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Nutritional Protocol for the Treatment of Intestinal Permeability Defects and Related Conditions

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Abstract

Under healthy conditions, the intestinal mucosa permits the absorption of vital nutrients from the gut lumen while presenting a barrier against the passage of pathogenic substances into the body. Leaky gut syndrome describes a pathological increase in permeability of the intestinal mucosa that causes increased absorption of intestinally derived endotoxin, antigens, inflammatory mediators, and, in some cases, intact bacteria. These agents can cause local and systemic reactions associated with a broad range of acute and chronic diseases. In some cases, atrophic changes in the mucosal epithelium can lead to the seemingly paradoxical condition of decreased permeability and malabsorption of essential nutrients concurrent with increased permeability and absorption of pathogenic macromolecules.

Research indicates that certain nutritional factors may help to support mucosal health and promote normal intestinal permeability (IP). These factors include antioxidants, mucosal nutrients, digestive enzymes, probiotics, and dietary fiber. Some of these nutrients have also been shown to lead to improvement in diseases associated with leaky gut syndrome. This article outlines evidence of efficacy for a number of these agents. It also includes recommendations for a nutritional protocol to treat IP defects. A number of the recommendations in this article are based on double-blind, placebo-controlled clinical studies that show statistically significant benefit for certain dietary supplements in the treatment of IP defects and related conditions. In most cases, however, the recommendations are based on indirect evidence of efficacy from *in vitro* human studies or animal research. The nutritional protocol, nutrient forms and dosages presented are the author's recommendations and have not been studied in controlled clinical trials.

Introduction

The human gut contains enough endotoxin, inflammatory mediators, and bacteria to kill the host many times over.[1] A healthy functioning intestinal mucosa is the body's primary line of defense against these potentially lethal agents. Catastrophic failure of the gut mucosal barrier has been identified as the main cause of multiple organ failure, the leading cause of death seen in surgical intensive care units with a mortality rate of approximately 70% .[2]

In critically ill individuals, toxins escaping from the gut lumen activate a local inflammatory response, which leads to further intestinal inflammation, tissue destruction, and production of cytokines and inflammatory mediators. Mucosal damage also causes increased IP with further release of inflammatory mediators and translocation of gut bacteria.[3] Intestinally derived inflammatory mediators lead to a systemic inflammatory and autoimmune response. Circulating inflammatory mediators lead to further increases in gut permeability and the release of gut-derived mediators in a vicious cycle that can culminate in multiple organ failure and death. In addition to surgical emergencies, multiple organ failure can also be seen in response to trauma, burn injuries, sepsis, pancreatitis, and shock.[4] Leaky gut syndrome represents a less severe example of pathologically increased IP that can often be seen in clinical practice. The resulting leakage of luminal toxins and inflammatory mediators is associated with a number of chronic inflammatory, autoimmune, and functional disorders. (See Table 1.)

TABLE 1

Conditions Caused By Or Seen In Connection With Intestinal Permeability Defects

- Multiple organ failure[5,6]
- Chronic fatigue syndrome[7,8,9,10]
- Ulcerative colitis[11,12]
- Crohn's disease [13,14,15,16,17]
- Celiac disease[18,19]
- Diarrhea-predominant irritable bowel syndrome[20]
- Inflammatory joint disease [21,22,23,24]
- Ankylosing spondylitis[25,26,27,28]
- Juvenile onset arthritis[29]
- Psoriatic arthritis[30]
- Food allergy[31,32,33,34]
- Atopic dermatitis, eczema[35]
- Chronic heart failure[36,37]
- Psychological conditions[38,39]
- HIV/AIDS[40,41]
- Chemotherapy[42,43]
- Pelvic radiotherapy[44,45]

Diagnosis

The lactulose-mannitol permeability test is one of the methods most widely used to diagnose IP defects.[46,47] The test is based on an oral challenge with lactulose and mannitol, two non-metabolized sugar molecules. Under normal conditions, small water-soluble molecules such as mannitol are absorbed readily through mucosal epithelial cell membranes by passive diffusion (transcellular uptake). Larger molecules like the disaccharide lactulose are normally excluded by cell membranes but can be slightly absorbed through the tight junction apparatus between cells (paracellular uptake). The amount of lactulose and mannitol recovered in the urine after 6 hours and the ratio between them are used as indicators of IP and mucosal barrier function.

Recent studies have examined the sensitivity and specificity of the lactulose-mannitol (L/M) test for the diagnosis of IP defects in a number of specific conditions. A 2008 controlled clinical trial found that the L/M ratio showed 100% specificity and 89.5% sensitivity in assessing IP defects in patients with Crohn's disease. Values for Crohn's patients differed significantly from the control group ($P < 0.0001$).[48] A 2009 clinical study in 47 patients with celiac disease found that the L/M test had a sensitivity of 85% but a specificity of only 46.2% for detecting severe mucosal damage on follow-up investigation in patients with celiac disease. That study also found that assays of saccharose excretion and serum endomysial antibodies (EMA) showed sensitivities and specificities of 60% and 52.6%, and 50% and 77.8% respectively. Investigators concluded that these noninvasive tests were not an accurate substitute for biopsies in follow-up investigations of patients with celiac disease.[49] In a group of 22 adult celiac patients on a gluten-free diet for 12 months, a 2007 controlled clinical study found that urinary lactulose excretion and the L/M ratio were significantly less than in the control group, and mannitol excretion was greater than in controls ($P < 0.0001$). Investigators concluded that the L/M test allowed a more precise physiologic correlation than serum antigliadin antibodies and offered more information for monitoring of patients.[50] A prospective cohort study in 261 patients with chronic diarrhea found that the L/M test was an effective screening tool for differentiating between organic and functional causes of chronic diarrhea. The L/M test accurately predicted the final diagnosis of organic cause of chronic diarrhea with an odds ratio of 1.5 (95% CI = 1.29–1.78).[51] A 2006 study concluded that dietary lactose and fructose could interfere with gas chromatography peaks in the measurement of lactulose and mannitol. Investigators found that a new gas chromatographic assay method permitted simultaneous quantification of urinary lactulose, mannitol, sucralose, and sucrose without interference from dietary lactose and fructose and was therefore an accurate method for evaluating IP.[52] The L/M test may have limited sensitivity or specificity in certain conditions; however, it appears to be a widely used screening tool for the diagnosis of leaky gut syndrome and may have value in monitoring clinical progress of patients undergoing treatment for conditions that are caused by or related to IP defects.

Causative Factors

In addition to surgery, trauma, burns, sepsis, pancreatitis, and shock, a number of other risk factors have been identified in the literature as potential causes of IP defects. (See Table 2.) In most cases of altered intestinal barrier function, mucosal inflammation and oxidative stress have been identified as central pathophysiological mechanisms.[53,54,55,56]

Nutritional Treatment Protocol

Interventions aimed at reducing or eliminating these causative factors may be of value in correcting IP defects. Of note, IP defects are characteristic of inflammatory bowel diseases (IBD) such as ulcerative colitis and Crohn's disease.[73,74] Studies have shown that intestinal inflammation and mucosal oxidative stress are pathophysiological features common to both IBD and abnormally increased IP in general.[75,76,77,78] Alteration of tight junction proteins, reduction in tight junction strands, and strand breaks are characteristic in Crohn's disease.[79] In ulcerative colitis, epitheleal barrier leaks occur as a result of tight junction protein changes, microerosions, and upregulated epithelial apoptosis.[80] Therefore, it seems reasonable to postulate that nutritional treatments aimed at reducing intestinal inflammation and mucosal oxidative stress in IBD may also lead to improved mucosal barrier function and normalized IP in other conditions.

TABLE 2

Causative Factors Associated With Development Of Intestinal Permeability Defects

Intestinal inflammation[57,58]
Mucosal oxidative stress[59,60]
Stress[61,62]
Nonsteroidal inflammatory drugs (NSAIDs)[63]
Alcohol consumption[64,65]
Cow's milk intolerance[66,67]
Small intestine bacterial overgrowth[68,69]
Pancreatic insufficiency[70]
Intestinal infections[71]
Obstructive jaundice[72]

Evidence is presented below indicating that a number of antioxidants, mucosal nutrients, enzymes, probiotics, and fiber may be of benefit in the treatment of leaky gut syndrome and related conditions. In addition, a treatment protocol is presented that includes proposed combinations and dosages of these nutrients. As noted, the combinations, forms of nutrients, and dosages are the author's recommendations and have not been studied in controlled clinical trials.

Antioxidants

Leaky gut syndrome is associated with intestinal inflammation, mucosal oxidative stress, lipid peroxidation, and depletion of antioxidant reserves in the intestinal mucosa.[81,82,83,84,85,86] Human and animal studies have shown evidence of potential benefit from supplementation with antioxidant nutrients and plant extracts in preventing oxidative damage and restoring normal mucosal barrier function.

Quercetin is a naturally occurring flavonoid with antioxidant, anti-inflammatory, and anticancer properties.[87] Quercetin has been shown to enhance intestinal barrier functions in human intestinal cells.[88] Mast cells play an important role in the pathogenesis of intestinal mucosal inflammation and increased IP.[89] Quercetin helps to control intestinal inflammation by inhibiting histamine release from human intestinal mast cells.[90,91] It has also been shown to inhibit gene expression and production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha), interleukin (IL) 1-beta, IL-6, and IL-8 from human mast cells.[92] The anti-allergic drug disodium cromoglycate is structurally related to quercetin.[93]

A number of studies have demonstrated bioavailability of quercetin on oral administration or shown significant benefit in a number of conditions including systolic hypertension, interstitial cystitis, and chronic prostatitis.[94,95,96] For example, a 2009 double-blind, placebo-controlled, cross-over trial examined the effects of supplementation with 150 mg per day of quercetin over a 6-week treatment period in a group of 93 overweight or obese subjects aged 25–65 years with signs of metabolic syndrome. Mean fasting plasma quercetin increased from 71–269 nmol/l during the treatment period ($P < 0.001$) and quercetin decreased systolic blood pressure by 2.6 mmHg compared to placebo ($P < 0.01$) Quercetin also significantly decreased plasma-oxidized low-density lipoprotein (LDL) concentrations.[97] However, it appears that no published human clinical studies have investigated the effects of quercetin supplementation on IP.

Ginkgo biloba extract (GBE) has antioxidant and free radical–scavenging properties with cytoprotective effects on cells of the gastrointestinal mucosa.[98,99] Oral supplementation with GBE has been shown to

reduce macroscopic and histological damage to the colonic mucosa *in vivo* and to significantly decrease pro-inflammatory cytokines in experimentally induced ulcerative colitis.[100] Ginkgo has also been shown to prevent increased IP and mucosal damage associated with small intestinal ischemia in a dose-dependent manner in animal models.[101] Pre-treatment with GBE was found to attenuate mucosal damage and significantly decrease markers of oxidative stress in ischemia and reperfusion of the small intestine *in vivo* in animals.[102] While evidence from animal research indicates that GBE may help to promote normal intestinal barrier function, there do not appear to be any published controlled trials on the use of GBE to treat IP defects in humans.

Vitamins C and E play essential roles in protecting intestinal mucosal cells from oxidative damage and free-radical pathology. In one clinical trial, oral supplementation with 300 mg of vitamin E resulted in evidence of decreased inflammation in the colonic mucosa of ulcerative colitis patients.[103] A 1995 study in patients with IBD showed significantly decreased levels of vitamin C in mucosal tissues compared to non-IBD controls.[104] In light of the shared pathophysiological mechanisms of intestinal inflammation and mucosal oxidative stress found in both IBD and IP as described above, it seems reasonable to postulate that vitamins C and E may also help to promote normal IP function, however this does not appear to have been investigated in published controlled clinical studies. Treatment with vitamin C (ascorbic acid) and vitamin E (alpha-tocopherol) has been shown to reduce the incidence of bacterial translocation from the intestinal lumen and decrease mucosal lipid peroxidation in chronic portal hypertension and common bile duct ligation in animals.[105]

N-acetyl-L-cysteine (NAC) is an antioxidant, detoxifier, and precursor for glutathione synthesis on oral administration in humans. NAC and glutathione quench free radicals that can contribute to oxidative damage of the intestinal mucosa. Pre-treatment with NAC has been shown to prevent increased IP following intestinal ischemia and reperfusion in animals.[106] Dietary zinc appears to play a critical role in the maintenance of normal IP and control of inflammation. Zinc deficiency has been shown to cause disruption in mucosal barrier function and increased secretion of inflammatory mediators in human intestinal epithelial cells.[107] Zinc has cytoprotective activity in the gastrointestinal tract and helps to stabilize intestinal mast cells.[108] Table 3 outlines a proposed combination of antioxidants and daily dose ranges to reduce intestinal oxidative stress, modulate release of inflammatory mediators, and support normal mucosal permeability.

TABLE 3

Antioxidant Supplementation

Antioxidant Combination to Provide:	
Quercetin	400–800 mg
Ginkgo biloba extract (24% ginkgo flavone glycosides)	40–80 mg
Vitamin C (calcium, magnesium ascorbates)	1,000–2,000 mg
Vitamin E (d-alpha tocopheryl succinate)	200–400 mg
N-acetyl-L-cysteine (NAC)	150–300 mg
Zinc (Zinc picolinate)	45–90 mg
(Consider copper supplementation at 0.75–1.5 mg in light of zinc intake.)	

Mucosal Nutrients

Certain nutrients have been shown to help maintain healthy structure and function of mucosal cells and promote normal IP. These include L-glutamine, phosphatidylcholine, N-acetyl-D-glucosamine and gamma-linolenic acid.

L-glutamine is an important energy source for cells of the intestinal mucosa and has been shown to be conditionally essential for normal mucosal structure and function.[109,110,111] Glutamine appears to be required for normal production of secretory immunoglobulin A (IgA) in the intestines. Secretory IgA is the most abundant immunoglobulin in external secretions and is central to the normal function of the intestinal mucosa as an immune barrier. Glutamine has been shown to help maintain gut mass and intestinal barrier function against bacteria and may be essential to host survival during critical illness in humans.[112]

Addition of L-glutamine to total parenteral nutrition (TPN) prevents pathologic increase in IP in humans.[113] A 1993 controlled study in 20 randomly assigned hospital inpatients compared the effects of standard total parenteral nutrition (STPN) to glutamine-enriched total parenteral nutrition (Gln TPN). Mucosal biopsy specimens were taken from the lower duodenum and IP was measured with the L/M test before and after 2 weeks of treatment. IP remained unchanged in the Gln TPN group but increased in the STPN group. Villous height was also unchanged in the Gln TPN group but was decreased in the STPN group. Investigators concluded that supplementation of TPN with glutamine prevented deterioration of gut permeability and preserved mucosal structure. Glutamine-enriched TPN also preserves gut-associated lymphoid tissue (GALT) function and intestinal IgA levels in animal studies.[114] A 2005 controlled animal study showed that glutamine added to the diet led to a significant reduction of increased IP and bacterial translocation in experimental biliary obstruction.[115]

N-acetyl-D-glucosamine (NAG) is a naturally occurring aminoglycan found in large concentrations in intestinal mucus, secretory IgA, and other immunoglobulins. Intestinal mucus plays a critical role in protecting the host by providing a mechanical and immunological barrier against toxins, antigens, and bacteria in the gut lumen. Studies have shown that NAG blocks the adherence of *Candida albicans* to the gastrointestinal mucosa *in vivo* in animals and stimulates the growth of beneficial *Bifidobacteria in vitro*.[116,117] Studies indicate that a defect exists in the glycoconjugate composition of intestinal mucin in many patients with IBD.[118,119] One clinical study found that NAG is deficient in the mucin of IBD patients compared to non-IBD controls. This appears to be due to a defect in the biosynthesis of NAG involving N-acetylation of glucosamine-6-phosphate to form NAG.[120] NAG can be absorbed from the gut lumen and directly incorporated into glycosaminoglycans and glycoproteins of the intestinal mucosa.[121]

A pilot study in 2000 investigated the efficacy of NAG administration in children with severe ulcerative colitis and Crohn's disease who were unresponsive to conventional treatment. Patients were given NAG orally or rectally, 3–6 g daily. Histochemical assessment of epithelial and matrix NAG and glycosaminoglycans was performed where biopsy specimens were available. Eight of 12 children who received oral NAG showed clear improvement. Of the children with symptomatic Crohn's stricture, 4 out of 7 showed endoscopic and radiological improvement and were able to avoid surgery over a mean follow-up period of 2.5 years. Investigators concluded that NAG administration may be useful in IBD with stricture but that further trials were needed to confirm efficacy.[122] No published controlled studies appear to have been conducted to investigate the effects of NAG supplementation on IP defects in humans. However, it may be reasonable to postulate that similar benefits exist as those seen in the above trial in IBD patients due to the shared pathophysiological mechanisms of intestinal inflammation and mucosal oxidative stress commonly found in both IBD and IP defects.

Phosphatidylcholine (PC) is a constituent of human bile and a key component of the hydrophobic mucus gel that protects the gastrointestinal mucosa.[123] Exposure to lipopolysaccharides (LPS) can cause injury to both gastrointestinal and non-gastrointestinal tissues. A 2008 controlled animal study showed that oral administration of PC prior to LPS exposure significantly prevented pathological increases in IP. Investigators concluded that enteral formulations containing PC may be useful adjuncts in preventing intestinal injury and increased permeability from exposure to intestinal endotoxins.[124]

In vitro human studies have shown that PC administration can enhance the protective effect of conjugated bile salts by reducing IP to endotoxin and suppressing production of inflammatory cytokines.[125] A

2009 study showed that the addition of PC to conjugated primary bile salts can reverse ethanol-induced increases in IP to endotoxin and prevent inflammatory activation of leukocytes. Ethanol is known to enhance transepithelial permeability to endotoxin and subsequent activation of human leukocytes. Human intestinal epithelial cells (Caco-2) co-cultured basolaterally with mononuclear lekocytes were challenged apically with endotoxin from *E. coli* K12 and incubated with or without the addition of conjugated primary bile salts (CPBS), PC, and pooled human bile in combination with ethanol. Investigators found that ethanol-induced transepithelial permeability of endotoxin and transepithelial stimulation of leukocytes were nearly completely abolished after apical supplementation of CPBS with PC but not by CPBS alone.[126]

Other nutrients shown to support epithelial barrier integrity and normal mucosal permeability include the polyunsaturated fatty acids gamma-linolenic acid (GLA), docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). GLA, DHA and EPA have been shown to be incorporated in to the membrane phospholipids fraction of human mucosal epithelial cells and to reduce mucosal permeability defects caused by inflammatory cytokines.[127] Table 4 contains a recommended combination of nutrients and daily dose ranges to support mucosal structure and normal barrier function.

TABLE 4

Targeted Mucosal Nutrients

Mucosal Nutrient Combination to Provide:	
L-glutamine	750–1,500 mg
N-acetyl-D-glucosamine (NAG)	375–750 mg
Phosphatidylcholine	75–150 mg
Gamma-linolenic acid (GLA)	200–400 mg

Digestive Enzymes and Intestinal Permeability

Adequate digestion is a prerequisite for normal gastrointestinal function and overall health. Deficiencies in digestive enzymes and imbalances in gastrointestinal pH can cause impaired digestion that can contribute to malabsorption of nutrients, food intolerance, food allergy, autoimmune conditions, bacterial overgrowth, and signs and symptoms of gastrointestinal discomfort.[128,129,130,131,132,133,134] Insufficient pancreatic enzyme activity can also cause increased IP and leaky gut syndrome.[135] Supplementation with digestive enzymes can help to treat enzyme deficiencies and improve conditions related to impaired digestion.

Oral supplementation with acid-stable fungal enzymes, also known as plant enzymes or microbial enzymes, has been shown to be safe and effective in the treatment of pancreatic insufficiency in humans and animals. In patients with gastrointestinal pH imbalances, these enzymes may offer advantages over conventional and enteric-coated pancreatic enzyme preparations.[136,137,138,139,140,141]

Acid-Stable Fungal Enzymes

Pancreatic enzymes have optimal activity in the neutral to alkaline pH range and are unstable in acidic conditions. Exposure to gastric acid can destroy up to 90% of supplemental pancreatic lipase and 65% of pancreatic trypsin.[142] Enteric coatings designed to protect pancreatic enzymes from gastric acidity may not dissolve reliably in all cases.[143,144] Some patients with pancreatic insufficiency are not able to concentrate bicarbonate sufficiently to alkalinize the upper small intestine for normal release of enteric coatings. The resulting jejunal hyperactivity can also inhibit pancreatic enzyme activity even if enteric coatings do dissolve as intended.[145,146]

Studies show that certain acid-stable fungal enzyme preparations are naturally stable and active in both acid and alkaline pH conditions. As a result, they are effective without the need for enteric coatings or coadministration of pH-altering drugs, even in individuals with gastrointestinal pH imbalances that could limit the effectiveness of pancreatic enzymes. Due to their broad pH range of activity, they begin digesting food in the stomach and continue working in the intestine.[147,148,149]

Studies have compared the efficacy of pancreatic enzymes and acid-stable fungal lipase in the treatment of exocrine pancreatic insufficiency in humans and animals. Some of these studies have shown that acid-stable fungal lipase is effective at a substantially lower dose than pancreatin in reducing steatorrhea and relieving symptoms of diarrhea and digestive discomfort.[150,151]

A controlled, crossover design clinical trail in 17 patients with severe pancreatic insufficiency, steatorrhea, diarrhea, and abdominal discomfort compared the effects of an acid-stable fungal enzyme preparation with conventional pancreatic enzymes and enteric-coated pancreatin. In one group, 9 surgical patients with duodenopancreatectomy and bowel resection (Whipple's procedure) 3–8 months prior to the study had pre-trial stimulated pancreatic enzyme secretion less than 10% of normal. In the other group of 8 nonsurgical patients with intact GI tracts had pre-trial stimulated pancreatic enzyme levels less than 29% of normal. Both groups were placed on a diet containing 100 g/day of fat. Stools were collected for 72 hours, 5 days after discontinuing all medications and supplemental enzymes. Thereafter, all patients were placed on 2-week periods of treatment using enteric-coated pancreatin (100,000 lipase units [LU]) followed by conventional pancreatin (360,000 LU) and finally, acid-stable fungal lipase (75,000 LU). Stools were collected for the last 72 hours of each treatment period and analyzed for fecal fat content and stool weight. All 3 treatment protocols lead to a significant reduction in fecal fat excretion in both groups ($P < 0.05$). All patients also became virtually symptom-free with regard to diarrhea and abdominal discomfort. In this study, the acid-stable fungal lipase was effective at an enzyme dose 25% lower than enteric-coated pancreatin and more than 4 times lower than conventional pancreatin.[152]

A similar placebo-controlled, randomized crossover design study in dogs compared the effectiveness of 4,000 LU of acid-stable fungal lipase to 60,000 LU of lipase from pancreatin in the treatment of surgically induced pancreatic insufficiency and steatorrhea. Dogs in the placebo group had significant weight loss due to malabsorption along with pathologically elevated fecal fat and stool weight. Dogs in both treatment groups had significant reductions in fecal fat and stool weight with no significant weight loss. The acid-stable fungal lipase was effective at an enzyme dose 15 times lower than the pancreatin.[153]

Clinical studies in humans show that intestinal secretion of lactase, sucrase, and maltase are decreased in conditions with intestinal mucosal injury and morphological changes including celiac disease and chronic diarrhea.[154,155,156,157] Lactase (beta-galactosidase) deficiency occurs in more than half of the adult human population.[158] A study of 232 children with intestinal biopsies found that lactase activity decreased significantly with age and correlated with degree of intestinal injury.[159] Lactose intolerance produces abdominal pain, bloating, diarrhea, and increased breath hydrogen excretion. A number of controlled human studies have shown that fungal lactase administered orally or added to milk at mealtime is effective at preventing or reducing signs and symptoms of intolerance in individuals exposed to dietary lactose.[160,161,162,163]

Bioavailability of minerals can be considerably reduced by dietary phytate. Humans and monogastric animals produce little or no endogenous phytase in the stomach and small intestine.[164] A controlled clinical trial in human subjects showed that dietary supplementation with an acid-stable fungal phytase from *Aspergillus niger* increased iron absorption. The study also showed that the fungal phytase was stable and active across a broad pH range from 1.0 to 7.5 and that it initiated digestion of dietary phytate beginning in the stomach.[165] Animal studies have shown that supplementation with fungal phytase helped to improve zinc, calcium, and phosphorus bioavailability and to increase bone strength in a dose-dependent manner.[166,167]

Studies have shown that supplementation with fungal cellulase helps to increase nutritional value of dietary grains in animals.[168,169] Cellu-

lase significantly improved digestibility of dietary cell wall components and increased solubility of calcium, phosphorus, iron, zinc, and copper associated with cell walls.[170] Studies using multienzyme combinations including fungal amylase, protease, invertase, phytase, and cellulase have shown increased digestibility of nutrients and improved growth in pigs and chickens.[171,172] Table 5 contains a recommended combination of acid-stable fungal enzymes to be taken at mealtime as part of a nutritional protocol to support healthy digestion and normal IP.

TABLE 5
Digestive Plant Enzymes

Acid-Stable Enzyme Combination Totaling 613 mg to Provide:	
Protease	30,000 USP
Amylase	32,000 USP
Lipase	2,100 FIP
Lactase	1,600 ALU
Sucrase	300 INVU
Maltase	32,100 DP°
Phytase	1.7 PU
Cellulase	350 CU

Probiotics

Intestinal microflora have been described as a postnatally acquired organ comprised of a large diversity of bacteria that perform a range of important functions for the host.[173] Probiotics are orally administered microorganisms that help to maintain or restore beneficial intestinal microflora and prevent or treat gastrointestinal disorders and related systemic conditions. A number of review articles have shown that supplementation with probiotics may be of benefit in the treatment or prevention of IP defects and related disorders, including IBD, irritable bowel syndrome, food allergy, atopic dermatitis, eczema, infectious diarrhea, antibiotic-associated diarrhea, chemotherapy-induced intestinal damage, and other conditions in humans.[174,175,176,177,178,179,180,181,182,183,184,185] In order to be effective, probiotic preparations must be able to survive gastrointestinal conditions and colonize the intestine, at least temporarily, by adhesion to the intestinal mucosa.[186]

Ulcerative colitis (UC) is associated with IP defects in addition to other characteristic signs and symptoms.[187,188] *Bifidobacterium longum* supplementation was found to significantly improve emotional function scores from an inflammatory bowel disease questionnaire (IBDQ) in a randomized, controlled trial involving 120 outpatients with UC. Dosage of *B. longum* in the study was 2 billion colony forming units (CFU) daily. The same dosage of *B. longum* in combination with 8 g of psyllium was even more effective at improving quality of life with significant improvement in total IBDQ scores ($P = 0.03$). The combination also significantly reduced C-reactive protein levels ($P = 0.04$).[189] A double-blind, placebo-controlled, crossover clinical study showed that *B. longum* is also effective in the treatment of antibiotic-associated diarrhea. Ten healthy adult volunteers were given erythromycin 1g orally twice daily for each of two 3-day treatment periods separated by a 3-week washout period. Subjects were given yogurt with *B. longum* (BY) or placebo yogurt without *B. longum* (PY) randomly assigned during each treatment period. Stool weight, stool frequency, and presence of abdominal discomfort were recorded 1 day before (D-1) and on the third day (D-3) of each treatment period. Subjects taking PY had significant increases in stool weight and frequency on D-3 compared to D-1 of the placebo period ($P < 0.005$) and significant increases in the same parameters compared to D-3 of the BY period. Incidence of abdominal discomfort was also greater during the PY period with 6 of 10 participants experiencing symptoms while taking PY compared to 1 of 10 during BY treatment.[190]

IP is increased in patients with diarrhea-predominant irritable bowel syndrome (D-IBS). A 2008 randomized single-blind, placebo-controlled study in 30 D-IBS patients compare the effects of supplementation with probiotic fermented milk containing *Lactobacillus acidophilus*, *B. longum,* and other lactic acid bacteria to a placebo milk beverage without probiotics. After 4 weeks, small bowel permeability decreased significantly ($P = 0.004$) and global IBS scores decreased significantly ($P < 0.001$) in the probiotic group versus placebo.[191]

A randomized, placebo-controlled trial in 2009 examined the effects of oral supplementation with *Bifidobacterium breve* Yakult in 42 children undergoing cancer chemotherapy. Frequency of fever and use of intravenous antibiotics were lower in the probiotic group versus placebo. Incidence of *Enterobacteriaceae* overgrowth was lower in the probiotic group, and only the probiotic group maintained normal fecal organic acid and pH levels.[192]

A 2009 randomized, double-blind, placebo-controlled trial evaluated the effects of prenatal and postnatal probiotic supplementation with *B. bifidum* BGN4, *B. lactis* AD011 and *L. acidophilus* AD031 in 112 pregnant women with family histories of allergic disease. Probiotic supplementation was started 4–8 weeks before delivery and continued for 6 months after delivery. Babies were breastfed exclusively for 3 months and fed with breast milk or cow's milk from 4–6 months of age. After 1 year, children in the probiotic group had a significantly lower incidence of eczema than controls (18.2% vs. 40.0%, $P = 0.048$).[193]

A double-blind, placebo-controlled, crossover study in 2004 investigated the effects of *L. rhamnosus* 19070-2 and *L. reuteri* DSM 12246 in 41 children with moderate to severe atopic dermatitis, increased IP, and gastrointestinal symptoms. IP was measured with the lactulose-mannitol oral challenge. Investigators found a positive association between the lactulose-mannitol ratio and severity of eczema. After 6 weeks of probiotic supplementation, gastrointestinal symptoms were significantly improved ($P = 0.002$) and the lactulose to mannitol ratio was significantly lower ($P = 0.001$). Investigators concluded that probiotic supplementation may improve intestinal barrier function and decrease gastrointestinal symptoms in children with atopic dermatitis.[194]

L. rhamnosus Lcr35 has been shown to be effective in shortening the duration of acute diarrhea in children. A 2009 open-label randomized trial in 23 children with acute rotaviral gastroenteritis found that *L. rhamnosus* significantly reduced fecal rotavirus concentrations in a dose-dependent manner ($P = 0.012$). The minimal effective dose was found to be 0.6 billion CFU per day for 3 days.[195] Table 6 contains a recommended combination of probiotic bacteria to help maintain healthy intestinal microflora and normal mucosal permeability.

TABLE 6
Probiotic Intestinal Microflora

Probiotic Combination to Provide 1–5 billion CFU:
Lactobacilli: L. acidophilus, L. rhamnosus
Bifidobacteria: B. bifidum, B. lactis, B. longum, B. breve

Dietary Fiber

Dietary fiber plays an important role in maintaining normal gastrointestinal function and health. Studies indicate fiber helps maintain normal barrier function of the intestinal mucosa.[196,197,198,199] Soluble fiber is fermented by colonic microflora, promoting the growth of beneficial *Bifidobacteria*. Fermentation of dietary fiber by colonic microflora is the primary source of intestinal short-chain fatty acids including butyric acid. Butyric acid is an important energy source for intestinal epithelial cells and plays a key role in colonic homeostasis. Butyrate has been shown to inhibit inflammation, reduce oxidative stress and maintain normal barrier function of the colonic mucosa.[200,201]

Psyllium seed and flaxseed fiber each demonstrate benefits of both soluble and insoluble dietary fiber in humans.[202,203,204] Both soluble and insoluble dietary fiber have been shown to help maintain normal barrier function in the distal colon in animal studies.[205,206,207] In a study of 26 healthy young adult volunteers, consumption of 9 g/day of flax for a period of 2 weeks resulted in effective laxation and fecal bulking capacity of about 3:1 for each gram of flax consumed. In a second arm of this study, 11 subjects consumed flax in a test meal baked into bread versus placebo bread without flax. Flax consumption significantly controlled peak postprandial blood glucose levels and area under the curve compared to control bread without flax ($P < 0.05$ and $P = 0.015$ respectively).[208]

A randomized controlled trial in 2009 investigated the effectiveness of psyllium or bran supplementation versus placebo for control of symptoms in 275 patients with irritable bowel syndrome. Patients in 3 groups took 10 g of fiber, bran, or placebo daily. After 3 months of treatment, patients in the psyllium group had significant reduction in symptom severity ($P = 0.03$). Patients taking bran had a nonsignificant trend toward reduced symptom severity.[209] In a 2007 clinical trial, combined treatment with psyllium and probiotic *Bifidobacteria* and *Lactobacilli* was found to significantly improve symptoms of diarrhea and abdominal pain in patients with Crohn's disease.[210] Table 7 contains a recommended combination of dietary fiber for daily supplementation to promote healthy gastrointestinal function and normal mucosal permeability.

TABLE 7
Dietary Fiber Supplementation

Dietary Fiber Combination to Provide:	
Psyllium Seed Husk	1 – 5 g
Flax Seed	1 – 5 g

Case Study of Nutritional Intervention in Leaky Gut Syndrome with Joint Pain and Fatigue

A 1993 pilot study investigated the effects of dietary supplements and diet restrictions on musculoskeletal complaints and IP in patients with nontraumatic inflammatory joint pain and fatigue of at least 60 days duration. Ten patients enrolled in the study were given a baseline symptom questionnaire and a lactulose-mannitol oral challenge test to measure IP. Patients were placed on a restricted diet that eliminated wheat, dairy, eggs, and refined carbohydrate products. They were also placed on a protocol of dietary supplements consisting of a digestive plant enzyme preparation (e.g., acid-stable fungal protease, amylase, lipase), a plant enzyme protease, an antioxidant combination formula, and a probiotic and prebiotic combination formula. No other drugs or pain medications were permitted during the study.

At the end of the 60-day treatment period, follow-up study questionnaires and repeat IP tests were administered. Seven patients completed the two-month study protocol and follow-up testing. This group included 2 patients who had been previously diagnosed with psoriatic arthritis and 1 patient with systemic lupus erythematosis. Results reported in the study showed that all 7 patients had reduced IP on follow-up testing. All patients reported decreased fatigue with 1 reporting a small improvement, 4 moderate, and 2 patients reporting significant improvements in energy. Six out of 7 reported modest to moderate decreases in musculoskeletal complaints. Study limitations included an open-label, uncontrolled design, small sample size, lack of quantitative or statistical analysis of study results, and subjective reporting of improvements in joint pain and fatigue. The author concluded that study results indicated a correlation between IP, musculoskeletal pain, and chronic fatigue, and that a program of dietary changes and supplements may exert an influence on gut permeability, musculoskeletal complaints, and fatigue in some patients.[211]

Conclusion

IP defects can cause severe illness and death in highly compromised individuals. Under less-critical conditions encountered in clinical practice, leaky gut syndrome can often be identified as an associated or causative factor in a broad range of chronic disorders. A number of double-blind, placebo-controlled studies provide evidence that dietary supplementation with certain antioxidants, mucosal nutrients, enzymes, probiotics, and fiber may be significantly effective in the treatment of IP defects and related conditions. In most cases, however, evidence is indirect and based on *in vitro* human studies or animal research.

This article presents evidence of efficacy for a number of nutritional agents along with the author's recommendations for a treatment protocol consisting of various combinations, forms, and dosages of these nutrients. The article does not address in any detail diet or lifestyle factors or drug therapies that may be important for certain individuals in the etiology or treatment of IP defects. Some of the proposed combinations and dosages in this protocol have been used anecdotally for nearly 20 years; however none of them have been evaluated for efficacy under controlled clinical conditions. Nonetheless, it may be reasonable to postulate that nutritional supplementation with a protocol similar to the one outlined here could be of benefit for some patients in the treatment of permeability defects and related conditions.

Disclosure

The author of this review paper is a consultant for Integrative Therapeutics. The ingredients reviewed are contained in products sold by Integrative Therapeutics.

About the Author

Corey Resnick, ND, has been a licensed naturopathic physician for over 30 years. He graduated from National College of Naturopathic Medicine where he served on the board of directors and taught on the faculty. He also served as a director of the American Association of Naturopathic Physicians. Dr. Resnick also had a naturopathic family practice near Portland, Ore. Dr. Resnick co-founded Tyler Encapsulations and currently serves as a consultant for Integrative Therapeutics specializing in dietary supplements for healthcare practitioners. He has lectured internationally on clinical nutrition and is a contributing author to the Textbook of Natural Medicine.

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