Integrative Medical Treatment of Inflammatory Bowel Disease

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Inflammatory bowel disease (IBD) is a condition that fits very well into the patient-oriented format used in integrative medicine. Patients with a genetic predisposition are subject to environmental exposures that can modify the body's response. This leads to a maladaption response, with inflammatory, immunological, hormonal, and nutritional dysregulation. The resulting symptom complex includes intestinal pain, cramps, diarrhea, bleeding, fistula formation, and possible obstruction. The diagnosis is made clinically, radiologically, and pathologically, utilizing endoscopic techniques. Conventional treatment regimes utilize corticosteroids, anti-inflammatories, and other immunosuppressive therapies.

Current research is shedding light on the etiology and perpetuation of IBD. This article will address the mechanisms involved in IBD, integrative diagnostic testing that one can add to his or her regime, and a progressive treatment approach that combines conventional and complementary methods.

Cause of Illness and Mechanisms of Action

Current thought is that inflammatory bowel disease is a genetically determined, overactive immune response to luminal bacteria. A defect in gut barrier function and/or immune dysregulation appears to mediate this response.(1)

Studies suggest that IL-IB gene polymorphism helps determine the cause and severity of inflammatory bowel disease.(2) The ratio between interleukin 1 receptor antagonist/interleukin-1 is decreased in inflammatory bowel disease. This reflects the importance of balance between inflammatory and anti-inflammatory forces, and it correlates clinically with disease severity.(3) Epidemiological data shows that inflammatory bowel disease is a polygenic disease with extensive heterogeneity.(4,5,6) An estimated 10-20 genes may be involved.(7) Human lymphocyte antigens (HLA) associations exist for both ulcerative colitis and Crohn's disease.(8)

Family studies show that anti-mucosal cytoplasmic antibodies are present in ulcerative colitis patients as well as their healthy relatives.(9,10) The site of production of peri-nuclear-antineutrophilic cytoplasmic antibody (P-ANCA) is the GI mucosa, and the antigen is mucosa-specific.(11) Mucosal inflammation and associated immune response are involved.(12)

Currently, ulcerative colitis is thought to be a genetically heterogenous set of disorders that creates a mucosal susceptibility to certain commensal bacteria. The resulting response to host mucosal antigens is a spreading phenomenon, possibly facilitated by a lack of regulatory suppressor cells.(13)

Viral infection, possibly early exposure to measles, has been associated with the etiology of inflammatory bowel disease.(14) As in ulcerative colitis, Crohn's disease has a genetic susceptibility.

Abnormalities of non-immune mechanisms, such as gastric acidity, intestinal enzyme production, luminal antigens, and intestinal permeability, could contribute to the overall immune reactivity to an antigen. Specific T-cell regulatory cells accomplish the normal protective immune response to intraluminal bacteria flora. Increased T-cell recognition of intestinal bacteria helps to up-regulate immune activities.(15) Loss of oral tolerance to one's own bacterial flora is probably involved. Normally, the immune system tolerates the bacteria in the colon. However, if the immune cells aren't regulated, they lose their tolerance and they cause the immune cells to react against the bacteria. This can spread to the mucosa. Interestingly, Crohn's disease manifests mostly in the colon and terminal ilium, sites that have the largest concentration of normal flora. Studies on rodents show that a non-invasive luminal bacteria, citrobactor, elicits a strong Th1 activation. This helps stimulate TNF alpha and massive epithelial cell hyperplasia.(16)

The gut is normally in a state of tolerance. Th3, a novel T-helper cell, helps regulate the activity, and prostaglandins mediate the process.(17) It is likely that the occurrence and production of immunoglobulins in inflammatory bowel disease is related to increased reaction of B cells to the intestinal flora.(18,19) Crohn's disease is characterized by a predominance of IgG2, which is consistent with a Th1 cytokine pattern. However, ulcerative colitis features an IgG1 predominant pattern, which is associated with a Th2 pattern.(20) Crohn's disease is associated with increased TNF alpha, IL6, IL1, and IL8 levels.(21)

Inflammatory bowel disease is associated with increased inflammatory prostaglandin and leukotriene levels. An elevated platelet count is a marker of inflammatory bowel disease activity. This is evidenced by a procoagulant and microvascular thrombosis state in the pathogenesis of inflammatory bowel disease.(22)

Eicosanoids mediate inflammation by releasing arachidonic from membrane phospholipids (phospholipase A2 reaction). They are metabolized to prostaglandins (cyclo-oxygenase pathway) or to leukotrienes, (lipo-oxygenase pathway).

Studies show that heparin can achieve 66% to 90% clinical remission in cases of ulcerative colitis, as measured by decreased bleeding, normalization of TNF alpha levels, and decreased C-reactive protein (CRP).(23) Heparin effects the binding of fibroblast growth factor to receptors on colonic epithelial cells. This allows ulcerated mucosa to regenerate and accelerate healing.(24)

A theory of glycoaminoglycan deficiency, leading to increased permeability of the mechanical and electrostatic barrier in the intestine, has been suggested as a contributing factor in inflammatory bowel disease.(25) There is positive correlation between smoking and Crohn's disease, and a negative association of smoking and ulcerative colitis.(26) Nicotine actually has a beneficial effect on ulcerative colitis. The mechanisms are not known, although nicotine decreases IgA production and impairs production of free radicals by neutrophils.(27) Transforming growth factor (TGF)-beta may increase epithelial regeneration. However, it may also facilitate scar formation and fibrosis in the bowel.

In summary, several mechanisms are involved in Crohn's disease, all resulting in pro-inflammatory responses:

1. Increased inflammatory mediators (e.g., leukotrienes, prostaglandins, PAF, NO, ROS);

2. Reaction against luminal antigens;

3. Increased adhesion molecule release;

4. Cytokine imbalance; and

5. Abnormalities of oral tolerance.

Diagnostic Testing

The standard diagnostic testing for inflammatory bowel disease includes a complete blood count (CBC) and sed rate. A complementary approach involves looking at systems that may contribute to the multifactorial problems. One looks for marginal nutritional deficiencies, deficiencies of precursor anti-inflammatory compounds, imbalanced immune parameters, altered adrenocortical function, allergies, particularly food allergies, and infectious etiologies involving both pathological and normal flora.

This type of testing will provide clues to any antecedents in the medical history that contribute to inflammatory or immune imbalance. Looking at dietary patterns can help determine which food allergy testing is indicated. Medical evaluations also include IgE and IgG RAST testing, intradermal testing, and antigliadin antibodies.(28) Electrodermal testing may be used to identify possible food sensitivities.

Intradermal testing for candida and/or anti-candida antibody levels can reflect immune balance concerning candida. After testing, one should always recommend an elimination diet with food challenges, to test allergens clinically. Adrenal function can be assessed using a serum DHEA-S, an ACTH stimulation test, and studies of salivary cortisol.

Nutritional testing can assess differences that affect the immune system, as well as nutrient deficiencies associated with IBD. Serum vitamin testing measures levels of nutrients, such as vitamins A,C, and E, essential antioxidants, vitamin B6, pantothenic acid, and other B vitamins. Red blood cell (RBC) testing can pick up mineral deficiencies, particularly zinc, magnesium, and selenium. RBC fatty acid testing can evaluate the balance of omega-3, omega-6, and arachidonic acid. It can also determine the eicosanoid balance between pro-inflammatory/anti-inflammatory mediators. A comprehensive stool analysis can be used to explore the intestinal milieu. This provides data on homeostasis and functional parameters in the gut. A stool analysis includes pH, enzyme activity, secretory IgA levels, colonic bacteria balance, and candida albicans overgrowth. Intestinal overgrowth can be assessed using the H2 Glucose Breath Test.(29) Proper hydrochloric acid production by the stomach can be ascertained by utilizing the Heidleberg Gastrogram.

Conventional Treatments

Conventional treatment of inflammatory bowel disease involves the use of corticosteroids, orally, rectally, or parenterally. They work by suppressing the immune response and inhibiting the action of cytokines and inflammatory mediators.(30,31) Rectal preparations of corticosteroids are used to treat inflammatory bowel disease that occurs in the rectum and/or sigmoid areas.(32) Prolonged use can cause adrenal suppression and/or hypercorticosteroidism. (33) Complications of corticosteroid usage include intestinal perforation, ulcers, osteoporosis, cataracts, sugar intolerance, and adrenal dysfunction. By adding alternative therapies to our conventional regime, hopefully the dosages of these potent medications can be minimized, decreasing the risks of adverse effects.

Amino salicylates, sulfasalazine, and 5-aminosalicylic acid are used to treat mild to moderate IBD. These compounds can inhibit products of the inflammatory cascade and reactive oxygen species. They decrease macrophages' production of IL1, and plasma cells' production of immunoglobulin.(34,35) However, adverse reactions include nausea, fatigue, headache, rash, hemolytic anemia, bone marrow suppression, and decreased sperm function in men.

Immunosuppressive drugs are now used regularly for chronic inflammatory bowel disease. These include 6MP, azathioprine, methotrexate, cyclosporin, and tacrolimus. These drugs inhibit T lymphocyte function and decrease the activity of natural killer cells. They have adverse reactions, such as paresthesias, lymphoma, bone marrow suppression, and renal dysfunction. Other potential side effects are toxic neurologic symptoms, including seizures, hepatic toxicities (e.g., possible hepatic fibrosis), and increased incidence of infections.(36,37) Patients need to be monitored clinically with a CBC and liver function test. If methotrexate is used, folic acid supplementation is

recommended.

Antibiotic treatment has been used for enteric infection. Metronidazole and ciprofloxacin have been tried for both ulcerative colitis and Crohn's disease.(38) It is effective in treating perianal disease in Crohn's patients.(39) Rifaximin, an antibacterial medication that inhibits bacterial RNA synthesis, is not absorbed in the lumen, and has been shown to reduce bacterial overgrowth, as measured on the Hydrogen Breath Test.(40,41,42) It is effective against bacteroides, lactobacillus, clostridia, and other anaerobic bacteria.(43) However, studies show that a positive effect only lasts for two to four weeks.

Complementary Approaches

When we use complementary modalities to treat inflammatory bowel disease, we need to be aware of patients' clinical responses. We need to work with their gastroenterologist or other practitioner in tapering their medication as they improve, or adding certain medications when the condition flares up and symptoms become distressing. It is important for the patients to set their own goals (e.g., greater well-being, relief of symptoms, or no medication). Different patients may aspire to different achievable targets.

Malnutrition can occur in inflammatory bowel disease through many mechanisms (see sidebar on p. 23). Recent evidence has shown that nutritional support, in addition to correcting specific nutritional deficiencies, influences endogenous production of inflammatory mediators. Nutritional abnormalities are often overlooked in patients with inflammatory bowel disease.(44)

Evaluation of dietary regimes is paramount in the treatment of inflammatory bowel disease. Any allergenic food or other substance that is found, through various methods of testing, should be avoided.(45) Sugars and certain fats should be limited.(46) Meat intake should be decreased. These foods contain arachidonic acid, a precursor of the pro-inflammatory prostaglandin PGE2. A diet low in disaccharides, called the "specific carbohydrate diet" by Gottshall, is very helpful.(47)

Patients with symptoms consistent with candidiasis, and positive findings in stool and antibody testing, can be placed on yeast-free, sugar-free dietary regimes. Dietary modifications can be combined with nystatin therapy, systemic antifungals, or natural antifungals such as citricidal, tanalbit, and berberine. When patients exhibit weight loss or increased GI symptoms, the addition of parenteral nutrition or IV nutrient therapy can be instituted. Parenteral use of IV vitamins, amino acids, and antioxidants can be helpful in these situations.

As discussed previously, the intestinal flora are a major area of consideration. Bentonite, a medical clay with a large surface area, absorbs antigens and toxins. It can provide symptomatic relief for gas and diarrhea. In an adult, start with 1/2 tablespoon two times a day, going up to 2 tablespoons two times a day. Bentonite should be taken apart from meals and vitamins to prevent interference with absorption of nutrients.

Bacterial dysbiosis can be treated with antibiotics, or herbal extracts such as artemesia, garlic, goldenseal, uva ursi, and berberine (the active alkaloid in goldenseal), barberry, and Oregon grape.

Intestinal Permeability

L-glutamine can be used to diminish intestinal permeability. Animal studies show that a variety of stressors (e.g., starvation, infection, and injury) increase the movement of bacteria from the bowel lumen to mucosal and regional lymph nodes. This causes an energy-dependent change in barrier permeability.(48) Glutamine enhances immune-cell growth and improves gut barrier function.(49)

Rhodes demonstrated that glutamine activates early receptor genes that govern proliferation responses of colonocytes. Glutamine also enhances growth functions and activity of orthithine decarboxylase (ODC), which is important for intestinal cell regeneration.(50) Furthermore, glutamine supplementation increases the intestinal glutamine level, which protects against oxidant damage and provides an anti-cancer effect.(51) When glutamine was administered to Crohn's patients, increased body weight and improvement in bowel permeability were noted.(52) Fructooligosaccharides can be utilized for improved health of colonocytes, provided there are no adverse reactions to the carbohydrate content.

Probiotics, such as lactobacillus and bifido bacterium, help restore normal intestinal flora. When combined with L-glutamine and aloe, probiotics increase secretory IgA, which is often low in these patients. Lactoferrin contributes to intestinal host defenses against antigenic factors, toxic metabolites, as well as limiting the mucosal inflammatory cascade.(53)

Nutrients in Inflammatory Bowel Disease

Low zinc levels can be found in inflammatory bowel disease. This may be secondary to poor intake, decreased absorption, excessive losses, and increased metabolic demands. Decreased levels are associated with poor healing, decreased cell-mediated immunity, and anorexia. Studies suggest that we may need to supplement parenterally to get adequate levels.(54,55)

Magnesium, calcium, and potassium are other essential minerals that can be depleted in inflammatory bowel

disease.(56) They also protect against osteoporosis, which is increased in patients on steroids.(57)

Studies show that fish oils reduce the relapse rate of Crohn's disease.(58) They decrease inflammatory markers such as leukotriene B1 and thromboxane A2.(59)

Symptoms of inflammatory bowel disease have shown improvement using the omega-3 fatty acids in fish oil. Studies on rats with inflammatory stress, after six weeks of EPA, have found decreased levels of IL1 and TNF alpha.(60) In clinical studies, Crohn's patients have shown improvement on omega-3 fatty acids.(61) Small-chain fatty acids, such as butyrate, serve as food for colonocytes. Butyrate enemas have helped patients with ulcerative colitis.(62)

Production of free radicals is increased in inflammatory bowel disease. Trace elements are a critical component of antioxidants. Therefore, trace mineral deficiencies can adversely affect antioxidant defenses. Levels of trace elements are decreased in ulcerative colitis.(63) Increased reactive oxygen intermediates and decreases in copper, zinc, and superoxide dismutase (SOD) are found in both ulcerative colitis and Crohn's disease.(64)

Oxidative stress may contribute to the increased incidence of colonic carcinoma.(65) Reduced levels of ascorbic acid and other antioxidants (e.g., tocopherol, ubiquinol, glutathione) provide strong rationale for antioxidant therapy in IBD.(66) Quercetin, an anti-inflammatory, inhibits phospholipidase A2 and lipoxygenase.(67) Taurine administration has been shown to reduce the inflammatory parameters in inflammatory bowel disease in rats.(68)

In IBD, there is a 30% cumulative incidence of colon rectal carcinoma over 35 years. IBD accounts for 1% of new cases of colon rectal carcinoma. Natural compounds such as vitamin E, beta-carotene, indole 3-carbinol, curcumin, folic acid, glutathione, and selenium can help reduce the risk of cancer.(69)

Peptide-based diets can modulate bowel permeability, thereby decreasing bacterial translocation in the gut.(70) One such peptide product is derived from fish protein, and contains peptides and essential fatty acids.

Herbs Useful in Inflammatory Bowel Disease

Anti-inflammatory compounds such as Curcuma longa, Boswellia serrata, Uncaria tomentosa, and Ginkgo biloba are recommended. Nuclear factor Kappa B (NF Kappa B) controls transcription of inflammation genes.(71) Cat's claw has an anti-inflammatory action and inhibits transcription of NF-KB.(72) It negates the expression of i-NOS and reduces nitric oxide production, thereby decreasing reactive nitrate production. Boswellia serrata, an Ayurvedic herb, contains boswellic acids. These act as 5 lipo-oxygenase inhibitors.(73) In studies, Boswellia serrata was equal to sulfasalazine in the treatment of inflammatory bowel disease.(74)

Other beneficial herbs include Echinacea angustifolia, Baptista tinctoria, and Ulmus fulva (slippery elm). Hydrastis canadensis contains berberine, a plant alkaloid, which exerts anti-microbial, anti-fungal, anti-parasitic, anti-inflammatory, and anti-neoplastic activity. Berberine extracts were shown to inhibit bacterial adhesions to mucosal surfaces.(75) Ulmus fulva (slippery elm) has a demulcent effect on mucosal membranes. Baptista tinctoria, containing active flavonoids, is useful for its anti-microbial and anti-inflammatory effect on the intestinal tract.(76)

Chinese Medical Treatment

Comprehensive treatment of IBD combines both acupuncture and Chinese herbs. One can cool heat with herbs such as akebia, gardenia, moutan, Alisma plantago-aquatica (water plantain), and bupleurum. Liver herbs include Angelica sinensis (dong quai), and Paeonia officinalis (red peony). A classical formula called 6 gentlemen can be used to strengthen the spleen and remove what the Chinese classify as dampness. This formula contains codonopsis, atractylodes, Glycyrrhiza glabra (licorice), poria, pinellia, and citrus. Be mindful of any adverse effects from Chinese herbs. They may occasionally increase inflammation in the GI tract. Acupuncture can be done at spleen points (spleen 6, bladder 20), stomach points (stomach 36, stomach 37, stomach 25), and general points (Ren 6, Ren 4, bladder 23). This treatment tonifies the spleen and drains dampness.(77)

Additional Complementary Therapies

Dealing with psychospiritual issues complements treatment. Learning to cope with stress in healthy ways can positively affect immune function and neuroendocrine status, and can help with the frustration of a chronic illness.(78) Body/mind techniques, such as meditation and hypnosis, can have a favorable impact on inflammatory bowel disease.

Conclusion

Fiocchi outlines the "intestinal homeostasis" that is dysregulated in inflammatory bowel disease.(79) One is immediately struck by the complexity of the inflammatory response. Chronic inflammation develops in the body when an initial inflammatory focus is not cleared. The sequela of chronic changes are gradual inflammation with increased accumulation of macrophages and lymphocytes, tissue fibrosis, involvement of cytokine imbalance, and increased NF-Kappa B. This cascade leads to the accelerated production of adherence molecules and then chemotactic cytokines.

While conventional treatment tries to inhibit inflammation and suppress the immune system, the integrative approach is to stimulate the body's defenses and to eliminate the noxious stimuli. By combining complementary remedies with conventional treatment and allergic, nutritional, herbal, immunologic, and detoxification methods, one can best treat this complex condition.

Patients with inflammatory bowel disease commonly use complementary therapies, especially patients with increased duration of illness, a history of hospitalization, and experience with medication side effects and a general long-term decrease in the effectiveness of conventional treatments.(80) Many are utilizing vitamins and herbs, and about 9% use homeopathy. Often, they do not tell their conventional physicians because they feel they are not knowledgeable on the subject.

Listen to and treat the whole patient, and observe the outcome of your combined integrative therapies. This approach will greatly benefit your patients. Those of us in integrative medicine feel this type of treatment should be the norm, not the exception.