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CASE REPORT

Post-Infectious Irritable Bowel Syndrome with Functional Diarrhea Following C. difficile Infections: Case Studies of Responses Using Serum-Derived Bovine Immunoglobulin

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ABSTRACT

Introduction: Post-infectious irritable bowel syndrome with diarrhea (PI-IBS-D) may occur after any number of enteric infections. Because these patients tend to experience chronic loose and frequent stools, serum-derived bovine immunoglobulin/protein isolate (SBI) was considered for the management of two patients with IBS-D following recurrent *Clostridium difficile* infections (CDI). Furthermore, *C. difficile* toxin binding has been described in an animal model which added to the consideration for its use in two challenging cases. SBI is a prescription medical food intended for the management of chronic loose and frequent stools in patients with IBS-D, inflammatory bowel disease (IBD) and HIV-associated enteropathy.

Case Presentations: Both patients were treated for relapsing CDI and eventually cleared. Despite negative retesting for *C. difficile*, a 39-year old Caucasian female patient developed persistent diarrhea in the setting of intolerance to common therapies. The severity of her condition led her to file for disability. Within two weeks of starting SBI 5 g QID, her frequent loose stools were completely managed but returned upon discontinuation. SBI was restarted resulting again in complete management of frequent loose stools. She now continues on SBI 5g QD and has returned back to work. The second patient, a 57-year old Caucasian female, experienced ongoing diarrhea with alternating bouts of constipation after clearance of her recurrent CDI. Upon use of SBI 5g BID, she noticed better management within a few days. Therapy was reduced to SBI 5g QD to avoid possible constipation and she reports regulation of her bowel habits.

Discussion: These cases highlight specific symptoms that result from *C. difficile*-associated PI-IBS, the management that SBI can provide when considered an option for therapy, and the impact disease manifestations can have on quality of life. These cases further suggest the need for additional study of this nutritional agent in post-*C. difficile* infectious IBS patients.

Key words: Irritable Bowel Syndrome; Diarrhea, Post-Infectious; Serum-derived; Immunoglobulin; IgG; Bovine; Medical Food

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INTRODUCTION

Irritable bowel syndrome (IBS) has been defined by the presence of abdominal pain in association with an alteration of bowel habits[1,2]. Stool consistency is part of diagnosis and determines whether the patient's IBS is with constipation (IBS-C), diarrhea (IBS-D), or mixed (IBS-M). The symptom classification of IBS has been defined as a functional bowel disorder, and more recently as an inflammatory disease[3,4]. While IBS is a common disorder noted in 9-22% of the population[5], post-infectious IBS (PI-IBS) may occur in up to nearly a third of gastroenteritis patients and these patients exhibit symptoms

similar to IBS-D[6-8]. Debate continues on the specific causes of IBS but there is growing evidence that IBS may be triggered by a number of issues including bouts of infectious enteritis, low grade inflammation, epithelial permeability, and altered gut flora, though the specific mechanisms are still being investigated[6-10].

IBS can have a detrimental impact on patient quality of life. Compared to patients with gastroesophageal reflux disease (GERD), IBS patients have significantly greater impairment in the ability to carry out daily living activities and work activities leading to greater loss of work[11]. IBS patients often suffer from other comorbidities such as anxiety, depression, fibromyalgia, migraine headaches, interstitial cystitis and temporomandibular joint syndrome[2]. The impact from changes in quality of life and activities of daily living results in an estimated annual economic burden of $25-50 billion[2,9].

The management of IBS is dependent upon the symptoms. For those with diarrhea, the effort is to generally address or manage the abdominal symptoms (pain and discomfort) and bowel symptoms (loose stools, frequency, urgency, incontinence, and bloating). For years, tricyclic antidepressants have been used to help target pain and take advantage of the side effect of constipation to help address stool consistency[12]. Alosetron, a 5HT3 antagonist, was approved for women with severe IBS-D because serotonin has been shown to affect motility and pain, but the side effect profile has limited use of the product[13,14]. Rifaximin, an oral antibiotic, has demonstrated some potential for some IBS-D patients[15,16]. FODMAP diets help address discomfort, bloating and flatulence by minimizing the ingestion of certain sugars and vegetables[17]. SBI (EnteraGam) is a prescription medical food product intended for the clinical dietary management of patients with chronic loose and frequent stools who have a limited or impaired capacity to ingest, digest, absorb, or metabolize certain nutrients used under physician supervision[18], and specifically for patients with IBS-D[19], IBD[18], or HIV-associated enteropathy[20].

METHODOLOGY AND CASES

Consideration for the Use of SBI Therapy

SBI was considered in these two cases where the patients presented with PI-IBS-D following a *C. difficile* infection (CDI) based upon several factors including indication for patients with IBS-D[19], mechanism of action[21], microbial binding[22-24], and general clinic practice experience. Antibiotic therapy is a major cause of antibiotic-associated diarrhea and results in increased risk for CDI as well as persistent concurrent alteration of gut flora[25]. There are no specific treatment options for PI-IBS so treatment was based upon the primary symptoms. However, there are potential side effects and implications for the masking of CDI relapses which can limit the options for PI-IBS patients with diarrheal symptoms (Table 1).

Animal models with SBI have noted binding to several bacterial toxins[21]. In particular, SBI *in vitro* specifically binds to and neutralizes *C. difficile* toxins A and B[22-24]. In an HIV population, SBI demonstrated a decrease in Clostridium bacteria over an eight week period[25].

The mechanism of action of SBI is postulated to involve binding to microbial components, maintaining immune balance in the gastrointestinal tract, restoring normal expression of tight junction proteins including Claudin-1 (Figure 1) which assists in managing gut barrier function and improving nutrient uptake[21]. Clinical studies have demonstrated that SBI is safe and improves gastrointestinal symptoms (e.g., chronic loose and frequent stools, abdominal discomfort, bloating, and urgency) in patients with IBS-D[19] and HIV-associated enteropathy[20]. SBI is a specially-formulated protein source consisting of >90% protein of which >50% is immunoglobulin G (IgG)[18]. Approximately 25-50% of orally administered IgG survives digestion in the stomach and small intestine[18].

In clinical practice, SBI has been used in numerous patients as a therapeutic option to help manage chronic loose and frequent stools in patients as well as patients with IBS-D[26,27]. While SBI may not be effective in all patients, clinical experience would suggest that SBI is safe and effective in many patients with chronic loose and frequent stools. Given the challenges of these two cases, SBI was considered as an option for the management of the patients' condition.

Table 1 Medication Complication for PI-IBS and CDI.

Medication	Complication for PI-IBS or CDI
Alosetron	Ischemic colitis , severe constipation , may mask CDI
Cholestyramine	Bloating and constipation
Low FODMAP diet	Low energy, poor diet
Bismuth subsalicylate	Bismuth toxicity long term
Rifaximin	Altered flora and cost, not indicated for treatment
Loperamide	May mask CDI
Diphenoxylate/atropine	May mask CDI

Case Presentation #1

This case involves a 39-year old, 5 foot-5 inch, 120 pound (BMI - 20.0) Caucasian female diagnosed with PI-IBS following several relapses with CDI. Her medical history is notable for antiphospholipid antibody syndrome (APS), methylenetetrahydrofolate reductase (MTHFR) homozygous, and HSV-1. Her surgical history includes a cholecystectomy after her first CDI.

The patient initially presented in January 2014 with abdominal discomfort and multiple episodes of bloody diarrhea. A CT scan was negative and a colonoscopy with biopsies and stool aspirates revealed no ulcers or pseudomembranes but biopsies were positive for focal active colitis. Stool aspirates confirmed CDI by PCR. A 10 day course of fidaxomicin 200 mg po BID was started which resulted in a cessation of the rectal bleeding and normally formed stools. Two weeks later she complained of abdominal pain and diarrhea but no blood in her stool. She was treated empirically with vancomycin (125 mg po QID) for 10 days, recovered, but developed abdominal pain related to acute cholecystitis and underwent a cholecystectomy. She developed diarrhea 2 weeks after discharge and recurrent CDI was confirmed by PCR where she was treated with fidaxomicin (200

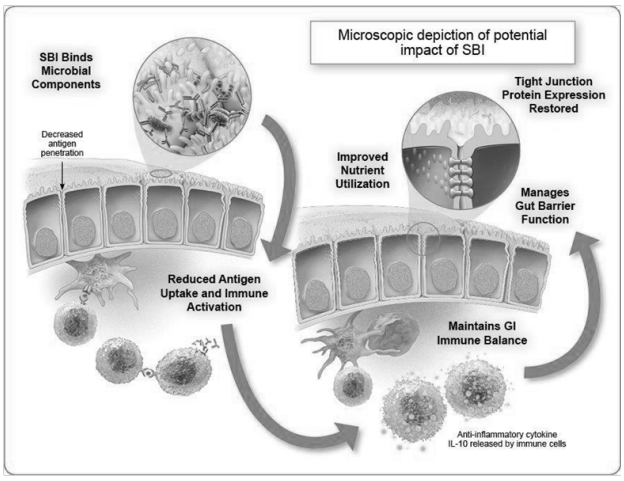

Figure 1 Postulated Mechanism of Action of Serum-derived Bovine Immunoglobulin.

mg po BID) for 10 days. Although her symptoms resolved while on antibiotic therapy, her abdominal discomfort and diarrhea returned days later despite a negative follow-up PCR for *C. difficile*. She was given cholestyramine (1 packet BID – QID) for possible bile acid induced diarrhea post-cholecystectomy, but stopped due to significant abdominal discomfort and bloating. A post cholecystectomy (low fat) diet made no clinical change. Anti-diarrheals made her constipated and were avoided to prevent masking of possible recurrent CDI. She was diagnosed with PI-IBS, and due to the severity of her condition, she was unable to work and filed for disability. SBI was considered at this point as a therapeutic option for management of her PI-IBS which included symptoms of abdominal discomfort and pain as well as chronic loose and frequent stools.

Case Presentation #2

The patient is a 57 year old Caucasian female diagnosed with possible PI-IBS following initial flu-like symptoms and several relapses with *C. difficile* infection. She weighs 214 pounds with a BMI of 34.72 kg/m^2. Her concurrent medical history includes hypothyroidism, high cholesterol, neuropathy, appendectomy, hysterectomy, cervical fusion, total knee replacement, angioplasty for coronary artery disease x 3, and idiopathic gastroparesis. Concurrent medications included levothyroxine, furosemide, duloxetine, pravastatin, and aspirin. For the patient's immediate issues, her history provided a detailed summary of the events leading to her office visit for possible PI-IBS. In December 2013, she was treated by her primary care provider for flu-like symptoms which developed into wheezing and possible pneumonia with antibiotics. Five days later she developed diarrhea (7 watery bowel movements/day) with mucus and blood. Her symptoms persisted for nearly 2 months until she was seen at an outside emergency department and sent home with ciprofloxacin and metronidazole. After one day her symptoms worsened and she was hospitalized and treated with metronidazole and vancomycin (125 mg po QID) for a positive *C. difficile* infection. After 5 days, she was discharged with a 10 day course of metronidazole (500 mg po TID). Approximately one week later, she was readmitted for dehydration and continued on vancomycin (125 mg po QID) for a positive CDI and discharged 3 days later on vancomycin (125 mg liquid po QID). At her office visit (March 2014), she was feeling better and was negative for *C. difficile* toxins. Approximately 4 days later (April 2014), she developed nausea and bloody diarrhea similar to her prior CDI. She was started on fidaxomicin for 10 days after which blood in her stool resolved but her diarrhea had only moderate improvement. A week later she developed alternating diarrhea and constipation. At the end of April 2014, she was seen at this office and diagnosed with PI-IBS given her prior history with alternating bowel habits, and current laboratory findings: normal thyroid studies, negative celiac serologies, negative *C. difficile* PCR, stool cultures, fecal leukocytes, ova and parasites. Anti-diarrheals were avoided in the setting of a history of recent recurrent CDI. Dietary changes made no difference and she could not tolerate a low FODMAPs diet. She was considered for SBI therapy to help manage her PI-IBS condition which included chronic loose and frequent stools.

RESULTS

Case #1

In May 2014, the patient was started on SBI (EnteraGam^{TM}) 5 g QID for two weeks and within 48 hours her frequent loose stools had resolved. However, approximately one week after stopping the SBI her diarrhea returned. Since her repeat *C. difficile* PCR was negative, SBI was restarted again resulting in complete management of frequent loose stools and abdominal discomfort. Given the management of her PI-IBS-D, the patient continued the use of SBI 5g BID and was able to return to work and get off disability. SBI therapy has been reduced to a maintenance dose of SBI 5g QD a month later with ongoing management of the patient's PI-IBS-D and no further relapses in *C. difficile*. The goal is to wean off SBI therapy over time.

Case #2

At the end of April 2014, she was started on SBI (EnteraGam^{TM}) 5 g BID initially for 2 weeks. Within a few days she noticed better management of her condition. At the end of May 2014, she developed a urinary tract infection where she was treated with metronidazole given her history for CDI and continued on SBI 5 g BID. Since she indicated that she had some constipation, her SBI was reduced to 5 g/day to avoid the potential for constipation. She continues to report normal regulation of her bowel habits and her SBI therapy continues at 5 g/day prn for the ongoing maintenance of her PI-IBS-D.

DISCUSSION

Irritable bowel syndrome has been attributed to many triggers with numerous studies suggesting that up to one third of IBS-D cases result from a prior bacterial infection including *C. difficile*[4,6]. IBS can also have a detrimental impact on patient quality of life leading to impairment of activities of daily living and loss of work[9]. The patients from these two case studies are representative of a PI-IBS subset of this population. Following relapsing episodes of CDI, the first patient experienced significant ongoing diarrhea despite resolution of the infection leading to the patient filing for disability. Following unsuccessful attempts to control the PI-IBS-D, the patient was eventually started on SBI which was able to modulate the patient's condition. Essentially, SBI improved the patient's quality of life and allowed her to return to work. For the second patient, there was a significant effort to get the patient's relapsing CDI under control and SBI was able to completely manage the patient's PI-IBS symptoms. In both cases, the use of SBI was able to completely manage the patient's PI-IBS symptoms which included chronic and frequent loose stools as well as abdominal discomfort, allowing the patients to have normal bowel habits and improved quality of life.

PI-IBS and functional diarrhea related to CDI is a unique entity because CDI has an apparent built in recurrence rate. The risk of a CDI relapse is often a source for anxiety and PI-IBS symptoms may resemble a recurrent CDI episode making matters worse. As a result, patients may undergo multiple repeated stool testing, hospital admissions and unnecessary empiric antibiotic treatments which may further delay restoration of the flora, resulting in impaired colonization and dysbiosis. Anti-diarrheals such as loperamide and diphenoxylate/atropine should be used with extreme caution, if not avoided if possible, since it may mask a recurrence of CDI and has also been associated with increased morbidity and mortality in the setting of active CDI. Because SBI is intended for use to manage IBS-D[18] and has the added ability to bind to *C. difficile* toxins[22-24], it may have a valuable role in both the management of PI-IBS as well as binding of *C. difficile* toxins A and B if reinfection occurs. This may help normalize the gut environment to allow normal flora to outgrow *C. difficile*. The outcomes of both cases reported in this manuscript suggest that there is a distinctive nutritional requirement for SBI unique to patients with PI-IBS. SBI provides for distinct nutritional requirements in other enteropathies[29] as well and this has been illustrated in nutritionally deficient mice models of CDI[30].

For decades, medical foods have been used in hospital settings but

are also utilized under prescription use by patients at home through retail pharmacy. SBI is a specially formulated, immunoglobulin-enriched product that works through a multi-faceted mechanism of action, including binding endotoxins and other microbial components from bacteria such as *C. difficile*[22,23,30]. SBI has been shown to also neutralize hypervirulent ribotype toxins from *C. difficile* including 027A/B, 078A/B and 087B in cell assays[24]. Such mechanisms may help to stabilize microbiota, maintain a homeostatic immune environment in the intestine, manage gut barrier function, and promote increased nutrient metabolism and utilization with this nutritional agent[19,20,29]. Together, the mechanisms of SBI (Figure 1) may be effective in management of the chronic loose and frequent stools brought on by PI-IBS while helping to provide a normal microbiota environment which may help avoid recurrent *C. difficile* infections. The findings from these two cases indicate that further study is warranted into the beneficial effects of SBI on managing PI-IBS caused by *C. difficile* or other bacterial agents that may lead to PI-IBS.

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Authors Contributions: Dr. Crawford had full access to review and pull available data from the medical records. Dr. Crawford and Dr. Panas consolidated and analyzed the collected data. Dr. Panas developed and organized the draft manuscript. Dr. Crawford and Dr. Panas reviewed and approved the final manuscript.

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CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

REFERENCES

1 Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology* 2006; **130**: 1480-1491. [PMID: 16678561 doi: 10.1053/j.gastro.2005.11.061]

2 American College of Gastroenterology Task Force on Irritable Bowel Syndrome, Brandt LJ, Chey WD, Foxx-Orenstein AE, Schiller LR, Schoenfeld PS, Spiegel BM, Talley NJ, Quigley EM. An evidence-based position statement on the management of irritable bowel syndrome. *Am J Gastroenterol* 2009; **104(Suppl 1)**: S1-S35 [PMID: 19521341 doi: 10.1038/ajg.2008.122]

3 Spiller R, Lam C. The shifting interface between IBS and IBD. *Curr Opin Pharmacol* 2011; **11(6)**: 586-592. [PMID: 22000604 doi: 10.1016/j.coph.2011.09.009]

4 Stanisic V, Quigley EM. The overlap between IBS and IBD–what is it and what does it mean? *Expert Rev Gastroenterol Hepatol* 2014; **8(2)**: 139-145. [PMID: 24417262 doi: 10.1586/17474124.2014.876361]

5 Saito YA, Schoenfeld P, Locke GR III. The epidemiology of irritable bowel syndrome in North America: a systematic review. *Am J Gastroenterol* 2002; **97**: 1910-1915. [PMID: 12190153 doi: 10.1111/j.1572-0241.2002.05913.x]

6 Spiller R, Garsed K. Postinfectious irritable bowel syndrome. *Gastroenterology* 2009; **136**: 1979-1988. [PMID: 19457422 doi: 10.1053/j.gastro.2009.02.074]

7 Dunlop SP, Jenkins D, Spiller RC. Distinctive clinical, psychological, and histological features of postinfective irritable bowel syndrome. *Am J Gastroenterol* 2003; **98**: 1578-1583. [PMID: 12873581 doi: 10.1111/j.1572-0241.2003.07542.x]

8 Schwille-Kiuntke J, Frick J-S, Zanger P, Enck P. [Post-Infectious Irritable Bowel Syndrome-A Review of the Literature]. *Zeitschrift fur Gastroenterologie* 2011; **49(8)**: 997-1003. [doi: 10.1055/s-0031-1281581]

9 Ohman L, Simrén M. Pathogenesis of IBS: role of inflammation, immunity and neuroimmune interactions. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 163-173. [PMID: 20101257 doi: 10.1038/nrgastro.2010.4]

10 Zhou Q, Verne GN. New insights into visceral hypersensitivity--clinical implications in IBS. *Nat Rev Gastroenterol Hepatol* 2011; **8**: 349-355. [PMID: 21643039 doi: 10.1038/nrgastro.2011.83]

11 Locke GR, Clark S, Cerulli A, Marehbian J, Kahler KH, Shetzline MA. Work productivity is more impaired in functional gastrointestinal disorders compared to GERD: six-month data from PROGRESS [abstract 1052]. *Am J Gastroenterol* 2007; **102**: S504. [doi: 10.1111/j.1572-0241.2007.01491_10.x]

12 Clouse RE. Managing functional bowel disorders from the top down: lessons from a well-designed treatment trial. *Gastroenterology* 2003; **125**: 249-253. [PMID: 12851889 doi: 10.1016/S0016-5085(03)00808-4]

13 Krause R, Ameen V, Gordon SH, West M, Heath AT, Perschy T, Carter EG. A randomized, double-blind, placebo-controlled study to assess efficacy and safety of 0.5 mg and 1 mg alosetron in women with severe diarrhea predominant IBS. *Am J Gastroenterol* 2007; **102**: 1709-1719. [PMID: 17509028 doi: 10.1111/j.1572-0241.2007.01282.x]

14 Chey WD, Chey WY, Heath AT, Dukes GE, Carter EG, Northcutt A, Ameen VZ. Long-term safety and efficacy of alosetron in women with severe diarrhea-predominant irritable bowel syndrome. *Am J Gastroenterol* 2004; **99**: 2195-2203. [PMID: 15555002 doi: 10.1111/j.1572-0241.2004.30509.x]

15 Lembo A, Zakko SF, Ferreira NC. T1390 rifaximin for the treatment of diarrhea associated irritable bowel syndrome: short-term treatment lending to long- term sustained response. *Gastroenterology* 2008; **134**: A545. [doi: 10.1016/S0016-5085(08)62544-5]

16 Pimentel M, Park S, Mirocha J, Kane SV, Kong Y. The effect of a nonabsorbed oral antibiotic (rifaximin) on the symptoms of the irritable bowel syndrome: a randomized trial. *Ann Intern Med* 2006; **145**: 557-563. [PMID: 17043337]

17 Halmos EP, Power VA, Shepherd SJ, Gibson PR, Muir JG. A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. *Gastroenterology* 2014; **146**: 67-75. [PMID: 24076059 doi: 10.1053/j.gastro.2013.09.046]

18 Entera Health, Inc. (2015/02). EnteraGam Prescribing Information. [www.enterahealth.com]

19 Wilson D, Evans MD, Weaver E, Shaw AL, Klein GL. Evaluation of serum-derived bovine immunoglobulin protein isolate in subjects with diarrhea-predominant irritable bowel syndrome. *Clin Med Insights Gastroenterol* 2013; **6**: 49-60. [PMID: 24833942 doi: 10.4137/CGast.S13200]

20 Asmuth DM, Ma ZM, Albanese A, Sandler NG, Devarai S, Knight TH, Flynn NM, Yotter T, Garcia JC, Tsuchida E, Wu TT, Douek DC, Miller CJ. Oral serum-derived bovine immunoglobulin improves duodenal immune reconstitution and absorption function in patients with hiv enteropathy. *AIDS* 2013; **27**: 2207-2217. [PMID: 23660579 doi: 10.1097/QAD.0b013e328362e54c]

21 Petschow B, Burnett B, Shaw A, Weaver E, Klein G. Serum-derived bovine immunoglobulin/protein isolate: postulated mechanism of action for management of enteropathy. *Clin Exp Gastroenterol* 2014; **7**: 181-190. [PMID: 24904221 doi: 10.2147/CEG.S62823]

22 Warny M, Fatimi A, Bostwick EF, Laine DC, Lebel F, LaMont JT, Pothoulaki C, Kelly CP. Bovine immunoglobulin concentrate-

clostridium difficile retains C difficile toxin neutralising activity after passage through the human stomach and small intestine. *Gut* 1999; **44(2)**: 212-217. [PMID: 9895380]

23 Henderson AL, Detzel CJ, Horgan A, Chen X, Kelly CP, Weaver EM. Serum-derived bovine immunoglobulin/protein isolate enhances overall survival of Clostridium difficile infection accentuated by malnutrition. Advances in Inflammatory Bowel Disease, Orlando, FL, 4-6 December 2014.

24 Henderson AL, Horgan A, Detzel CJ, Maas KJ, Weaver EM. Serum-derived bovine immunoglobulin/protein isolate binds and neutralizes clostridium difficile toxins A and B. Digestive Disease Week, Chicago, IL, 2014. [doi: 10.1016/S0016-5085(14)61030-1]

25 Zilberbeg MA, Reske K, Olsen M, Yan Y, Dubberke ER. Risk factors for recurrent clostridium difficile infection (CDI) hospitalization among hospitalized patients with an initial CDI episode: a retrospective cohort study. *BMC Infect Dis* 2014; **14**: 306. [PMID: 24898123 doi:10.1186/1471-2334-14-306]

26 Asmuth DM, Strombaugh J, Ursell L, Ma ZM, Albanese A, Hodzic E, Troia-Canico P, Flynn NM, Yotter T, Miller CJ, Knight R. Changes in stool microbiota, bacterial translocation and mucosal immunity after oral serum-derived bovine immunoglobulin (SBI) administration. 20th Conference on Retroviruses and Opportunistic Infections (CROI), Atlanta, GA, 3-6 March 2013.

27 Hilal R, Mitchell P, Guerra Jr E, Burnett BP. Case series of 10 drug-refractory IBS patients who respond to oral serum-derived bovine immunoglobulin/protein isolate (SBI). *Open J Gastroenterol* 2014; **4**: 321-328. [doi:10.4236/ojgas.2014.410046]

28 Weinstock LB, Jaison, VS. Serum-derived bovine immunoglobulin/protein isolate therapy for patients with refractory irritable bowel syndrome. *Open J Gastroenterol* 2014; **4**: 329-334. [doi:10.4236/ojgas.2014.410047]

29 Petschow BW, Burnett B, Shaw AL, Weaver EM, Klein GL. Dietary requirement for serum-derived bovine immunoglobulins in the clinical management of patients with enteropathy. *Dig Dis Sci* 2015; **60**: 13-23. [doi: 10.1007/s10620-014-3322-0]

30 Weaver EM, Klein GL, DeVries BK, Maas KJ, & Shaw A. Endotoxin neutralization activity (ENA) of bovine plasma and bovine Immunoglobulin (IgG)-rich fractions as compared to human plasma. FASEB, Boston, MA, 2013. [doi: 10.1096/fj.1530-6860]

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