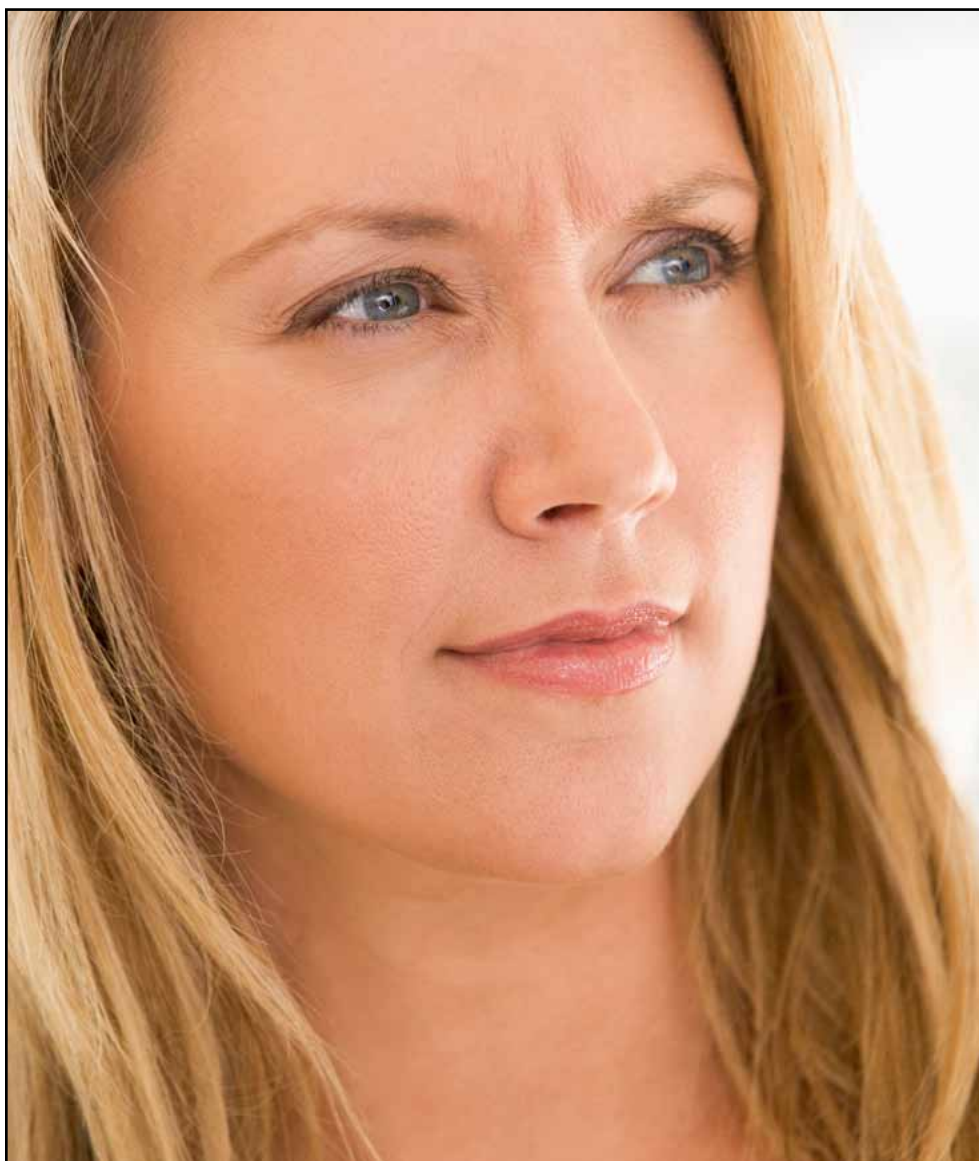


1

29-Year-Old Female with
Ulcerative Colitis



ULCERATIVE COLITIS

Ulcerative colitis (UC) and Crohn disease are the principal constituents of the gastrointestinal inflammatory condition group known as Inflammatory Bowel Disease (IBD). IBD is one of the five most common gastrointestinal diseases in the United States. Because there is no recognized cure, patients require a lifetime of care. Annually, the health care cost of IBD exceeds \$1.7 billion and more than 115,000 patients are placed on disability.¹ IBD is associated with an increased risk for intestinal cancers.² Up to 75% of Crohn disease patients and 33% of UC patients will require surgery (colectomy).¹ The case below describes a patient with pancolitis, a severe form of UC that involves the whole colon. Pancolitis that is non-responsive to medications, as was the case with this individual, frequently requires surgical intervention.³

29-Year-Old Female with Ulcerative Colitis/Pancolitis

Additional Symptoms and Conditions	Chronic diarrhea, erythema nodosum, weight loss, fatigue; medications ineffective
Lifestyle Factors	Standard American diet, high stress due to illness
Medications	Mesalamine (Asocol®), azathioprine (Imuran®), prednisone
Tests Used	Food-specific IgG4 antibodies, microbial stool analysis using DNA identification; celiac genes and serology
Imbalances Identified	Elevated food-specific IgG4 antibodies, intestinal dysbiosis and parasitosis
Treatments	Diet modification, albendazole, digestive enzymes, antimicrobial and nutritive botanicals, probiotics
Outcome	Weight normalization (gain), 80% resolution of symptoms, improved energy, daily use of medications no longer required
Discussion/Significance	The testing and treatment used in this case resulted in dramatic clinical improvement and enhanced quality of life. It is probable that the treatment prevented the need for surgical intervention. Given the grim epidemiological statistics of IBD, research investigating the efficacy of this cost-saving, multifactorial, integrative approach is highly recommended.

CASE HISTORY

EM was a 29-year-old female presenting with extremely active ulcerative colitis (UC). Colonoscopy had detected pancolitis. She was at her lowest body weight since adulthood. She was taking prednisone, mesalamine (a cyclooxygenase and prostaglandin blocker), and azathioprine (an immunosuppressive drug with unknown mechanism), but these medications were not bringing her relief. She had chronic diarrhea and severe fatigue. She also had erythema nodosum (nodular erythematous eruptions on the lower legs) which presented as large, multiple oozing lesions which were preceded by bruises. For the erythema nodosum, she was prescribed a two-month course of the antibiotic cephalexin. Because of the debility of her illness, EM stated that she couldn't be a mother to her two children.

For most of her life, EM had eaten a standard American diet (SAD) characterized by high intake of red meat, sugary desserts and drinks, high-fat foods, dairy products, eggs, and refined grains. Ten months prior to her initial visit, an IgG4 food antibody test reported significant reactions to yeast, gluten, and dairy, and she eliminated foods containing these components from her diet. Celiac serology and genes were also tested for and found to be negative. Even with the adoption of this oligoantigenic diet based on her specific reactions, she noted no significant change to her condition at the time of her initial visit.

Because this patient's pancolitis could not be medically managed using prednisone, mesalamine and azathioprine, it is likely that surgery would have been her next step.

EM's family history did not include inflammatory bowel disease or other autoimmune conditions. Her husband had irritable bowel syndrome. Although EM was under a great deal of stress because of her condition and had eaten the SAD for most of her life, there were no other apparent contributing lifestyle factors.

Initial Laboratory Results

Laboratory tests ordered and rationale:

1. **Previous testing:** Celiac serology and celiac genes were tested and found to be negative. IgG4 food-specific antibody testing identified significant antibody elevations to yeast, gluten and dairy. Adverse food reactions, including an association with celiac disease, have been identified in IBD.⁴⁻⁵ Removal of offending foods has been noted to improve symptoms. Note laboratory findings demonstrate a positive gluten IgG4 reaction, but frank celiac disease (gluten intolerance) was ruled out, suggesting an alternative inflammatory response to gluten.
2. **Microbial stool analysis using DNA identification:** Gastrointestinal microbiota imbalance (dysbiosis) is a common and significant finding in inflammatory bowel disease.⁶ Dysbiosis was suspected to be a significant etiopathogenic factor in this case, particularly given the lack of favorable response to the removal of potential antigenic foods.

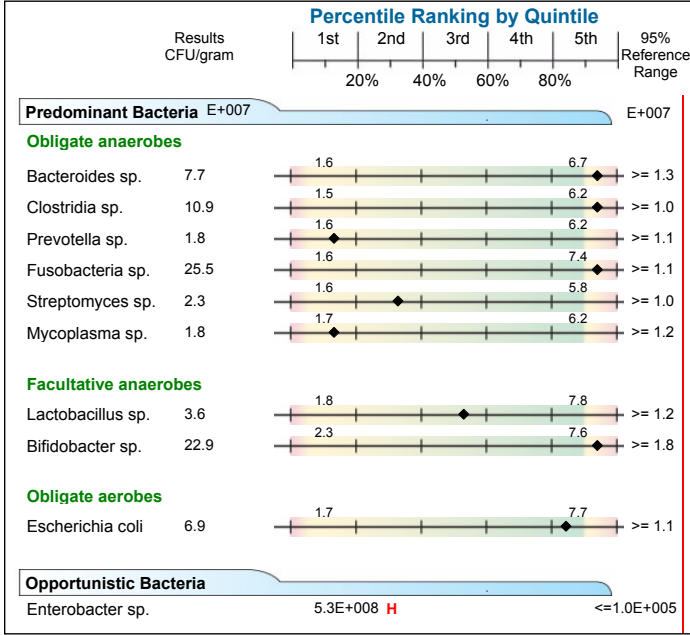


Figure 1. Microbial stool analysis using DNA identification. Opportunistic bacteria present. Imbalance in the pattern of predominant bacteria suggested dysbiosis.

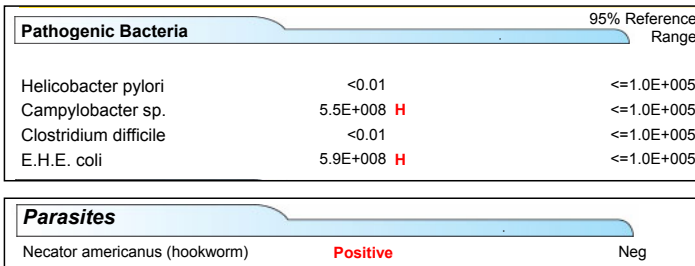


Figure 2. Microbial stool analysis using DNA identification. Pathogenic bacteria and a parasite detected in patient's stool.

NOTES

Pharmaceuticals		
Amoxicillin		R
Ampicillin		R
Cefuroxime		R
Ciprofloxacin	S	
Clindamycin	S	
Erythromycin		R
Levofloxacin	S	
Penicillin		R
Potassium Clavula		R
Sulfamethoxazole	S	
Tetracyclin	S	
Trimethoprim-Sulfa	S	

Botanicals		
5-Hydroxy-1,4-naphthoquinone Black Walnut	S	
Alliin Garlic		R
Arbutin Uva Ursi		R
Artemisinin Wormwood		R
Berberine Goldenseal	S	
Caprylic acid Octanoic acid	S	
Carvacrol Oregano	S	
Oleuropein Olive Leaf		R
Quinic Acid Cats Claw	S	
Thymol Oil of Thyme	S	
Undecylenic acid Undecylenic acid	S	

Figure 3. Bacterial sensitivities to pharmaceutical and botanical interventions. Findings suggested that bacteria detected in stool may have resistance to cefuroxime, among other antibiotics and botanicals. S = sensitive; R = resistant.

Assessment

- ◆ Pancolitis with associated weight loss, fatigue and diarrhea
- ◆ Erythema nodosum
- ◆ Dysbiosis
- ◆ Antibiotic resistance

Treatment Plan

- ◆ Albendazole 250 mg: 1 tab PO BID for 3 days; then 1 tab on day 8, day 30, and day 90
- ◆ Berberine (botanical antimicrobial formula): 1 tab PO BID
- ◆ Multi-botanical antimicrobial formula: 2 caps PO BID (contains: bilberry extract (25% anthocyanosides), noni, milk thistle, echinacea (purpurea & angustifolia), goldenseal, shiitake, white willow (bark), garlic, grapeseed extract, black walnut (hull and leaf), raspberry, fumitory, gentian, tea tree oil, galbanum oil, lavender oil (plant and flower), oregano oil (plant and flower))
- ◆ Deglycyrrhizinated licorice (DGL): 2 tabs PO TID AC
- ◆ Aloe vera capsules: 2 caps PO BID
- ◆ Vegetable greens powder: 1 scoop PO QD
- ◆ Probiotic 1: *Lactobacillus rhamnosus* strain GG
- ◆ Probiotic 2: *Saccharomyces boulardii*
- ◆ Probiotic combination: *Lactobacillus sp.*, *Bifidobacter sp.*, and *Streptococcus thermophilus*
- ◆ Digestive enzymes: 2 tabs PO TID AC
- ◆ Continue:
 - » Diet: Eliminate gluten, dairy, and yeast
 - » Mesalamine (COX/PG blocker) 400 mg: 1 tab PO TID

NOTES

Treatment plan rationale: It was decided that the potentially pathogenic parasite would be treated with albendazole, and the pathogenic and opportunistic bacteria would be addressed using a combination of antimicrobial botanicals that were identified as sensitive on laboratory testing (Figure 3). Botanicals were chosen because the patient had an extensive exposure history to antibiotics. Botanicals may be less disruptive to the predominant flora for a number of reasons. For example, some antimicrobial botanicals contain prebiotic substances such as polysaccharides.⁷ They are also suggested to be less likely to contribute to antibiotic resistance.⁸ The mucilaginous botanicals aloe vera and licorice (DGL) were used to reduce GI inflammation and support healing of the mucosa.⁹⁻¹⁰ A vegetable-greens powder was employed with the expectation that it would provide bioavailable nutritional support. Comprehensive probiotics, including *Saccharomyces boulardii*, were used to normalize microflora, reduce inflammation and support intestinal health.¹¹ Digestive enzymes were given to optimize macronutrient breakdown to facilitate improved bioavailability and absorption of micronutrients. The dietary restrictions and mesalamine were continued. Note that this relatively low-risk protocol was directed at addressing the suspected causal factors of EM's IBD as identified on laboratory analysis, rather than suppressing the symptoms and pathogenic mechanisms, as the higher-risk medications were designed to do.

Ten-Month Follow-Up

EM was feeling approximately 80% better from her initial presentation. She had gained weight and the erythema nodosum resolved. Her energy level was much better. She had stopped the azathioprine and titrated off the steroids by the completion of the antimicrobial regimen. Her dose of mesalamine was reduced then discontinued, although she occasionally used it for flare-ups. The flare-ups were mostly caused by inadvertent exposure to foods she was reactive to. These exposures to foods would throw her off track for a few days, but she recovered more quickly than in the past. She thought that if she was successful in avoidance of these foods, her recovery would be 100%. To EM, the most important benefit of her healing was that she could once again be a mother to her two children. As she described it, she was doing “incredibly well.” For maintenance treatment, it was recommended that EM continue with dietary restrictions, probiotics and digestive enzymes; periodic clinical and laboratory assessments would determine need for additional interventions.

To EM, the greatest benefit of her healing was that she could once again be a mother to her two children.

Ten-Month Follow-up Laboratory Results

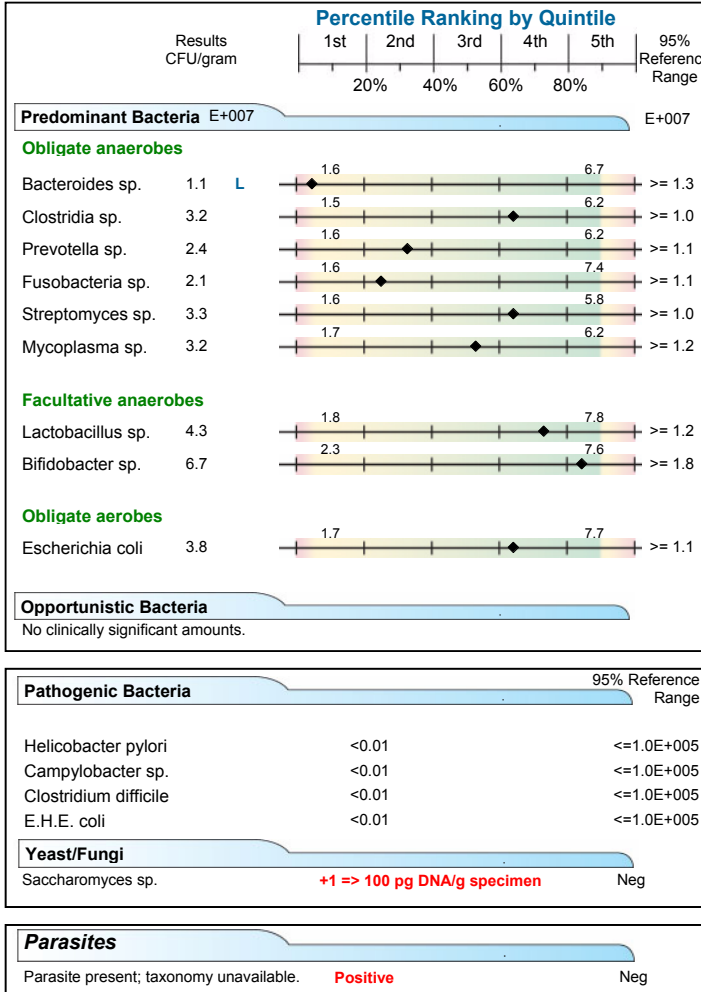


Figure 4. Follow-up microbial stool analysis using DNA identification. Findings were negative for *Enterobacter sp.*, *Campylobacter sp.*, EHEC, and hookworm. *Saccharomyces* species were detected, probably as a result of supplementation. Parasite was detected; taxonomy was unavailable but was probably dietary exposure to parasitic DNA rather than a pathogen. Predominant bacteria were improved, although *Bacteroides* species were low.

DISCUSSION

EM’s pancolitis and erythema nodosum were evidence of an intense systemic inflammatory reaction. Factors involved in the pathogenesis of inflammatory bowel disease (IBD) include the host’s intestinal microflora, the host’s genetic and immune predisposition, infection, psychological stress, environmental stimuli, and intestinal barrier permeability.¹²⁻¹⁴

Immunological reactivity to foods, including gluten intolerance, have been reported as causes of colonic inflammation and IBD.⁴⁻⁵

In this case, EM did not have a family history of IBD, but she was under a good deal of stress caused by her limited ability to care for her children due to her illness. While this particular stressor was not a causative factor, it may have exacerbated her IBD. Components of the SAD she ate most of her life were very antigenic for her, as identified on IgG4 testing. The severe reactions, while not numerous enough to indicate intestinal hyperpermeability, do reflect a pronounced inflammatory response. IgG4 is an immunoglobulin that forms a complex with the offending food protein. This antigen-antibody complex may initiate an immune response, leading to a wide variety of symptoms, ranging from gastrointestinal symptoms including diarrhea, skin changes, headaches or joint inflammation and myopathy. Indeed, symptoms associated with IgG reactions are found associated with most organ systems.¹⁵ It is interesting to note that EM had a severe reaction on IgG4 testing to gluten, but was negative for celiac disease, suggesting that an inflammatory response to foods in UC is not limited to a single pathogenic mechanism.

This patient's laboratory results point to several factors that may have contributed to the etiopathogenesis of ulcerative colitis.

This patient's laboratory results pointed to several factors that may have contributed to the pathogenesis of UC. As shown in Figure 1, very high levels of predominant bacteria spp. (*Bacteroides* sp., *Clostridia* sp., *Fusobacteria* sp., and *Bifidobacter* sp.) and *Enterobacter* sp. (an opportunistic bacterium) demonstrated significantly altered microflora (dysbiosis). Imbalances of predominant anaerobic bacteria (both high and low) have been reported in IBD. Specifically, *Bacteroides*, *Eubacterium* (such as *E. coli*, *Enterobacter*, *Shigella*, *Salmonella*, *Yersinia*, etc.), and *Lactobacillus* have been identified.¹⁶ Similar to EM's findings, studies have also shown increased anaerobes (especially gram-negative anaerobes such as *Bacteroides*) in Crohn disease (CD), UC, and pouchitis. In one study, 50% of CD patients had either *E. coli* or *Bacteroides* as the predominant GI bacterial group.¹⁷

Enterobacter spp, the opportunistic bacteria shown in Figure 1, are asymptomatic in healthy individuals but are a leading cause of nosocomial bacterial infections, including urinary tract infections, bacteremia, skin and soft tissue infections, and septic arthritis.¹⁸ However, there are not many cases in the literature of *Enterobacter*-induced colitis or gastroenteritis.

Two pathogens, *Campylobacter* sp. and *Enterohemorrhagic Escherichia coli* (EHEC), were also detected (Figure 2), illustrating the severity of dysbiosis. Bacterial enteritis can induce or exacerbate IBD.¹³ *Campylobacter* sp. and *EHEC* have been reported as causes of bacterial colitis.^{14,19-20}

Campylobacter specifically has been detected in IBD,²¹ and has been cited as a rare cause of pancolitis.¹⁹

Campylobacter specifically has been detected in IBD, and has been cited as a rare cause of pancolitis.

Erythema nodosum is the most common dermatologic manifestation of IBD, and UC specifically is known to trigger this condition, especially with flare-ups.²² Further, it can be caused by bacterial or fungal infection, and *Campylobacter* sp. has been specifically implicated.²² Erythema nodosum has also been associated with celiac disease.²³ In this case, it may

be that the combination of immunosuppressive steroids, IBD, GI *Campylobacter*, and gluten sensitivity led to the expression of this condition.

Hookworm, *Necator americanus*, was detected (Figure 2). UC has been exacerbated or even caused by helminth infections, specifically *Strongyloides* species.²⁴⁻²⁵ However, “worm therapy” using the helminth *Trichuris suis* has been reported to significantly improve IBD symptoms.²⁶

Given the dearth of evidence connecting *Enterobacter sp.* and *Necator americanus* to pancolitis, it is not clear the contribution these played in EM’s condition, although they may have added to her overall inflammatory burden.

It is noteworthy that the bacterial culture and sensitivity (Figure 3) showed resistance to cefuroxime, a second generation cephalosporin antibiotic. At the time of her first visit, EM had been on two months of cephalixin which is a first-generation cephalosporin antibiotic. Resistance to this class of antibiotics could explain why she had high predominant bacteria, opportunistic bacteria, and pathogenic bacteria even after two months of cephalixin. Because of her history of antibiotic use, this patient was a candidate for antimicrobial botanicals, to which microbes may have more difficulty developing resistance.²⁷

Based on research findings, *Campylobacter sp.* and *EHEC* were most likely involved in the pathogenesis of EM’s pancolitis. As EM’s remarkable clinical response and normalized follow-up laboratory results in Figure 4 demonstrated, she responded favorably to treatment with albendazole, antimicrobial herbal formulas, digestive enzymes, DGL, aloe vera, vegetable greens powder, and a variety of probiotics. This relatively low-risk protocol addressed the suspected causal factors of IBD, rather than inhibiting symptoms and pathogenic mechanisms as her high-risk medication was

In this case, it may be that the combination of immunosuppressive steroids, IBD, GI *Campylobacter*, and gluten sensitivity led to the expression of erythema nodosum.

designed to do. Consistent with published research, the aggressive protocol of probiotics appears to have been quite therapeutic in EM’s case.^{16-17,28} Certain species of *Lactobacillus* and *Bifidobacteria* have been shown to attenuate colitis in animal models.²⁸ Treatments with *Lactobacillus sp.*, *Bifidobacteria sp.*, and *Saccharomyces boulardii* have been shown to bring about remission in UC.¹⁶

The presence of taxonomically unidentified parasitic DNA (Figure 4) was considered to be clinically irrelevant, as evidenced by her significant improvement. It is suggested that if the major pathogenic parasites in humans have been tested for using PCR technology and ruled out, the finding of parasitic DNA is likely from a transient, food-based exposure and not indicative of parasitic infection. The *Saccharomyces* species detected on follow-up was most likely from supplementation of *Saccharomyces boulardii*. While the predominant *Bacteroides sp.* were low after treatment, it may have actually been a desirable finding. It has been shown that *Bacteroides vulgatus* causes inflammation and that increased *Bacteroides fragilis* may be involved with CD.¹⁶ The fact that *Bacteroides sp.* were high when she was symptomatic and were lower after treatment that resulted in clinical improvement suggests that the *Bacteroides* in her stool included *B. vulgatus* or *B. fragilis*.

A comprehensive protocol designed to remove GI microbial imbalances and antigenic foods, replace digestive enzymes and nutrients, repair the intestinal lining, and reinoculate with beneficial microflora resulted in an 80% improvement from the initial presentation. The patient experienced a significant improvement or resolution of all of her major symptoms, including diarrhea, erythema nodosum, fatigue and weight loss, and was able to stop regular use of all medications. She observed that it was likely that hidden exposures to antigenic foods resulted in the periodic flare-ups that kept her from a full, 100% recovery.

It is interesting to note that the removal of antigenic foods from EM's diet appears to have clearly contributed to her improvement, as evidenced by the fact that accidental ingestion of those substances triggered symptomatic flare-ups. However, it was only after normalization of bowel microbial status that the effect of antigenic foods was experienced. This suggests that the GI microbial imbalances in EM were the significant underlying etiological factors.

CONCLUSION

Pancolitis that is non-responsive to medications frequently requires surgical intervention (colectomy), resulting in significant quality-of-life issues.³ Because this patient's condition could not be medically managed using the high-risk, immunosuppressive combination of prednisone, mesalamine and azathioprine, colectomy would most probably have been her next step.

Laboratory testing identified IgG4 food reactions and severe gastrointestinal microbial imbalances, including disruption of the predominant flora, the presence of opportunistic and pathogenic bacteria and a parasite. The low-risk and non-invasive protocol employed was designed to address underlying causes of the patient's IBD, and in doing so, dramatically reduced GI inflammation and may have prevented the need for surgical intervention.

The fact that this UC case showed such dramatic improvements once the microbiota were normalized strongly suggests that this approach might have great benefit for any inflammatory bowel case, particularly in light of the numerous reports in the literature that significant microbial imbalances are associated with the etiopathogenesis of inflammatory bowel diseases. Given the epidemiological statistics of IBD, research investigating the efficacy of this cost-saving, safe, multifactorial and integrative approach is highly recommended.

The fact that this UC case showed such dramatic improvements once the microbiota were normalized, strongly suggests that this approach may have benefit for any IBD case.

References

1. Hanauer SB. Inflammatory bowel disease: epidemiology, pathogenesis, and therapeutic opportunities. *Inflammatory bowel diseases*. Jan 2006;12 Suppl 1:S3-9.
2. O'Connor PM, Lapointe TK, Beck PL, Buret AG. Mechanisms by which inflammation may increase intestinal cancer risk in inflammatory bowel disease. *Inflamm Bowel Dis*. Feb 12 2010.
3. Cuffari C, Present DH, Bayless TM, Lichtenstein GR. Optimizing therapy in patients with pancolitis. *Inflammatory bowel diseases*. Oct 2005;11(10):937-946.

4. Yang A, Chen Y, Scherl E, Neugut AI, Bhagat G, Green PH. Inflammatory bowel disease in patients with celiac disease. *Inflamm Bowel Dis*. Jun 2005;11(6):528-532.
5. MacDermott RP. Treatment of irritable bowel syndrome in outpatients with inflammatory bowel disease using a food and beverage intolerance, food and beverage avoidance diet. *Inflamm Bowel Dis*. Jan 2007;13(1):91-96.
6. Marteau P. Bacterial flora in inflammatory bowel disease. *Dig Dis*. 2009;27 Suppl 1:99-103.
7. Guo FC, Williams BA, Kwakkel RP, et al. Effects of mushroom and herb polysaccharides, as alternatives for an antibiotic, on the cecal microbial ecosystem in broiler chickens. *Poult Sci*. Feb 2004;83(2):175-182.
8. Abascal K YE. Herbs and Drug Resistance: Part 1—Herbs and Microbial Resistance to Antibiotics. *Alternative and Complementary Therapies*. August 2002 2002 8(4):237-241.
9. Davis RH, Donato JJ, Hartman GM, Haas RC. Anti-inflammatory and wound healing activity of a growth substance in Aloe vera. *J Am Podiatr Med Assoc*. Feb 1994;84(2):77-81.
10. Stewart PM, Prescott SM. Can licorice lick colon cancer? *J Clin Invest*. Apr 2009;119(4):760-763.
11. Mengheri E. Health, probiotics, and inflammation. *J Clin Gastroenterol*. Sep 2008;42 Suppl 3 Pt 2:S177-178.
12. Goodhand JR, Wahed M, Rampton DS. Management of stress in inflammatory bowel disease: a therapeutic option? *Expert review of gastroenterology & hepatology*. Dec 2009;3(6):661-679.
13. Kalischuk LD, Buret AG. A role for Campylobacter jejuni-induced enteritis in inflammatory bowel disease? *American journal of physiology*. Oct 29 2009.
14. Singh J. Colitis. *medicine from WebMD* 2009; <http://emedicine.medscape.com/article/927845-overview>. Accessed 12/31/09, 2009.
15. Lord RS BJ. Laboratory Evaluations for Integrative and Functional Medicine. Atlanta: Metamatrix Institute; 2008:435-437.
16. Ott SJ, Musfeldt M, Wenderoth DF, et al. Reduction in diversity of the colonic mucosa associated bacterial microflora in patients with active inflammatory bowel disease. *Gut*. May 2004;53(5):685-693.
17. Tamboli CP, Neut C, Desreumaux P, Colombel JF. Dysbiosis in inflammatory bowel disease. *Gut*. Jan 2004;53(1):1-4.
18. Fraser SL, Arnett M. Enterobacter infections. *medicine from WebMD* 2009; <http://emedicine.medscape.com/article/216845-overview>. Accessed 1/05/2010, 2010.
19. Siegal D, Syed F, Hamid N, Cunha BA. Campylobacter jejuni pancolitis mimicking idiopathic ulcerative colitis. *Heart Lung*. Jul-Aug 2005;34(4):288-290.
20. Sumrall A, McMullan L, Abrasley C, East H. A case of severe hemorrhagic diarrhea. *Journal of the Mississippi State Medical Association*. Dec 2007;48(12):366-369.
21. Gradel KO, Nielsen HL, Schonheyder HC, Ejlersten T, Kristensen B, Nielsen H. Increased short- and long-term risk of inflammatory bowel disease after salmonella or campylobacter gastroenteritis. *Gastroenterology*. Aug 2009;137(2):495-501.
22. Hebel JL, Habif T. Erythema Nodosum. *medicine from WebMD* 2009; <http://emedicine.medscape.com/article/1081633-overview>. Accessed 12/31/09, 2009.
23. Bartyk K, Varkonyi A, Kirschner A, Endreffy E, Turi S, Karg E. Erythema nodosum in association with celiac disease. *Pediatric dermatology*. May-Jun 2004;21(3):227-230.
24. Ghoshal UC, Alexander G, Ghoshal U, Tripathi S, Krishnani N. Strongyloides stercoralis infestation in a patient with severe ulcerative colitis. *Indian journal of medical sciences*. Mar 2006;60(3):106-110.
25. Weight SC, Barrie WW. Colonic Strongyloides stercoralis infection masquerading as ulcerative colitis. *Journal of the Royal College of Surgeons of Edinburgh*. Jun 1997;42(3):202-203.
26. Summers RW, Elliott DE, Urban JF, Jr., Thompson RA, Weinstock JV. Trichuris suis therapy for active ulcerative colitis: a randomized controlled trial. *Gastroenterology*. Apr 2005;128(4):825-832.
27. Sibanda T, Okoh A. The challenges of overcoming antibiotic resistance: plant extracts as potential sources of antimicrobial and resistance modifying agents. *African J of Biotechnology*. December 2007;6(25):2886-2896.
28. Sheil B, Shanahan F, O'Mahony L. Probiotic effects on inflammatory bowel disease. *J Nutr*. Mar 2007;137(3 Suppl 2):819S-824S.