBTs have high success rates for recurrent CDIs, however, a recent meta-analysis of recurrent CDI therapeutics qualified most fecal bacteriotherapy (FBT) studies as low quality studies [30]. There is a “synthetic stool” in development which consists of 62 difference bacterial isolates, this would replace the use of donor feces in FBT and had promising results in a pilot study [31]. Susceptible host humoral immune system is also implicated in the pathophysiology of CDIs [6-9]. As such, there is a *C. difficile* toxoid vaccine (ACAM-CDIFF) vaccine in phase 3 clinical trials [32]. Once a patient has presented with a CDI, however, the humoral immune system can be augmented by passive immunity strategies. Currently in phase 3 clinical trials, there are human monoclonal antibodies specific for *C. difficile* toxin A (MK-3415), *C. difficile* toxin B (MK-6072) and *C. difficile* toxins A and B (MK-3415A) [33]. This is an example of directed systemic passive-immunity, using monoclonal antibodies against *C. difficile*, but not enteric passive-immunity. IVIG remains expensive so broad adoption in CDIs is limited by the poor quality of the studies [15] and cost [20].

Patients who are hospitalized with CDI infections are more than 2.5 times more likely to die in the hospital than other patients [34]. This patient was admitted to the hospital, presenting with a severe case of CDI and pseudomembranous colitis. She was unresponsive to standard antibiotic therapies until SBI, a non-probiotic medical food specially formulated to contain >50% bovine IgG, was added to the therapeutic arsenal. Antibiotics have been shown to alter the gut metabolome to a nutritional environment which favors *C. difficile* proliferation to include: increased primary bile acids and sugar alcohols with decreased secondary bile acids, glucose, free fatty acids and dipeptides [5]. The direct alterations to gut metabolome after SBI administration have not yet been studied; however, other studies suggest SBI ingestion may alter the gut microbiota [15]. Overall, the purpose of this case report is to demonstrate the potential utility of nutritional therapeutics in the overall management of CDI patients.

Disclosures

Bruce P Burnett is an employee of Entera Health, Inc.

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