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**Bovine immunoglobulin protein isolates for the nutritional management of enteropathy**

Petschow BW *et al*. Bovine immunoglobulin protein isolates for enteropathy

Bryon W Petschow, Anthony T Blikslager, Eric M Weaver, Joy M Campbell, Javier Polo, Audrey L Shaw, Bruce P Burnett**,** Gerald L Klein, J Marc Rhoads

**Bryon W Petschow, Eric M Weaver, Audrey L Shaw, Bruce P Burnett, Gerald L Klein,** Entera Health, Inc., Cary, NC 27518, United States

**Anthony T Blikslager,** College of Veterinary Medicine, North Carolina State University, Raleigh, NC 27606, United States

**Joy M Campbell,** APC, Inc., Ankeny, IA 50021, United States

**Javier Polo,** APC Europe, S.A., Barcelona, E-08403, Spain

**J Marc Rhoads,** University of Texas Health Sciences Center, Houston, TX 77030, United States

**Author contributions:** Petschow BW, Weaver EM, and Rhoads JM wrote the paper and made critical contributions to its intellectual content; Blikslager AT, Campbell JM, Polo J, Shaw AL, and Burnett BP reviewed and edited the paper; Klein GL and Rhoads JM had primary responsibility for the final content.

**Correspondence to:** **Bryon W Petschow, PhD,** Entera Health, Inc., 2000 Regency Parkway, Suite 255 Cary, NC 27518, United States. bryon.petschow@enterahealth.com  
**Telephone:** +1-919-6160014 **Fax:** +1-919-3191437

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**Abstract**

The gastrointestinal tract is responsible for a multitude of digestive and immune functions which depend upon the balanced interaction of the intestinal microbiota, diet, gut barrier function, and mucosal immune response. Disruptions in one or more of these factors can lead to intestinal disorders or enteropathies which are characterized by intestinal inflammation, increased gut permeability, and reduced capacity to absorb nutrients. Enteropathy is frequently associated with human immunodeficiency virus (HIV) infection, inflammatory bowel disease (IBD), autoimmune enteropathy, radiation enteropathy, and irritable bowel syndrome (IBS), where pathologic changes in the intestinal tract lead to abdominal discomfort, bloating, abnormal bowel function (*e.g.*, diarrhea, urgency, constipation) and malabsorption. Unfortunately, effective therapies for the management of enteropathy and restoring intestinal health are still not available.

An accumulating body of preclinical studies has demonstrated that oral administration of plasma- or serum-derived protein concentrates containing high levels of immunoglobulins can improve weight management, normalize gut barrier function, and reduce the severity of enteropathy in animal models. Recent studies in humans, using serum-derived bovine immunoglobulin (SBI)/protein isolate demonstrate that such protein preparations are safe and improve symptoms, nutritional status, and various biomarkers associated with enteropathy. Benefits have been shown in patients with HIV infection or diarrhea-predominant IBS (IBS-D). This review summarizes preclinical and clinical studies with plasma/serum protein concentrates and describes the effects on host nutrition, intestinal function, and markers of intestinal inflammation. It supports the concept that immunoglobulin-containing protein preparations may offer a new strategy for restoring functional homeostasis in the intestinal tract of patients with enteropathy.

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**Key words:** Immunoglobulins; Plasma proteins; Inflammation; Gut barrier; Enteropathy

**Core tip:** This review article summarizes previous preclinical and clinical studies with serum- or plasma-derived protein preparations with an emphasis on potential benefits for intestinal health and recovery from intestinal disorders. Specifically, how serum-derived bovine immunoglobulin/protein preparations may be useful in restoring intestinal homeostasis (*e.g.* gut barrier function, immune regulation) following episodes of enteropathy associated with various human disease conditions, such as human immunodeficiency virus infection, inflammatory bowel disease, or irritable bowel syndrome.

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**INTRODUCTION**

The intestinal epithelium is contiguous with the external environment and adaptively organized to both amplify surface area for nutrient absorption and provide a barrier against harmful microorganisms and toxins[1]. The lumen of the gastrointestinal (GI) tract is occupied by a complex assortment of microbial species, the gut microbiota, which changes in response to diet, age, disease, and medical or pharmaceutical intervention[2,3]. This complex array of bacteria and other microbes exist in symbiosis with the intestinal mucosa and play an important role in nutrient absorption, immune regulation, and gut barrier function. At the same time, a variety of immune and physiological adaptations exist within the GI tract to maintain constant vigilance against potentially harmful pathogens and luminal antigens, while preventing the development of uncontrolled inflammation[4].

A variety of factors, both host-related and environmental, can disrupt intestinal homeostasis and lead to development of intestinal disorders or enteropathies. Such enteropathies are characterized by inflammation in the epithelium and lamina propria of the intestine and occur in association with a variety of human conditions or disease states, including: gluten-sensitivity[5], protein-losing enteropathy[6], environmental enteropathy[7,8], radiation-induced enteropathy[9], drug-associated enteropathy[10], irritable bowel syndrome (IBS)[11,12], inflammatory bowel disease (IBD)[13], and human immunodeficiency virus (HIV) infection[14]. In the small intestine, pathologic mucosal changes include blunting of villi associated with inflammation that reduces absorptive capacity and tends to increase gut permeability. In the colon, inflammatory changes may be associated with overt epithelial damage or loss. Clinical signs associated with inflammatory mucosal changes may include abdominal pain or discomfort, nausea, bloating, and abnormal bowel function (*e.g.*, urgency, diarrhea, constipation). The pathophysiologic mechanisms leading to enteropathy are not well understood but may involve the effects of exposure to luminal antigens, toxins, or alterations in intestinal microbiota, as well as host diet, genetics, or dysregulated immune responses.

Certain genetic mutations may also predispose to conditions that are associated with enteropathy. For example, more than 200 polymorphisms have been linked to Crohn’s disease. These polymorphisms may predict disease manifestations (stenosis, fistulization, or inflammation), location, and need for surgery[15]. The mutations fall broadly into categories reflecting toll-like receptor-mediated bacterial recognition, autophagy, organic cation transport, lymphocyte differentiation, and barrier function [16,17]. There is some evidence that genetic polymorphisms also play a role in ulcerative colitis[18,19] and IBS[20]. Metabolomic studies have found that malabsorption leads to depleted levels of alanine, glutamine, glutamic acid, isoleucine, leucine, and valine, choline and select dietary organic acids, including formate, lactate and succinate, in patients with ulcerative colitis[19,21]. Interestingly, altered expression of genes involved in the production of metabolites from tryptophan through the kynurenine pathway has also been associated with IBS. Clarke *et al*[22] found significantly higher kynurenine: tryptophan ratios in IBS subjects compared to controls, and acute depletion of tryptophan has been associated with higher levels of abdominal pain and lower levels of serotonin production in IBS[23,24]. Altered tryptophan metabolism through the kynurenine pathway has also been implicated in the events leading to intestinal inflammation in HIV-infected individuals[25] and in IBD[26]. In summary, a variety of enteropathies occur with various human health conditions which are governed by a harmful and continuing cycle of gut barrier dysfunction, immune activation, altered gut microbiota, and impaired nutrient absorption[1,13](Figure 1). Unfortunately, available therapies are often directed at symptoms and not causative factors and include such things as dietary modifications or restrictions, steroids, broad spectrum antibiotics, Crofelemer (antiretroviral HIV diarrhea), or supportive IV fluids. Due to a broad range of potential causes, multidimensional approaches may be needed, including nutritional interventions alongside current drug treatments to manage these complex disorders. It is well established that plasma-derived protein concentrates (PPC) from bovine, porcine and other sources, when added to the diets of several species of animals, leads to improvements in appetite, weight gain, intestinal growth, and gut barrier function in a number of intestinal disorders[27-30]. Serum-derived bovine immunoglobulin/protein isolate (SBI), specially-formulated to increase IgG levels, has been extensively studied in animal models and recently has been found to be safe and effective in the management of the enteropathy associated with IBS-D and HIV infection[31,32]. The purpose of this review is to summarize the scientific evidence supporting the benefits of orally-administered, immunoglobulin-containing protein preparations for host nutrition and protection of gut barrier integrity, particularly as it relates to conditions associated with enteropathy. Studies on the impact of these protein preparations [PPC, bovine serum concentrate (BSC), serum-derived bovine immunoglobulin (SBI)] on host nutrition, gut barrier function, tight junctions, and immune regulation will be summarized.

**COMPOSITION OF BOVINE PLASMA- AND SERUM-DERIVED PROTEIN ISOLATES**

Plasma-derived protein concentrates are commonly used in animal husbandry to promote growth and modulate intestinal inflammation in immunocompromised young animals[27-30]. Agricultural PPC products are prepared from blood obtained from abattoirs using hygienic collection and processing procedures to ensure high quality plasma products. Preparation first involves the addition of an anticoagulant with subsequent centrifugation to separate the cellular fraction. The plasma is then concentrated by filtration, using inverse osmotic membranes, or ultrafiltration and then spray-dried to create a plasma protein powder. During spray drying, plasma proteins are exposed to high temperatures for a very short period of time to avoid denaturation of proteins and to preserve their biological activity[33,34]. In contrast, SBI is produced through a series of shifts in pH and specific salt additions to chilled, edible grade plasma [United States Department of Agriculture (USDA) approved] to reduce the albumin and fibrinogen content and increase the immunoglobulin concentration[35].

Plasma protein concentrates used for animals typically contain over 80% protein on a weight basis, with over 15% of the protein consisting of immunoglobulins (Ig), mainly IgG. In contrast, SBI preparations are specially formulated to increase protein content and reduce levels of albumin and fibrinogen, which results in proportionally higher levels of immunoglobulins. EnteraGam™ is a specially formulated commercial SBI preparation, manufactured according to FDA good manufacturing practice guidelines and intended for human use as a prescription medical food product. It contains ~92% protein (> 50% IgG) with high levels of essential amino acids, including lysine, threonine, tryptophan, and leucine, and is indicated for the clinical dietary management of enteropathy for patients under medical supervision[36]. Arginine and glutamic acid are also found in relatively high levels compared to common dietary sources of protein and the total caloric content of EnteraGam™ is 372 Kcal per 100 g.

**NUTRITIONAL BENEFIT**

While the purpose of this review is not to provide an extensive summary of all studies conducted on this topic, several representative studies are summarized in Table 1 and the reader is referred to review articles on this topic[27,30]. Torrallardonareviewed the results from 75 trials in 43 publications, involving more than 12000 pigs, to evaluate the feeding and nutritive benefits of PPC from a variety of sources for weaning piglets[30]. Most studies evaluating PPC showed improvements in caloric intake, growth and metabolism, as well as utilization of feed nutrients. Replacement of several high quality protein sources (*e.g.*, meat extracts, soy, pea, potato, skimmed milk, whey, and fishmeal) with PPC at comparable levels led to improved weight gain and feed intake in piglets. Jiang *et al*[37] evaluated growth performance in piglets after pair-feeding a diet containing soy protein or PPC for 24 d. Protein intake was similar among groups while the rate of weight gain and protein conversion efficiency was significantly higher in the PPC group, especially during early weaning period. Pigs fed PPC also had improved body weight and absolute mass of protein with no difference in fat mass, suggesting a higher efficiency of dietary protein utilization for lean tissue growth. Feeding PPC reduced the circulating concentrations of urea, arginine, citrulline and ornithine, suggesting a reduction in the catabolism of amino acids to urea and increased availability of dietary amino acids for lean tissue mass. In addition, there were also significant increases in bone mineral content and bone mineral density in the PPC-fed compared to the soy protein-fed group.

Pierce *et al*[28] conducted several experiments to evaluate the growth and feed intake of weaned piglets fed porcine PPC, bovine PPC, or different molecular weight fractions of PPC. Collectively, the results demonstrated that both porcine and bovine PPC enhances growth rate and feed intake of weaned piglets, while the IgG fraction of porcine or bovine plasma appeared to stimulate growth performance that was comparable to intact PPC and superior to the albumin or low MW fractions of PPC. This data suggests that a distinct nutritional role may exist for the IgG-rich fraction of PPC to support growth performance.

**SAFETY AND DIGESTIBILITY**

Plasma-derived protein concentrates (*e.g.* PPC, SBI) are composed of > 50% IgG and other proteins and peptides that reflect the composition of plasma and are similar to other serum proteins present in colostrum and milk. Such products typically do not contain milk ingredients such as lactose, casein, or whey, so adverse reaction rates would be expected to be minimal. However, patients who have an allergy to beef should not take SBI or PPC products. The rigorous process used to prepare commercial forms of SBI meets strict industry standards to ensure that finished products do not become contaminated with infectious agents, including the Bovine spongiform encephalitis (BSE) agent. In addition, SBI has been self-affirmed as Generally Recognized as Safe (GRAS) with no safety-related questions by the US Food and Drug Administration (FDA) for doses up to 50 g/d. SBI has not yet been tested in pregnant or nursing mothers or immunocompromised individuals, so use in such patients should be at the discretion of the patients’ physician.

The safety of SBI has been evaluated in both pediatric and adult subjects. Tolerance and digestibility of SBI was evaluated in 12 healthy adult volunteers by Hanning *et al*[38]. Volunteers were administered 10 g of SBI orally and blood samples were obtained at various time points, which showed elevated levels of plasma total amino acids and leucine at 1-2 h following SBI administration. Bovine IgG was not detected in serum samples from study subject, suggesting that bovine IgG remains in the intestinal tract and does not pass the luminal barrier into the blood stream. Subjects then consumed 5 g of SBI daily for 2 wk and completed daily diaries for general health and adverse events (AEs). No serious AEs were reported by test subjects. The following AEs were reported: increased urination (3); stomach cramps (3); fatigue (2); headache (2); sore throat, softened stools, nausea, constipation, and irritability (1 each). Bovine IgG was detected by enzyme-linked immunosorbent assay (ELISA) in stool samples from test subjects on day 14 but not at baseline (day 0), suggesting survival of some IgG following GI transit, which is similar to previously reports[39,40].

A standard diet with graded amounts of SBI (starting at ~1.25 g/d) was also fed to infants 9 to 25 mo of age at entry (*n* = 10) recovering from severe protein-energy malnutrition to evaluate acceptability, safety, and digestibility[41]. Study diets were well accepted by study subjects with no evidence of intolerance and no AEs were reported. In another study, malnourished infants (age 6-7 mo of age at entry; *n* = 107) fed a diet containing SBI (~3.5 g/d) for up to 8 months showed no side effects or adverse impact on growth or morbidity rates when compared to infants fed diet supplemented with whey protein concentrate[42]. Studies in HIV+ patients (*n* = 8)[31], a longer term open-label exposure in HIV+ patients (*n* = 35) (data on file), and subjects with IBS-D (*n* = 66)[32] also showed only minor or non-medication related adverse events, as well as no clinically relevant changes in blood chemistries or hepatic or renal markers in any studies. Collectively, the results from available clinical studies suggest that SBI is safe and well-tolerated when consumed up to 8 mo in doses ranging from 1.25 to 10 g per day in infants, children and adults.

In order for PPC supplementation to provide benefits to dysfunctional intestinal mucosa, the immunoglobulin and other active protein components must resist digestion and remain active in the lumen of the intestine. Morel *et al*[39] used radial immunodiffusion to evaluate survival of IgG at various points along the intestine in weaned piglets fed PPC. They found 50% undigested IgG located in the proximal small intestine, 17% in mid-small intestine and 10% in the distal small intestine, but none in the cecum and colon. Rodriguez *et al*[40] also found IgG survival through the intestinal tract at 8% and 5%, in adult dogs and cats fed PPC or purified IgG, respectively, which suggests partial resistance to digestion. The authors found that the immunoglobulin fraction present in the feces of these animals was the Fab fraction.

**IMPACT ON GUT BARRIER AND INTESTINAL RECOVERY**

The ability of PPC and SBI to modulate intestinal barrier function, permeability, and malabsorption has been evaluated in a number of preclinical and clinical studies.

***Preclinical studies***

Studies on the effects of bovine immunoglobulin isolates (PPC or SBI) on inflammation in the GI tract have primarily come from preclinical models in which animals were challenged by infection or exposure to bacterial toxins (Table 2). In one study of piglets infected with rotavirus, PPC was effective at reducing diarrhea, improving intestinal recovery and maintaining growth[43]. Infected soy-fed pigs had significantly greater diarrhea scores (*P* < 0.001) from day 1 to 7 post-infection, while diarrhea scores of infected pigs fed PPC ranked the same as uninfected controls. Administration of PPC was not able to attenuate the reductions in intestinal villus height and the villus height/crypt depth ratio caused by rotavirus infection. Nevertheless, oral feeding of PPC maintained greater intestinal mucosa protein and estimated total lactase activity than infected, soy protein-fed piglets. In a second study, weaned pigs were challenged with enterotoxigenic *Escherichia coli* K88 (ETEC K88), used as a model of *in vivo* pig IBD, to investigate whether PPC could improve growth, immune defense and reduce intestinal inflammation[44]. Compared to a diet based on fish protein, ETEC K88 infected pigs fed PPC showed higher calorie intake and daily weight gain, less intestinal mucosal damage and inflammatory cell infiltration, and reduced expression of pro-inflammatory cytokines.

In a third study of infectious enteritis -- *Cryptosporidium parvum* infection in neonatal calves, a disease which produces moderate intestinal inflammation, watery diarrhea, and increased intestinal permeability -- Hunt *et al*[45]showed that the daily addition of a bovine serum product (compared with a soy protein control) reduced diarrheal volume, oocyte shedding, and intestinal permeability, while facilitating villus re-growth and increasing mucosal surface area. Lactase activity was significantly improved in response to bovine serum concentrate.

Other data in preclinical models have specifically evaluated tight junction protein expression in response to early weaning and toxin challenge. Peace *et al*[46] evaluated the effects of PPC in piglets undergoing early weaning, a condition known to induce impairment in intestinal epithelial barrier function. Piglets were fed a control diet containing PPC for 7 or 14 d to evaluate impact on ileal and colonic barrier function. Co-administration of PPC with radiolabeled nutrients reduced paracellular permeability as indicated by significant reductions in colonic 14C-inulin permeability on day 7 post-weaning and reduced ileal 3H-mannitol and 14C-inulin permeability on day 14. Protein plasma concentrate also reduced the predominantly lymphocytic cellular infiltration in the lamina propria in both ileum and colon, concomitantly reducing levels of pro-inflammatory cytokines in colon (see below). As shown by immunofluorescence staining, claudin-1, a tight junction protein was more highly expressed and localized to tight junctions in animals fed PPC.

The protective effects of spray-dried porcine PPC in a rat model of intestinal inflammation were also evaluated[47]. Weaned rats were fed a diet with or without PPC for 14 d then exposed to intraperitoneal challenge with *Staphylococcus aureus* enterotoxin B (SEB) known to disturb barrier function and ion transport. Addition of PPC to diets significantly ameliorated SEB-induced increases in intestinal permeability as measured by dextran flux (*P* < 0.05) flux and horseradish peroxidase (HRP) paracellular flux (*P* < 0.05) across the intestinal epithelium. Plasma protein concentrate was also shown to increase β-catenin expression, part of the adherens complex positioned adjacent to the tight junction. These data suggest that PPC beneficially promoted endogenous repair of the tight junctions, modulated inflammation, reduced permeability, and improved the diarrhea in pigs challenged with enterotoxin B.

Collectively, the results of these experimental studies suggest that dietary plasma protein preparations strengthen intestinal barrier function and prevent alterations in intestinal epithelium during inflammation. Two reviews have been published on the effects of PPC and the proteins in SBI on intestinal barrier function in animal models of human disease[48,49].

***Clinical studies***

Two clinical trials evaluated the efficacy of dietary SBI for improving intestinal absorption, GI symptom scores, and quality of life measures in patients with HIV-associated enteropathy or IBS-D (Table 3). An open-label study was conducted by Asmuth *et al*[31] to evaluate the impact of oral SBI on GI symptoms and systemic markers of immune activation in patients with a diagnosis of HIV-associated enteropathy. To qualify, patients with enteropathy were given an extensive evaluation to exclude other GI disease. Eight patients were enrolled in the study and received 5 mg of SBI/day for 8 wk followed by a 4 wk washout period. Administration of SBI led to consistent improvement in symptoms associated with HIV enteropathy. After 8 wk of SBI administration, bowel movements per day decreased from 5.7 to 2.0 (*P* = 0.013) and stool consistency scores improved from 5.3 to 3.0 (*P* = 0.013). A GI symptom questionnaire showed a marked decrease in score from 6 to 0.5 (*P* =0.013). After a 4 wk washout period, 5 patients continued on for another 9 mo maintaining similar bowel movements and stool consistency. An additional open-label, in-market analysis of 31 patients taking various nutritional formulas which contained 2.5 to 5.0 g SBI showed improved management of loose stools, thus providing further evidence for the management of HIV-associated enteropathy (Table 3).

A randomized, double-blind, placebo-controlled study was conducted in individuals with IBS-D to investigate the efficacy of SBI on decreasing gastrointestinal symptom scores and improving the quality of life of[32]. Study subjects (*n* = 66) with a diagnosis of IBS-D for at least 6 mo prior to enrollment met the Rome II diagnostic criteria for IBS, and had a recent history of elevated stool frequency. Test groups received SBI at either 5 or 10 mg/d or 10 mg/d of control soy protein isolate (SPI) for 6 wks and completed an IBS-36 questionnaire at baseline (Day 0) and at the end of the study (Wk 6). The daily symptom diary assessed the presence and severity of the following symptoms: nausea, abdominal pain, flatulence, bloating, hard stools, loose stools, urgency, straining, incomplete evacuation and mucus. Forty-five subjects completed the study per protocol and were included in the analysis: 10 g/d  SBI (*n* = 15), 5 g/day SBI (*n* = 15), and 13 subjects in the placebo group. Results showed that subjects receiving 10 g/d of SBI experienced significant within-group reductions in abdominal pain (*P* < 0.01), loose stools (*P* < 0.01), bloating (*P* < 0.05, flatulence (*P* < 0.01), urgency (*P* < 0.05) and any symptom (*P* < 0.01) at EOT *vs* baseline (Table 4). Subjects receiving 5 g/d of SBI (*n* = 15) reported statistically significant within-group reductions in days with flatulence (*P* < 0.035), incomplete evacuation (*P* < 0.05), and ‘any symptom’ (*P* < 0.01). No significant within group improvements were seen in the placebo arm. There were no significant changes in quality of life (QoL) scores or in hematology or clinical chemistry values among treatment groups.

Studies have also been performed in infants and children recovering from malnutrition. A standard diet with graded amounts of SBI was also administered to infants or children 9 to 25 mo of age at entry (*n* = 10) recovering from severe protein-energy malnutrition to evaluate acceptability, safety, and digestibility during three randomly ordered 7-d periods[41]. Replacing 50% of the protein in the standard diet with SBI led to significant reductions in fecal wet and dry weights, and lower fecal fat and energy losses, suggesting greater absorption of fat and energy compared with the control diet (*P* < 0.05)(Table 3). Investigators suggested that SBI enhanced intestinal recovery from severe malnutrition.

Another randomized, controlled, community-based intervention study evaluated the effects of SBI and/or multiple micronutrients on children’s growth, morbidity, and micronutrient status[42]. A total of 259 children who were initially 6 to 7 mo of age received 1 of 4 maize-based dietary products daily for 8 mo with or without protein supplementation. Groups studied: SBI, whey protein concentrate (WPC, control group), SBI plus multiple micronutrients, or WPC plus multiple micronutrients. Two hundred and twenty-five (225; 86%) children completed ≥ 60 d of observation, 184 (71%) completed ≥ 180 d of observation, but only 132 (51%) distributed among the 4 treatment groups finished the full 8 mo of observation. There were no significant differences in growth or morbidity by treatment group for those children who completed 8 mo of observation. Although not statistically significant, there were trends toward weight gain and upper arm circumference (a measure of lean body mass) increases in the SBI+ micronutrient group suggesting better utilization of these nutritional substances (Table 3).

**EFFECTS ON GUT MICROBIOTA**

Changes in gut microbiota has been identified as one potential factor in causing inflammation that leads to alterations in gut barrier function with associated increases in mucosal permeability. An increase in firmicutes over bacteroidetes bacteria has been reported in IBS patients[50-52]. Another study in IBS-D patients found an increase in bacteroides and clostridia with an associated reduction in bifidobacteria[53]. Pediatric IBS-D patients were reported to show significant differences compared to healthy controls having statistically greater numbers of gammaproteobacteria[54]. There is also a well-recognized dysbiosis that occurs in IBD, although the colonic bacterial imbalances are less well-characterized for ulcerative colitis compared to Crohn’s disease[55-58]. Recently it was also reported that the microbiota in both ulcerative colitis and Crohn’s disease was relatively unaltered, but metabolism by bacteria in the microbiota was significantly changed[59]. There were notable shifts in fecal metabolome showing reduced carbohydrate processing and alterations in various amino acid biosynthesis pathways. This alteration in gut microbiota may contribute to increased tight junction permeability with associated decreases in barrier function, and changes in bacterial metabolic products and host nutrient malabsorption. Diet may play a role in the causality and/or in the progression of both IBS and IBD[60,61]. Therefore, it is reasonable to assume that diet may play a role in restoring a natural balance to the gut microbiota and metabolome.

In the HIV-associated enteropathy population treated with SBI, the firmicutes and bacteriodales were the dominant phyla in all 8 patients[62]. When SBI was administered to these patients, proinflammatory gammaproteobacteria decreased from 0.70% to 0.12%. *Clostridium* (genus) decreased from 6.5% to 3.4% in the stool and correlated with duodenal CD3+/CD4+ density (*r* = -0.63; *P* < 0.01). Ruminococcus and the bacteroidetes/firmicutes ratio, which increased in 6/8 SBI-treated subjects in the study, have been shown to contribute to better calorie utilization from the diet[63,64]. Changes in gut microbiota in the study also correlated with local lymphocyte populations that increased significantly with short-term SBI administration over 8 wk. These results suggest that some component in the formulation may be normalizing gut bacteria, perhaps the IgG fraction. Work is underway to further characterize these interactions.

**EFFECTS ON INTESTINAL INFLAMMATION**

The release of inflammatory mediators, such as reactive oxygen species, prostaglandins, leukotrienes, and cytokines from mucosal leukocytes is associated with the altered barrier function and increased permeability caused by intestinal inflammation. Cytokines such as interleukin (IL)-1β and tumor necrosis factor (TNF)-α play an important governing role in such inflammatory responses while other cytokines such as IFN-γ, IL-12 and IL-18 affect the production and cellular response to IL-1β and TNF-α[65]. In models of inflammation where several cytokines are produced, specific blockade of IL-1β and/or TNF-α results in a reduction in the severity of the inflammation[65]. Dietary PPC has been shown to reduce the expression of proinflammatory cytokines and alter the lymphocyte response during immune activation in weaned piglets[46] as well as experimental models of intestinal inflammation in mice[66,67], rats[68-70] and pigs[44] (Table 4). For example, a study by Pérez-Bosque *et al*[71] investigated the effects of dietary SBI on immune responses of mucosal-associated lymphoid tissue in mice with a genetic predisposition to IBD. Wild type (WT) mice and mice lacking the *mdr1a* gene (KO) were fed diets supplemented with either SBI (2% w/w) or milk proteins (control diet) starting on day 19 (weaning). At day 56, SBI reduced the production of proinflammatory cytokines and chemokines IL-17, IL-6 and CCL4 (*P* < 0.05), prevented the expression of IFN-γ (*P* < 0.05), and blocked the increase in colon crypt permeability that was found in the mdr1a KO model. SBI treatment produced increases in mucosal concentration in anti-inflammatory TGF-β and in the percentage of regulatory T lymphocytes (both *P* < 0.05), thus reducing the activated Th1 to regulatory Treg lymphocyte ratio. PPC and immunoglobulin-enriched protein isolates have also been demonstrated to affect Peyer’s patch lymphocyte populations in weaned rats challenged with *S. aureus* superantigen B (SEB)[70]. In this study, it was shown that the mild intestinal inflammation associated with the SEB model was reduced by dietary PPC as measured by decreased diarrhea. Furthermore, the administration of PPC significantly increased the number of T-helper cells, while reducing the number of activated T-helper cells as compared with animals not fed PPC or immunoglobulin-enriched protein isolates[70]. This same trend was observed for changes in the population of γδ-T cells and natural killer (NK) T cells in the Peyer’s patches of rats fed diets containing PPC or immunoglobulin isolates.

In an initial clinical trial in HIV patients with decimated lamina propria CD4+ counts, SBI ingestion significantly increased jejunal CD4+ lymphocyte densities over 8 wks, but had no effect on circulating CD4+ counts[31]. In addition, levels of I-FABP, a marker for enterocyte damage, initially rose in 7/8 subjects after 8 wk, but then fell below baseline in 4/5 who continued taking SBI after 48 additional weeks on product, suggesting that damage to enterocytes caused by inflammation had ceased (Table 4). Collectively, data from these preclinical and clinical studies support the hypothesis that the distinct protein composition of SBI can play a role in the modulation of the immune response in the intestine.

**MECHANISM OF ACTION**

SBI contains immunoglobulins, particularly IgG, that are directed against a wide array of pathogens and foreign antigens due to the fact that SBI is prepared from plasma obtained from hundreds of animal donors. The Fab regions of IgG recognize antigenic targets and provide diversity to antibodies, while the Fc region interacts with Fc gamma receptors on certain immune cells to enhance phagocytic activity by macrophages, monocytes, and polymorphonuclear neutrophils (PMNs). Several mechanisms may explain how oral immunoglobulins modulate intestinal inflammation and support gut barrier function. For example, immunoglobulins in SBI may simply bind directly to specific microbial pathogens or their toxins, thereby interfering with their ability to migrate through the mucus layer and enter or damage epithelial cells.

A more likely explanation of how oral immunoglobulins work to maintain intestinal homeostasis may involve binding to highly-conserved microbial antigens such as bacterial lipopolysaccharide (LPS), also known as microbe-associated molecular patterns (MAMPs), and interfere with signaling pathways that lead to inflammation (Figure 3). Under normal conditions, cells of the innate immune system play a crucial role in maintaining intestinal homeostasis through a highly-regulated process involving the recognition of MAMPs through pattern recognition receptors (PRRs), such as toll-like receptors (TLRs). TLRs are differentially expressed by various cells of the GI tract (*e.g.*, macrophages, dendritic cells, endothelial cells, myofibroblasts)[72,73] and play a key role in signaling the recognition of MAMPs by activating several inflammatory pathways, including the NF-қB pathway which is a key regulator of proinflammatory TNF-α, IL-1β, IL-6 and IL-8 cytokine production[74]. Prolonged recognition of MAMPs can lead to a persistent state of inflammation associated with numerous chronic inflammatory disorders such as IBS, IBD, and HIV enteropathy. Studies have shown that the IgG, IgA, and IgM contained in SBI bind to bacterial endotoxins and a wide array of other bacterial, viral, and fungal MAMPs[75,76]. Therefore, it is possible that SBI binding of microbiota components results in less binding of MAMPs by macrophages and dendritic cells which may interfere with release of IL-1, IL-6, and TNF-α[77]. Similarly, less presentation of antigens by dendritic cells and macrophages may result in a decrease in activated T cell populations and more regulatory cell phenotypes that produce IL-10 to dampen inflammation[70].

Alternatively, SBI may contain a large fraction of natural antibodies (Nabs) that work in other ways to maintain immune homeostasis. For example, studies with intravenous immunoglobulin (IVIG) have shown that binding of the Fc portion of IgG to Fc receptors on target cells may govern some of the anti-inflammatory mechanisms involved with IVIG therapy by up-regulating the expression of inhibitory classes of Fc receptors and down-regulating the activating class of Fc receptors[78]. Autoreactive antibodies in IVIG have also been shown to modulate Th1 and Th2 cytokine production[79], trigger the production of interleukin-1 receptor antagonist, abrogate the capacity of mature dendritic cells to secrete IL-12 upon activation *in vitro*, and enhance anti-inflammatory IL-10 production[80]. Collectively, such immune modulating effects of SBI might explain previous reports of reduced expression of pro-inflammatory cytokines and altered lymphocyte response to immune activation in weaned piglets[46] and experimental models of intestinal inflammation[66-69].

The ability of SBI to modulate inflammation may also benefit the patient with enteropathy by improving gut barrier function. A developing body of evidence indicates that intermittent or even minor inflammation in the intestinal mucosa can elicit changes in intestinal structure and function leading to increased mucosal permeability[12,81]. For example, increased production of pro-inflammatory cytokines such as TNF-α, IFN-γ, and various interleukins during certain chronic inflammatory disorders[4,82,83] have been shown to increase paracellular permeability by impacting the expression or degradation of claudin and occludin tight junction proteins[84,85]. Conversely, certain anti-inflammatory cytokines such as IL-10 and TGF-β appear to maintain tight junction barrier and protect against intestinal inflammation[82].

In addition to the IgG content of PPC and SBI, the effect on lean body mass may also be in part due to the amino acid content of the complex protein mixture. Plasma protein concentrate and SBI contain amino acids which have been identified to be important for recovery after intestinal damage from infectious agents[43,44,47]. For example, glutamine serves as a preferential energy source for rapidly proliferating immune cells and enterocytes, is a nontoxic transporter of ammonia, and has been linked with maintenance of gut barrier function and cell differentiation[86]. Amino acids absorbed into the blood from PPC or SBI may also play an anabolic role in the body such as tryptophan which may support the generation of serotonin or metabolite formation in the kynurenine pathway[22-24].

**CONCLUSion**

Chronic intestinal disorders or enteropathies occur in a variety of human disease conditions such as IBS, IBD, and HIV infection which are characterized by intestinal inflammation, increased gut permeability, and reduced capacity to absorb nutrients. Most therapies used to treat enteropathy are aimed at managing symptoms or target single pathways. However, a multifaceted approach may be needed to manage enteropathy associated with these complicated disease states, or in some cases the side effects of pharmaceutical treatment protocols.

There is a developing body of evidence indicating that intermittent or even relatively minor inflammation can lead to changes in intestinal structure and barrier function[87]. Translocation of bacterial antigens may result in increased production and secretion of pro-inflammatory cytokines, including TNFα, IFN-γ, and interleukins[4,82], which degrade structural tight junction proteins (*e.g.*, occludins[84], claudins[85]), and contribute to symptoms associated with enteropathy. Inflammation-driven disruption of barrier function has been shown to negatively influence growth in young animals, and also has a range of health consequences in humans [1]. For example, post-infectious IBS is recognized to have inflammatory involvement which may persist months after the initial resolution of infection[88,89] with associated intestinal histological changes and increased intestinal permeability[12,83,90,91]. HIV-associated enteropathy has long been associated with inflammatory damage, decreased barrier function, increased permeability and malabsorption of nutrients[92-94]. Due to increased permeability, microbial translocation markers in HIV patients have been shown to be significant predictors for disease progression and death[95,96]. Serum-derived bovine immunoglobulin protein isolates may provide a distinct protein composition to counter intestinal inflammation and the resulting changes in barrier function as well as tight junction permeability to help maintain proper functioning of the intestine. Enteropathy is also associated with chronic undernutrition[97,98]. Malabsorption of nutrients such as bile acids, polyols, fructose, and lactose has been reported to contribute to increased symptoms in patients with IBS[99-101]. A nutritional deficiency of vitamin B6 may also be correlated with IBS symptoms[102]. Nutritional interventions may be needed alongside current drug treatments to effectively manage these complicated disorders.

Results from numerous research studies consistently demonstrate beneficial physiological effects for IgG-containing PPC and SBI protein preparations[27,28,30,33]. SBI contains distinct nutritional factors that may impart growth and protective benefits by several different mechanisms including binding endotoxin, supporting intestinal barrier function, fostering the growth and maintenance of the normal microbiota, reducing pro-inflammatory cytokine production, and maintaining epithelial tight junctions. In environmentally stressed or disease states, increased cytokine production can promote an increase in enteric epithelial tight junction permeability with resultant antigenic penetration of the gut barrier. These effects may be ameliorated through PPC and SBI preparations *via* the reduction of pro-inflammatory cytokine expression, including TNF-α, IFN-γ, IL-1β, IL-6, IL-8, IL-17, thus facilitating restoration of normal GI function and improved nutritional utilization of accompanying SBI proteins[44,66-70,103].

The protein composition in SBI has been tested in five studies that confirmed its safety in humans. Four clinical trials have reported results that are consistent with the hypothesis that SBI may improve intestinal dysfunction. The study of SBI in HIV-enteropathy patients[31] in which D-xylose uptake was increased and in infants with malnutrition[41] where fecal wet/dry weights as well as lower fecal fat and energy losses were prevented suggest that this distinct and specially formulated protein mixture is able to restore intestinal structure and functional damage caused by proteolytic enzymes, lymphocytic cytokines, or chemokine-induced damage. Oral SBI may represent a safe and effective option with multiple modes of action to provide for distinctive nutritional requirements in patients with disease-related enteropathy to increase digestion, absorption, metabolism, and utilization of a variety of macro- and micronutrients and facilitate resolution of their abdominal symptoms and diarrhea.

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**Table 1 Weight gain and growth following dietary supplementation with plasma protein concentrates**

|  |  |  |
| --- | --- | --- |
| **Animal Model** (Age) | **Impact of dietary supplementation with SBI** | **Ref** |
| Piglets: 14-21 d | Superior growth and feed intakes during the first week in 4 of 5 experiments.  Growth performance improved by the IgG-rich fraction. | Pierce *et al*[28] |
| Piglets:  Varying age groups | Consistent improvement in growth, feed intake and sometimes feed conversion; similar results with spray dried plasma from porcine, bovine, and mixed origin. | Torrallardona *et al*[30] |
| Piglets: Weaned at 14 d | Significantly increased mean daily body weight gains and food conversion efficiencies; no difference in protein intake.  Significantly greater lean body mass and total carcass mass (*P* < 0.05).  Significantly lower circulating urea concentrations (*P* < 0.05), indicating greater retention of nitrogen and reduced amino acid catabolism. | Jiang *et al*[37] |
| Piglets: Weaned at 21 d, infected with ETEC K88 | Increased average daily weight gain and food intake.  Protected against *E. coli*-induced inflammation. | Bosi *et al*[44] |

SBI: Serum-derived immunoglobulin/protein isolates; *E. coli*: *Escherichia coli;* ETEC K88: Enterotoxigenic *E. coli*, K88 strain.

**Table 2 Effects of plasma-derived protein concentrates on intestinal function in animal models**

|  |  |  |  |
| --- | --- | --- | --- |
| **Species** | **Model/ Indication** | **Impact of dietary supplementation with SBI** | **Ref** |
| **Pig** | Postweaning | Reduced colonic paracellular permeability.  Reduced ileal permeability.  Fewer lamina propria cells in ileum and colon.  Reduced transepithelial electrical resistance in the colon - improved tight junction.  Significantly improved fecal scores. | Peace *et al*[46] |
| Rotavirus infection | Significantly reduced clinical signs of diarrhea  Significantly greater intestinal mucosal protein and lactase activity. | Corl *et al*[43] |
| Infection by ETEC K88 | Decreased inflammatory cell infiltration and mucosal damage.  Increased crypt depth, reduced intestinal expression of proinflammatory TNF-α and IL-8. | Bosi *et al*[44] |
| **Rat** | Exposure to SEB | Improved ion transport function, as measured by reductions in the potential difference across the jejunum and Na-K-ATPase activity.  Improved mucosal permeability (dextran flux and HRP paracellular flux) | Perez-Bosque *et al*[47] |

SBI: Serum-derived immunoglobulin/protein isolates; ETEC K88: Enterotoxigenic *Escherichia coli*; K88 strain; TNF-α: Tumor necrosis factor alpha; IL-8: Interleukin 8; SEB: *Staphylococcus aureus* enterotoxin B; Na-K-ATPase: Sodium-potassium adenosine triphosphatase; HRP: Horse radish peroxidase.

**Table 3 Human studies with serum-derived immunoglobulin/protein isolates to evaluate intestinal benefits and quality of life**

|  |  |  |  |
| --- | --- | --- | --- |
| **Species** | **Model/ Indication** | **Impact of dietary supplementation with sbi** | **Ref** |
| Human  *n* = 8, HIV positive adults | HIV-associated enteropathy | Significant reduction in mean bowel movements/day and improvement in stool consistency scores after 8 wk (*P* = 0.008).  Significant reduction in GI questionnaire scores from 17 at baseline to 8.0 at 8 wk (*P* =0.008).  No change in gut permeability (disaccharide absorption); increase in D-xylose absorption in 7/8 subjects.  Maintained stool frequency and consistency for an additional 9 mo (*n* = 5) | Asmuth *et al*[31] |
| Human *n* = 31, HIV positive adults | HIV-associated enteropathy | Improved management of chronic and loose stools. | Data on file |
| Human  *n* = 66 adults | IBS-D | 10 g/d showed significant decrease in # symptom days with abdominal pain, flatulence, bloating, loose stools, urgency or any symptom over 6 wk (*P* < 0.05).  5 g/d showed significant improvements in loose stools, hard stools, flatulence and incomplete evacuation (*P* < 0.05). | Wilson *et al*[32] |
| Human *n* = 10 infants or children (9-25 mo) | Malnutrition | Significant reductions in fecal wet and dry weights, and lower fecal fat and energy losses compared with the control diet (*P* < 0.05) in relation to the amount of SBI in the diet during three randomly ordered 7-d periods. | Lembcke *et al*[41] |
| Human *n* = 259 infants (6-7 mo) | Malnutrition | Trends toward weight gain and upper arm circumference (a measure of lean body mass) increases were found in the SBI + micronutrient group *vs* SBI alone. | Begin *et al*[42] |

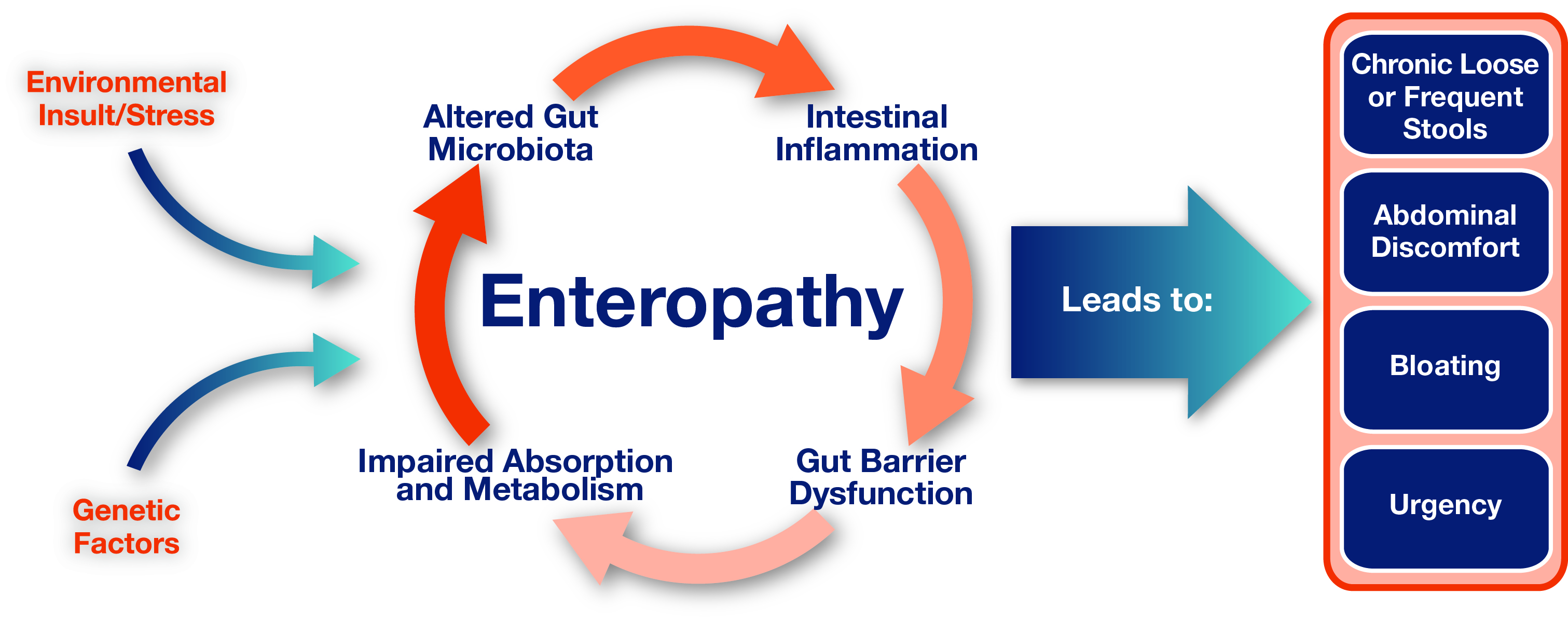
HIV: Human immunodeficiency virus; IBS-D: Irritable bowel syndrome, diarrhea predominant.

**Table 4 Effects of serum-derived immunoglobulin/protein isolates administration on immune and inflammatory markers**

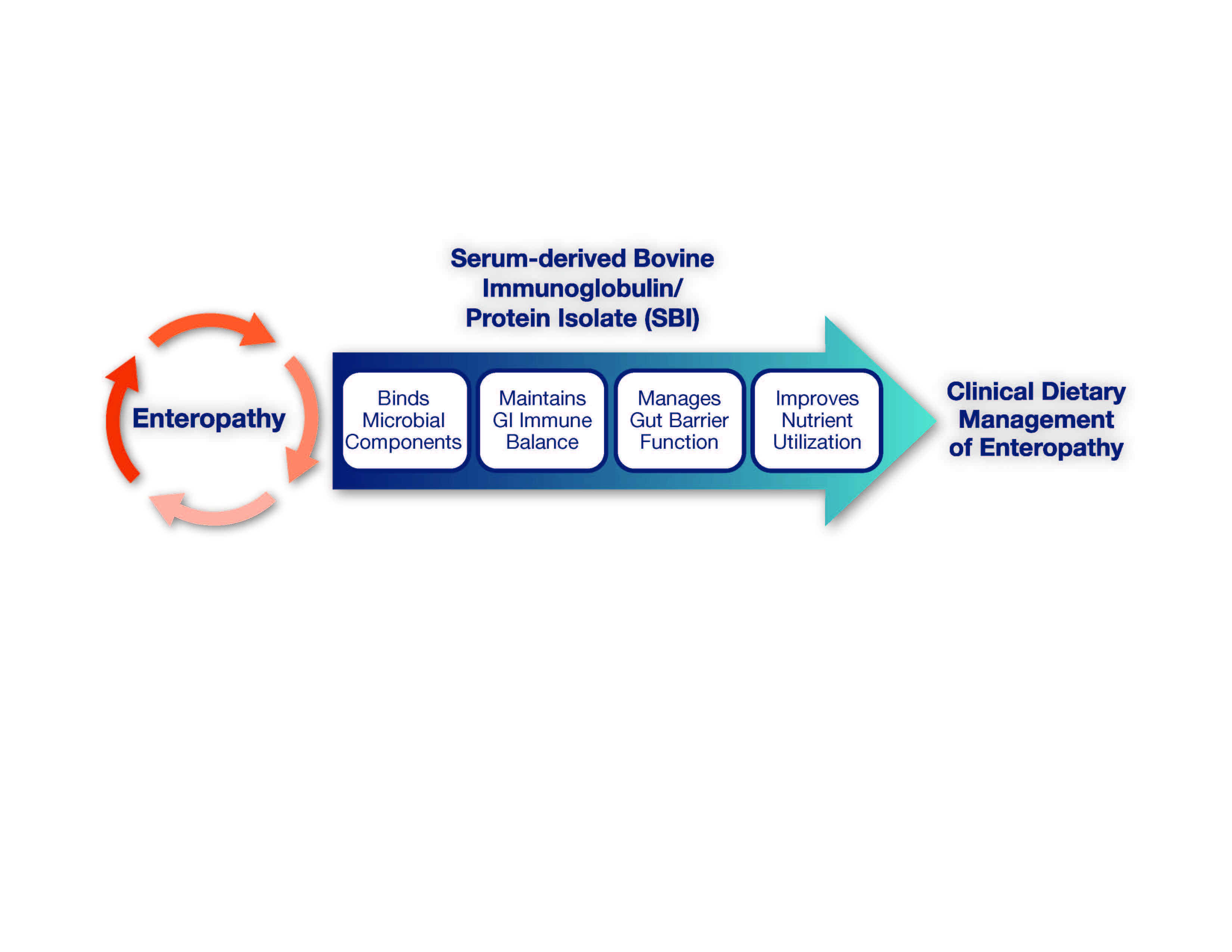
|  |  |  |  |
| --- | --- | --- | --- |
| **Species** | **Model/ Indication** | **Impact of dietary supplementation with SBI** | **Reference** |
| Pig | ETEC K88 | Reduced expression of TNF-α and IL-8 in the gut. | Bosi *et al*[44] |
| Postweaning | Reduced TNF-α in the colon  Reduced IFNγ levels in the ileum and colon day 7, but not day 14 post weaning | Peace *et al*[46] |
| Rat | SEB | Prevented the SEB-induced increase in IFN-γ, IL-6, and LTB4 in Peyer's patches and in the mucosa.  Increased anti-inflammatory cytokines (IL‑10 and mature TGF-β) in intestinal mucosa. | Perez-Bosque *et al*[69] |
| Reduced SEB-induced increase in cytotoxic lymphocyte populations of γδ-T cells, natural killer cells, and the number of activated T lymphocytes in lamina propria. | Perez-Bosque *et al*[68] |
| Mouse | Mdr1-/- knockout mouse model of spontaneous colitis | Reduced the percentage of activated Th lymphocytes.  Reduced INF-γ and TNF-α expression in the colon.  Significantly reduced the expression of cytokines IL-2 and IL-17, chemokines MCP-1 and MIP-1b, and iNOS in the mucosa. | Moreto´*et al*[48] |
| Mouse | 2% DSS-induced IBD model | Reduced elevation of IL-1α, IL-4, IL-6, IL-10, MCP-1, and KC | Jiang *et al*[67] |
| Human  (HIV+ adults) | HIV enteropathy | I-FABP fell below baseline in 4/5 patients who continued receiving SBI (*P* < 0.12) out to 48 wk.  MMP-9/TIMP-1 ratios in subjects were significantly lower than controls at baseline (*P* < 0.007)  MCP-1 levels decreased in 5/5 patients who continued receiving SBI (*P* < 0.06) out to 48 wk | Asmuth *et al*[31] |

ETEC K88: Enterotoxigenic *Escherichia coli*, K88 strain; TNF-α: Tumor necrosis factor α; IL: Interleukin; SEB: *Staphylococcus aureus* enterotoxin B; IFNγ: Interferon-γ; LTB4: Leukotriene B4; TGF-β: Transforming growth factor β; MCP‑1: Monocyte chemotactic protein 1; MIP-1b: Macrophage inflammatory protein; iNOS: Inducible nitric oxide synthase; KC: Keratinocyte-derived cytokine; HIV: Human immunodeficiency virus; I-FABP: Intestinal-fatty acid binding protein; MMP-9: Matrix metalloproteinas-9; TIMP: Tissue inhibitor of metalloproteinase.

**Figure 1 Factors involved in the pathogenesis of enteropathy associated with certain human disease states or conditions (*e.g.,* diarrhea-predominant irritable bowel syndrome or human immunodeficiency virus infections).**



**Figure 2 Proposed mechanism of action for serum-derived bovine immunoglobulin   
 protein isolates to aid management of enteropathy.**



**Figure 3 Summary of postulated mechanism of action for serum-derived immunoglobulin/protein isolates.** Immunoglobulins in SBI support intestinal homeostasis by binding MAMPs (endotoxins, *etc.*), toxins or other antigens in the lumen of the intestinal tract. Immunoglobulin binding interferes with downstream antigen detection by cell surface receptors on IELs or APCs such as DCs and macrophages that influence T cell activation, cytokine production, and barrier fortification. Additionally, biologically active compounds in immunoglobulin isolates may interact directly with mucosal immune cells in the lamina propria to influence mucosal inflammatory responses and with epithelial cells to influence barrier function. SBI: Serum-derived immunoglobulin/protein isolates; MAMP: Microbe-associated molecular patterns; IEL: Intraepithelial lymphocytes; APC: Antigen presenting cells; DC: Dendritic cells; T-reg: Regulator T-lymphocytes; Th1: T helper type 1; Th2: T helper type 2. Reprinted with permission from Moretó *et al*[48].

