

## **Serum-Derived Bovine Immunoglobulin/Protein Isolate Therapy for Patients with Refractory Irritable Bowel Syndrome**

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Abbreviations: Irritable Bowel Syndrome (IBS), Diarrhea-Predominant Irritable Bowel Syndrome (IBS-D), Constipation-Predominant Irritable Bowel Syndrome-Alternating (IBS-C), Irritable Bowel Syndrome-Mixed (IBS-M), Lactulose Breath Test (LBT), Small Intestinal Bacterial Overgrowth (SIBO), Serum-Derived Bovine Immunoglobulin/Protein Isolate (SBI), three times per day (TID), two times per day (BID)

### **ABSTRACT**

**Background:** A small double-blind study showed benefit of serum-derived bovine immunoglobulin/protein isolate (SBI), for diarrhea-predominant irritable bowel syndrome (IBS-D). The purpose of this study was to assess safety and clinical outcomes of SBI in refractory IBS patients.

**Methods:** A retrospective review of 35 IBS patients with diarrhea or mixed diarrhea/constipation pattern (IBS-M) who were administered SBI 5 gm/twice daily was performed. Clinical response (“good response” or “no response”) and adverse events were determined by follow-up after four weeks of therapy. Patients were included for evaluation if a lactulose breath test (LBT) had been performed prior to SBI. All patients were refractory to common IBS therapies. The response rate to the inclusion of SBI was calculated in three separate groups: dividing patients based on their LBT results (positive or negative), dividing patients by their IBS diagnosis (IBS-D or IBS-M) and grouping all patients together.

**Results:** Analysis was carried out on 26 IBS-D/-M patients with LBT results. Two patients were lost to follow-up and were excluded from data analysis. The positive LBT group (N=11) had a 73% (p=0.117) positive response rate to SBI. The negative LBT (N=13) had a significant response rate of 77% (p=0.040). If patients were divided by IBS diagnosis or grouped together, the response rate to SBI was similar ranging from 69-75%. Adverse events leading to cessation of SBI occurred in 3/24 (12.5%) patients.

**Conclusion:** SBI appeared to be a safe and effective nutritional moiety in refractory IBS patients. Larger, double-blind studies are needed.

### **INTRODUCTION**

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder affecting 10-15% of adults (1). An estimated 28% of visits to gastroenterologists and 12% of visits to primary care offices are from patients with IBS (2). The pathophysiology of IBS is complex. Recently, gastrointestinal inflammation gut inflammation and altered gut microflora have been implicated (3, 4).

Therapeutic options are diverse and include: dietary modification, fiber supplementation, psychological therapy (counseling, hypnosis, relaxation, etc.) and pharmacological therapy (prescription drugs, over-the-counter medications, herbs and dietary supplements) (5). The number of FDA-approved medications indicated for IBS are limited. New algorithms for IBS therapy based on the role of bacterial overgrowth, in particular small-intestinal bacterial overgrowth (SIBO), have been proposed (6).

Serum-derived bovine immunoglobulin/protein isolate (SBI), an FDA-regulated medical food product, is composed of greater than 50% immunoglobulin and has been shown to survive the stomach environment and bind microbial components in the intestine, thereby neutralizing their effect in many different animal models (7). In a double-blind, randomized, placebo-controlled IBS-diarrhea (IBS-D) study, 10 gm of SBI per day was shown to statistically decrease the number of days per week in which patients experience: abdominal pain, flatulence, urgency, loose stools, bloating or any symptom (8). The microbial binding activity of SBI may have downstream effects in maintaining GI immune balance and managing gut barrier function, which ultimately leads to improved nutrient utilization. In addition to the gut microflora being a key player in the complex pathophysiology of IBS, it has recently been shown that IBS-D patients have abnormal tight junction proteins in the jejunal mucosa versus healthy adults (9). Thus, both the endotoxin binding and barrier function maintenance properties of SBI are particularly relevant in this patient population for nutritional management of their condition(s).

The purpose of this retrospective chart review is to assess IBS-patient response to the inclusion of a nutritional therapy, SBI, into their diet in a community gastroenterology practice. This chart review summarizes the response to 5 gm SBI twice daily administered over four weeks in patients who were first screened for SIBO using the lactulose breath test (LBT).

## METHODS AND MATERIALS

### Patient population

Initial IBS diagnosis of all patients in this chart review was based upon patient-reported symptoms and all patients were diagnosed by the same physician, using the Rome II criteria. The initial patient questionnaire asks the patient to identify bowel habit: “no problems,” “mainly constipation,” “alternating diarrhea and constipation,” and “mainly diarrhea.” The patient form also has a six-point scale (0 – not at all, 6 – a very great deal) assessing how bothersome the following symptoms are to patients: abdominal discomfort, abdominal bloating and flatulence/lower gas. Finally, patients are asked whether or not the discomfort has occurred at least 3 months per year. If a patient was diagnosed with either diarrhea-predominant IBS (IBS-D) or mixed diarrhea/constipation pattern (IBS-M) from this questionnaire, a lactulose breath test (LBT) was performed to screen for SIBO. At a routine four-week follow-up, the patients were seen in the office for follow up and when this did not occur, the office nurse called patients to assess progress. Since the follow-up does not consist of the same questionnaire, this data is not reported. Only patients who had the LBT performed prior to adding SBI into their diets were included in this review.

All LBT were performed using the QUINTRON Breath Tracker HC. A positive lactulose hydrogen breath test (LBT) is considered 20 ppm over the basal amount of breath hydrogen, at or before 90 min of ingesting lactulose. Methane excretion of 3 ppm or more was determined to be clinically significant and two antibiotics were administered if both hydrogen was abnormal and methane was present.

### Data Extraction and Analysis

Inclusion criteria for this chart review were: diagnosis of IBS with either diarrhea or mixed diarrhea/constipation pattern (IBS-D/-M) according to Rome II criteria, pre-therapeutic results from LBT and patients ingesting 5 gm SBI BID for four weeks. Of 35 potential IBS patients, 26 patients fulfilled those criteria and were divided into two groups: patients who either had a positive LBT (+LBT) or those with negative LBT (-LBT) prior to any therapy. Prior to being placed on SBI, all patients with a positive

LBT were first placed on a 14-day course of 550 mg rifaximin TID with or without metronidazole or neomycin. Many of these patients were then placed on a variety of other common IBS treatments including: tricyclic anti-depressants, loperamide, anticholinergics and diet modification (FODMAP). If there was an incomplete response after these therapies they were prescribed SBI as a nutritional moiety. All patients who initially had a negative LBT and who had failed conventional IBS treatments (FODMAP diet, probiotics, tricyclic anti-depressants and/or alosetron) were placed on 5 gm SBI BID for four weeks. From each group, one patient was lost to follow-up. For data analysis, these patients were not included in the total sample size or analysis. The primary goal of this report is to assess patient satisfaction and response to SBI so patients were categorized as either “good response” or “no response” within their LBT groups. This outcome was asked and recorded in patient’s chart as standard-of-care in the clinicians practice (LW) at a four-week follow-up interval.

Since the previous clinical trial of SBI was only in IBS-D populations and not IBS-M, the same patients were removed from the LBT groups and re-grouped as either IBS-D or IBS-M. The clinical response rate was then calculated in each of these populations regardless of their LBT results. Finally, all patients were grouped together and a broad response rate was calculated.

Overall, the percentage of patients who responded to SBI was calculated within either their LBT group, their IBS category (IBS-D or IBS-M) or the entire patient group. A one-sample t-test between the percentages of “good response” versus “no response” within both groups was used to determine if patient outcomes were significant.

## RESULTS

Twenty four patients were included in this retrospective chart review. Table 1 outlines the patients as organized by the LBT outcomes, either positive or negative. In the positive LBT group, the number of patients who had failed common therapies was as follows: rifaximin (10), low dose naltrexone (4), tricyclic antidepressants (3), probiotics (4), neomycin (3), metronidazole (3), ampicillin (1), Imodium (1), linaclotide (1) and FODMAP diet (1). In the negative LBT group, the number of patients who had failed common therapies was as follows: rifaximin (8), low dose naltrexone (4), probiotics (4), neomycin (4), metronidazole (1), trimethoprim/sulfamethoxazole (1), tricyclic antidepressants (3), SSRI (1), linaclotide (2), cromalyn (1), alosetron (1), colestipol (1), bismuth (1) and gluten-free diet (2).

The percentage of patients who responded positively to the inclusion of SBI into their diets was high for all patient groups. The positive LBT group (N=11) had a response rate of 73%,  $t(10) = 1.718$ ,  $p=0.117$  and the negative LBT group (N=13) had a significant response rate of 77%,  $t(12)=2.31$ ,  $p=0.040$  (Table 1). If patients were separated by their diagnosis, a similar high-response rate was noted. IBS-D patients (N=16) had a 69% response rate,  $t(15)=1.64$ ,  $p=0.121$  and IBS-M patients (N=8) had a significant response rate of 88%,  $t(7)=3.2$ ,  $p=0.015$ . When all patients were pooled (N=24), the response rate of 75% was significant with  $t(23)=2.83$ ,  $p=0.010$ .

The adverse events included constipation, diarrhea and nausea and led to cessation of therapy in 3/24 (12.5%) of patients. These adverse events were short-lived and self-limited.

## DISCUSSION

The data presented shows positive clinical response from this patient population to the inclusion of 5 gm SBI BID over four weeks as a nutritional therapy. Whether patients were divided by LBT outcome,

initial IBS diagnosis, or pooled together, the response rate was between 69-75%. The LBT group was composed of two groups: either IBS-D/-M patients with positive LBT who were refractory to rifaximin therapy and other IBS therapies, with an SBI response rate of 73% ( $p=0.117$ ), or IBS-D/-M patients with negative LBT who were also refractory to common IBS therapies had a significant response rate of 77% ( $p=0.040$ ). Although the former group did not obtain statistical significance, both groups have a similar response rate. When patients were divided by diagnosis, IBS-D patients had a 69% response rate ( $p=0.121$ ) and IBS-M patients had a significant response rate of 88% ( $p=0.015$ ). This suggests that SBI might be useful for IBS-M, yet the clinical trial of SBI was only conducted in IBS-D populations (8). When lumped together, the clinical response rate to the inclusion of SBI as a nutritional therapeutic for these intractable IBS-D/IBS-M patients was statistically significant at 75% ( $p=0.010$ ). The statistical variation observed in this small case analysis between groups suggests a need for a larger and well-powered study to examine this particular population the LBT positive group of IBS-D and -M subjects.

This is the first formal report of a clinical response to using SBI in IBS-D/-M patients with a positive LBT, an indication of SIBO, who were refractory to antibiotic therapy and other common IBS therapies. The patients with a negative LBT had also failed previous therapies and had a statistically significant response rate to SBI. The reason that patients are grouped into their pre-therapeutic LBT outcomes is because this is the only objective measurement a clinician can use in IBS patients. This is also the first formal report of a significant response rate to SBI in IBS-M patients. However, by regrouping patients into their IBS diagnosis (IBS-D or IBS-M) and disregarding their LBTs, the outcomes lack any objective variables. The same can be said regarding the statistically significant response rate of 75% when all patients were grouped together. Nonetheless, all patients had intractable IBS-D/-M, illustrating that SBI could be useful in refractory patients. This clinical study presents general clinical data that is supportive the finding of the double-blind pilot study of SBI in IBS-D, which illustrated improvements in the number of days per week that patients reported loose stools, abdominal pain, flatulence, urgency and bloating (20). The safety of SBI in this present study was such that 87.5% of patients were able to complete 4 weeks of therapy.

There are several caveats to this chart review. This is a retrospective analysis so results were based upon standard-of-care patient outcomes utilizing SBI for nutritional management without a control group. In addition, there were no follow-up LBTs after recording a clinical response to SBI. The patient-reported improvement is limited to a simple "good response" or "no response", meaning there is no detailed gauge for clinical outcome. This is also a relatively small chart review as well, with only 26 patients fulfilling the inclusion criteria and 24 patients with complete follow-ups. Given the inclusion criteria of this retrospective review, there are groups which are not included in this study, so it is difficult to make broader conclusions outside of those already mentioned. Specifically, there is no group of IBS (IBS-D/-M) patients with a positive LBT who declined rifaximin and were immediately placed on SBI for nutritional management of their condition(s). In addition, there is no group of IBS-D/-M patients without any LBT testing who were placed on SBI though current clinical results seem to already support this use (20). Finally, it is impossible to make conclusions which directly compare the clinical response rate between +LBT and -LBT groups reported in this review since there are factors which are inherently confounding: all patients in the +LBT were first treated with antibiotic therapy and had failed this therapy.

As aforementioned, the purpose of chart review is to analyze the patient response to SBI and report that in-office clinical observation. The data suggests that despite the presence of absence of SIBO, SBI appears to have a similar effect in IBS-D/IBS-M patients who are refractory to common IBS treatments. In animal models SBI has been beneficial reducing inflammation and binding bacterial toxins (7, 10).

Oral immunoglobulins in animals have been shown to neutralize bacterial infection and reduce inflammation (11). In a HIV positive population with enteropathy, SBI was shown to decrease proinflammatory Gammaproteobacteria and decrease *Clostridium* (genus) over a period of eight weeks (12). Other *in vitro* results have demonstrated that SBI binds to and neutralizes *C. difficile* toxin A and B (13).

Further controlled clinical studies are needed to elucidate the utility of SBI for therapy of IBS patients diagnosed with and without SIBO and in IBS-M populations. Based on its mechanism of action, SBI may have broad potential for use in the management of several different infective and non-infective enteropathies in combination with antibiotics or as part of dietary modification protocol.

**Table 1. Clinical Response from IBS-D/-M Patients Ingesting 5 g SBI Twice Daily for Four Weeks.**

	Group	
	IBS-D/M with positive LBT <sup>†</sup>	IBS-D/M with negative LBT
<b>Total # Patients</b>	11	13
<b># IBS-D</b>	7	9
<b># IBS-M</b>	4	4
<b># Male</b>	3	6
<b># Female</b>	8	8
<b>Average Age</b>	44	47
<b># Responded to SBI</b>	8	11
<b># Without Response to SBI</b>	3	3
<b>Percent Response</b>	73%, p=0.117	77%, p=0.040
<b># AE</b>	1	2

<b>Reported AE</b>	constipation	diarrhea, nausea and constipation
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‡Before being administered SBI, patients had reported an incomplete clinical response to a 14-day course of rifaximin, 550 mg TID.

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