A REVIEW OF NATURAL & NUTRACEUTICAL THERAPIES FOR CLINICAL PRACTICE

THE STANDARD

Volume 9, No. 1

2009

POINT INSTITUTE OF NUTRACEUTICAL RESEARCH

Inflammatory Bowel Disease

by Jason Sailesh Dave, NMD, MS

Introduction:

Inflammatory Bowel Disease (IBD) is comprised of various chronic inflammatory conditions that affect the large and small intestines. The most common subcategories of IBD include Crohn's Disease (Cr) and Ulcerative Colitis (UC), which account for the vast majority of patients with IBD. It is estimated that both of these diseases affect up to 1.4 million people in the U.S., and are most commonly diagnosed in adolescence and young adulthood although they can affect people of any age.[1] While these two conditions share many common features such as abdominal pain, diarrhea and weight loss – each has distinctive features (described in more detail below). Periods of remissions and exacerbations commonly occur. IBD patients can experience long periods of time without symptoms, but acute attacks occur intermittently lasting from weeks to months. Since similar symptoms are seen in both of these conditions, it is difficult to distinguish one from the other. Endoscopy and laboratory tests are useful tools that can help assist clinicians with the exact diagnosis. As this review will make clear, while conventional diagnosis is helpful, determining the status of key gastrointestinal (GI) functions can direct the clinician to the root underlying cause(s)- which can be the basis of therapies designed to optimize GI health.

Crohn's Disease is a relapsing and transmural (spanning the entire depth of the intestinal wall) inflammatory condition of the GI mucosa that can affect any portion of the GI tract from the mouth to anus, but mostly involves the terminal ileum and colon.[2] Inflammation and ulceration seen in Cr occurs in "skip lesions," or areas of affected tissue interspersed with normal tissue. Clinical presentation depends mainly on disease location and can include abdominal pain, diarrhea, fever, weight loss, signs of bowel obstruction, and a right lower quadrant mass upon examination (due to an inflamed ileum). Other characteristics of Cr include ulcers, fissures, strictures, as well as complications such as intestinal obstruction, abscess formation, fistulas, colon cancer and systemic manifestations.

Ulcerative Colitis is a relapsing and non-transmural inflammatory condition that affects the inner lining of the colonic mucosa, resulting in continuous areas of ulceration and abscesses without skip lesions.[2] Patients with UC usually present with bloody diarrhea or bowel movements accompanied with the passage of pus and/or mucus. Abdominal cramping, rectal bleeding and weight loss (in severe cases) can also be seen in these patients. Hemorrhage is a frequent complication and the colon may become dilated and perforate. UC increases the risk of colon cancer and other extracolonic complications. Table 1 below shows the differences between Cr and UC.

Table 1. Differentiation between Crohn's Disease and Ulcerative Colitis

	Crohn's Disease	Ulcerative Colitis
Location of lesions	Mostly affects the terminal ileum and colon, but can affect any portion of GI tract	Inner lining of the colonic mucosa
Depth of pathology	Entire bowel wall	Mucosa and submucosa
Blood in stool	Usually absent	Frequently present
Weight loss/anorexia	Weight loss and anorexia are common	Weight loss in more severe cases
Diarrhea	Moderate	Present
Immune response	Exaggerated Th1 cytokine response	Exaggerated Th2 cytokine response
Complications	Small bowel abscesses, obstruction, and fistulas Perianal disease Malabsorption Toxic megacolon Colon cancer	Perforation Hemorrhage Toxic megacolon Colon cancer

edited by

Thomas G. Guilliams Ph.D.

Etiology and Risk Factors

The exact etiology of IBD is largely unknown, but appears to be largely related to genetic susceptibility, environmental triggers, and the immune response. Evidence suggests familial tendency is less pronounced in UC than Cr.[3] For first-degree relatives of UC patients, the lifetime risk of developing IBD is 1.6% (5.2% within the Jewish population); and for relatives of Cr patients, the risk increases to 5.2% (7.8% for Jews).[3] Genome-wide scans have found several susceptible regions on different chromosomes.[3,4] Mutations of the NOD2 gene (also known as the CARD15 gene) on chromosome 16 appear to have the most significant impact on the risk for developing Cr. This genetic mutation may be responsible for the disruption of the intestinal mucosal barrier, stricturing activity of the small bowel and an abnormal immune response to the normal bacterial flora present in the gut.[3,5,6,7,8]

Several studies have found an association between environmental factors in the pathogenesis of IBD.[1] It has been well-established that cigarette smoking increases the risk of developing Cr, but conversely, may improve the disease severity in some patients with UC.[9,10,11] Despite these well-described associations, the mechanism by which cigarette smoking affects IBD is not exactly known. Hypoxia, nicotine, and carbon monoxide have all been implicated as mediators of the effects of smoking on IBD.[11] Dietary factors can contribute to the development of IBD in certain individuals. Suggestive evidence has shown that increased consumption of foods high in trans fats (such as margarine and fast food) may be involved in the etiology of both UC and Cr.[12,13] Furthermore, two studies have suggested that diets with increased refined sugar intake and high overall carbohydrate intake may precede the development of Cr.[14,15]

Besides the genetic and environmental impact, the mucosal immune system of the gut plays a central role in the pathogenesis of IBD. Normally, the mucosal immune system is responsible for the balance between pro- and anti- inflammatory mediators. This system helps to defend against luminal pathogens, as well as prevent an immune over-reaction against harmless luminal antigens (such as beneficial bacteria or food). In IBD, this immunological balance is impaired and shifted toward a more pro-inflammatory state, which is caused primarily by the increased activation of effector immune cells. These immune cells produce high levels of pro-inflammatory cytokines (such as TNF-α, IL-6 and interferon-γ), resulting in tissue damage and inflamed intestinal mucosa. Nuclear transcription factor kappa B (NF-κB) is one of the major regulatory components of pro-inflammatory cytokine production in this inflammatory cascade, and can be initiated by many different factors such as bacteria, viruses, and toxins that damage the DNA.[16] Several studies have shown that elevated NF-κB levels were found in macrophages and epithelial cells in patients with IBD, consequently increasing the levels of pro-inflammatory cytokines.[17,18,19]

One interesting proposal to the increasing prevalence of IBD is the fact that certain lifestyle decisions have a profound impact on the gut microflora, which can lead to the development of IBD. Imbalanced gut microflora can contribute to the pathogenesis of IBD by causing dysregulated immune-mediated tissue damage. Two of the most profound influences on gut microflora imbalance are the increased use of antibiotics and poor dietary choices .[20] Increasing evidence shows that antibiotics play a role in causing dysbiosis in the gut, which leads to a disturbed systemic immune response.[21,22] Starting at birth, the microbiota colonizing the gut plays a primary role in "educating" the immune system in appropriate responses. If there is any disturbance or deficit in the quality of educational development of the immune system, it can leave the host susceptible to higher risk of inappropriate responses to harmless environmental stimuli later in life.[20] As a result, disorders such as auto-immune diseases and allergic reactions can result. Also, there has been speculation of specific infectious agents as a possible cause of Cr; *Mycobacterium avium* subspecies *paratuberculosis* has been shown to have the strongest association.[23] This association, however, has limitations due to the lack of reliable and reproducible culture or detection assays.[24 20] In addition, diet has been shown to influence the composition and metabolic behavior of the gut flora. Diets high in saturated fats have been shown to increase gut inflammation by the activation of NF-κB , which can be suppressed by omega-3 fatty acids.[25] Obviously, diets high in fermentable fibers will increase the growth of beneficial strains of gut microbes with positive impact on the immune system.

In addition to understanding the etiology of IBD from the conventional medical model, it is equally important to consider a functional medicine approach to complex GI disorders . The "Pillars of GI Health" is a holistic model that describes the essential functions that maintain the optimal health of the GI system.[26] These pillars include: Digestion/absorption, Elimination, Microflora balance and Gut integrity. This model looks at the overall health of the GI tract and assesses basic underlying dysfunctions. Unlike the conventional medical model that seeks a differential diagnosis for every patient, the "Pillars of GI Health" approach can help the clinician find the unique root cause(s) of the particular patient by assessing their particular functions. This approach looks at each patient as an "individual," with a unique set of circumstances that resulted in a condition which may be labeled as "IBD." This allows the clinician flexibility in outlining an appropriate treatment tailored to each patient, rather than merely treating all IBD patients with the same conventional therapy.

Laboratory Assessment

While radiology and endoscopy testing are used in conventional medicine for the diagnosis of IBD, they both have severe limitations when assessing functional components of the disease (such as activity and prognosis). Several laboratories have developed multi-analyte stool tests called comprehensive digestive stool analysis (CDSA) that allow for an assessment of multiple GI functions. These tests include stool microbial analysis, markers of digestive efficiency, metabolites of

healthy gut microbes and markers of immune functions. Calprotectin, a marker included in some CDSA tests, is a useful test for identifying disease progression in IBD patients and also helps to determine the severity of intestinal inflammation. Calprotectin belongs to a group of calcium-binding neutrophil-specific proteins. Fecal calprotectin has been shown to be increased in over 95% of patients with IBD, and is associated with clinical disease activity. It also helps to differentiate between patients with Irritable Bowel Syndrome (IBS) and active IBD (especially in Cr).[27,28] More importantly, in patients with non-active IBD, the test has a high level of sensitivity and specificity in predicting clinical relapse of disease.[27 29]

Conventional Treatment

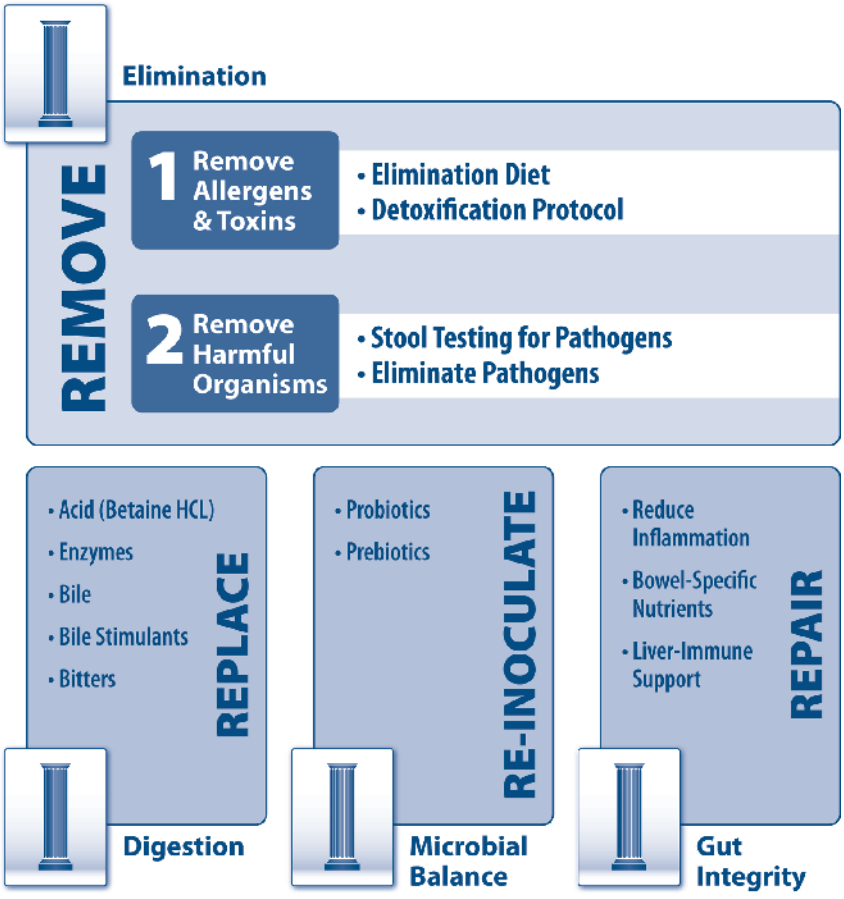
The conventional medical treatment of IBD involves an approach that focuses on both symptomatic relief as well as controlling overstimulation of the immune system. Exacerbations of Cr and UC usually require treatment of 5-aminosalicylic acid (5-ASA), which is the active ingredient found in the pharmaceutical preparations sulfasalazine and mesalamine. 5-ASA helps to reduce inflammation and tissue damage by neutralizing reactive oxygen molecules produced by neutrophils and inhibiting the production of pro-inflammatory mediators such as leukotrienes and prostaglandins. Patients with Cr are given the antimicrobials ciprofloxacin or metronidazole when complications such as infected abscesses or fistulas occur.[30,4]

Corticosteroids are often employed for IBD patients presenting with moderate to severe disease, and are also an option for patients with mild symptoms who do not benefit from 5-ASA. Corticosteroids are also used for short-term therapy in IBD patients who experience acute exacerbations – this reduces the side effect profile related to its long-term use. If these patients do not respond to corticosteroid therapy or need to be tapered off of them, then immunosuppressive agents such as azathioprine, mercaptopurine, methotrexate, cyclosporine, and infliximab are utilized. These medications have several mechanisms of action – from inhibiting purine synthesis to neutralizing TNF-α (consequently inhibiting the production of inflammatory cytokines). If medication fails, then surgical management is often the last conventional treatment.[30,2,5,19,4]

Most of these medications have serious adverse effects in patients, which is a concern for many clinicians. 5-ASA has been known to commonly cause nausea, diarrhea, headaches, abdominal cramping; and occasionally, thrombocytopenia. Long-term use of corticosteroid therapy is associated with the development of cataracts, diabetes, osteoporosis, and other adverse effects. Common serious side effects of immunosuppressive agents include increased risk of developing cancer, increased vulnerability for opportunistic infections, nausea or vomiting, abdominal pain, loss of appetite and other GI complaints.[30,2,5,19,4]

Complementary & Alternative Medicine Treatments

Lack of effectiveness as well as side effects associated with conventional medical therapy are reasons why half of all patients with IBD use alternative (non-conventional) therapies – either integrating it with their conventional medical therapy, or using it in place of conventional medical therapy.[31] Functional medicine is an evidence-based systems biology approach that some clinicians use to assess, prevent, and treat chronic diseases. This type of personalized medicine uses treatments that address the underlying root cause of chronic disease unique to an individual, rather than treating symptoms alone. A functional medicine approach also considers the role that environmental toxins, diet, and nutritional imbalances play in predisposition to illness, aggravation of symptoms, and modulation of the activity of biochemical mediators through a diverse set of mechanisms. One popular functional medicine approach for treating GI dysfunction is known as the "4R" program, in reference to its four basic clinical steps: *Remove, Replace, Reinoculate,* and *Repair.*[117] This program helps clinicians to rebuild the Pillars of GI health by treating GI imbalances.



Remove – This is the first and most vital step that needs to be addressed before utilizing the other three Rs. In this step, the emphasis is on "removing" incoming toxic and immunological burden. This is accomplished by eliminating pathogenic organisms (bacteria, viruses, fungi, parasites), toxic burden and reactive foods. A common treatment approach used in this step is an elimination diet that focuses on both the avoidance of common allergenic food groups and decreasing food toxins (pesticides, herbicides, additives, artificial ingredients, etc.). An elimination diet is often combined with a detoxification protocol that allows for removal of toxins stored in the body and improves the process of the removal of toxins.

Replace – In this step, the replacement of digestive enzymes or other factors may be needed in order to properly address the GI pillar of "Digestion/absorption." While foods may often contain some of these components, these are usually provided through proper dietary supplementation until the patient's GI complaints can be normalized.

Reinoculate – This is the third "R" in this program, which involves the introduction of viable micro-organisms (or ingredients such as prebiotics that feed these organisms) which will help support the GI pillar of "Microflora Balance." Treatment usually consists of probiotic and/or prebiotic therapies.

Repair – This step involves the full healing of the intestinal mucosa. The three keys to repairing the integrity of the gut include: reducing inflammation, providing nutrients for specific GI cell growth, and strengthening immune and liver function. Herbs such as curcumin and boswellia are often used to repair the gut due to their powerful anti-inflammatory effects. Supplementation with glutamine also enhances gut mucosal growth and repair.

Dietary Treatment Approaches

It is essential that patients with IBD receive nutritional therapy during the entire course of their treatment. Dietary therapy is used in IBD patients for two main reasons: supportive (to correct nutrient deficiencies), or primary (to help attain remission). A wide array of vitamin and mineral deficiencies exists in patients with IBD, with varying degrees of clinical significance.[32] An example of this is folate deficiency – in IBD patients this may result from dietary insufficiency, enhanced intestinal loss, or competitive inhibition of sulfasalazine therapy.[32] Since each patient's disease progression and diet is different, clinicians should look for a wide variety of micronutrient deficiencies in patients with IBD.

An elemental diet is composed of predigested free-form amino acids. Observationally, patients adhering to this diet have experienced some improvement (in UC primarily), but evidence of its effectiveness (in the literature) has been very limited.[33] Compliance among patients on this diet is also difficult. Hospitalization is often needed for proper administration and relapse is common once the patient resumes a normal diet. These diets can also be quite unpleasant to many patients,and diarrhea may result (due to the hyperosmolality of the diet).[19]

An elimination diet reduces allergic or intolerant food reactions, as well as empirically test individuals for food allergies (upon reintroduction). One study looked at the effect of an elimination diet in 78 Cr patients who achieved remission with an elemental diet. These patients were randomly assigned to corticosteroids or elimination diet. The corticosteroid group received 40 mg of prednisone daily, which was tapered and stopped after 12 weeks; dietary advice and tips on healthy eating were given to this group. The diet group received a tapered placebo, and were recommended to introduce one new food daily (avoiding any food that was known to cause or aggravate symptoms). After treatment, the results showed that the median remission time was 7.5 months in the diet group vs. 3.8 months in the corticosteroid group. Particularly interesting was the relapse rates (statistically significant) among both groups after 2 years – 62% in the diet group vs. 79% in the corticosteroid group. The food intolerances noted among participants in this study were mainly to cereals, dairy products and yeast.[34] However, in two smaller trials, remission rates were not significantly better in Cr patients who were on an elimination diet vs. patients on an unrestricted diet.[35,36] Further investigation is needed because studies using elimination diets for Cr have produced conflicting results to date. Other dietary interventions, such as the utilization of probiotic and prebiotic therapies, are discussed below.

Probiotics

Probiotics have been one of the most widely used CAM treatments that have been extensively studied for use in patients with IBD. Although the exact mechanisms through which probiotics function are not entirely clear, the results of clinical trials have been favorable for UC. In three double-blind, placebo-controlled randomized clinical trials, researchers found that a non-pathogenic strain of *E. coli* (Nissle 1917) was equally effective as mesalazine in maintaining remission among UC patients. In one of these trials involving 120 patients, Kruis et al. reported that patients receiving this probiotic strain had a similar relapse-free time (106± 5 d) compared to UC patients who were given mesalamine (103± 4 d).[37] Similar outcomes were confirmed by Rembacken et al. in a trial involving 116 patients with UC. Relapse rates were 73% for the mesalazine group and 67% for the *E.coli* group, and the time to relapse was not significantly different between both groups.[38] In another larger clinical trial of 327 patients, researchers also found that *E.coli* was effective and safe in maintaining remission equivalent to the gold standard mesalazine in patients with UC.[39]

A probiotic preparation (containing 3 strains of bifidobacteria, 4 strains of lactobacilli, and 1 strain of *Streptococcus salivarius* ssp.) has also shown benefit in UC patients. In one open-label pilot study, 20 patients who were in remission with UC were evaluated using very high doses of this preparation (3 trillion cfu/day). At the end of the study (12 months), 15 of 20 patients (75%) remained in remission. The authors

of this study concluded that, "this probiotic preparation may be useful in maintaining the remission in UC patients intolerant or allergic to 5-ASA."[40] Another open-label study conducted by Bibiloni et al. involved testing this preparation (3.6 trillion cfu/day) on thirty-four patients with active mild-to-moderate UC who had not responded to conventional therapy. Over a six-week period, these patients experienced a combined remission/response rate of 77% with no adverse events.[41] One proposed mechanism by which this probiotic cocktail exerts its beneficial effects on IBD is thought to be due to the induction of dendritic cell secretion of IL-10 while attenuating T-cell production of IFN-γ.[42]

The non-pathogenic yeast, *Saccharomyces boulardii*, has also been shown to be beneficial in IBD patients. In a randomized double-blind trial involving 32 patients with Cr in remission, clinical relapses were observed at a significantly lesser extent among patients who received 1 g. mesalamine along with 1 g. *S. boulardii* (37.5%) compared to patients receiving 1 g. mesalamine only (6.25%).[43] Authors from a similar study assessed the effectiveness of *S. boulardii* among 25 UC patients with mild to moderate clinical flare-ups. In the past, these patients did not tolerate steroid therapy well. Patients were administered 250 mg. (three times daily) of *S. boulardii* for 4 weeks, with ongoing mesalamine treatment. At the conclusion of the study, out the 24 patients who completed the study, 17 attained remission.[44]

A number of published studies have examined the efficacy of *Lactobacillus casei* strain GG in the treatment of IBD. Malin et al. reported that among pediatric patients with Cr, consumption of *Lactobacillus* GG was associated with increased gut IgA levels, which can promote the gut immunological barrier.[45] Furthermore, Gupta et al. reported a similar finding in an open-label pilot study among a small number of pediatric Cr patients. At the end of the study, these patients had improved clinical scores, as well as improved gut barrier function.[46] A few studies have also reported benefit with using bifidobacteria-fermented milk (BFM) in active UC patients. In one of these small studies, patients were randomized into either a BFM group or a control group. Exacerbation of symptoms was seen in 3 out of 11 subjects in the BFM group, as opposed to 9 out of 10 in the control group. The authors concluded the study by stating that supplementation with the BFM product was successful in maintaining remission and had possible preventive effects on the relapse of UC.[47] Another pilot study showed that supplementation with BFM was safe and more effective than conventional treatment alone. In this trial, 20 patients with UC randomly received 100mL/day of BFM or placebo for 12 weeks with conventional treatment. Post-treatment clinical activity index, endoscopic activity index, and histological scores were significantly lower in the BFM group compared to the placebo group.[48]

Studies have also been conducted on the efficacy of probiotic preparations on cell cultures. These studies can help us better understand the mechanisms behind the beneficial effect of probiotic supplementation reported in the aforementioned clinical trials. One study performed on the intestinal mucosa of UC patients found that supplementation with a probiotic preparation containing *Bifidobacteria, Enterococci,* and *Lactobacilli* decreased the activation of NF-κB, TNF-α, and IL-1β and elevated the expression of IL-10. These findings suggest that this probiotic preparation may be effective in preventing exacerbations, as well as decreasing the relapse in patients with chronic UC.[49] In another study, the effect of a *Bifidobacteria* longum preparation was examined on inflamed colonic biopsies of patients with active UC. The investigators found that after probiotics were co-cultured with the colonic biopsies, the concentrations of TNF-α and IL-8 lowered. Also, probiotics were shown to inhibit NF-κB activation in lamina propria mononuclear cells levels when they were co-cultured with inflamed UC colonic tissue.[50]

In light of these studies, the clinician must remember that that the efficacy of a probiotic preparation may not be the same in all patients or in the same patient at different stages of disease. Success of treatment could also be dependent on several variables, such as characteristics of a patient (gender, lifestyle habits, age), lesions in IBD (location, extent, type of gross lesion), and risk factors (genetic predisposition, familial history). Most studies on probiotics have included women as a significant portion of the cohort, and men have traditionally been underrepresented. To date, there have not been any published dose-response studies on probiotics.

Prebiotics

Prebiotics are non-digestible functional foods that help to stimulate growth or activity of beneficial bacteria in the gut. Many types of dietary fiber are classified as prebiotics and have exhibited beneficial effects in both animal models and clinical studies of UC. In one animal study, rats who were given psyllium (*Plantago ovate, PO*) seeds experienced an increase in butyrate, an important short-chain fatty acid (SCFA) produced when intestinal flora ferment prebiotic fibers, and utilized by epithelial cells to help protect against intestinal mucosal damage and promote healing. These rats also experienced restored colonic glutathione levels, lower TNF-α levels, and recovery of damaged colonic mucosa when compared to untreated colitic rats.[51] Psyllium seeds were shown to benefit UC patients in a randomized clinical trial as well. In this trial, participants were either given 10 g psyllium seeds twice daily, 500 mg mesalamine three times daily, or a combination of mesalamine and psyllium. The greatest benefit was shown in the group taking both mesalamine and psyllium – only 7 of 30 patients relapsed – compared to 13 of 35 patients in the PO group and 13 of 37 in the mesalamine group. A separate group of patients were given PO seeds for 3 months to determine the effect of PO on SCFA production. Fecal samples that were collected at the end of the trial indicated that PO administration resulted in significantly higher total SCFA, butyrate, and acetate levels.[52]

Another prebiotic that has shown benefit in UC patients and animal models with colitis is germinated barley foodstuff (GBF), which mainly consists of a protein-rich insoluble fiber with glutamine. Kanauchi et al. reported an increase in SCFA production, a reduction in frequency of bowel movements, amelioration of severe bloody diarrhea, and an attenuation of colonic mucosal damage when rats (in an experimental colitis model) were administered GBF.[53,54,55] Furthermore, a clinical trial involving mild to moderate UC patients who took GBF showed that these

patients had an attenuation of symptoms.[56,57] Another report, in a murine model, found that GBF had anti-inflammatory activity by affecting two main pathways – first by downregulating Th1-mediated inflammatory activity (therefore decreasing levels of IL-6), and second, by attenuating NF-κB levels.[57] Currently, GBF is not commercially available in the US for therapeutic use.

Essential Fatty Acids

It is well-known that in today's Western diets, the ratio of omega-6 (n-6) to omega-3 (n-3) fatty acids (FAs) is very high – approximately 15:1 – which can cause pro-inflammatory effects. Many studies have been conducted showing the benefit of n-3 FAs for chronic inflammatory illnesses such as asthma,[58,59] cardiovascular disease[60,61] and autoimmune diseases.[62,63]

The n-3 FAs have been shown to have anti-inflammatory effects by suppressing NF-κB, IL-1β, TNF-α, and IL-6.[64] Omega-3 FAs also prevent inflammation by competitively inhibiting arachidonic acid, reducing the inflammatory mediators derived through the cyclooxygenase (COX) and 5-lipooxygenase enzymes: prostaglandin E2, thromboxane A2, and leukotriene B4.[65] Sources of n-3 FAs can be found in a wide variety of foods such as fish, walnuts, flaxseeds, soybeans, tofu, and vegetables; although therapeutic doses require supplementation.

Several studies have suggested that patients with IBD have unhealthy, pro-inflammatory fatty acid ratios. An observational study conducted by Siguel and Lerman demonstrated that patients with UC had high ratios of derivatives to precursors of n-6 FAs, a sign of essential fatty acid deficiency.[66] Two other studies investigating the serum FA levels of Cr patients found that n-3 FAs were significantly lower, and that the ratio of n-6 to n-3 was significantly higher in these patients compared with the control group.[67,68]

Animal models of IBD have also confirmed the benefits of n-3 fatty acids. Several studies using murine models of experimental colitis have shown that n-3 FAs helped protect against injury and helped augment the healing process. The researchers in these studies found varying mechanism to attenuate inflammation in these animal models of UC – from lowering NF-κB and TNF-alpha levels to downregulating COX enzyme activity.[69,70,71,72,73] Furthermore, several human studies have found that UC patients who were administered fish oils (a combination of EPA/DHA) improved clinically – even with a wide range of dosages utilized in these studies.[74,75] The dosages in these trials ranged from 2.7 to 3.24 grams per day for EPA, and 1.8 to 2.4 grams per day for DHA. Another trial even showed that 72% of patients in the active fish oil group weaned off or reduced their medication dose.[76] Similar results were shown in clinical trials utilizing varying doses of fish oils for maintenance of remission in patients with Cr over a one-year period. Overall, the doses of EPA and DHA given to these Cr patients were smaller than dosages given to the UC patients mentioned above. Despite these dosages, a significant number of Cr patients who were administered fish oil showed clinical improvement, measured by a decreased Crohn's Disease Activity Index (CDAI).[77,78,79] Based on these findings, it is recommended that patients with IBD take between 2-4 grams per day of EPA, and 1-3 grams per day of DHA.

Other Nutraceutical Therapies

Curcumin

Turmeric is a well-known flavorful spice derived from the herb *Curcuma longa*, a member of the ginger family. Turmeric is often used as a major cooking spice in curry, found predominantly in South Asian cuisines. Besides being a food flavoring and coloring agent, turmeric has been used in Ayurvedic medicine for numerous health benefits since ancient times. Curcuminoids are the major active constituents found in turmeric, the most prominent being curcumin. Given the recent interest of turmeric for many health benefits, many papers have been published showing its role in the treatment or prevention of many diseases – ranging from heart disease[80,81,82] to cancer.[83,84,85] Many encouraging studies have shown the beneficial effects of curcumin on IBD. A vast majority of studies in animal models have shown that curcumin primarily reduces inflammation through the inhibition of NF-κB.[86,87] Findings from another study using a murine model of colitis showed that curcumin administration resulted in a significant decrease in both neutrophil infiltration and lipid peroxidation in the inflamed colon.[88]

Human studies have yielded positive benefits after administration of curcumin. In an open-label pilot study, Holt and colleagues reported that curcumin reduced the inflammatory response in 9 out of 10 patients with IBD.[89] The first group consisted of 5 patients who had UC, and were treated with 550 mg of curcumin twice daily for 1 month and then 550 mg three times daily for another month. Another group consisted of 5 Cr patients that were treated with 360 mg of curcumin three times daily for 1 month and then 360 mg 4 times daily for the remaining 2 months. Serological tests in all patients from both groups indicated a reduction of inflammation, and out of 10 patients, 9 reported an improvement in clinical symptoms. Interestingly, 4 of 5 patients in the UC group were able to eliminate or decrease their medications. Curcumin was found to maintain remission among quiescent UC patients in a larger double-blind, placebo-controlled, randomized multicenter clinical trial. In this trial, 89 UC patients were enrolled in one of two groups to either receive 1 g of curcumin twice daily plus sulfasalazine (SZ) or mesalamine, or receive a placebo plus SZ or mesalamine. During this 6-month trial, patients enrolled in the curcumin group experienced clinical improvement and a statistically significant decrease in the rate of relapse.[90] In these studies, curcumin has demonstrated to also have an excellent safety profile.

Boswellia

Boswellia serrata, or Indian frankincense, has been used in traditional Ayurvedic medicine for its therapeutic properties. It has been widely studied for treating arthritis[91,92] and has also been used over the centuries for various inflammatory conditions such as bronchial asthma and wound healing. The exact mechanism of how *Boswellia* works in reducing inflammation is not known, however a few *in vitro* studies have shown it to inhibit 5-lipooxygenase, consequently lowering leukotriene formation.[93,94] *Boswellia* also inhibits NF-κB, which helps

to downregulate the pro-inflammatory cascade.[95] This action is similar to the anti-inflammatory mechanism of *Curcuma longa*.

To date, there have been a few human studies showing the efficacy of *Boswellia* in IBD. *Boswellia* (350 mg three times daily) was compared to SZ (1 g three times daily) during a 6-week intervention trial among UC patient. Patients that were administered *Boswellia* were found to have similar improvement as patients in the SZ group – in laboratory, clinical, and histopathological parameters. In addition, 82% of treated patients in the *Boswellia* group went into remission, while the remission rate was 75% in the SZ group.[96] Following this trial, the same group of researchers conducted an interventional study involving 30 UC patients that were given *Boswellia* (900 mg daily, divided in 3 doses) or SZ (1 g three times daily) for 6 weeks. The primary goal of treatment was to attain remission. Secondary endpoints included changes in stool property, sigmoidoscopic scores, histopathology of colonic mucosa, and various laboratory markers of inflammation and anemia. 18 of the 20 patients in the *Boswellia* treatment group had improvement in at least one secondary endpoint, and 14 experienced remission. Conversely, 6 of the 10 patients in the SZ group had improvement in at least one secondary endpoint and only 4 went into remission.[97] In a larger clinical trial consisting of 102 active Cr patients, Gerhardt et al. assessed changes in pre- and post treatment in Crohn's Disease Activity Index (CDAI) among patients receiving either *Boswellia* or mesalazine. Patients treated with *Boswellia* exhibited an average 90-point decrease in CDAI, while those taking mesalazine averaged a 53-point decrease in symptom severity. In terms of benefit-risk evaluation, the researchers concluded that Boswellia appeared to be superior to mesalazine. [98]

Glutamine

Glutamine, a non-essential amino acid, is an important source of fuel needed for intestinal enterocytes to function. If levels of glutamine are deficient, then increased intestinal permeability and mucosal atrophy occur, and enterocyte metabolism is adversely affected. There have been animal model and cell culture studies published on the effects of glutamine. In one of these studies, the administration of glutamine inhibited the expression of pro-inflammatory mediators that are regulated by the NF-κB pathway in rats with experimentally-induced colitis. These effects are possibly due to the reduced expression of pro-inflammatory cytokines, as well as the inhibition of oxidative stress.[99] Another study with animal models of UC has shown that glutamine added to elemental diets promotes quicker healing of colonic lesions[100] and decreases endotoxin levels.[101]

In rat studies, glutamine was found to not only improve mucosal integrity,[102] but also helped to preserve both intestinal and extra-intestinal levels of immunoglobulin A (IgA).[103] In an in-vitro study, duodenal biopsies from healthy volunteers were cultured in the presence of increasing amounts of glutamine and IL-1β (which enhances inflammatory cytokines). Researchers found that glutamine inhibited IL-1β, which furthermore, reduced production of pro-inflammatory cytokines IL-6 (found to be high in the mucosa and serum of Cr patients) and IL-8, and increased the production of anti-inflammatory cytokine IL-10.[104] Another study showed similar effects of decreased IL-6 and IL-8 production when high doses of glutamine (administered with low doses of arginine) were incubated on colonic biopsy cultures.[105]

Although supplementation with glutamine has shown promising results in animal and in-vitro studies, there have been limited human clinical studies in IBD patients. One small clinical study on the effects of glutamine in Cr showed no benefit. In this study, oral doses of 21 g per day for 28 days of glutamine in addition to a standard diet did not improve intestinal permeability.[106] Dosing recommendations for gut healing activity range from 1 to 10 grams per day.[107]

Vitamin D

Vitamin D has been long known for its role in optimal bone health. Increasing evidence now indicates that vitamin D plays an essential role in regulating the immune system and cancer prevention.[108] Vitamin D receptors have been found on virtually all cells involved in the modulation of the immune system. One mechanism vitamin D is thought to play a role in is modulating Th1 and Th2 pathways. If vitamin D levels are deficient, an increase in Th1 pathway occurs, resulting in a pro-inflammatory response.[108] Deficient vitamin D levels have been implicated in the pathogenesis of IBD - the incidence for IBD appears to be the highest in Northern Europe and North America, where direct sunlight exposure is lower than in other parts of the world.[65] Moreover, several studies suggest that even when IBD patients are well-controlled with therapy, their levels of vitamin D are lower than normal.[109] Past studies using animal models have assessed the role of vitamin D deficiency and/or supplementation on the development and severity of IBD. These studies consistently showed that the presence of vitamin D was associated with either delayed development or an improvement of certain parameters in animal models with colitis.[110,111,112] As with other therapies reviewed above, vitamin D has also shown to be anti-inflammatory by inhibiting NF-κB, causing a decrease in pro-inflammatory cytokines in Cr.[113]

Other Alternative Medicine Treatments

Various non-biologically based alternative medicine modalities have been researched for IBD. One study found that mind-body therapies may improve the quality of life in patients with UC who are in remission. In addition, patients in the intervention group showed significant improvement in mental health and bowel symptoms (assessed by questionnaire) compared to patients in the usual-care group.[114] A few studies have also looked at the benefit of acupuncture as a treatment modality in IBD patients. Two trials by Joos et al. (1 UC, 1 Cr) compared real acupuncture with moxibustion versus sham acupuncture (or placebo). In both trials, real acupuncture was significantly superior in regard to disease activity scores (primary outcomes), but not to the quality of life questionnaires and symptoms scores. However, quality of life and symptom scores improved significantly in both groups after treatment compared to baseline.[115,116] Further research is warranted with larger clinical trials to recommend these therapies for IBD.

Summary

The prevalence of inflammatory bowel disease (Crohn's disease and ulcerative colitis) has been on the rise in the United States, as well as in other developed nations. Patients who have IBD experience significant morbidity with potential life-threatening sequelae. In addition, these patients experience poor quality of life with constant remissions and painful exacerbations of disease throughout their lifetime. Conventional treatments have been only partially successful in treating IBD. Usually medication is employed as a first-line approach, but when they fail, patients are often left with no other treatment options except for surgery. These treatments may help treat acute episodes, but do not address the underlying cause of the disease, and can lead to many types of complications such as nutrient deficiencies. Natural therapies, when used alone or in conjunction with conventional therapies, have been shown in the literature to lower the risk of adverse events and help patients attain remission for a longer period of time. Most well-designed studies using natural therapies for IBD have shown to be as effective and beneficial by affecting similar physiological pathways as conventional therapy without the side effects.

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