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Inflammatory Bowel Disease & Irritable Bowel Syndrome

Understanding, Distinguishing and Addressing

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POINT INSTITUTE OF NUTRACEUTICAL RESEARCH

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Gastrointestinal complaints are one of the most common reasons individuals seek medical care. Many have been through numerous physician consultations and treatment modalities without relief. Unfortunately, millions more suffer silently, thinking that their GI symptoms are "normal"; while self-medicating with antacids, Pepto Bismal or food avoidance. Additionally, many GI complaints are embarrassing for patients to discuss with their health provider or they may fear invasive GI testing procedures.

In the past several decades research has changed the way we understand gastrointestinal disorders. These studies have illuminated the complex interaction of the immune system, neuroendocrine system and microbial environment within the gut. These advances in understanding have profound implications on the diagnosis and treatment of gastrointestinal disorders. Rather than describing only discreet independent GI disorders, common dysfunctions are at the root of many, seemingly unrelated, GI conditions. Combining these scientific advances with the understanding of the biological individuality of each patient has led to a new paradigm of patient care. Even while many patient complaints and irregularities are difficult to pigeonhole into a clear cut "ICD" diagnosis, this new paradigm of medicine has emerged to allow the practitioner to assess, evaluate and treat *patients* rather than *diseases*.

This new paradigm of medicine is generally referred to as "functional medicine."[1] While defined differently by various groups, functional medicine, in essence, combines the importance of patient-centered preventative care with the understanding of the complex interconnections between multiple organ systems. This form of medicine allows clinicians to begin to understand the complex network connecting each body system through a web of physiology and biochemistry. No longer is each body system isolated from the other; instead, the emphasis is on what connects the systems together—their common relationships (and deficiencies) that help explain the patient's chronic conditions. In general, this form of medicine asks, "What are the common threads that tell us about why the patient may be experiencing chronic illness?" rather than merely, "How can we differentiate one disease from another?" The result is therapies that focus on root causes of complex and chronic disease patterns that are tailored to the specific patient being treated.

Functional Medicine and GI health

The gastrointestinal (GI) tract represents our most intimate contact with the external environment. In our lifetime we will consume between 30–50 tons of food and routinely host more microbial cells in our gut than the number of human cells in our body. Our GI tract is tasked with the responsibility of extracting from foods the appropriate nutrients needed to thrive, maintaining an appropriate balance of helpful and harmful microbes while at the same time preventing the entrance of harmful substances into the bloodstream. Is it any wonder that the delicate balance in the gut is often disturbed, leading to one of many GI disturbances—for which many seek medical care?

The functional medicine approach does not begin by labeling the disease in order to begin treating the symptoms as the primary step. Instead, discovering the underlying dysfunction(s) unique to the patient experiencing the symptoms is the key. In basic terms, GI function can be grouped into four distinguishable functions. They are: Digestion, Elimination, Microbial Balance and Gut (mucosal) Integrity.

[1]Other terms such as complementary/alternative medicine, integrative medicine, evidence-based medicine and prospective medicine overlap with the definition of functional medicine. To gain some further insight into these different terms by one of the leading proponents of functional medicine- see www.functionalmedicine.org, the Website for the Institute for Functional Medicine—particularly their recent "manifesto" called *21st Century Medicine: A New Model for Medical Education and Practice.*

Digestion

Perhaps the most obvious of the four functions, the GI tract is tasked with digesting and absorbing the foods we eat. Through a complex coordination of enzymes, acids, bile salts, peristaltic action, transporters and microbial symbiosis, our GI tract is able to take complex food sources and break them down into the macronutrients (protein, carbohydrate, fat) and micronutrients (vitamins, minerals, phytonutrients etc.) that can be transported into the body. Each of the processes of digestion are important, as it only requires a deficiency in one or a few micronutrients to lead to some biochemical dysfunction.

Elimination

The process of elimination can be nearly as important as digestion. Ridding our body of the un-useable portions of our food, as well as the toxic metabolites produced by our own bodies, is critical to our health. Healthy liver detoxification (biotransformation), bile production and bowel movements are hallmarks of a healthy GI tract. Proper elimination also helps regulate bowel transit time, which has an effect on water-retention, electrolyte balance, healthy microbial fermentation of fiber and proper digestion. Stool frequency and morphology have been used to define overall health for millennia.

Microbial Balance

Our gut hosts upwards of 100 trillion bacteria, yeast and other microbes. A proper balance of this gut microflora (over 500 different strains) is vital for proper GI health. These microorganisms represent one of the most metabolically active systems within our bodies; affecting glycemic control, cholesterol and amino acid metabolism, short-chain fatty acid acid production (eg. butyrate for colon cell energy) and vitamin synthesis. Proper microbial balance helps regulate immune function, prevent overgrowth of harmful organisms and regulate bowel motility. When this healthy balance of organisms is disturbed, a condition known as dysbiosis, the GI tract becomes vulnerable to numerous pathologies.

Gut Integrity

While we think of the GI tract as primarily digestive and absorptive, maintaining proper mucosal barrier function is vital to GI health. Within the lumen of the gut are numerous entities (large antigenic/allergenic food particles, toxins, harmful microorganisms and their metabolites) that should never reach the blood stream or lymphatic system. The integrity of the mucosal barrier is maintained by a single layer of tightly fitted enterocytes that comprise a surface area the size of a tennis court. Not surprisingly, 70 percent of the immune system function is closely associated with the GI tract, in specialized lymphatic compartments within the mucosa and in the intercellular space along the epithelium. Gut integrity can be compromised by a number of factors such as dysbiosis, inflammation, food allergies and immune system dysregulation.

When all four functions of the GI are working properly and in harmony with one another, few GI symptoms are likely to occur. However, when one area is compromised, it places strain upon the other components. Often times it is difficult to determine which area triggered the downfall as the relationship between each of these functions is interdependent. For instance, the use of antibiotics will often trigger dysbiosis due to depletion in healthy microbial organisms. This dysbiosis may lead to mucosal damage caused by harmful bacteria, *Candida*, or other opportunistic organisms. The ensuing inflammatory process may lead to a disruption in microvilli function and gut permeability, which may manifest as lactose intolerance, food allergies/intolerance or changes in stool frequency just to name a few. Often times these symptoms will be non GI-related (headaches, skin irritations, chronic joint pain, depression). Assessing and supporting these basic GI functions is vital to ensure proper vitality and optimal health.

The companion articles in this edition of The Standard address the complex functional issues in two common bowel disorders. Inflammatory Bowel Diseases (IBD) and Irritable Bowel Syndrome (IBS) are often characterized in similar ways by patients and clinicians; both are chronic GI disorders that involve altered bowel habits and GI discomfort—although each presents a different model of adverse GI function. These papers will outline the basic components of these conditions, showing how the functional medicine approach differs from the common Western medical approach. This discussion is followed by the evidence for non-pharmacological approach, which can be integrated into a modern functional medicine practice.

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, though 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 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

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 percent (5.2 percent within the Jewish population); and for relatives of Cr patients, the risk increases to 5.2 percent (7.8 percent for Jews).[3] Genome-wide scans have found several susceptibility 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 decrease 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 a 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. This model is a holistic model that describes the essential functions that maintain the optimal health of the GI system, including digestion and 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 functional medicine 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 that 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 percent 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).[26,27] More importantly, in patients with non-active IBD, the test has a high level of sensitivity and specificity in predicting clinical relapse of disease.[26,28]

Conventional Treatment

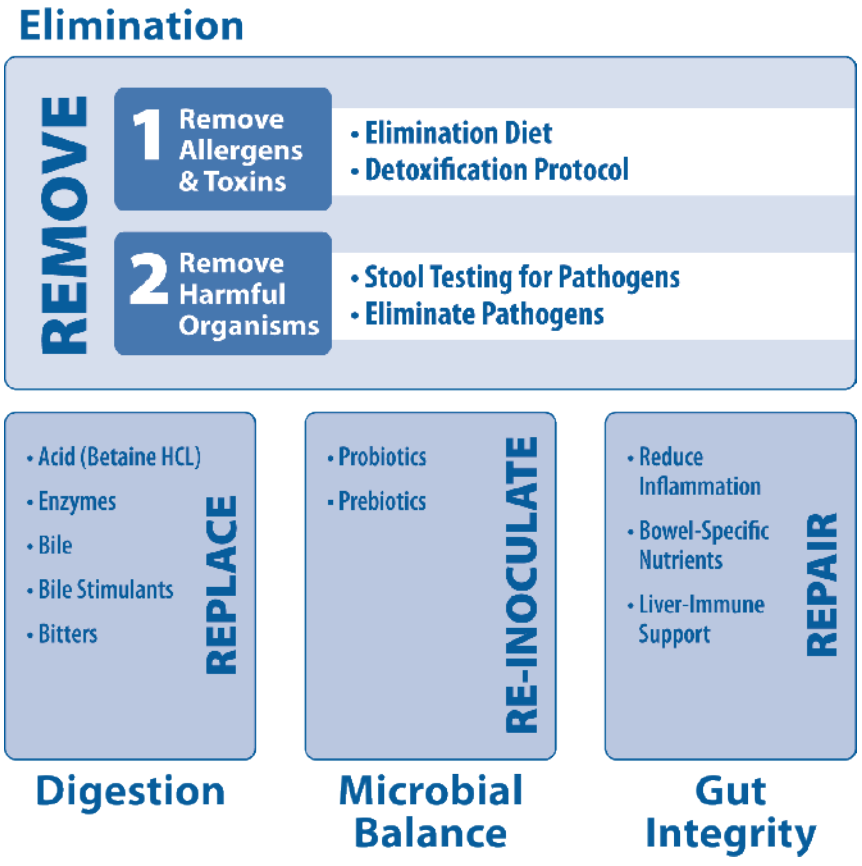
The conventional medical treatment of IBD involves an approach that focuses on both symptomatic relief as well as controlling overstimulation of the immune system. Exacerbations of Cr and UC usually require treatment of 5-aminosalicylic acid (5-ASA), which is the active ingredient found in the pharmaceutical 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.[29,4]

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.[29,2,5,19,4]

Most of these medications have serious adverse effects in patients, which is a concern for many clinicians. 5-ASA has been commonly known to 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.[29,2,5,19,4]

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.[30] 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.*[31]



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 the 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 both digestion and absorption. While foods may often contain some of these components, they 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. It involves the introduction of viable micro-organisms (or ingredients such as prebiotics that feed these organisms) that will help support overall 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 exist 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 are 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 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 tests 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 versus 3.8 months in the corticosteroid group. Particularly interesting was the relapse rates (statistically significant) among both groups after two years—62 percent in the diet group versus 79 percent 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 versus 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 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 percent for the mesalazine group and 67 percent for the *E.coli* group, and the time to relapse was not significantly different between both groups.[38] In a 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 three strains of bifidobacteria, four strains of lactobacilli and one 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 (three trillion cfu/day). At the end of the study (12 months), 15 of 20 patients (75 percent) 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 percent 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 one gram mesalamine along with one gram *S. boulardii* (37.5 percent) compared to patients receiving one gram mesalamine only (6.25 percent).[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 four 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 100 mL/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 clinical trials above. 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 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 of psyllium seeds twice daily, 500 mg of 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 three months to determine the effect of PO on SCFA production. Fecal samples 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 U.S. 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 mechanisms 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 percent 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 two to four grams per day of EPA, and one to three 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 and Indian 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 its 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 five patients who had UC and were treated with 550 mg of curcumin twice daily for one month and then 550 mg three times daily for another month. Another group consisted of five Cr patients that were treated with 360 mg of curcumin three times daily for one month and then 360 mg four times daily for the remaining two months. Serological tests in all patients from both groups indicated a reduction of inflammation and, out of 10 patients, nine reported an improvement in clinical symptoms. Interestingly, four of five 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 one gram of curcumin twice daily plus sulfasalazine (SZ) or mesalamine, or receive a placebo plus SZ or mesalamine. During this six-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, is used in traditional Ayurvedic medicine for its therapeutic properties. It has been widely studied for treating arthritis[91,92] and has 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 (one gram three times daily) during a six-week intervention trial among UC patients. 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 percent of treated patients in the *Boswellia* group went into remission, while the remission rate was 75 percent 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 three doses) or SZ (one gram three times daily) for six 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; 14 experienced remission. Conversely, 6 of the 10 patients in the SZ group had improvement in at least one secondary endpoint and only four 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]

Scutellaria

Scutellaria baicalensis is a widely used herb in traditional Chinese and Japanese medical systems, especially in the treatment of chronic inflammatory and ulcerative disease. The major flavonoids found in *S. baicalensis* (baicalein, baicalin and wogonin) have been found to have several biological and pharmacological activities, including anti-inflammatory, [99] anti-microbial,[100,101] anti-proliferatory[102] and anti-tumor properties.[103] Animal studies on colitis have provided significant insight into how *S. baicalensis* affects certain cellular and molecular pathways involved in reducing inflammation. One study examined the anti-inflammatory effect of *S. baicalensis* in a murine model of colitis.[104] The investigators found that baicalein (compared to baicalin and wogonin) improved inflammatory symptoms of colitis such as rectal bleeding, weight loss, blood hemoglobin content and other histological and biochemical parameters. Additionally it was found that baicalein lowered elevated levels of IFN-gamma and IL-4, which were associated with inflammation. Asimilar study looked at the effect of *S. baicalensis* on a rat model of colitis.[105] *S. baicalensis* was shown to have powerful anti-inflammatory and protective effects—histological preparations showed significant reductions in colonic ulcerations. A reduction in body weight and enhanced recovery of normal colonic secretory function was also observed. The effects of certain flavonoids isolated from *S. baicalensis* have been studied in animal models as well. Researchers studying wogonin in mice models of colitis found that it helped alleviate colitis-related damage by regulating cytokines such as IL-4, IL-5 and IL-10.[106] This effect can be beneficial in mediating inflammation in colitis brought about by an abnormal Th2 response. Various other studies have shown that wogonin inhibited NF-κB activity in different tissue types, which prevented the production of pro-inflammatory cytokines.[107, 108,109]

Presently there have not been any human studies examining the effects of *S. baicalensis* on IBD. Only one clinical study to date has been published. The study showed that Flavocoxid, a proprietary mixture of baicalin and catechin, was found to be as effective as naproxen for the management of osteoarthritis of the knee.[110] In the double-blind study, 103 subjects were randomly assigned to receive either flavocoxid (500 mg BID) or naproxen (500 mg BID) for one month. Primary endpoints were discomfort and global disease activity, and safety assessments were taken for both treatments as a secondary endpoint. Both flavocoxid and naproxen showed significant reduction in the signs and symptoms of knee OA. In addition, there were no statistically detectable differences in adverse events between the groups (although there was a trend toward a higher incidence of edema and nonspecific musculoskeletal discomfort in the naproxen group). The authors concluded that "flavocoxid was as effective as naproxen in controlling the signs and symptoms of OA of the knee, and would present a safe and effective option for those individuals on traditional nonsteroidal anti-inflammatory drugs or cyclooxygenase-2 inhibitors."

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.[111] Another study with animal models of UC has shown that glutamine added to elemental diets promotes quicker healing of colonic lesions[112] and decreases endotoxin levels.[113]

In rat studies glutamine was found to not only improve mucosal integrity,[114] but also helped to preserve both intestinal and extra-intestinal levels of immunoglobulin A (IgA).[115] In an invitro 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 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.[116] 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.[117]

Although supplementation with glutamine has shown promising results in animal and invitro 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.[118] Dosing recommendations for gut healing activity range from 1 to 10 grams per day.[119]

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.[120] 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 the Th1 pathway occurs, resulting in a pro-inflammatory response.[120] 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.[121] 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.[122,123,124] 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.[125]

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.[126] 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.[127,128] 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. And even as some conventional therapies may help treat acute episodes, they 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 reported to lower the risk of adverse events and help patients attain remission for a longer period of time. This review confirms that most well-designed studies using natural therapies in IBD patients show clear benefits, often affecting similar physiological pathways as conventional therapy without the side effects.

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Irritable Bowel Syndrome

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Introduction

Irritable Bowel Syndrome (IBS) is one of the more common gastrointestinal disorders seen in clinical practice today. The prevalence of IBS is high, affecting approximately 10–20 percent of the general population.[1,2] IBS is also responsible for significant health care costs—the estimated annual direct cost in the U.S. rose to an estimated $1.35 billion in 2003.[3] This disorder not only impacts the quality of life of those affected, but it also accounts for many missed work days and an increased financial burden upon patients seeking conventional medical treatments that often do not work.[4,5] These experiences can cause both the doctor and patient to become frustrated, often leading them to seek alternative treatment options.

Patients with this functional bowel disorder commonly experience non-specific gastrointestinal (GI) symptoms such as abdominal pain or cramping, change in stool consistency or frequency, and bloating.[6,1] The severity and occurrence of these symptoms in IBS patients can vary greatly—some experience minor infrequent episodes, while others experience more disabling episodes. Based on the alteration of stool habits, IBS is classified as either being diarrhea-predominant (IBS-D), constipation-predominant (IBS-C) or having an alternating stool pattern (IBS-A).[1,7,2] Although these classifications are useful for research purposes, symptom patterns may differ from one individual to another.

Because IBS is considered to be a functional disorder for which no specific conventional laboratory or imaging tests exist, many clinicians consider it to be a "diagnosis of exclusion."[7,8] Clinicians need to exclude conditions that can mimic IBS symptoms before making a definitive diagnosis; these include conditions such as lactose intolerance, parasitic (and other) infections, small bowel bacterial overgrowth and Celiac disease.[9,10,11,12] After this is done, a diagnostic algorithm is used to categorize the patient's symptoms. One common, well-known algorithm includes the Rome III Criteria (Table 1 below).[1,13,2] Doctors can choose to use one of these guidelines or may rely on their own clinical experience with past patients when diagnosing IBS.

Even though the Rome III criteria (and other diagnostic algorithms) can help assist with the diagnosis of IBS, it does not identify the underlying cause(s) driving the condition. Without addressing the underlying cause, persistence of non-specific G.I. symptoms will continue to occur. Symptoms of IBS are usually treated with various medications (long-term), which often are not effective or cause side effects in patients. A type of personalized medicine that takes into account the "entire picture" of a patient with chronic illness is the functional medicine approach. This approach uses an evidence-based systems biology approach that some clinicians use to assess, prevent and treat chronic diseases. Functional medicine utilizes treatments that address the underlying root cause of chronic disease unique to an individual rather than treating symptoms alone. Emphasis is placed on how environmental toxins, diet and nutritional imbalances play a role 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*.[14] These steps are discussed in greater detail under the "Complementary & Alternative Medicine Treatments" section.

Table 1: Rome III Criteria

12 weeks or more in the past 12 months of abdominal discomfort or pain that has 2 out of the 3 features:

- Relieved with defecation
- Associated with a change in frequency of stool
- Associated with a change consistency of stool

The following are supportive, but not essential to the diagnosis:

- Abnormal stool frequency (>3/day or <3/week)
- Abnormal stool form (lumpy/hard or loose/watery)>1/4 of defecations
- Abnormal passage (straining, urgency or feeling of incomplete evacuation)>1/4 of defecations
- Passage of mucus > ¼ of defecations

Causes

In the conventional medicine paradigm it is largely believed that there is no unique cause attributable to the development of IBS. On the other hand, the functional medicine approach helps to give clinicians additional tools in identifying potential underlying causes of the illness that the conventional medical model does not address. The interaction of certain lifestyle factors (along with the environment) can play a large role in predisposing an individual to develop IBS. These include:

• **Psychological Factors:** Stressful life events are well-known triggers for the onset and exacerbation of IBS symptoms. In one study, chronic stress (such as job loss, divorce, lawsuits, etc.) for more than six months correlated strongly with subsequent IBS symptom intensity. Furthermore, no patient exposed to any of these chronic stressors improved clinically over the subsequent study period (16 months).[15] Another study found that psychological distress (particularly anxiety and depression) was strongly correlated to the effects of GI symptoms in IBD patients.[16] It has also been shown that the symptoms of IBS itself can aggravate stress levels in IBS patients.[17]

Specifically, reaction to stress is mediated by corticotrophin-releasing hormone (CRH), which is released from the hypothalamus. CRH then stimulates the production of adrenocorticotropic hormone (ACTH) from the pituitary, affecting GI function through brain and peripheral receptors.[8,18,19] Researchers have shown that CRH (stimulated by stress) can cause abdominal pain and increase colonic motility and defecation, while at the same time, reduce gastric emptying.[20,21,22] In addition, increased levels of ACTH, cortisol and pro-inflammatory cytokines IL-6 and IL-8 were found in patients with IBS after infusion with CRH.[23] The over-activity of brain CRH and the CRH-receptor signaling system also contributes to a high prevalence of psychiatric disorders, such as anxiety and depression, in IBS patients.[24] Psychiatric illnesses, in general, have been identified in more than 50 percent of patients with IBS.[25] Patients with IBS may be assessed for hypothalamic-pituitary-adrenal (HPA) axis abnormalities using readily available salivary cortisol and DHEA profiles.

• **Active Infections:** Acute bacterial gastroenteritis is the strongest risk factor for the development of post-infectious IBS (PI-IBS).[26] Approximately six percent to 17 percent of patients with IBS believe their symptoms began with an infection; prospective studies have shown up to a 36 percent incidence of post-infectious IBS following an episode of gastroenteritis.[27] Patients with post-infectious IBS (compared to IBS from other causes) usually experience fewer psychiatric symptoms with more diarrhea-type symptoms[28] and increased intestinal inflammation. This inflammation is characterized by increased T-lymphocytes, mast cells and pro-inflammatory cytokines.[29,30,31] Other risk factors for the development of PI-IBS include infection with parasites such as *Giardia lamblia*, female gender, psychiatric disorders, smoking and longer duration of infectious illness.[32,33,34]

• **Dysbiosis:** Anytime the balance of organisms within the gut is disrupted, harmful organisms can gain an advantage, leading to systemic consequences. There are several factors known to disrupt this delicate balance which result in symptoms associated with IBS. These include:

Overgrowth of Opportunistic Yeasts: During immune-system stress, GI imbalances and antibiotic therapy, Candida in the gut can overgrow and act as an opportunistic pathogen.[35,36,37,38] Candida overgrowth can trigger the development of symptoms in patients with IBS. For example, the glycoprotein composition of yeast can cause inflammation by stimulating mast cells to produce pro-inflammatory substances (such as prostaglandin E2 and histamine), which may drive IBS-like symptoms.[38] Furthermore, yeast overgrowth can degrade secretory IgA, which is found in the intestinal mucosa and is crucial for gut immunity and defense.[38]

Depletion of Beneficial Bacteria: Disturbances of gut flora in IBS patients, including decreases in the concentrations of beneficial flora such as *Bifidobacterium* and *Lactobacillus*, have been reported in the literature.[39,40,41] In several studies probiotic supplementation was shown to provide symptomatic relief, leading to the conclusion that depletion of beneficial bacteria may be responsible for triggering symptoms.[42,43,44] Results from other studies suggest proliferation of bacterial species that produce more gas through fermentation may be responsible for symptoms in IBS patients.[45]

Specific triggers, such as antibiotic therapy, can have a detrimental effect the ecological balance of the GI microbiota by depleting beneficial bacterial populations in the gut. The possible role of antibiotics in the etiology of IBS has been reported in the literature. A study by Mendall et al. looked at a possible link between antibiotic use and the development of IBS.[46] After interviewing 421 participants at a general health screening, researchers found that 48 participants had symptoms of IBS. During further analysis, results showed that antibiotic use was strongly related to the presence of IBS [adjusted OR 3.70]. Another study in 2002 followed patients prescribed antibiotics for non-GI-related symptoms.[47] These patients were monitored for more than four months and compared against the control group who had not received antibiotics. The investigators found that among those who took antibiotics, 48 percent developed one or more bowel symptoms (compared to 22 percent in the control group). Also, 24 percent of the patients who took antibiotics developed two or more bowel symptoms (compared to only six percent in controls). The authors concluded that, "patients who are given a course of antibiotics are more than three times as likely to report more bowel symptoms four months later than controls."

Small Bowel Bacterial Overgrowth (SBBO): Several studies have shown a connection between SBBO and IBS.[48,49] One study found that up to 78 percent of IBS patients have SBBO,[50] which may be responsible for symptoms such as bloating, diarrhea and abdominal pain. In a study by Pimental et al, eradication of SBBO was shown to improve symptoms in IBS patients.[49]

SBBO usually occurs when bacteria normally found in the large intestines migrate up and colonize the small intestines. Symptoms of SBBO include gas and bloating after meals, steatorrhea, and deficiencies of iron, vitamin D and B12. SBBO is primarily caused by a reduction in bowel transit time, but numerous other causes can include:

- Anatomic and motor disorders that cause stasis of gut contents (surgery, diverticula, strictures, adhesions, diabetic enteropathy)[51,52]
- Achlorhydria and hypochlorhydria[52,53]
- Use of proton-pump inhibitors: A study published in Clinical Gastroenterology and Hepatology[54] linked PPI use to an increased risk of development of SBBO. More than 450 patients were recruited in this study (200 with gastroesophageal reflux disease who received PPIs for a median of 36 months; 200 with IBS, in absence of PPI treatment for at least three years; and 50 healthy control subjects that had not received PPI for at least 10 years). Researchers found that the incidence of SBBO among normal controls was six percent; in IBS patients it was 25 percent; and among patients that received long-term PPI, the incidence jumped to 50 percent. Based on the increasing accumulation of evidence, it is important that clinicians periodically re-evaluate the need for long-term PPI therapy.
- Stasis (dysmotility)[55,56]
- Abnormal communication between the colon and small bowel

Laboratory Assessment

The conventional medical approach may help in ruling out certain disorders that mimic IBS, but it has severe limitations when assessing functional components of IBS (such as activity and prognosis). The functional medicine approach, instead, takes a more holistic look at determining the status of key gastrointestinal (GI) functions that can direct the clinician in determining the root underlying cause(s) of GI dysfunction. This approach allows the doctor to prescribe appropriate therapies designed to optimize GI health. Several laboratories have developed multi-analytic stool tests, called comprehensive digestive stool analysis (CDSA), that allow for an assessment of multiple G.I. functions. These tests include stool microbial analysis (for yeast and parasites), markers of digestive efficiency, metabolites of healthy-gut microbes and markers of immune function. The CDSA can serve as an excellent non-invasive tool because it is recommended for patients with diffuse and non-specific GI-related symptoms such as indigestion, dysbiosis, constipation and diarrhea. Of particular note, calprotectin, a marker included in some CDSA tests, is a useful test to determine the severity of intestinal inflammation. This marker also helps to differentiate between patients with IBS and Inflammatory Bowel Disease (IBD).[57,58] In IBS patients there is either low-grade or no active inflammation present. However, in IBD patients, there is usually a much higher level of inflammation.

Conventional Treatment

Conventional medical therapy for IBS primarily focuses on alleviating individual symptoms with pharmacotherapy—particularly pain, diarrhea and constipation. However, these therapies do not address the underlying cause(s). Furthermore, evidence of long-term benefits of pharmacologic agents has been weak, and the development of new agents has raised many issues concerning safety and therapeutic efficacy.[59,60]

Anticholinergic (antispasmotic) drugs are commonly prescribed for pain associated with IBS.[61] Other medications such as tricyclic antidepressants[62] and selective serotonin reuptake inhibitors (SSRIs)[63] have also been used to treat comorbid psychiatric symptoms and pain. Side effects of anticholinergic drugs and tricyclic antidepressants are many, including dry eyes, dry mouth, anxiety and tachycardia. Patients taking SSRIs may also experience adverse effects such as sexual dysfunction, suicidal ideation, nausea and vomiting.

Diarrhea-predominant IBS is usually treated with diphenoxylate or loperamide.[64,2] In unresponsive cases, antibiotics are commonly prescribed.[65,59] As mentioned in the previous section, when beneficial bacteria are destroyed by antibiotic therapy, harmful organisms have an advantage; this can lead to negative systemic consequences (such as Candida overgrowth). Conversely, constipation-predominant IBS is treated with osmotic laxatives;[66,67,2] side effects of these agents include dependency, melanosis coli, dehydration and electrolyte imbalance (when used longer than intended).

Prior to March 2007 the FDA approved only two drugs to treat IBS: tegaserod (a serotonin receptor agonist that increases intestinal motility) and alosetron (a serotonin receptor antagonist that decreases abdominal sensitivity).[68,8,69] In March 2007, however, tegaserod was taken off the market due to increased adverse cardiovascular events; the use of alosetron has been restricted due to GI toxicity.[68,70]

In addition to the safety concern of these pharmacological agents, evidence suggests that the efficacy of these therapies for IBS have not shown clear benefit. In 2005 a Cochrane review was published that reviewed 40 studies on the evidence of efficacy of various drug therapies for IBS.[71] After reviewing these studies, the authors concluded that the efficacy of drug therapies was weak and that no clear evidence existed for the benefit of using antidepressants or bulking agents. Other studies report that no convincing evidence supports the use of antispasmodics.[72,61]

Complementary & Alternative Medicine Treatments

Based on lack of efficacy cost and side effects associated with conventional medical treatments, it is not surprising that half of all patients with IBS look for complementary and alternative medicine (CAM) therapies. As discussed earlier, the "4R" program is a popular functional medicine approach for treating GI dysfunction.[14] This program utilizes four basic clinical steps:

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 digestion and absorption. While foods may often contain some of these components, they 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. It involves the introduction of viable micro-organisms (or ingredients such as prebiotics that feed these organisms) that will help support 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 scutellaria are often used to repair the gut due to their powerful anti-inflammatory effects. Supplementation with glutamine also enhances gut mucosal growth and repair.

Peppermint Oil

Peppermint oil (PO) is one of the most widely used CAM treatments that have been extensively studied in IBS patients. PO has an antagonistic effect on calcium channels, helping to relax GI smooth muscle. This effect helps to relieve cramping and pain associated with IBS.[73] Enteric-coated PO is usually recommended over other forms because it dissolves lower in the GI tract; thus reduces the risk of esophageal reflux (PO may relax the lower esophageal sphincter).[74,75,73] Many recent studies have shown the benefit of using PO on IBS. A recent clinical trial of 110 patients who had IBS (excluding patients with small bowel bacterial overgrowth, lactose intolerance or celiac disease) was conducted.[76] After patients took four capsules of enteric-coated PO (225 mg/capsule) daily for four weeks, symptoms improved in 75 percent of those taking peppermint oil (compared with 38 percent of those taking placebo). A similar study involving 110 patients tested the effects of PO in patients with IBS.[77] Patients took one capsule of PO (187 mg) or placebo three to four times daily, 15-50 min before meals, for one month. At the completion of study, 79 percent of patients in the PO group (43 percent in placebo) experienced a reduction in the severity of abdominal pain; 83 percent (29 percent in placebo) had less abdominal distention; 83 percent (32 percent in placebo) had reduced stool frequency; and 79 percent (22 percent in placebo) had less flatulence. Another important study[78] looked at the use of enteric-coated PO in children between the ages of 8 and 17 with IBS. In this randomized, double-blind controlled trial, 43 children with IBS were given two PO (0.1–0.2 mL) or placebo capsules t.i.d. for two weeks. At the conclusion of the trial, 75 percent of the patients receiving PO reported a significant reduction in the severity of pain associated with IBS (compared with 19 percent receiving placebo). Based on this latest research, PO should be considered in IBS patients due to its safe, effective and low-cost profile. It has been successfully used to treat global IBS symptoms and pain due to its spasmolytic and antiflatulent effect. It is suggested that a dose of 500 to 900 mg of enteric-coated PO be administered per day, depending on the severity of symptoms.

Probiotics

Probiotics have been one of the most widely studied CAM treatments in patients with GI-related disorders, including IBS. In one comparison study,[79] 75 patients were randomized to receive *Bifidobacterium infantis, Lactobacillus salivarius* or placebo for eight weeks. Compared to the other two groups, the *B. infantis* group had significantly reduced IBS symptoms (including decreased abdominal pain and discomfort, bloating and distention, and bowel movement difficulty). The researchers also observed an immune-modulating effect (normalization of IL-10/IL-12 ratio) in the *B. infantis* group compared to placebo. Another study using *B. infantis* showed similar benefit in ameliorating many symptoms associated with IBS.[80] In this large-scale, multi-center clinical trial, 362 women with IBS were randomized to receive three different doses of *B. infantis* (1x1010, 1x108, or 1x106 cfu/ml) compared to placebo. After four weeks, patients administered the 1x108 cfu/ml dosage of *B. infantis* had significant benefit over the placebo and all other doses in reducing many global IBS symptoms (abdominal pain, bloating, bowel dysfunction, incomplete evacuation, straining and flatulence).

There have also been several studies that have evaluated probiotic combinations in IBS patients. One randomized, double-blind, placebo-controlled study looked at a mixture containing different species (*Lactobacillus rhamnosus GG, Bifidobacterium breve* and *Propionibacterium freudenreichii ssp. Shermanii JS*) with 103 IBS

patients. The patients received a probiotic capsule (8-9 x 109 CFU/day) or a placebo capsule daily for six months. GI symptoms and bowel habits (such as abdominal pain, distention, and flatulence) were recorded. At the end of the study, there was a mean reduction of 42 percent in the symptom score of the probiotic group compared with six percent in the placebo group.[43] A probiotic preparation containing three strains of bifidobacteria, four strains of lactobacilli and one strain of *Streptococcus* (*S. salivarius* subspecies *thermophilus*) has also shown benefit in alleviating symptoms in IBS patients. In one eight-week study involving 25 patients, treatment with this preparation (450 billion CFU/day) showed a reduction in abdominal bloating scores in patients with IBS-D.[81] A further trial (double-blind, placebo controlled study) was conducted by the same investigators. They found that after administration of the probiotic preparation for four weeks (at the same dose), IBS patients had reduced flatulence scores and delayed colonic transit time.[42] Another trial tested the efficacy of this probiotic combination in children (ages 4 to 18) with IBS for six weeks. The researchers found that the probiotic preparation was significantly associated with improvements in IBS symptoms (abdominal pain/discomfort, abdominal bloating/flatulence and family assessment of life disruption).[82]

In light of these studies, it is important for the clinician to remember that the efficacy of a certain probiotic preparation may not be the same in all patients. Success of treatment can also be dependent on several variables, such as characteristics of a patient (gender, lifestyle habits, age), etiology (parasites, Candida overgrowth, lactose intolerance) and type of IBS the patient has (IBS-C, IBS-D, IBS-A).

Other Nutraceutical Therapies

Carminative Herbs

Traditional carminative herbs have been historically used to support those with an upset stomach, cramping, gas and bloating. Since patients with IBS share many of these features, carminative herbs can be of benefit. Common carminative herbs include fenugreek, black caraway, coriander, cardamom, cumin and ginger. These herbs have been traditionally used extensively in ethnic cuisines, especially in East Indian, Southeast Asian, and Mexican cooking.

Coriander, along with other carminative herbs, has been used in patients with IBS for reduction of abdominal pain and bloating. One study evaluated the effects of a blend of three carminative herbs: *Melissa officinalis* (lemon balm), *Mentha spicata* (mint) and *Coriandrum sativum* (coriander).[83] In this randomized, double-blind, placebo-controlled trial, patients received this blend and loperamide or psyllium (based on their predominant IBS type) for eight weeks. The frequency and severity of abdominal pain/discomfort and bloating were significantly lower in the active group compared to the placebo group at the end of the study. Another study[84] evaluated the efficacy of a commercially available herbal preparation (containing extracts of bitter candytuft, chamomile flower, peppermint leaves, caraway fruit, licorice root, lemon balm leaves, celandine herbs, angelica root, and milk thistle fruit) in 208 patients with IBS. After four weeks with treatment, patients taking the herbal preparation had significant improvements in symptoms compared to placebo—particularly in reducing the total abdominal pain score and IBS symptom score (which measured the severity of symptoms such as flatulence, incomplete evacuation or changes in bowel habits).

Ginger has also been historically used as a carminative and as a calming agent for GI disturbance, its use is very popular among patients with functional bowel disorders.[85] In vitro, it has been shown to be a calcium-antagonist, resulting in spasmolytic activity.[86] This mechanism may explain how it helps to relieve diarrhea and cramping in patients with IBS. To date, no clinical studies have been published evaluating the effect of ginger in the management of IBS.

Fiber

Recommendations to increase fiber intake through diet or supplementation is commonly given to patients with IBS. It is important that clinicians understand that fiber may be beneficial in some and detrimental in others (depending on the type of fiber used and subtype of IBS). Also, careful consideration must be given before recommending fiber products to patients who present with severe IBS. Evidence has shown mixed results supporting the use of soluble fiber in alleviating global IBS symptoms, while insoluble fiber demonstrated no effect on IBS (in certain instances worsening the symptoms). A Cochrane review of 11 randomized controlled, trials[71] limited to bulking agents (seven trials using soluble fiber and four trials using wheat bran) did not show beneficial effects on abdominal pain, global assessment or symptom scores. The reviewed studies also had quality issues (such as double-blinding, method of randomization, concealment of treatment allocation, etc). Another systematic review[87] examined insoluble fiber (8 RCTs) and soluble fiber (9 RCTs) separately. In general, fiber was shown to improve global IBS symptoms (particularly constipation) but had no effect on IBS-related abdominal pain. Specifically, soluble and insoluble fiber had differing effects on global IBS symptoms. Soluble fiber (psyllium, ispaghula, calcium polycarbophil) showed significant improvement, but insoluble fiber (corn, wheat bran) worsened symptoms in certain cases. No significant difference was noted when compared to placebo. A randomized, placebo-controlled study by the same authors looked at the effects of soluble fiber and insoluble fiber among IBS patients.[88] 275 IBS patients were placed into one of the following groups: psyllium (10 g), bran (10 g) or placebo (10 g rice flour). After three months of treatment, IBS symptom severity in the psyllium group was reduced by 90 points, compared with 58 points in the bran group and 49 points in the placebo group. Early dropout occurred most commonly in the bran group because of worsening IBS symptoms. The authors concluded that "psyllium offers benefits in patients with IBS in primary care settings."

Other Alternative Medicine Treatments

Acupuncture

Acupuncture has been widely used by Chinese medicine practitioners for thousands of years to treat GI-related symptoms. Although there have been many claims of efficacy among practitioners of acupuncture, there is little evidence that demonstrates its efficacy in the treatment of IBS. Acupuncture was evaluated in a prospective, blinded, sham-controlled trial of 60 IBS patients.[89] The primary end-point was a predefined fall in symptom score at 13 weeks. Patients in the active and sham groups had significant improvement during the study; the mean improvements in scores were equal (-1.9) for both groups. It was also noted that there was a non-significant difference between response rates in patients receiving acupuncture (40.7 percent) and sham treatment (31.2 percent). Some secondary end-points marginally favored active treatment, but an improved symptom score occurred more often with sham therapy (65.6 percent vs 59.2 percent). Another double-blind, sham-controlled study involving 25 IBS patients was conducted using acupuncture.[90] The investigators found that there was a significant improvement in overall symptoms and abdominal pain in the active group after the first session; however, no comparable effect was seen in the second session (when compared to the sham group). The authors concluded that there was no therapeutic benefit of acupuncture in Irritable Bowel Syndrome.

Mind-Body Therapies

Mind-body medicine is an appealing approach for many practitioners because brain-gut interactions play an important role in the pathogenesis of IBS, and almost half of IBS patients have comorbid psychiatric disorders. One form of relaxation, mindful-based stress reduction, was shown to downregulate elevated pro-inflammatory cytokines.[91,92,93] Gut-directed hypnotherapy has also been explored in IBS patients, resulting in favorable outcomes.[94,95,96,97,98] However, there are only a few number of studies exploring hypnotherapy on IBS patients and data in these trials are weakened by small sample sizes. An early trial that examined hypnotherapy in IBS showed significant improvements in IBS symptoms when compared to psychotherapy.[97] The participants in the hypnotherapy group did not have any relapses over a three-month follow-up period. Although there was a considerably greater response in the hypnotherapy group, the patients in the psychotherapy group also had symptomatic improvements.

Summary

Irritable Bowel Syndrome is a multi-faceted GI disorder that affects a large portion of the U.S. population and is associated with a significant impairment in quality of life, high work absenteeism rates and increased health care costs. Despite recent advances in research, many patients and physicians are dissatisfied with both the efficacy and high cost of conventional medical therapies for IBS. Furthermore, over the past decade, the FDA withdrawal of three IBS medications from the market has caused increasing concern over the safety of medications used to treat IBS. These hurdles have led physicians and patients to seek unconventional (natural) therapies, that can help address the underlying cause of the disease. Unlike conventional therapy that targets only specific symptoms, certain natural therapies have been shown to help alleviate IBS symptoms by working on a multitude of biological pathways without causing many of the side effects often seen in conventional therapies.

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