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Alycia Leiby and Minal Vazirani

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Complementary, Holistic, and Integrative Medicine: Crohn Disease

Alycia Leiby, MD,*
Minal Vazirani, MD†

Author Disclosure
Drs Leiby and Vazirani have disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

Introduction

Crohn disease (CD) is a chronic inflammatory bowel disease (IBD) characterized by periods of relapse and remission. In a genetically predisposed individual, environmental factors lead to a dysregulated adaptive immune response resulting in chronic intestinal inflammation and the potential long-term complications of intestinal stricture and perianal disease. (1) In pediatric CD, there is the additional complication of corticosteroid dependence, resulting in growth failure and significant psychosocial impact. (2) The need for surgical intervention in children is considerable also, with 5% requiring surgery at 1 year from diagnosis and 18% at 5 years. (3)

The clinical severity and location of disease often dictate what agents are chosen to treat CD, with the goal being to induce and then maintain long-term remission. Conventionally, 5-aminosalicylate (5-ASA) therapy, such as mesalamine, is used often for mild disease, although the evidence for this approach is not considered robust. (4) For moderate to severe disease, data reveal that earlier use of immunomodulators, such as the thiopurines or methotrexate, may act to decrease corticosteroid exposure and hospitalizations. (5)(6) Recently, infliximab, a monoclonal antibody directed against tumor necrosis factor α , has been shown to be efficacious in the induction and maintenance of remission in moderate to severe pediatric CD. (7) Despite strong evidence for benefit, potential adverse effects, including infection and malignancy, affect the acceptance of immune modulating therapies. (8)

The incidence of complementary and alternative medicine (CAM) use in pediatric patients with IBD ranges from 40% to 70%, (9)(10)(11)(12) with concern over adverse effects and lack of efficacy of conventional therapies being common reasons for such use. Use of CAM is increased particularly in patients who have a worse quality of life (QoL). (10)(13) In this article, we review the evidence for CAM therapy in CD as drawn from adult and pediatric data available in the English language.

Supplements

Glutamine

The amino acid glutamine is the preferred substrate for enterocytes, essential in a catabolic state such as IBD. Animal studies reveal glutamine decreases damage in IBD models, potentially by improving intestinal epithelial cell integrity. At this time, however, the beneficial effects of glutamine on human intestinal inflammation have not been demonstrated clearly. (14) The authors of one pediatric and two adult studies have looked both at glutamine as a supplement (15) and as part of a glutamine-enriched polymeric diet (16) and have not supported the use of glutamine for CD. Another study revealed no difference in plasma glutamine and intestinal permeability in a mixed IBD sample of patients who were randomly assigned to glutamine-enriched total parenteral nutrition versus glutamine-free total parenteral nutrition. (17) At this time, the available data do not support a recommendation of glutamine for maintenance of remission or treatment of disease flares.

Omega-3 Fatty Acids (Fish Oil)

Fish oil and other sources of omega-3 fatty acids have been theorized to be effective in IBD therapy due to their inhibitory effect on the cyclooxygenase pathway, decreasing the formation of arachadonic acid as a substrate for the production of proinflammatory cytokines. (18) A 2009 Cochrane

Abbreviations

5-ASA: 5-aminosalicylate
CAM: complementary and alternative medicine
CD: Crohn disease
IBD: inflammatory bowel disease

*Pediatric Gastroenterology, Atlantic Health, Morristown Memorial Hospital, Morristown, NJ.

†Integrative Pediatrics and Internal Medicine, Atlantic Health, Morristown Memorial Hospital, Morristown, NJ.

meta-analysis reviewed the effectiveness and adverse events of fish oil when used for maintaining remission in CD. (19) Six randomized, placebo-controlled studies, including one pediatric trial, (20) were reviewed. The dose of fish oil ranged from 2 to 4 g per day, with varying blends of eicosapentaenoic acid and docosahexaenoic acid in differing delivery systems.

Two other trials (EPIC-1 and EPIC-2), with ~380 patients in each, revealed no significant difference in the relapse rate between omega-3 fatty acid supplementation and placebo. (21) The Cochrane review revealed that to date the existing studies do not support routine use of omega-3 essential fatty acids. The Cochrane analysis also revealed that adverse effects, including diarrhea and upper gastrointestinal symptoms, were more common in the fish oil groups compared with placebo, although the pediatric trial specifically did not reveal any adverse effects. (19) The type of fish oil preparation and delivery system would likely influence the rate of adverse reactions.

The authors of the single pediatric study compared 18 patients who received 5-ASA in combination with 3 g/day of omega-3 fatty acid with 20 patients who received 5-ASA and an olive oil placebo. (20) The omega-3 fatty acid group had a significantly lower relapse rate at 1 year compared with the placebo group (61% vs 95%, $P = .0016$). This small but well-designed trial is the only one to use fish oil supplementation in combination with other CD therapy. It is possible that the combination of 5-ASA and fish oil may have a synergistic anti-inflammatory effect. Additional large pediatric studies using a combination of omega-3 fatty acid supplementation and conventional immunosuppressive therapy are needed to demonstrate a role for routine fish oil use in CD.

Probiotics

Probiotic use is popular, with an average of 40% of pediatric patients with IBD having tried a probiotic preparation, (9)(10)(11)(12)(22) but evidence for clinical efficacy in CD is limited. In vitro and animal studies have revealed that probiotics can stimulate anti-inflammatory cytokine production and strengthen the intestinal epithelial cell barrier. (23) The authors of adult trials have examined the use of probiotics, including *Lactobacillus GG*, (24) *Lactobacillus johnsonii*, (25)(26) and a blend of pre- and probiotics (27) for prevention of postoperative recurrence; however, no effect was found. Some preliminary adult data reveal that *Saccharomyces boulardii* might be beneficial for CD by strengthening the intestinal barrier. (28) In a single randomized, double-blind trial of 75 children, *GG* versus placebo was used in addition to standard therapy. (29) There was no significant difference in time

to relapse. The authors of two studies looked at a *Lactobacillus* probiotic mixture VSL number 3 and found it to be efficacious for pediatric ulcerative colitis. (30)(31) Although theoretically beneficial, to date there is insufficient pediatric research done on the effects of probiotics to treat pediatric CD. Additional research using other strains or targeting specific CD phenotypes may show more promising results.

Diet

Diet and bacteria may play a significant role in the etiology of IBD because they are the most common antigens to which the gastrointestinal lumen is exposed. (32) Epidemiologic data demonstrating an increased incidence of CD in emigrants to countries with a more western diet has been used as evidence that diet may be an environmental factor in the rising incidence of CD. (33) The authors of a case-control study investigated dietary patterns in pediatric CD cases and reported a positive association of CD with diets high in meats, saturated fatty foods, and desserts, whereas a diet high in vegetables, fruits, olive oil, fish, grains, and nuts was inversely associated with CD. (34)

Enteral nutrition therapy is a purely dietary approach more commonly prescribed in Canada and Europe than in the United States. Treatment consists of 50% to 100% of the diet being formula, the aim being to induce and maintain remission in some patients. (35) Because oral consumption of the volume necessary is difficult, nasogastric administration of the formula is the route most commonly used and this modality may limit acceptance.

Diets such as the specific carbohydrate diet, elimination diets, and Ayurvedic diets are anecdotally purported to be beneficial but lack evidence, and therefore further study is needed. As more research is done in the fields of epigenetics and nutrigenomics, perhaps dietary modification may become a more useful and precise tool in the prevention and treatment of CD. Until then, it is important to enforce the basic principles of a healthy diet low in saturated fats and sugar for children with CD.

Acupuncture

Acupuncture is thought to act on many different mediators in the inflammatory cascade, including changing the cytokine profile to reset the imbalance between T helper 1 and T helper 2 cell activity and stimulating a sustained low-concentration release of calcitonin gene-related peptide, a neuropeptide with vasodilator effect. (36)

There is one randomized controlled study in adults in which acupuncture and moxibustion for the treatment of

CD were used. (37) Remission rates and inflammatory markers did not differ between groups, but QoL measures also improved in both groups, although not significantly. More research is needed to study the effectiveness of acupuncture for CD in adults and children.

Homeopathy

Homeopathy is used by 3% to 4% of pediatric patients with IBD who are using CAM modalities. (9)(10) Although there are no randomized controlled trials to recommend routine use of homeopathic remedies, there is also no evidence that it is harmful. In general, homeopathic remedies are considered to be safe and nontoxic due to their extreme diluteness (usually 10^{-6} or greater), and thus can be tolerated in conjunction with conventional care.

Biobehavioral Methods

The role that stress may play in triggering flares of IBD has been investigated in the adult IBD population. Stress has been shown to alter gut permeability and cause the release of neuropeptides that have immune modulatory effects. (38) Although some studies reveal conflicting results, several prospective studies have revealed a positive association between stress and IBD flares, particularly the perception of stressful events, as opposed to discrete events. (38)

Unpredictable and potentially embarrassing symptoms of IBD add to the stress and challenges of adolescence. The incidence of psychiatric disorders in children with CD is increased compared with healthy children and is comparable to the incidence in children with other chronic diseases, such as cystic fibrosis. (39) QoL may be impaired by pain and school absences, and patients having increased disease severity often have worse QoL. (39)

Biobehavioral CAM techniques, such as relaxation, meditation, and prayer, are popular and are used by adolescents with IBD, especially those with more severe disease. (13) Various strategies have been tried in order to improve QoL and psychosocial functioning in pediatric patients with IBD, such as a prospective analysis of children attending a 1-week camp sponsored by the Crohn's and Colitis Foundation of America, (40) cognitive behavioral therapy, (41) and a psychological program that included relaxation, imagery, and deep-breathing as part of

an overall cognitive behavioral therapy (CBT) program. (42)

Additionally, there is a potential role for "gut-focused hypnotherapy." The authors of a small study done in the United Kingdom in 2008 demonstrated a reduction of corticosteroid requirements after 12 sessions of gut-focused hypnotherapy. (43)

There has been significant adult and pediatric research in the therapeutic applications of yoga to prevent and treat medical conditions. (44)(45) Yoga has been shown to decrease functional disability and anxiety in children with irritable bowel syndrome. (46) Yoga may be helpful for similar reasons as stated above for IBD, but further studies are needed.

The use of biobehavioral techniques in conjunction with conventional care may improve QoL in children with CD and incorporate a holistic approach.

Summary

- Although the use of CAM in pediatric CD is common, quality evidence-based research is limited. There is clearly a need for further randomized controlled trials.
- The role of psychosocial distress in children with CD should not be overlooked and thus biobehavioral techniques should be considered and incorporated when possible.
- Considering the potential for growth failure and need for surgical intervention in CD, any CAM therapies that are not harmful should be used only in combination with conventional medical treatment.
- The importance of all health care providers partnering with their patients and asking about CAM use, as well as maintaining an awareness of efficacy, safety, harm, drug-supplement interactions, and appropriate referral sources, should be kept in mind when caring for those afflicted with this chronic disease.

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