INTEGRATIVE THERAPIES FOR

INFLAMMATORY BOWEL DISEASE

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PATHOPHYSIOLOGY

Crohn's disease (CD) and ulcerative colitis (UC) are thought to result from inappropriate activation of the mucosal immune system, facilitated by regulatory defects in the mucosal immune response and failure of the mucosal barrier that separates immune response cells from the contents of the intestinal lumen. The normal flora of the gut lumen act as triggers for the inflammatory response and appear to play a central role in pathogenesis.[1] In both diseases, an increased number of surface-adherent and intracellular bacteria have been observed in mucosal biopsies.[2 3] The immune responses provoked by these bacteria are different in the two disorders, however.[4] The immune response underlying the pathology of CD, as in other granulomatous diseases, is driven by lymphocytes with a type 1 helper-T-cell (TH1) phenotype and their cytokines: interleukin-2 (IL-2) and gamma-interferon (g-IFN). These TH-1 products promote a self-sustaining cycle of activation with macrophages that includes interleukin 12 (IL-12), which further increases TH-1 activity, and interleukins 1 and 6 (IL-1, IL-6) and tumor necrosis factor-alpha (TNF-a), which create a broader inflammatory response. Although macrophage-derived IL-6 and TNF-a are also important for the pathophysiology of UC,

the lymphocytes that organize the inflammatory response in UC demonstrate an atypical type 2 helper-T-cell (TH2) phenotype, with interleukin-5 (IL-5) as a distinctive cytokine mediator[5]. The anti-inflammatory cytokine, interleukin-1 receptor antagonist (IL-1ra), is decreased in both diseases.[6]

Malnutrition is a major reversible complication of inflammatory bowel disease (IBD). The mechanisms of malnutrition include: anorexia resulting from the systemic effects of IL-1, a catabolic state induced by TNF-a, malabsorption due to disease or surgical resection, nutrient losses through the inflamed and ulcerated gut, small bowel bacterial overgrowth resulting from strictures or fistulas, and the side effects of drug therapy.[7] Inflammation increases oxidative stress in the bowel mucosa and decreases levels of anti-oxidants.[8] Zinc and copper or the zinc- and copper-dependent enzyme, superoxide dismutase (Cu-Zn SOD), is reduced in mucosal biopsies from patients with IBD.[9] Oxidative stress caused by inflammation decreases the mucosal concentration of vitamin C.[10] Plasma levels of vitamins A and E are lower and plasma levels of the oxidative stress marker, 8-hydroxy-deoxy-guanosine (8-OHdG), are higher in IBD patients than in controls.[11] Compared to controls, children and adults with IBD have lower blood levels of zinc and selenium, mineral co-factors of antioxidant enzymes[12 13 14], and adults with UC may show lower levels of beta-carotene, magnesium, selenium and zinc[15]. Micronutrient deficits may favor self-perpetuation of IBD by causing defects in the mechanisms of tissue repair[16]. Micronutrient deficiencies may also contribute to some complications of IBD, such as growth retardation, osteopenia, urolithiasis and thromboembolic phenomena[17].

In CD, abnormal mucosal barrier function may play a primary role in pathogenesis. Small intestinal permeability is increased among healthy first-degree relatives of patients with CD[18] and is increased in non-inflamed enteric tissue obtained from patients[19]. Aspirin, a drug that increases intestinal permeability of healthy controls, causes an exaggerated increase in intestinal permeability of first-degree relatives of patients with CD[20]. The rate of relapse among patients who have entered remission is directly proportional to the degree of small intestinal hyperpermeability measured with chemical probes[21]. Hyperpermeability is associated with polymorphism of genes associated with regulation of epithelial barrier function[22]; it increases exposure of the intestinal immune system to luminal antigens. Intestinal epithelial lymphocytes of patients with CD are abnormally sensitive to antigens derived from *Enterobacteria* and *Candida albicans*, both normally present in the small intestine.[23] The other genetic polymorphism conferring susceptibility to CD involves genes that regulate the innate immune response to microbial antigens [ref 19].

The role of malnutrition, increased intestinal permeability and hypersensitivity to indigenous gut flora is significant for integrative therapies, because of the influence of diet and dietary supplements on nutritional status, intestinal permeability and the composition of the intestinal microflora.

INTEGRATIVE THERAPIES

ENTERAL FEEDING. Defined formula diets, either elemental or polymeric, are successful in improving nutritional status of patients with IBD and preventing

complications of surgery [ref 6]. In CD, but not in UC, enteral feeding of defined formula diets as primary therapy has been shown to induce remission of active disease in 30 to 80 percent of patients [ref 6]. Although enteral feeding is most commonly used in pediatric patients, because of growth-enhancing and steroid-sparing effects[24], it is equally effective in adults[25] and appears to have a direct anti-inflammatory effect on the bowel mucosa[26]. Theories to explain the anti-inflammatory effect of enteral feeding in CD include: alteration in intestinal microbial flora[27], diminution of intestinal synthesis of inflammatory mediators, nonspecific nutritional repletion or provision of important micronutrients to heal the diseased intestine [ref 21]. Decreased dietary antigen uptake, an early concept, is not a likely mechanism; polymeric diets, composed of whole protein, are as effective as elemental diets, in which nitrogen is supplied as free amino acids[28 29]. Furthermore, the addition of regular food may not diminish the effectiveness of defined formula feedings[30], although a recent pediatric study found that partial enteral nutrition with *ad libitum* food consumption was far less effective than total enteral nutrition without additional food.[31]

Part of the benefit derived from enteral feeding may reflect dietary fat content [ref 6]. Those liquid diets that are most effective in inducing remission of active CD are either very low in fat or supply one-third of their dietary fat in the form of medium-chain triglycerides (MCT) from coconut oil [32 33]. Addition of long-chain triglycerides derived from vegetable oils attenuates benefit[34], whereas diets enriched with MCT oil are as effective as very low fat diets[35]. MCT oil may have a direct anti-inflammatory effect, modulating expression of adhesion molecules and cytokines [ref 6]. The potential role of omega-3 fats in treatment of IBD is discussed below, under Supplements.

The main advantage to enteral feeding as primary therapy for CD is avoidance of medication side effects, especially in children[36]. Although no clear clinical predictors of response have been established, clinicians believe that patients treated early in the course of CD are more likely to respond than those with longstanding disease [ref 21], and small studies indicate that remission may be more likely in patients with ileal involvement than colonic involvement only[37] and with perforating/fistulating disease than with more superficial disease[38]. The main disadvantage to enteral feedings is poor compliance due to lack of palatability and the high rate of relapse (over 60 percent) following their discontinuation. The use of exclusion diets (discussed below) may significantly extend the benefit of enteral feeding regimens.

The specific carbohydrate diet (www.scd.org) is a food-based approach to enteral nutrition for patients with IBD for which there are many anecdotal reports of long-term remission without medication[39]. Its alleged mechanism of action is improvement of nutritional status and alteration in ileocecal flora by the proper choice of nutritious carbohydrate sources [40]. It is far more effective for patients with CD than UC (Elaine Gottschall, personal communication). In practice, the diet consists of meat, poultry, fish, eggs, most vegetables and fruits, nut flours, aged cheese, homemade yogurt and honey. Forbidden foods include all cereal grains and their derivatives (including sweeteners other than honey), legumes, potatoes, lactose-containing dairy products and sucrose. Early studies found that high sucrose intake predisposed to CD[41 42 43 44] and that control of disease was enhanced by its avoidance[45]

The author has used the specific carbohydrate diet as primary treatment for patients with CD for almost fifteen years, observing an overall response rate of 55 percent, unrelated to duration of illness but being most effective in those with ileitis[46]. Improvement occurred in symptoms and laboratory parameters, such as serum albumen and erythrocyte sedimentation rate, and permitted decreased use of glucocorticoids.

Diets that induce remission of CD do not usually induce remission of UC, although they improve patients' nutritional status and prevent complications related to surgery [ref 6]. Recent dietary approaches to treatment of UC have examined the therapeutic potential of short chain fatty acids (SCFA), butyric acid in particular [ref 6]. Not only do SCFA nourish the colonic epithelium, they lower intraluminal pH, favoring growth of *Lactobacilli* and *Bifidobacteria* (considered to be beneficial organisms, or probiotics) and inhibiting the growth of *Clostridia, Bacteroides,* and *Escherichia coli,* potential pathogens. In addition to serving as the preferred energy substrate for colonic epithelial cells, butyrate has a true anti-inflammatory effect, preventing activation of the pro-inflammatory nuclear transcription factor, NF-kappa-B[47]. When added to 5-ASA enemas, butyrate (80 mM per liter) induces remission in ulcerative proctitis that is resistant to combined 5-ASA/ hydrocortisone enemas[48]. Because butyrate is normally produced by bacterial fermentation of indigestible carbohydrate in the colon, studies have examined the effect of fiber supplementation on the course of UC. These studies are described below in the section on Prebiotics.

Patients with UC are not deficient in butyrate, but appear unable to utilize it, perhaps because organic sulfides produced by their enteric flora inhibit the epithelial effects of butyrate[49] [50]. Protein consumption is a major determinant of sulfide production in the human colon[51]. For patients with UC in remission, the risk of relapse is directly influenced by higher consumption of protein, especially meat protein, and by total dietary sulfur, and sulfates[52]. A low sulfur diet has been advocated for maintenance of remission in UC. This diet, which is markedly different from the specific carbohydrate diet, eliminates beef, pork, eggs, cheese, whole milk, ice cream, mayonnaise, soymilk, mineral water, nuts, cruciferous vegetables, and sulfited alcoholic beverages. Controlled studies have not been performed, but a small preliminary study demonstrated the feasibility and safety of a low sulfur diet for patients with UC over a five-year period.[53]

The differences in dietary response patterns between patients with CD and patients with UC make clarity of diagnosis essential for proper nutritional therapy.

EXCLUSION DIETS. Exclusion diets eliminate specific symptom-producing foods and have been used to maintain remission of IBD. Although self-reported food intolerance is common among patients with IBD[54], most of the data from controlled studies has been gathered from patients with CD. In the East Anglia Multicentre Controlled Trial, 84% of patients with active CD entered clinical remission after two weeks of a liquid elemental diet [55], which produced a significant decrease in erythrocyte sedimentation rate and C-reactive protein and an increase in serum albumen. Patients were then randomized to receive treatment with prednisolone or treatment with a specific food exclusion diet. To determine which foods each patient needed to avoid, a structured series of dietary

challenges was conducted. Patients would introduce foods of their choice, one at a time. Any food that appeared to provoke symptoms was excluded from further consumption; foods that did not provoke symptoms were included into a maintenance diet. At six months, 70 percent of patients treated with diet were still in remission, compared with 34 percent of patients being treated with prednisolone. After two years, 38 percent of patients treated with specific food exclusion were still in remission, compared to 21 percent of steroid-treated patients. In previous uncontrolled studies, some of the same authors had used a diet consisting of one or two meats (usually lamb or chicken), one starch (usually rice or potatoes), one fruit and one vegetable instead of the elemental diet, in order to induce remission. Structured food challenges were then used to construct a maintenance diet free of symptom-provoking foods. Compliance with the specific food elimination diet was associated with a rate of relapse under 10 percent per year[56]. Individual foods found most likely to provoke symptoms in this study were wheat, cow's milk and its derivatives, cruciferous vegetables, corn, yeast, tomatoes, citrus fruit and eggs.

A large proportion of CD patients develop antibodies to baker's and brewer's yeast, Saccharomyces *cerevisiae* (ASCA) [57]. Lymphocytes of ASCA-positive patients proliferate after stimulation with mannan, an antigen common to most types of yeast. For these patients, lymphocyte proliferation is associated with increased production of the key inflammatory mediator, TNF-a.[58] A small placebo-controlled study found that patients with stable, chronic CD experienced a significant reduction in the CD activity index during 30 days of dietary yeast elimination and a return to baseline disease activity when capsules of *S. cerevisiae* were added to their diets [59].

An observational study of patients with UC suggested that dietary practices based upon food avoidance did not appear to modify the risk of relapse[60], but a small experimental study from South Africa found that diarrhea, rectal bleeding and the appearance of the colon on sigmoidoscopy improved significantly more for patients receiving a diet that systematically eliminated symptom-provoking foods than for those assigned to only monitor their diets[61]. Patients in the diet group were given a defined menu of fish, meat, grains, vegetables and fruit from which to choose and were instructed to eat only one food at breakfast and lunch and two at dinner, rotating foods so that no specific food was eaten more than once during the first week and no food group was consumed more than once in 48 hours. Fried foods, dairy products, sugar, all condiments other than salt and all beverages other than boiled water were eliminated during the first week. At the end of week one, the menu was slowly expanded to include as many foods as tolerated. Four out of eleven patients in the diet group and no patients in the control group achieved clinical and endoscopic remission by the end of six weeks. Eight months later, three of the four patients remained in remission, despite having returned to their usual diets. The potential value of this study is reduced by the small number of patients and the maintenance of remission despite return to an unrestricted diet. Earlier reports from dietary trials led to an estimate that 15 to 20 percent of patients with UC have specific food intolerance that effects severity of illness, with cow's milk protein being the leading offender[62]. This is consistent with the author's clinical experience.

SUPPLEMENTS. Nutritional supplements may be used to correct or prevent the deficiencies that are common among patients with inflammatory bowel disease or to achieve an anti-inflammatory effect.

FOLIC ACID. 5-ASA derivatives, sulfasalazine in particular, impair folic acid transport.[63] Reduced folic acid in patients with IBD is associated with hyperhomocysteinemia[64], a risk factor for deep vein thrombosis[65], an extra-intestinal complication of inflammatory bowel disease. Co-administration of folic acid with 5-ASA derivatives prevents folic acid depletion and has been shown to reduce the incidence of colon cancer in patients with ulcerative colitis[66 67]. One study found that a high dose of folic acid (15 mg/day) reversed sulfasalazine-induced pancytopenia in two patients[68].

VITAMIN B12. Because vitamin B12 absorption may be impaired by ileal inflammation and by small bowel bacterial overgrowth, deficiency of vitamin B12 has long been described as a potential complication of CD[69]. Although frank vitamin B12 deficiency is unusual, lower vitamin B12 levels are associated with increased serum homocysteine in patients with CD[70]. Ischemic strokes in a woman with CD were associated with vitamin B12-reversible hyperhomocysteinemia.[71] A single dose of 1000 micrograms of cobalamin by injection corrects the megaloblastic anemia associated with CD[72].

VITAMIN B6. Median vitamin B6 levels are significantly lower in patients with IBD than controls; low levels are associated with active inflammation and hyperhomocysteinemia[73]. Although some homocysteine is removed by folate-B12-dependent remethylation, the bulk of homocysteine is converted to cystathionine in a reaction catalyzed by vitamin B6. Ischemic stroke and high-grade carotid obstruction in a young woman with CD were attributed to hyperhomocysteinemia, vitamin B6 deficiency and a heterozygous methylene-tetrahydrofolate reductase gene mutation. The authors believed that vitamin B6 deficiency was the principal cause of hyperhomocysteinemia in this patient[74].

VITAMINS E AND C. Blood levels of vitamins E and C are often reduced in patients with IBD[75] Administration of alpha-tocopherol 800 IU per day and vitamin C 1000 milligrams per day to patients with stable, active CD decreased markers of oxidative stress but had no effect on the CD activity index[76].

VITAMIN A. Although levels of carotenoids[77] and retinol[78] are diminished in patients with active CD, low levels appear to be related not malabsorption but to inflammation[79 80] and a reduction in circulating retinol binding protein [81]. Supplementation with vitamin A at doses of 100,000 to 150,000 IU per day had no effect on symptoms or disease activity[82 83].

VITAMIN D. Reduced blood levels of 25-OH cholecalciferol, the major vitamin D metabolite, are common in patients with CD, and are related to malnutrition and lack of sun exposure[84 85]. Administration of vitamin D, 1000 IU per day for one year, prevented bone loss in patients with active disease[86]. The major causes of bone loss in IBD, however, are the effects of inflammatory cytokines and glucocorticoid therapy[87], not vitamin D status. Calcitriol (1,25 dihydroxycholecalciferol), the most active metabolite of vitamin D, may actually be increased in patients with inflammatory bowel disease, because activated intestinal macrophages increase its synthesis; elevated calcitriol is associated with increased risk of osteoporosis and may serve as a marker of disease activity[88]. Hypercalcemia is a rare complication of excess calcitriol and serum calcium should be monitored in patients with IBD receiving vitamin D supplements[89].

VITAMIN K. Biochemical evidence of vitamin K deficiency has been found in patients with ileitis and in patients with colitis treated with sulfasalazine or antibiotics[90]. Serum vitamin K levels in CD are significantly decreased compared with normal controls and

are associated with increased levels of undercarboxylated osteocalcin, indicating a low vitamin K status in bone. In patients with CD, undercarboxylated osteocalcin is inversely related to lumbar spine bone density[91]. Furthermore, the rate of bone resorption in CD is inversely correlated with vitamin K status, suggesting that vitamin K deficiency might be another etiological factor for osteopenia of IBD[92]. Optimal dose of vitamin K for correction of deficiency is not known. Patients with active disease may not absorb oral vitamin K, even at high dosage[93].

CALCIUM. Although calcium supplementation is recommended for maintaining bone density in patients with IBD, especially those receiving glucocorticoids, **c**alcium supplementation (1000 milligrams per day) with 250 IU of vitamin D per day, conferred no significant benefit to bone density at one year in patients with corticosteroid-dependent inflammatory bowel disease and osteoporosis.[94] Nonetheless, calcium supplementation should be given to patients with low dietary calcium intake. In experimental animals, low dietary calcium increases severity of IBD[95].

ZINC. Low plasma zinc is common in patients with CD and may be associated with clinical manifestations such as acrodermatitis, decreased activity of zinc-dependent enzymes like thymulin and metallothionein, reduction in muscle zinc concentration and poor taste acuity [ref 6]. Zinc absorption is impaired and fecal zinc losses are inappropriately high[96]. Zinc deficient adolescents with CD grow and mature more normally when zinc deficiency is treated. Anecdotally, correction of zinc deficiency as a specific intervention has been associated with global clinical improvement, suggesting that zinc replacement may have beneficial effects on disease activity[97]. A small study of patients in remission from CD found that high dose supplementation with zinc sulfate, 110 milligrams three times a day for eight weeks, significantly decreased small intestinal

permeability for a period of twelve months[98]. In patients with active disease, zinc sulfate, 200 milligrams per day (but not 60 milligrams per day) significantly increased plasma zinc and thymulin activity[99].

SELENIUM. Low selenium levels in patients with CD are associated with increased levels of TNF-a and decreased levels of the antioxidant enzyme, glutathione peroxidase (GSHPx) [100]. Although selenium supplementation raised plasma selenium to the level of a control population, it did not significantly increase activity of GSHPx[101]. Patients with small bowel resection are at risk for severe selenium deficiency; monitoring of selenium status and selenium supplementation have been recommended for this group in particular[102]. Patients on enteral feeding with liquid formula diets experience decreased selenium concentrations proportional to duration of feeding, suggesting that additional selenium supplementation is also needed by them[103].

MAGNESIUM. Magnesium deficiency is a potential complication of IBD, a result of decreased oral intake, malabsorption and increased intestinal losses due to diarrhea. Urinary magnesium is a better predictor of magnesium status than serum magnesium in this setting[104]. Reduced urinary magnesium excretion is a significant risk factor for urolithiasis, one of the extraintestinal manifestations of IBD[105]. For patients with IBD, the urinary ratio of magnesium and citrate to calcium is a better predictor of lithogenic potential than urinary oxalate excretion[106]. Supplementation with magnesium and citrate may decrease urinary stone formation, but diarrhea is a dose-related, limiting side effect.

CHROMIUM. Glucocorticoid therapy increases urinary chromium excretion and chromium picolinate, 600 micrograms per day, can reverse steroid-induced diabetes in humans, with a decrease in mean blood glucose from 250 milligrams per dL to 150 milligrams per dL. Chromium supplementation may be of benefit for patients receiving glucocorticoids who manifest impaired glucose tolerance[107].

IRON. Anemia occurs in about 30 percent of patients with IBD[108]. Its causes include iron deficiency due to blood loss, cytokine-induced suppression of erythropoiesis and side effects of medication. Some authors have speculated that iron deficiency actually increases the IFN-g response in TH-1 driven inflammation and may contribute to aggravation of CD [ref 109]. Most clinicians, however, avoid oral iron supplements, believing they can increase oxidative stress in the gut, because very high dose iron supplementation consistently aggravates experimental colitis in rodents[109]. The doses used in rodent studies, however, are orders of magnitude greater than the doses given to patients. The relative risks and benefits of oral iron supplementation for patients with IBD are uncertain.

FISH OILS. Biochemical studies indicate that 25 percent of patients with IBD show evidence of essential fatty acid deficiency[110]. In experimental animals, fish oil feeding ameliorates the intestinal mucosal injury produced by methotrexate[111]. In tissue culture, omega-3 fatty acids stimulate wound healing of intestinal epithelial cells[112]. For patients with UC, a fish oil preparation supplying 3200 milligrams of eicosapentaneoic acid (EPA) and 2400 mg of docosahexaenoic acid (DHA) per day decreased symptoms and lowered the levels of leukotriene B4 (LTB4) in rectal dialysates, with improvement

demonstrated after 12 weeks of therapy[113]. A similar preparation improved histological score and symptoms of patients with proctocolitis[114]. At a dose of 4200 milligrams of omega-3 fatty acids per day, fish oils were shown to reduce dose requirements for anti-inflammatory drug therapy of UC[115]. At a dose of 5,100 milligrams of omega-3 fatty acids per day, fish oils combined with 5-ASA derivatives prevented early relapse of UC better than 5-ASA derivatives plus placebo, but fish oils alone did not maintain remission[116].

In all studies of UC, the fish oil preparations consisted of triacylglycerols. A delayed-release preparation of free fatty acids derived from fish oil, supplying 1,800 milligrams per day of EPA and 800 milligrams per day of DHA, was much more effective than placebo in preventing relapse of CD in patients not taking 5-ASA derivatives[117]. Based upon clinical symptoms and laboratory indices of inflammation, 59 percent of those receiving fish oil remained in remission at one year, compared to 26 percent of those receiving placebo. The main side effect of fish oil was reversible diarrhea, which occurred in 10 percent.

GLUTAMINE. Glutamine appears to have a special role in restoring normal small bowel permeability and immune function. Patients with intestinal mucosal injury secondary to chemotherapy or radiation benefit from glutamine supplementation with less villous atrophy, increased mucosal healing and decreased passage of endotoxin through the gut wall[118]. Although integrative practitioners often advocate glutamine therapy for treatment of IBD, controlled studies have shown no benefit from glutamine supplementation at doses as high as 20 grams per day in patients with CD[119 120]. Glutamine excess aggravates experimental colitis in rodents[121].

N-ACETYLGLUCOSAMINE (NAG): NAG is a substrate for synthesis of glycosaminoglycans, glycoproteins that protect the bowel mucosa from toxic damage. Synthesis of NAG by N-acetylation of glucosamine is impaired in patients with IBD[122]. In explants of bowel tissue from patients, incorporation of added NAG was depressed in patients with inactive UC, increasing to control levels in those with active colitis, probably indicating response of gut tissue to inflammation[123]. In a pilot study, NAG (3 to 6 grams per day for more than two years) given orally to children with refractory IBD produced symptomatic improvement in the majority of patients and an improvement in histopathology [124]. In children with distal colitis or proctitis, the same dose of NAG was administered by enema with similar effects [ref 123].

PROBIOTICS. Probiotics are beneficial microorganisms. Their therapeutic use in IBD is attracting considerable attention, because of the recognition that alteration of intestinal microflora may modulate intestinal immune responses[125]. Because of the large number of probiotic preparations available, this section will only discuss those preparations that are commercially available in the United States and that have been studied in clinical trials of patients with IBD. More data exist for their benefits in UC than in CD.

VSL-3 is a proprietary mixture of *Lactobacillus acidophilus, L. bulgaricus, L. casei, L plantarum, Bifidobacteriium brevis, B. infantis, B. longum and Streptococcus salivarius ssp thermophilus*, supplied in sachets containing 900 billion organisms each. When added to therapy with the 5-ASA derivative balsalazide, VSL-3 (one sachet twice a day) induced faster remission of active UC than balsalazide or mesalazine alone[126]. In an uncontrolled trial, two sachets of VSL-3 twice a day for six weeks as monotherapy yielded clinical and endoscopic remission of mild to moderate UC in 54 percent of patients treated[127]. VSL-3

also prevents relapse of pouchitis (post-colectomy inflammation of the ileal pouch)[128], with two sachets once a day producing remission rates far better than placebo over a one-year period.[129] A survey done at the Cleveland Clinic, however, found poor compliance with this therapy in patients not participating in clinical trials[130].

LACTOBACILLUS GG. *Lactobacillus rhamnosus var GG* at a dose of 10 to 20 billion organisms per day, was found to prevent onset of pouchitis in patients with ileal pouch-anal anastomosis during the first three years after surgery in a placebo-controlled trial[131] Lactobacillus GG has been ineffective in inducing or maintaining remission of patients with CD[132] or in preventing relapse of CD after surgical resection[133].

SACCHAROMYCES BOULARDII. This plant-derived yeast has shown benefit in the treatment or prevention of traveler's diarrhea[134], *C. difficile* diarrhea[135] and antibiotic-induced diarrhea[136]. Experimental data suggest that the yeast owes its antibacterial effects to stimulation of secretory IgA secretion[137] and macrophage activation[138]. Despite its stimulation of mucosal immune responses and its antigenic similarity to baker's yeast, *S. boulardii* has shown benefit in both UC and CD. The addition of *S. boulardii* (250 milligrams three times a day) to maintenance mesalamine therapy of patients with chronic, active UC was associated with induction of remission within four weeks in 17 out of 25 patients[139]. This trial was uncontrolled. In a placebo-controlled trial, the same dose was given to patients with stable, active CD and mild to moderate diarrhea. *S. boulardii* reduced the frequency of diarrhea and the clinical activity index when given over a ten-week period, with benefits apparent within two weeks[140]. When added to mesalamine therapy of patients with CD in remission, *S. boulardii* (1000 milligrams per day) reduced the frequency of relapse from 37.5% to 6.25% during six months, when

compared to mesalamine alone[141] Although *S. boulardii* is considered non-pathogenic, case reports of *S. boulardii* fungemia have been described in critically ill or immunocompromised patients exposed to *S. boulardii*. At least eighteen reports of this complication have been published, including one in which airborne spread of *S. boulardii* occurred in an intensive care unit[142].

PREBIOTICS. Prebiotics are non-digestible food ingredients that stimulate the growth or modify the metabolic activity of intestinal bacterial species that have the potential to improve the health of their human host. Criteria associated with the notion that a food ingredient should be classified as a prebiotic are that it remains undigested and unabsorbed as it passes through the upper part of the gastrointestinal tract and is a selective substrate for the growth of specific strains of beneficial bacteria (usually *Lactobacilli* or *Bifidobacteria*), rather than for all colonic bacteria. Prebiotic food ingredients include bran, psyllium husk, resistant (high amylose) starch, inulin (a polymer of fructofuranose), lactulose, and various natural or synthetic oligosaccharides, which consist of short chain complexes of sucrose, galactose, fructose, glucose, maltose or xylose. The best-known effect of prebiotics is to increase fecal water content, relieving constipation. Bacterial fermentation of prebiotics yields short-chain fatty acids like butyrate. Fructooligosaccharides (FOS) have been shown to alter fecal biomarkers (pH and the concentration of bacterial enzymes like nitroreductase and beta-glucuronidase) in a direction that may convey protection against the development of colon cancer[143]. Several studies have suggested benefits of various prebiotics for the treatment of UC:

Oat bran, 60 grams per day (supplying 20 grams of dietary fiber), increased fecal butyrate by 36 per cent in patients with UC and diminished abdominal pain[144]. A dietary

supplement containing fish oil and two types of indigestible carbohydrate, FOS and xanthum gum, allowed reduction of glucocorticoid dosage when compared to a placebo, in patients with steroid-dependent UC[145]. A Japanese germinated barley foodstuff (GBF) containing hemicellulose-rich fiber, at a dose of 20 to 30 grams per day, increased stool butyrate concentration[146], decreased the clinical activity index of patients with active UC[147] and prolonged remission in patients with inactive UC[148]. Wheat grass juice, 100 milliliters twice daily for one month, tested in a small placebo-controlled trial of patients with distal UC[149], produced a significant reduction in rectal bleeding, abdominal pain and disease activity as measured by sigmoidoscopy. A mixture of *B. longum* and inulin-derived FOS administered for one month as monotherapy to patients with UC produced improvement in sigmoidoscopic appearance, histology and several biochemical indices of tissue inflammation when compared to a placebo control[150].

BOVINE COLOSTRUM. Colostrum is the first milk produced after birth and is particularly rich in immunoglobulins, antimicrobial peptides (eg, lactoferrin and lactoperoxidase), and other bioactive molecules, including growth factors. Recent studies suggest that the peptide growth factors in colostrum might provide novel treatment options for a variety of gastrointestinal conditions[151]. Colostrum enemas, 100 milliliters of a 10 percent solution, administered twice a day by patients with distal UC, proved superior to a control enema in promoting healing; all patients were also taking a fixed dose of mesalazine[152]. Studies of oral colostrum in IBD have not been reported, but 125 milliliters three times a day fed to healthy human volunteers was shown to prevent the increase in intestinal permeability produced by indomethacin[153], suggesting that peptide growth factors survive passage through the stomach and upper small bowel.

DEHYDROEPIANDROSTERONE (DHEA). DHEA is the steroid hormone produced in greatest quantity by the human adrenal cortex, circulating primarily in the sulfated form, DHEA-S. DHEA inhibits activation of nuclear factor kappa B (NF-kappaB), which is activated in inflammatory lesions. Patients with IBD have lower levels of DHEA-S in serum and intestinal tissue than controls[154], partially associated with prior treatment with glucocorticoids[155]. In men with IBD, low DHEA-S is associated with increased risk of osteoporosis[156]. In a pilot study, six of seven patients with refractory CD and eight of thirteen patients with refractory UC responded to DHEA (200 milligrams per day for 56 days) with decrease in the clinical activity index[157] A case report demonstrated benefit of the same dose of DHEA in a woman with severe refractory pouchitis, with relapse occurring 8 weeks after discontinuation of DHEA[158].

BOTANICALS. In traditional Chinese medicine and Ayurveda, herbal extracts are the mainstay of treatment for IBD and appear to be effective when used by practitioners trained in those systems. Botanicals commonly taken by patients with IBD include slippery elm, fenugreek, devil's claw, *Gingko biloba, Angelica sinensis* (Dong quai), and licorice. Although these all express antioxidant or anti-inflammatory activity *in vitro*[159 160 161], data from clinical trials is lacking. Two botanical therapies readily available in the United States have been studied in clinical trials, primarily of UC:

BOSWELLIA. The Ayurvedic herb, *Boswellia serrata* (Indian frankincense) contains boswellic acids, which inhibit leukotriene biosynthesis in neutrophilic granulocytes by noncompetitive inhibition of 5-lipoxygenase.[162] During a small six-week trial, 350 milligrams three times a day of Boswellia gum resin was as effective as sulfasalazine 1000 milligrams three times a day in reducing symptoms or laboratory abnormalities of

patients with active UC[163]. The rate of remission was 82 percent with *Boswellia* and 75 percent with sulfasalazine[164]. A proprietary *Boswellia* extract, H15, was found as effective as mesalazine in improving symptoms of active CD, in a randomized, double-blind study from Germany[165].

ALOE VERA. *Aloe vera* gel has a dose-dependent inhibitory effect on production of reactive oxygen metabolites, prostaglandin E2 and (at high doses) IL-8, by human colonic epithelial cells grown in tissue culture.[166]. Oral A*loe vera* gel, 100 milliliters twice a day for four weeks, produced a clinical response significantly more often than placebo (response ratio 5.6) in patients with UC[167]. Remission occurred in 30 percent of patients taking aloe vera gel and 7 percent of patients receiving placebo. Aloe also reduced histological disease activity, whereas placebo did not. No significant side effects were described, although it should be noted that aloe vera gel is often used as a laxative. Acemannan, an extract of Aloe vera, concentrated to a mucopolysaccharide (MPS) concentration of thirty per cent of solid weight, has been demonstrated to reduce symptoms and indices of inflammation in controlled studies of patients with UC[168].

MIND-BODY THERAPIES. Although it is widely believed that stress aggravates IBD, a German study found no relationship between symptoms of CD or UC and stressful life events, feelings of pressure, conflict or fear of separation.[169] A prospective study did not validate the notion that stressful life events can trigger relapse[170]. Three prospective studies of different types of psychotherapy for patients with IBD failed to show any improvement in medical outcome compared with standard care.[171] [172] [173]

SELF-MANAGEMENT TRAINING. This patient-centered educational approach has a significant impact on health care utilization. In a study from the University of Manchester, when compared to a control group that received customary care, the intervention group required one-third as many doctor visits and one third as many hospitalizations. The difference in outcome was not related to specific treatments employed but rather to the empowerment of patients to be actively involved in managing their own care.[174] The method used: During a 15 to 30 minute consultation, physicians specifically ask patients about the symptoms they have experienced during past relapses and review past and current treatments that have been used to control symptoms, emphasizing the specific effectiveness of each and its acceptability to the patient. Physician and patient then design a personalized self-management strategy based upon the patient's recognition of symptoms and a mutually acceptable treatment protocol for the patient to initiate at onset of a relapse.

ACUPUNCTURE. Acupuncture and moxibustion are commonly employed by practitioners of Chinese medicine for treatment of UC. Uncontrolled studies from China claim excellent results[175] [176]. One small study of moxibustion found evidence of enhanced cellular immunity and decreased antibody production associated with improvement of diarrhea in patients with UC,[177] suggesting down-regulation of the TH-2 response network. A review of studies from both the Chinese and Western literature supports the efficacy of acupuncture in the regulation of gastrointestinal motor activity and secretion through opioid and other neural pathways.[178] Controlled clinical trials of patients with inflammatory bowel disease have not yet been reported.

ANTIBIOTICS. Antibiotics are sometimes helpful for exacerbations of IBD, especially for Crohn's colitis and for draining fistulae[179] [180]. Metronidazole is the most commonly

used agent; it is the first-line drug for treatment of pseudomembranous colitis caused by *Clostridium difficile* toxin, a complication of IBD that, in patients with active colitis, may occur spontaneously without prior antibiotic exposure. *S. boulardii* (1000 milligrams per day) enhances therapeutic efficacy of metronidazole in the treatment of recurrent *C. difficile* colitis[181]. Some other natural products may interfere with the efficacy of metronidazole: Silymarin, a group of flavonoids extracted from milk thistle, at a dose of 140 milligrams per day for nine days, decreased the peak plasma concentration and bioavailability of metronidazole and its major metabolite by 30 percent in healthy volunteers[182]. Vitamin E (400 international units per day) with vitamin C (500 milligrams per day) reduced effectiveness of metronidazole against metronidazole-sensitive *Helicobacter pylori* infection by 40 percent[183].

Always ask patients about the effect of antibiotics, including those used for unrelated illnesses, on their gastrointestinal symptoms. Improvement of symptoms during antibiotic therapy may be an indication to use that antibiotic empirically during an exacerbation of symptoms. Aggravation of symptoms during antibiotic therapy may be an indication to avoid the specific antibiotic and employ probiotics.

5-ASA DERIVATIVES. Mesalazine, sulfasalazine, balsalazide, and olsalazine are used for inducing remission in mild cases of ulcerative or Crohn's colitis and for maintenance of remission. The value of continuous therapy with 5-ASA derivatives at relatively high doses for maintenance of remission in ulcerative colitis is now well established. Side effects may include folic acid deficiency (discussed above), exacerbation of diarrhea, hair loss and skin rash.

The efficacy of 5-ASA derivatives in inducing remission of IBD can be enhanced by fish oils supplying 4000 milligrams of EPA plus DHA per day and by probiotics (VSL-3 2 packets a day or *S. boulardii* 250 milligrams three times a day).

GLUCOCORTICOIDS. Steroids are used to induce remission of IBD, but have shown no benefit in maintaining remission. Not only do they suppress adrenal function, causing a decline in release of DHEA (discussed above) and impair immune function, their side effects include cataracts, growth failure, hypogonadism and osteopenia. They decrease intestinal calcium absorption, increase renal calcium excretion and induce parathyroid hormone secretion.

IMMUNOSUPRESSANTS. 6-mercaptopurine and its derivative, azothioprine, are used for maintenance of remission or for induction of remission in patients with chronic, stable disease. Although usually well tolerated at low doses, they may cause leukopenia, anemia, and hepatic dysfunction and promote opportunistic infection. Immune stimulating herbs, like *Echinacea* and *Astragalus* species, may reverse the benefits of immune suppressants in the treatment of autoimmune disorders[184] [185]. Concomitant use should be avoided. Cyclosporine is occasionally used for inducing remission in refractory UC. Its absorption is drastically reduced by St. John's wort[186] and may be dangerously increased by peppermint oil[187]. Cyclosporine nephrotoxicity is diminished by administration of fish oil supplying 3000 to 4000 milligrams of omega-3 fatty acids per day[188][189] and by vitamin E (D-alpha tocopherol, 500 international units per day)[190].

Ipriflavone, a semisynthetic isoflavonoid used for prevention of bone loss, may produce lymphopenia[191]. Patients receiving immunosuppressants should avoid it.

TNF-ALPHA BLOCKADE. Infliximab (Remecade) is a major advance in drug therapy for inducing remission of IBD. Adverse events reported in patients treated with anti-TNF agents include acute infusion reactions, delayed hypersensitivity-type reactions, autoimmune diseases like drug-induced lupus and demyelination, and infection[192]. Cigarette smoking interferes with response to infliximab in patients with CD[193].

SURGERY. Surgical resection of inflamed bowel is today considered a last resort in the management of patients with IBD. Correction of malnutrition and the use of probiotics (discussed above) may enhance responses to surgery for IBD.

SECONDARY PREVENTION

Despite abundant speculation about the reasons for the dramatic increase in incidence of IBD in industrialized nations over the past century, no convincing strategy for primary prevention has been devised. Secondary prevention may benefit from the following interventions:

- Prolonged use of 5-ASA derivatives and folic acid (typically one milligram per day) to maintain remission and prevent colon cancer. Fish oils supplying about 5000 milligrams per day of omega-3 fatty acids and *S. boulardii* 1000 milligrams per day may enhance efficacy of 5-ASA derivatives in maintenance of remission.
- Folic acid, vitamin B6 and vitamin B12 at doses that keep circulating homocysteine low, to prevent thrombotic complications.

- Vitamin D (1000 international units per day) and vitamin K (optimal dosage unknown) to prevent bone loss.
- A specific food exclusion diet, individually tailored (described above), cessation of tobacco use and reduced consumption of sucrose for maintenance of remission in patients with CD.
- A high fiber, low meat diet for maintenance of remission in patients with ulcerative colitis.

LABORATORY TESTING

All patients with IBD should be under the care of a gastroenterologist for regular endoscopic examination and prescription of appropriate drug therapy. The main role of the integrative practitioner is to enhance conventional treatment with a nutritional prescription and the use of nutritional and botanical supplements. A number of laboratory tests are useful for fulfilling this role effectively. Commonly used tests include the complete blood count, erythrocyte sedimentation rate, C-reactive protein and serum albumen. Useful markers of nutritional status in IBD also include plasma zinc and homocysteine, serum and urine magnesium, serum iron, ferritin and transferrin, and 25-OH vitamin D. In steroid-treated patients with refractory disease, serum DHEA-S may be useful. Patients with recent onset, relapse or exacerbation of IBD--especially those with diarrhea--should undergo stool testing for parasites, pathogenic bacteria and *C. difficile* toxins.

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