



Alternative & complementary treatment for pediatric inflammatory bowel disease

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Alternative medicine includes treatments that are not considered mainstream and is suggested to replace the accepted treatment, while complementary treatment is added to the conventional treatment. The estimated prevalence of their use in patients with inflammatory bowel diseases (IBD) is high, ranging between 21–60%. This review summarizes the data on these treatments and their efficacy in the setting of IBD.

Keywords: Alternative therapy; complementary therapy; inflammatory bowel disease (IBD); children

Submitted Jun 29, 2019. Accepted for publication Aug 30, 2019.

doi: 10.21037/tp.2019.09.02

View this article at: <http://dx.doi.org/10.21037/tp.2019.09.02>

Introduction

Inflammatory bowel diseases (IBD) are chronic autoimmune inflammatory diseases that may involve the entire intestinal tract as in Crohn's disease (CD) or can be confined to the colon as in ulcerative colitis (UC).

Alternative medicine includes treatments that are not considered mainstream and is suggested to replace the accepted treatment, while complementary treatment is added to the conventional treatment. The estimated prevalence of their use in patients with IBD is high, ranging between 21–60% (1). This review summarizes the data on these treatments and their efficacy in the setting of IBD.

Probiotics

The current most accepted theory is that IBD develops due to an inappropriate inflammatory response to the gut microbiome in genetically susceptible individuals (2). It has also been demonstrated that the diversity of the microbiome in IBD patients is low compared to healthy controls (3).

A multicenter study that investigated the microbiome

composition of treatment-naïve children with CD in comparison to healthy controls found that patients with CD had an increased level of aerobic and facultative anaerobes (Enterobacteriaceae, Fusobacteriaceae, Veillonellaceae and Pasteurellaceae). These may invade the epithelium and potentially exacerbate inflammation. Patients with CD have also been demonstrated to have decreased levels of obligate anaerobes (Bacteroides and Clostridiales). These organisms are considered beneficial to the host by increasing colonic Treg cells and downregulating intracellular signal transduction pathways, such as nuclear factor (NF)- κ B and by producing short chain fatty acids, which are an important energy source for the colonic epithelium (4,5). This shift is considered to be due to an increased oxygen concentration in the inflamed environment.

It has also been demonstrated that the use of antibiotics negatively affects the diversity of the microbiome, thereby contributing to the development of a dysbiotic state (4).

Probiotic microorganisms influence the intestinal microbiota by changing intestinal pH, competing for nutrients, synthesis of antimicrobial compounds such as defensins, bacteriocins and blockage of bacterial adhesion

and invasion to epithelial cells (6).

Whether probiotics have a positive effect in patients with CD is controversial. A recent systematic review on the effect of *Saccharomyces bouladaii* in patients with IBD concluded that there is insufficient evidence to show that this probiotic is effective for the treatment of UC or CD due to the small number of trials (2 in CD and 1 in UC that showed a positive effect and 1 trial in CD that didn't find any effect in CD) (7).

Another systematic review with meta-analysis on the efficacy of probiotics in IBD, included 22 randomized controlled trials (RCTs) (8). There was no beneficial effect of probiotics in patients with CD for neither induction of remission or prevention of relapse of quiescent CD.

In patients with UC, however, it seems that probiotics may have a positive effect on induction of remission and prevention relapse when the high-dose multi-bacterial agent VSL#3 is administered (8). VSL#3 is a probiotic preparation that is composed of 8 bacterial strains: *S. thermophiles*, *L. paracasei*, *L. plantarum*, *L. acidophilus*, *L. delbrueckii*, *B. longum*, *B. breve*, *B. infantis*.

In 2015, Fedorak *et al.* (9) evaluated the effect of VSL#3 on patients with CD who were post small intestinal resection. The patients that were treated immediately after the surgery had lower inflammatory cytokines and lower recurrence rate compared to the patients who started treatment on the 90th day post operation. However, the rate of severe recurrence and CD activity index were not significantly different between the two groups.

In a pediatric placebo controlled, double-blind study, 29 patients with UC were randomized to receive either placebo or VSL#3 in addition to steroid therapy for induction of remission and mesalamine for maintenance (10). This study demonstrated that VSL#3 is beneficial for induction of remission and for preventing relapse in 1-year follow-up. In another open label trial of children with mild to moderate UC, VSL#3 taken for a period of 8 weeks in addition to the maintenance therapy or low steroid dose, induced endoscopic and clinical remission in 56% of patients, which was statistically significant (11). No adverse events were reported.

VSL#3 has also been found to be effective in maintenance of remission in two double-blind, placebo controlled trials in adults with chronic or recurrent pouchitis (12,13).

Lin *et al.* (14) also demonstrated that in mice gut, *Lactobacillus rhamnosus* GG (LGG) prevents tumor necrosis factor alpha (TNF- α)-induced NF- κ B activation and blocks inflammatory response *in vitro* and *in vivo*.

In a recent study, LGG has been shown to reduce the expression of TNF- α and IL-17 in colonic biopsies taken from patients with UC (15). *In vivo*, the reduction of expression of TNF- α and IL-17 in these patients was dose dependent.

A systematic review and meta-analysis published in 2015, concluded that *Escherichia coli* Nissle 1917 is as effective as mesalazine in induction and maintenance of remission in UC patients (16).

In the European Crohn's and Colitis Organization (ECCO) and European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines, published in 2018, it is suggested that VSL#3 or *E. Coli* Nissle 1917 may be used as an adjuvant therapy in mild UC for induction or maintenance of remission or as the sole treatment in mild UC with intolerance to 5-aminosalicylic acid (5-ASA) preparations. However, probiotics are not recommended in patients with CD due to lack of supporting evidence (17).

Fecal microbiota transplantation (FMT)

Several studies have indicated that an early alteration in the microbiome, either by the use of antibiotics or gastrointestinal (GI) infection, influences the risk to develop IBD.

FMT is an administration of processed feces from a donor into the patient's gut, hence increasing the diversity of the microbiome (18). Couturier-Maillard *et al.* (19) demonstrated that wild type (WT) mice that were cohoused with NOD2 mice, were more susceptible to develop colitis after dextran sodium sulfate (DSS) exposure. It was suggested that the NOD2 mice microbiome sensitized the mucosa to injury. Broad spectrum antibiotics and FMT decreased the risk of developing colitis in both WT and NOD2 mice.

One small pediatric study involving four patients with UC and one RCT in adults that were treated with FMT via nasogastric tube (NT) found no efficacy for NT administered FMT (20,21).

In another small pediatric trial, 10 patients with mild-moderate UC received FMT via daily enemas for 5 days (22). Clinical response was observed in 78% of the patients and clinical remission was achieved in 33% within 1 week. Two thirds of the patients maintained clinical response for 1 month after the treatment. The reported adverse events were mild self-limited GI symptoms and fever.

In a recent randomized, double-blind trial in 73 adult patients with mild-moderate UC, 32% of patients achieved

steroid free remission at 8 weeks after FMT *vs.* 9% of control (autologous FMT) (23). The FMT was performed by colonoscopy followed by two enemas over 7 days.

Similar results were obtained in two other RCTs, where FMT was given by enemas or colonoscopy (24,25). In a recent trial that included 41 steroid dependent adults with UC, 46% achieved clinical remission at week 24, 75.6% had clinical response and 63.4% had endoscopic remission after colonoscopy administered FMT (26).

The data on the efficacy of FMT in patients with CD is limited compared to UC. A systematic review with meta-analysis of 10 CD clinical trials and 29 UC clinical trials reported a remission rate of 47.5% and 39.6%, respectively, but there was high variability among the trials and most of them were uncontrolled (27).

Another meta-analysis of 23 cohort studies and four RCTs of CD and UC patients reported lower success rates—clinical remission rate of 28.8% and 30% for UC and CD, respectively (28). Clinical remission did not correlate with endoscopic findings in the individuals with CD. There was better clinical remission rate in more severe disease for both UC and CD, however, there was high variability among the trials and most of them were uncontrolled.

Neither of the meta-analysis found any advantage to either route of administration nor to the feces type (frozen/fresh). For conclusion, it seems that there might be beneficial effect of FMT in patients with IBD, mainly UC. More research is needed before it can be recommended.

Curcumin and resveratrol

Curcumin is the main component of turmeric and resveratrol is a polyphenolic compound found in grapes, red wine and berries. Both of these components have been reported to have an anti-inflammatory effect.

Curcumin modulates inflammatory activity by blocking arachidonic acid cascade and NF- κ B activity, which affects CRP, TNF- α and IL-1. It downregulates genes that are involved in oxidation and fibrogenesis, regulates proliferation and activation of T cells, B cells and macrophages. It also suppresses IL-2 synthesis and inhibits neutrophils chemotaxis (29).

In a mice colitis model, subjects that were treated with DSS combined with curcumin or resveratrol had better survival rate and decreased body weight loss, diarrhea and rectal bleeding compared to the controls that were treated with DSS alone (30). Colonic TNF- α and IL-6 levels were significantly lower and histology was normal in the

treatment groups compared to overt colitis histology in the controls.

Two multicenter randomized, placebo controlled, double-blind studies of 50 patients with mild to moderate UC and 89 patients with UC in remission on 5-ASA treatment showed significant advantage from the addition of curcumin to 5-ASA treatment compared to the 5-ASA plus placebo in clinical remission rates, clinical response, endoscopic remission rate (Mayo score ≤ 1), and recurrence rate during 6 months of follow-up (31,32). No adverse events were reported.

In the recent ECCO and ESPGHAN guidelines, curcumin was suggested to be used as a complementary treatment for induction of remission and maintenance in mild-moderate UC (17). Nevertheless, a recent systematic review and meta-analysis of the three UC curcumin RCT studies concluded that there is no beneficial effect to curcumin over placebo in maintaining remission (33).

Resveratrol has been demonstrated to reduce the number of Th17 cells in a mouse model of UC mouse and to increase the number of Treg cells in a dose dependent manner (34). Its anti-inflammatory effect has been demonstrated through inhibition of production of nitric oxide (NO), TNF- α and PGE2 and reduction of colonic epithelial cells neutrophil infiltration (35,36). It was suggested that resveratrol may also have an anti-fibrotic effect (37).

Two randomized, double-blind, placebo controlled study on 50 patients with UC treated with 500 mg resveratrol for 6 weeks found a significant reduction in markers of oxidative stress, CRP, NF- κ B and TNF- α levels and a significant improvement in quality of life (38,39). More clinical trials are needed to assess its efficacy and safety in IBD patients.

Marijuana

Cannabinoid receptors in the enteric nervous system influence the gut motility by decreasing gastric acid secretion and gastric and colonic emptying (40). The cannabinoids also have been demonstrated to have an anti-inflammatory effect and reduction of inflammation-related pain in rats (41,42).

Two randomized, double-blind, placebo controlled trials in patients with CD and one in patients with UC have failed to demonstrate any beneficial effect to the cannabis in clinical remission rate or biochemical markers, however, in one trial there was a significant clinical response in the cannabis group versus the placebo group (43-45). In

addition, in a retrospective study in patients with CD, there was a significant improvement in Harvey-Bradshaw index and a reduction in the number of stools per day (46).

Cannabis has also been demonstrated to improve daily activity, ability to work, health perception, reduce abdominal pain and emotional stress. It has a positive impact on the weight gain in IBD patients as well as in quality of life (43,47).

Cannabis may be effective in improving symptoms such as abdominal pain and reduced appetite. It may also improve quality of life, but data suggests it has no effect on enteric inflammation. So, it can mask disease progression and may increase the risk of developing disease complication. An association between cannabis use and an increased risk for surgical intervention was demonstrated in CD patients (48).

Its chronic use, especially in the pediatric population, is of concern due to its adverse events: altered brain development, cognitive impairment with lower IQ, increased risk of psychosis disorders in susceptible patients, and addiction (49).

Massage

There is one recently published RCT that tested the effect of 30 sessions of massage therapy in patients with CD (50). There was an improvement in quality of life scores, but no effect on pain reduction was seen.

Cognitive behavioral treatment (CBT)

There is high prevalence of anxiety and depression among children with IBD (51). CBT has been demonstrated to be an effective treatment in children and adolescents with depression or anxiety disorders (52,53).

Stress has been shown to induce the translocation of GI bacteria to lymphoid organs in mice (54). The parasympathetic system has an anti-inflammatory effect, while sympathetic activity has a pro-inflammatory effect. However, there is limited data to support the assumption that stress induces mucosal inflammation (55). Although stress has been shown as a contributor to mucosal damage in IBD animal models (8,56), there is still limited data to support the assumption that stress induces mucosal inflammation (55).

Szigethy *et al.* (57) conducted an RCT of CBT on 41 adolescents with IBD. The authors concluded that CBT can lead to significant improvement in depression and global functioning compared to standard treatment.

In another large RCT that included 185 children with IBD, patients were assigned to 3 sessions of CBT *vs.* educational lecture that focused on nutrition, food labels and the GI system (58). There was a significant reduction in health care visits in the 12 months post intervention, improved coping ability and quality of life in the CBT group compared to the control group.

However, in contrast a recent RCT involving 70 adolescents and young adults with IBD found no advantage of CBT over standard medical care in reducing subclinical anxiety, depression or quality of life (59).

Hypnotherapy

The brain gut axis is the suggested mechanism through which hypnotherapy affects patients with IBD and IBS. There are only a few studies that have explored the efficacy of hypnotherapy in patients with IBD.

In one RCT involving 54 adults with UC, hypnotherapy was found to be effective in maintaining remission for 78 days compared to the control group (50). Two other adult studies conducted in patients with severe IBD found hypnotherapy effective in reducing the need for corticosteroid therapy, reducing disease severity and improving quality of life (60,61). However, the sample size in both studies was small (n=15 patients in both).

Mawdsley *et al.* found that hypnotherapy significantly reduced substance P, IL-13 and TNF α levels in the rectal mucosa and reduced serum concentration of IL-6 in 17 subjects with UC (62).

In children with IBD, there is only one small study from our group (63). This study included six children—five with CD and one with UC. In this set of patients, CBT resulted in the resolution of most of the clinical symptoms and reduction of inflammatory markers.

Acupuncture and moxibustion

Acupuncture is a Chinese traditional medicine that involves placing thin needles into the patient's skin in specific points. In variations of this, an electrical current or heat is added to the treatment.

Moxibustion is another Chinese traditional medicine that involves burning mugwort cones and placing them on particular points on the skin (64).

The mechanism of acupuncture in pain relief is through several mechanisms: decreasing acetyl choline esterase levels, which are increased during inflammatory processes

and downregulating mast cells and 5-hydroxytryptamine (5-HT) release from mast cells, thus mediating visceral afferent cells sensitization (65). Acupuncture was also found to reduce substance P, vasoactive intestinal peptide (VIP) and neurokinin-1 receptors levels found to be overexpressed in patients with abdominal pain compared to healthy controls (65). Further, it has also been demonstrated to attenuate excitation of the colonic dorsal root ganglion, an effect that was reversed by naloxone (65).

In mouse and rat models of IBD, acupuncture has been shown to decrease the levels of TNF- α , TNF receptors, IL-6, IL-8 and NF- κ B (64).

Moxibustion improved microscopic colonic inflammation and significantly reduced the levels of several pro inflammatory cytokines in rat models of UC (66). It also up-regulated the anti-inflammatory cytokine IL-10 (67). In other work, moxibustion resulted in upregulation of tight junction proteins and decreased epithelial cell apoptosis in rat model of CD (68).

A systematic review and meta-analysis published in 2013 found that these Chinese techniques were superior to sulphasalazine (69). Nevertheless, the included trials were of low methodological quality with most of them selected clinical efficacy as an outcome, and only few used objective measurements.

In a further RCT that included 92 patients with mild to moderate CD there was a significant advantage to the treatment group (herb moxibustion combined with acupuncture) compared to the control group (wheat bran moxibustion combined with superficial acupuncture) (70). The two groups were treated for 12 weeks and were followed up for 24 weeks. There was a statistically significant difference in favor of the treatment group in the quality of life, increased hemoglobin level and the reduction of CRP levels in the post treatment period. Crohn's Disease Activity Index (CDAI) scores improved both in the post treatment and the follow-up period. There was no significant change in erythrocyte sedimentation rate (ESR) levels or the post treatment endoscopic evaluation. However, there was a significant difference in the relapse rate between the groups during the follow-up period in favor of the treatment group.

Summary

Based on the current data, it appears that probiotics have no effect in the setting of CD. However, *VSL#3* and *E. coli Nissle 1917* have a beneficial effect as a complementary

treatment for the induction of remission and maintenance in UC. *VSL#3* may also be effective in maintenance of remission in chronic pouchitis.

Current data suggests that there might be a beneficial effect for FMT in patients with IBD, however more high-quality studies are needed especially in the setting of CD.

The latest published ECCO guidelines on Complementary Medicine and psychotherapy in IBD suggests curcumin as an adjuvant treatment for the induction of remission and maintenance of UC (71).

Preliminary data on the anti-inflammatory effects of resveratrol is promising, however, more clinical trials should be conducted. Cannabis may be effective in improving symptoms such as abdominal pain and reduced appetite. It may also improve quality of life, but current data indicated that it has no effect on the inflammatory process.

There is limited evidence to support the use of CBT in children or adults with IBD for the reduction of anxiety, depression and quality of life. Hypnotherapy may be an effective adjuvant therapy in improving quality of life, symptoms and inflammation in IBD, however, the current data is limited and more studies are needed. There is insufficient data to support the use of acupuncture or moxibustion as complementary treatments in IBD.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Magen R, Shaoul R. Alternative & complementary treatment for pediatric inflammatory bowel disease. *Transl Pediatr* 2019;8(5):428-435. doi: 10.21037/tp.2019.09.02