

## Non-pulmonary allergic diseases and inflammatory bowel disease: A qualitative review

David S Kotlyar, Mili Shum, Jennifer Hsieh, Wojciech Blonski, David A Greenwald

David S Kotlyar, Medical Oncology Service, NIH National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, United States

Mili Shum, Department of Medicine, New York/Presbyterian Medical Center, New York, NY 10021, United States

Jennifer Hsieh, Division of Gastroenterology, Department of Medicine, SUNY Stony Brook, Stony Brook, NY 11790, United States

Wojciech Blonski, Department of Medicine, SUNY Upstate, Binghamton Campus, Binghamton, NY 13902, United States

Wojciech Blonski, Medical University, 53-111 Wrocław, Poland  
David A Greenwald, Division of Gastroenterology and Liver Diseases, Department of Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY 10461, United States

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**Correspondence to:** David A Greenwald, MD, Professor, Division of Gastroenterology and Liver Diseases, Department of Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, 625 Ullman Building, 1300 Morris Park Avenue, Bronx, NY 10461, United States. [dgreenwa@montefiore.org](mailto:dgreenwa@montefiore.org)  
Telephone: +1-718-4302098 Fax: +1-718-4302098

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### Abstract

While the etiological underpinnings of inflammatory bowel disease (IBD) are highly complex, it has been noted that both clinical and pathophysiological similarities exist between IBD and both asthma and non-pulmonary allergic phenomena. In this review, several key points on common biomarkers, pathophysiology, clinical manifestations and nutritional and probiotic interventions for both IBD and non-pulmonary allergic diseases are discussed.

Histamine and mast cell activity show common behaviors in both IBD and in certain allergic disorders. IgE also represents a key immunoglobulin involved in both IBD and in certain allergic pathologies, though these links require further study. Probiotics remain a critically important intervention for both IBD subtypes as well as multiple allergic phenomena. Linked clinical phenomena, especially sinonasal disease and IBD, are discussed. In addition, nutritional interventions remain an underutilized and promising therapy for modification of both allergic disorders and IBD. Recommending new mothers breastfeed their infants, and increasing the duration of breastfeeding may also help prevent both IBD and allergic diseases, but requires more investigation. While much remains to be discovered, it is clear that non-pulmonary allergic phenomena are connected to IBD in a myriad number of ways and that the discovery of common immunological pathways may usher in an era of vastly improved treatments for patients.

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**Key words:** Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Food intolerance; Food allergies; Biomarkers; Pathophysiology; Nutrition; Probiotics

**Core tip:** There are multiple clinical, pathophysiological and therapeutic commonalities between nonpulmonary allergic disease and inflammatory bowel disease (IBD). In particular, in terms of pathophysiology, histamine expression is upregulated in both IBD and allergic diseases. Ulcerative colitis, in particular, shows upregulation of the Th2 pathway which is seen in a large number of allergic phenomena including sinonasal disease. Both probiotics and nutritional interventions are promising therapies for both IBD and allergic disease (especially food intolerance, food allergies, and eczema) but these require more investigation. Recommending mothers breastfeed their infants, and for a longer duration also shows potential promise in prevention of both IBD and food allergies, but also requires further study.

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## INTRODUCTION

Inflammatory bowel disease (IBD) is comprised of two major disorders, ulcerative colitis and Crohn's disease (CD). The exact pathophysiology of IBD remains unclear; however immune dysregulation plays a substantial role, with likely significant involvement of the Th1 and Th17 pathways in Crohn's and the Th2 pathway in ulcerative colitis. Intriguingly, some clinical manifestations of allergic disorders and IBD overlap, as well as expression of selected cytokines and immune responses. In particular, both disorders feature histamine release and IgE overexpression. Certain probiotics have been found to be useful in both disorders. There have been some studies that have shown a correlation between sinonasal allergic disease and IBD. Moreover, some food allergies and intolerances have been linked to IBD. Finally, sulfasalazines are often used to treat patients with IBD; such therapy can require desensitization for an individual patient to successfully use. It is evident that allergic disorders and IBD share common etiological characteristics and also share potential common treatment pathways.

## HISTAMINE AND OTHER BIOMARKERS ASSOCIATED WITH IBD AND ALLERGY

### Role of histamine and mast cells

In 1978, Dvorak *et al*<sup>[1]</sup>, followed by Levo and Livni<sup>[2]</sup>, found ultrasonographic and morphological evidence of degranulation of mast-cells in the submucosa of ileal specimens from patients with CD. They found release of mediators including histamine, platelet activation factor, and eosinophil chemotactic factor, all of which may play a role in the pathophysiology of CD. Subsequently, Dvorak *et al*<sup>[1]</sup>, using transmission electron microscopic studies discovered a markedly increased number of mast cells that were located in the edematous submucosa and between smooth muscle cells in the ileum of subjects with CD. In addition, evidence of degranulation of mast-cells, basophils and eosinophils in the affected area of ileum was also observed<sup>[1]</sup>. Similarly, an increased number of mast-cells with intense degranulation was found in the active stage of ulcerative colitis (UC)<sup>[3]</sup>. Moreover, it was also demonstrated that the median number of mast-cells in normal colonic tissue was significantly greater in patients with UC than controls (patients examined for colonic adenomas) or those with CD (1500 per milligram of tissue *vs* 1250 per milligram of tissue,  $P < 0.05$ )<sup>[4]</sup>. Furthermore, median mast-cell counts obtained from inflamed colonic tissue were significantly ( $P < 0.01$ ) greater than the number of mast-cells in non-inflamed tissue in patients with

IBD (2000 per milligram of tissue *vs* 1500 per milligram of tissue in UC and 1700 per milligram of tissue *vs* 1250 per milligram of tissue in CD)<sup>[4]</sup>. On the other hand, King *et al*<sup>[5]</sup> showed an increased mean number of mast cells (19.5) at the demarcation line between active and inactive areas of colonic inflammation in 12 of 20 (60%) UC patients. Finally, a Japanese group determined that patients with IBD or collagenous colitis had a greater number of mast cells in the upper part of the lamina propria of the colon than healthy controls and that patients with IBD had a higher number of mast cells in the lower part of the lamina propria of the colon as compared to those with collagenous colitis and healthy controls<sup>[6]</sup>.

Knuston *et al*<sup>[7]</sup> observed that patients with CD of the distal ileum had a significantly greater mean histamine secretion rate within the small intestine than did healthy controls (152 ng/cm *vs* 71 ng/cm small intestine per hour,  $P < 0.01$ ), and that histamine secretion was related to disease activity (active disease defined as CDAI  $> 150$ : 193 ng/cm per hour *vs* inactive disease defined as CDAI  $< 150$ : 105 ng/cm per hour). Further study also suggested that histamine secretion was significantly increased in inflamed colonic mucosa in patients with both CD and UC when compared to their non-inflamed colonic mucosa or colonic mucosa in healthy controls<sup>[8]</sup>. A more recent study showed that urinary excretion of N-methylhistamine was significantly increased in patients with active IBD when compared to inactive IBD or non-IBD controls and such urinary histamine excretion strongly correlated with endoscopic activity of CD measured by the CD Endoscopic Index of Severity ( $r^2 = 0.70$ ,  $P < 0.0001$ )<sup>[9]</sup>. Greater expression of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) by mast cells was also found in the submucosa and muscularis propria of the ileum in patients with CD when compared to controls; significantly greater numbers of TNF- $\alpha$ -labeled mast cells were noted in the muscularis propria both in uninflamed (1.7-fold,  $P < 0.05$ ) and in inflamed ileum (4.6-fold,  $P < 0.002$ )<sup>[10]</sup>. In addition, TNF- $\alpha$  expression was found to be greater in the submucosa in inflamed *vs* uninflamed ileum in CD patients (1.6-fold,  $P < 0.01$ ), while it was lower in the lamina propria in inflamed *vs* uninflamed ileum in CD patients (0.4-fold,  $P < 0.05$ )<sup>[10]</sup>. This is noteworthy as TNF- $\alpha$  has been shown to be an important factor in the inflammatory cascade leading to the inflammatory response in the murine model for IBD<sup>[11]</sup>.

### IgE

**IgE as a biomarker of disease activity in IBD:** It has been suggested that IgE may mediate an allergic response in patients with IBD. Evidence supporting this hypothesis includes the presence of peripheral and tissue eosinophilia in IBD patients<sup>[12,13]</sup>, increased numbers of mast cells or cells containing IgE in rectal mucosa of patients with IBD<sup>[14,15]</sup>, concomitant atopic disease in patients with IBD<sup>[16,17]</sup> and a good response to disodium cromoglycate in IBD patients<sup>[18-20]</sup>.

Several studies have assessed IgE levels in patients with IBD. Pepys *et al*<sup>[21]</sup> suggested that some patients with IBD (25% of UC patients and 31% of CD patients) may

have elevated serum IgE levels. These data were further supported by Levo *et al.*<sup>[22]</sup>, who claimed that patients with IBD have significantly increased mean serum level of IgE when compared to healthy controls (358 IU/mL *vs* 103 IU/mL,  $P < 0.05$ ). On the other hand, several studies report normal serum IgE levels in IBD patients<sup>[23-26]</sup>. Becker *et al.*<sup>[25]</sup> determined that specific serum IgE levels to food allergens such as egg white, whole milk,  $\beta$ -lactoglobulin and wheat were undetectable in IBD patients and thus suggested that the allergic hypothesis of IBD should be rejected. However, a prior study by Mee *et al.*<sup>[26]</sup> observed a significantly higher frequency of positive reactions to food allergens using the skin prick test in IBD patients when compared to healthy controls.

### Role of IgE in desensitization to therapies for IBD:

Desensitization to sulfasalazine (SASP) has been found to be effective in patients who experienced hypersensitivity reactions to SASP<sup>[27-30]</sup>. This is achieved by administration of successively larger doses of SASP, thereby allowing the presence of specific IgE in a controlled fashion without causing massive histamine release from mast cells<sup>[29]</sup>. In the largest published study, reporting on 47 patients with IBD, desensitization was successful in 85% of patients with IBD, and there was no recurrence of hypersensitivity reactions in 82.5% of those who were successfully desensitized<sup>[29]</sup>. In addition, among the successfully desensitized patients, 100% of UC patients and 78% of CD patients remained in long-term remission on SASP alone or in combination with intermittent prednisone<sup>[29]</sup>. Caution is advised in attempting desensitization in patients with agranulocytosis, toxic epidermal necrolysis, or fibrosing alveolitis<sup>[30]</sup>. The risks of these severe reactions may outweigh the benefit of continuing to take SASP containing medications.

## PROBIOTICS

At a workshop held at Yale University in 2007, recommendations were made with regards to the use of probiotics in clinical settings for a variety of indications, including IBD<sup>[31]</sup>. For IBD, the recommendations included a class “A” recommendation (defined as one made on “strong, positive, well-conducted controlled” studies) for the use of VSL#3 for the prevention and maintenance of remission in pouchitis<sup>[31]</sup>. In addition, some probiotics were given a class “C” recommendation (one “based on some positive studies”) for IBD<sup>[31]</sup>. These included VSL#3 for the induction of remission of pouchitis, and for inducing remission and maintenance of remission in ulcerative colitis<sup>[31]</sup>. The probiotic *Lactobacillus* GG (LGG) was noted to be beneficial in both IBD and allergic diseases; LGG has a “C” class recommendation in the treatment of CD, and a class “A” designation treatment of atopic eczema<sup>[31]</sup>. Probiotics may also help with cow milk allergy<sup>[31]</sup>. See Tables 1-3 for other disease indications and probiotic regimens, with additional recommendations from the workshop in 2007.

*Lactobacillus* also has specific bacteriocidal effects, including against *Lactococcus*, *Streptococcus*, *Staphylococcus*, *Listeria* and *Mycobacteria*<sup>[32]</sup>. The bacterium uses two different pathways to neutralize competing bacteria. First, it uses a

**Table 1 Recommendations for probiotic use**

Clinical condition	Effectiveness	Organism
Diarrhea		
Infectious-adult-treatment	A	<i>Saccharomyces boulardii</i> , LGG
Infectious-childhood-treatment	A	LGG, <i>Lactobacillus reuteri</i>
Prevention of infection	B	<i>S. boulardii</i> , LGG
Prevention of AAD	A	<i>S. boulardii</i> , LGG, <i>L. casei</i> , <i>L. bulgaricus</i> , <i>S. thermophilus</i>
Treatment of recurrent CDAD	B	<i>S. boulardii</i> , LGG
Prevention of CDAD	B	LGG, <i>S. boulardii</i>
IBD		
Pouchitis		
Preventing and maintaining remission	A	VSL#3
Induce remission	C	VSL#3
Ulcerative colitis		
Inducing remission	C	<i>Escherichia coli</i> Nissle, VSL#3
Maintenance	C	<i>E. coli</i> Nissle, VSL#3
Crohn's	C	<i>E. coli</i> Nissle, <i>S. boulardii</i> , LGG
IBS	B	<i>Bifidobacterium infantis</i>
IBS	C	<i>Bifidobacterium animalis</i> , VSL#3, <i>Lactobacillus plantarum</i>
Immune response	A	LGG, <i>Lactobacillus acidophilus</i> , <i>L. plantarum</i> , <i>Bifidobacterium lactis</i> , <i>Lactobacillus johnsonii</i>
Allergy		
Atopic eczema assoc. with cow milk allergy		
Treatment	A	LGG, <i>B. lactis</i>
Prevention	A	LGG, <i>B. lactis</i>
Radiation enteritis	C	VSL#3, <i>L. acidophilus</i>
Vaginosis and vaginitis	C	<i>L. acidophilus</i> , LGG, <i>L. reuteri</i>

Reproduced with permission from reference Floch *et al.*<sup>[31]</sup>. An “A” recommendation is based on strong, positive, well-conducted, controlled studies in the primary literature, not abstract form; A “B” recommendation is based on positive, controlled studies but the presence of some negative studies; A “C” recommendation is based on some positive studies. IBD: Inflammatory bowel disease; LGG: *Lactobacillus* GG; *S. boulardii*: *Saccharomyces boulardii*.

small molecule to inhibit growth of competitor bacteria, likely a short chain fatty acid, and also uses hydrogen peroxide to alter the bacterial microenvironment from an aerobic one to an anerobic one<sup>[32]</sup>. In addition, *Lactobacillus* also has immunomodulatory abilities. First, the bacillus increases transepithelial resistance, and it also upregulates the key toll-like receptors TLR2 and TLR9. These toll-like receptors recognize foreign hostile viral and bacterial antigens and their activation causes a large expansion of cytokine expression and amplifies the immune response against hostile antigens<sup>[32]</sup>.

## ATOPY, NASAL DISEASE AND URTICARIA IN IBD

Prior studies have described a relationship between IBD

**Table 2 Results of random controlled trials which reported efficacy of probiotics in patients with inflammatory bowel disease**

Probiotic	Situation	Control	No. of subjects	Duration (mo)	Relapse probiotic vs control	Ref.
<i>E. coli</i> Nissle 1917	Ulcerative colitis	5-ASA	120	4	16% vs 11.3%	[70]
<i>E. coli</i> Nissle 1917	Ulcerative colitis	5-ASA	120	12	67% vs 73%	[71]
<i>E. coli</i> Nissle 1917	Crohn's disease	Placebo	28	12	30% vs 70% <sup>a</sup>	[72]
VSL#3	Pouchitis	Placebo	40	9	15% vs 100% <sup>a</sup>	[73]
VSL#3	Prevention of pouchitis	Placebo	40	12	10% vs 40% <sup>a</sup>	[74]
VSL#3	Crohn's disease <sup>1</sup>	5-ASA	28	12	20% vs 40% <sup>a</sup>	[75]
<i>S. boulardii</i>	Ulcerative colitis	5-ASA	31	12	30% vs 35% <sup>a</sup>	[76]
<i>S. boulardii</i>	Crohn's disease	5-ASA	28	6	6.3% vs 37.5% <sup>a</sup>	[77]

Reproduced with permission from reference Marteau<sup>[69]</sup>. <sup>1</sup>Postoperative. <sup>a</sup>*P* < 0.05 vs control. 5-ASA: 5-aminosalicylic acid; *E. coli*: *Escherichia coli*; *S. boulardii*: *Saccharomyces boulardii*.

**Table 3 Probiotics in treatment of inflammatory bowel disease: Randomized controlled trials**

Entity	Ref.	Population (n)	Probiotic(s)	Treatment group	Effect
Crohn's disease	Bousvaros <i>et al</i> <sup>[79]</sup>	Children (75; age, 5-21 yr)	LGG	Maintenance of remission	No benefit
	Plein <i>et al</i> <sup>[80]</sup>	Adults (20)	<i>S. boulardii</i>	Maintenance of remission	Reduced diarrhea vs placebo
	Malchow <sup>[72]</sup>	Adults (28)	<i>E. coli</i> Nissle 1917	Maintenance of remission	No benefit
	Prantera <i>et al</i> <sup>[81]</sup>	Adults (45)	LGG	Maintenance of surgically induced remission	No benefit
Ulcerative colitis	Schultz <i>et al</i> <sup>[82]</sup>	Adults (11)	LGG	Treatment of active Crohn's disease	No benefit
	Kruis <i>et al</i> <sup>[70]</sup>	Adults (120)	<i>E. coli</i> Nissle 1917	Maintenance of medically induced remission	Equal to mesalamine
	Rembacken <i>et al</i> <sup>[71]</sup>	Adults (120)	<i>E. coli</i> Nissle 1917	Maintenance of medically induced remission	Equal to mesalamine
	Kruis <i>et al</i> <sup>[83]</sup>	Adults (327)	<i>E. coli</i> Nissle 1917	Maintenance of medically induced remission	Equal to mesalamine
Pouchitis	Ishikawa <i>et al</i> <sup>[84]</sup>	Adults (21)	<i>B. breve</i> and <i>B. bifidum</i> and <i>L. acidophilus</i> YIT 0168	Maintenance of medically induced remission	Superior to placebo
	Gionchetti <i>et al</i> <sup>[73]</sup>	Adults (40)	VSL#3	Maintenance of antibiotic-induced remission of chronic pouchitis	Superior to placebo
	Mimura <i>et al</i> <sup>[85]</sup>	Adults (36)	VSL#3	Maintenance of antibiotic-induced remission of chronic pouchitis	Superior to placebo
	Gionchetti <i>et al</i> <sup>[86]</sup>	Adults (40)	VSL#3	Maintenance of antibiotic-induced remission of chronic pouchitis	Superior to placebo
	Kuisma <i>et al</i> <sup>[87]</sup>	Adults (20)	LGG	Treatment of active pouchitis	No benefit

Reproduced with permission from reference Szajewska *et al*<sup>[78]</sup>. LGG: *Lactobacillus GG*; *E. coli*: *Escherichia coli*; *S. boulardii*: *Saccharomyces boulardii*; *B. breve*: *Bifidobacterium Breve*; *B. bifidum*: *Bifidobacterium bifidum*; *L. acidophilus*: *Lactobacillus acidophilus*.

and allergy. It is unclear whether this association is manifested as atopy (consisting of atopic dermatitis, allergic rhinitis, asthma, and food allergy) or nasal disease. The association was hypothesized because patients with allergy have an abnormal IgE antibody response to common environmental antigens and earlier findings of peripheral and tissue eosinophilia in patients with IBD had suggested an IgE mediated response. Furthermore, because some allergic symptoms were associated with other systemic inflammatory disorders, it was felt that patients with colitis might also have an increased likelihood of developing atopic illnesses.

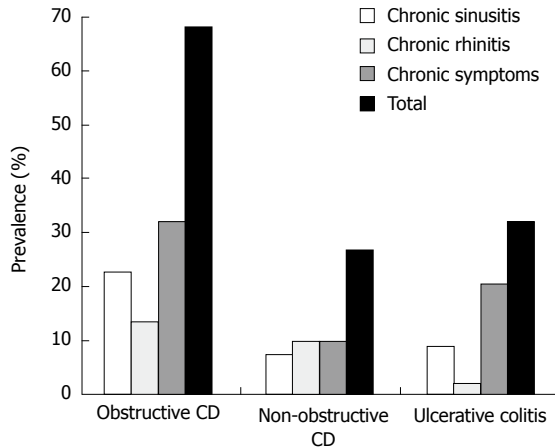
A review of prior studies has shown that these results may be equivocal and may only be pertinent in relation to food allergies and possibly sinonasal disease. One study showed that in children with atopic eczema, food allergy is associated with increased intestinal inflammation, as manifested by elevated levels of fecal eosinophil cationic protein, TNF- $\alpha$  and  $\alpha$ 1 antitrypsin<sup>[33]</sup>. Similarly, in another study, while there was no correlation observed between

frequency of personal history of atopy, serum IgE levels and prick test response between IBD patients and controls, it was observed that IBD patients had a higher frequency of positive prick test when tested against food allergens<sup>[26]</sup>. There also seemed to be a positive relationship between IBD and chronic sinonasal disease, since the prevalence of chronic sinonasal disease was elevated in patients with IBD, specifically in patients with CD and especially in those also with obstructive bowel complications<sup>[34]</sup>. Interestingly, nearly 70% of these patients had some degree of sinonasal disease; see Figure 1 for a graph depicting the prevalence of sinonasal disease in patients with IBD.

Other atopic features (asthma, hay fever and allergic rhinitis) were investigated in patients with UC and CD with the results indicating that atopic features were twice as common in patients with UC, but no different between patients with CD and controls, suggesting that hypersensitivity may play a part in UC but not in CD<sup>[17]</sup>.

In contrast, other studies found no association be-





**Figure 1** Prevalence of sinonasal disease in inflammatory bowel disease patients. Reproduced with permission from reference Book *et al*<sup>[34]</sup>. CD: Crohn's disease.

tween controls and IBD patients in terms of atopic symptoms. Personal history analyses for atopic symptoms (asthma, allergic rhinitis, eczema, urticaria, and allergic symptoms) were assessed in another study where the prevalence of atopy with skin-prick tests (using five allergens - mixed grass pollens, dog hair, cat fur, *Dermatophagoides pteronyssinus* and *Aspergillus fumigatus*) and serum IgE concentrations among 122 patients with IBD and 103 age-matched controls was examined<sup>[35]</sup>. The authors showed no statistical difference in the percentage of patients with positive skin tests between controls and IBD patients and also no difference between the subgroups of IBD patients (CD, ulcerative colitis, and ulcerative proctitis)<sup>[35]</sup>.

Another study assessed skin test reactivity in IBD patients. In this study, two different populations were examined, one in the United States and another in Czechoslovakia, and patients were classified as having CD or UC by clinical, pathological and radiological criteria; those who had been treated with immunosuppressives were taken off these medications for three weeks. The authors found no evidence of skin test anergy (assessed by using multiple antigens - candida, mumps, PPD, streptokinase-streptodornase, and trichophyton) when all patients were compared to controls<sup>[36]</sup>.

Despite initial studies that suggested an association between IBD and IgE mediated allergic reactions, direct evidence is still lacking and the role of IgE mediated reactions remains unclear.

## NUTRITION AND IBD

### Epidemiology of food intolerance and IBD

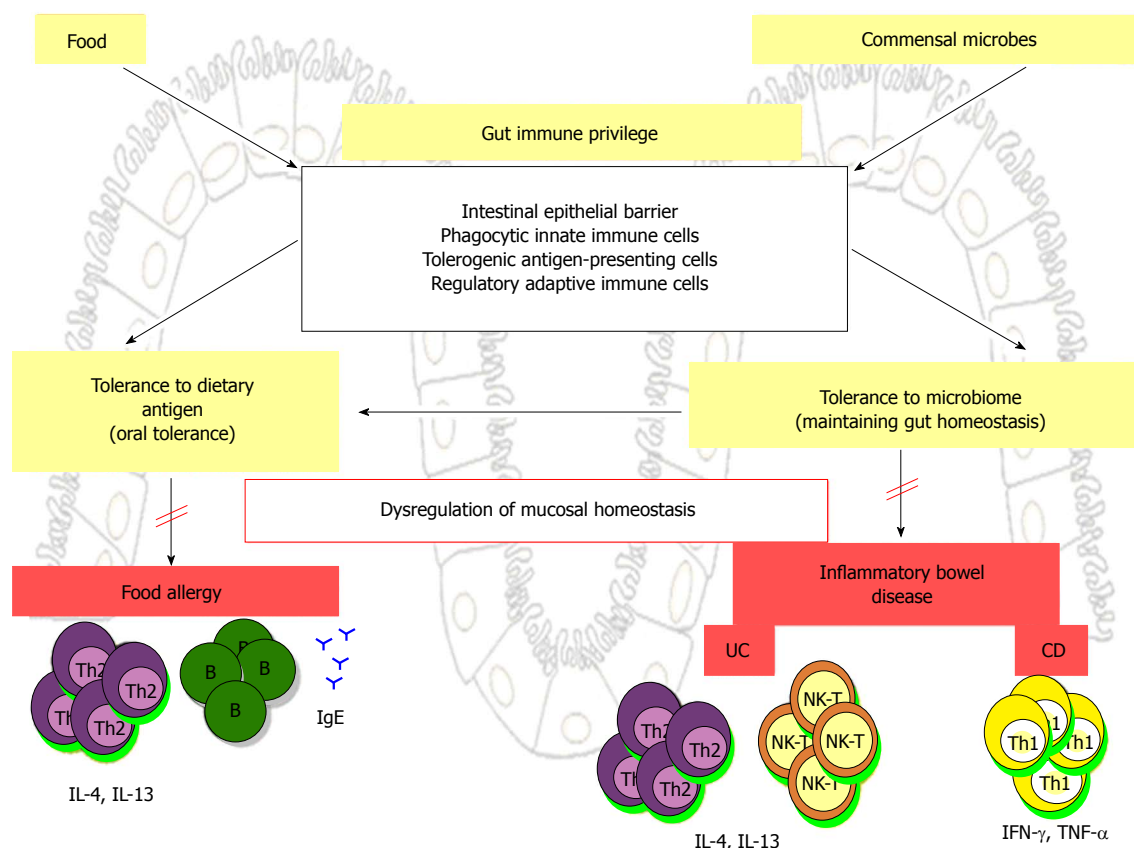
IBD is characterized by chronic inflammation of the gastrointestinal tract. The etiology of IBD is complex and probably multi-factorial. Nutrition is an important modulator of IBD<sup>[37]</sup>. In particular, it is felt that relationships between food antigens and immune pathways may alter the course of IBD<sup>[38]</sup>. Gut bacteria and the inflammatory response are altered by the ingestion of differing foods<sup>[39]</sup>.

Most patients with IBD are intolerant to selected (or

specific) food items. Food intolerance has been evaluated in multiple studies. In a survey administered to 132 patients (along with 70 controls) with IBD, food intolerance was reported by 66% of patients with CD, and 64% of UC patients<sup>[40]</sup>. The most common symptoms included diarrhea and abdominal pain<sup>[40]</sup>. In a study that evaluated the antibody response to cow's milk antigen, it was found that IgG and IgM antibodies to beta-lactoglobulin were significantly elevated in patients with UC and CD when compared with normal subjects<sup>[41]</sup>. Elevation of IgG further correlated with involvement of the ileum, increase in inflammatory markers, and was higher in untreated patients; interestingly there was no change in IgM levels after sulfasalazine or steroid therapy<sup>[41]</sup>. Another study reported on a questionnaire examining dietary habits, the amount of food consumed, and whether patients had problems with specific foods<sup>[42]</sup>. A total of 122 foods were evaluated. Intolerance to chocolate, dairy products, fats and artificial sweeteners were seen in both UC and CD, and patients with CD seemed to have a greater range of problems with specific foods<sup>[42]</sup>. From 80%-100% of bacteria in the colonic flora of CD patients are bound by immunoglobulin whereas, in controls only 20% are bound; when enteral feeds are given the percentage bound in CD significantly decreases<sup>[43,44]</sup>.

The prevalence of food reactions was studied in 375 adult patients attending a gastroenterology outpatient clinic: 32% complained of food allergies as being the source of their abdominal complaints and in 14.4% laboratory testing was consistent with intestinal food allergy<sup>[45]</sup>. Laboratory testing included counts of eosinophils, the presence of specific IgE against food antigens, increased total IgE, specific clinical signs of atopy, and cromoglycate sensitivity<sup>[45]</sup>. Confirmation of the diagnosis of food allergy was found in 3.2%<sup>[45]</sup>. This was confirmed through elimination diet and subsequent rechallenge or allergen provocation testing during EGD<sup>[45]</sup>.

Breastfeeding may have a protective effect against developing IBD<sup>[37,46]</sup>. Of thirteen reported case-control studies, 3/13 (23.1%) found that patients with IBD were less likely to have been breast fed as compared to controls<sup>[37]</sup>. In another study of 308 matched patients, the patients with CD were found to have had an average breast-feeding duration of 4.6 mo as compared to controls who had an average duration of 5.8 mo<sup>[47]</sup>. Postulated mechanisms have been suggested to include a protective effect of immunoglobulins and antibacterial proteins in breast milk<sup>[37]</sup>. In addition, breast milk may accelerate maturation of the GI tract in infants, and may also delay the introduction of cow's milk, a potentially allergenic food<sup>[37]</sup>. Another population based case-control study examined three cohorts of patients: one with 638 CD patients, one with 653 UC patients, and 600 controls<sup>[46]</sup>. Specific factors associated with a lower odds ratio of CD and UC included breast-feeding (CD: OR = 0.55; 95%CI: 0.41-0.74; UC: OR = 0.71; 95%CI: 0.52-0.96), and having a vegetable garden during infancy, childhood or adolescence (CD: OR = 0.52; 95%CI: 0.36-0.76; UC: OR = 0.65; 95%CI: 0.45-0.94)<sup>[46]</sup>. In addition, those living in the countryside had a lower odds ratio of having CD (OR = 0.64; 95%CI: 0.46-0.89).



**Figure 2** Immune privilege in the gut consists of tolerance to dietary antigens and to commensal microbes<sup>[49]</sup>. Reproduced with permission from reference Iweala *et al*<sup>[49]</sup>. CD: Crohn's disease; UC: Ulcerative colitis; TNF- $\alpha$ : Tumor necrosis factor- $\alpha$ ; IL: Interleukin; IFN: Interferon.

The duration of breastfeeding was also significant in decreasing both IBD and UC, with those having 0-2 mo of exposure having no protection, as compared with those having 3 or more mo<sup>[46]</sup>.

### Relation between pathophysiology of food insensitivity and IBD

While 20%-30% of the general population have undesirable reactions to food, only 10%-25% of these are actual food allergies<sup>[48]</sup>. The gastrointestinal mucosa is however predisposed to develop allergic reactions, since the tissue in the GI tract is exposed to various food and bacterial allergens in addition to containing all cells required to develop allergic reactions, such as eosinophils, mast cells, and lymphocytes<sup>[48]</sup>.

Proteins in food usually act as the primary foreign antigens that trigger most allergic reactions in the gastrointestinal tract<sup>[49]</sup>. The border between intra and extraluminal sites in the intestine plays a vital role in preventing inappropriate inflammation or allergic disease in the gut<sup>[49,50]</sup>. The gut barrier works in at least five different ways to prevent such diseases. These include (Figure 2): (1) a physical barrier preventing foreign or microbial invasion; (2) the presence of specialized immune cells, including macrophages, to phagocytize microbes and other proinflammatory or allergic antigens; (3) release of IgA, which sequesters microbes away from the gut in the intraluminal space; (4) promotion of antigen presenting cells which upregulate immune tolerance; and (5) expansion of regu-

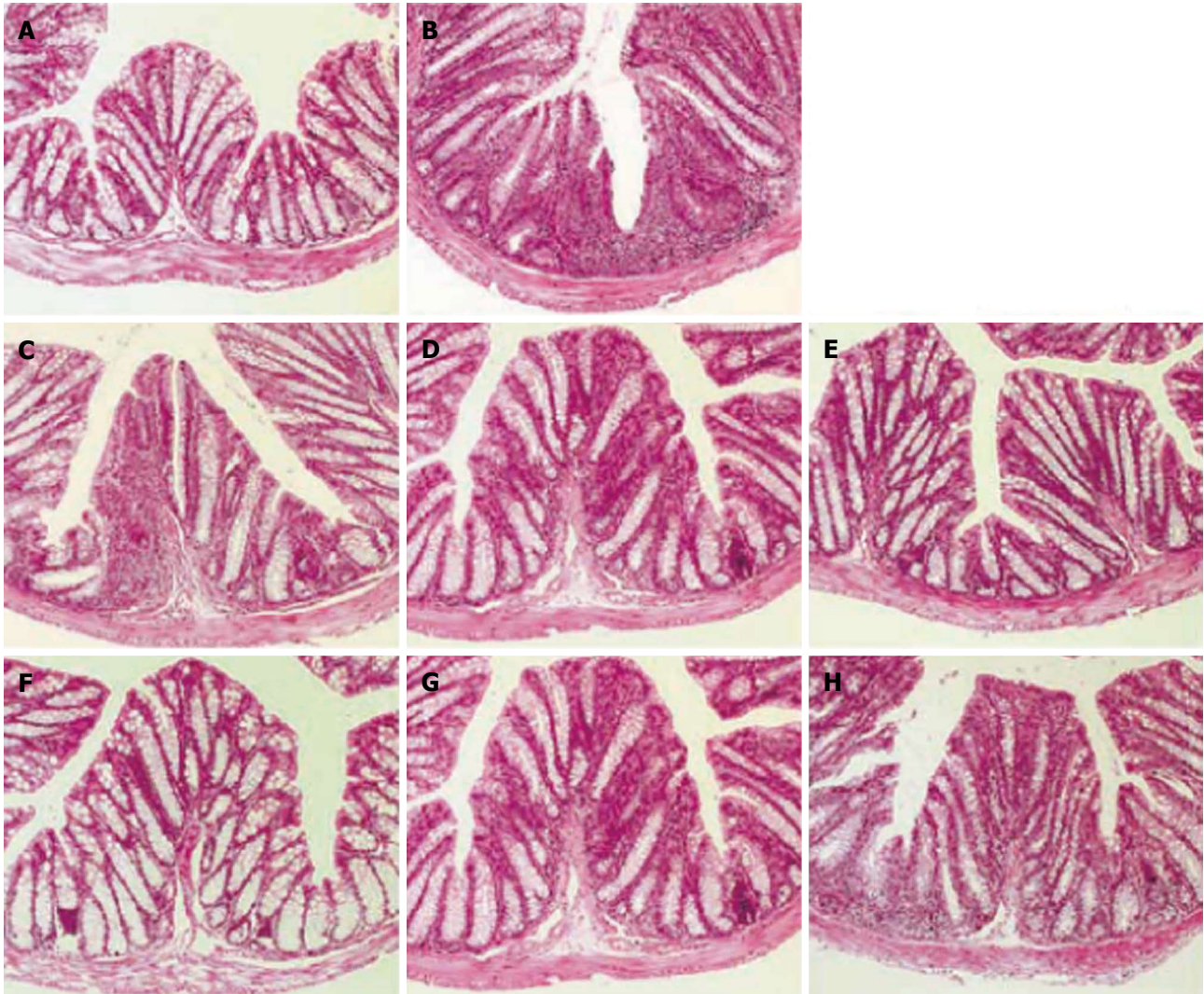
latory T cells which dampens the immune response<sup>[49]</sup>. Chronic inflammation in the gut may act in an ongoing fashion with increasing inflammation leading to additional damage to the physical barrier of the gut, leading in turn to more proinflammatory antigens which can then pass into the extraluminal space<sup>[51]</sup>.

A disruption of one of these five regulatory barriers may contribute to inflammation and/or allergic responses. Mast cells and eosinophils also play a critical role in modulating intestinal allergic reactions and have also been found to be stimulated in IBD and eosinophilic gastroenteritis<sup>[52]</sup>.

In addition, the main inflammatory mechanisms of IBD and of the pathophysiology of intestinal allergic phenomena are related concepts. In particular, the Th2-like response seen in ulcerative colitis is driven by NK-T cells activated by glycolipid and CD1 on epithelial cells, which facilitates their production of proinflammatory cytokines including IL-13 and IL-5<sup>[53]</sup>. Interestingly, this process does not result in the production of IL-4. Upregulation and maladaptive Th2 responses have been implicated in chronic rhinosinusitis<sup>[54]</sup>. In addition, *Staphylococcus aureus* (*S. aureus*), a common colonizer of the nasal tract, has been shown to upregulate IL-5 and IL-13 in nasopharyngeal lymphocytes<sup>[54]</sup>.

Additionally, there is also maladaptive activity of T regulatory T cells (Tregs) both in IBD and in food intolerance<sup>[49]</sup>. Adoptive transfer of Tregs has been shown to prevent intolerance to the food antigen OVA<sup>[55]</sup>. In addition it has been found that TLR4 signaling is critical for





**Figure 3** Histologic analysis of the colon in C57BL/6 mice. A: Normal architecture of the colonic mucosa from mice treated with 50% ethanol alone; B: Erosions of the epithelium, distortion of crypts, loss of goblet cells, and massive mononuclear cell infiltration in lamina propria in mice after administration of trinitrobenzene (TNBS); C-E: TNBS-induced colitis is dose-dependently improved by curcumin. Mice were treated with 0.5% (C), 2.0% (D), or 5.0% (E) curcumin just after administration of TNBS; F-H: Mice were treated with 2% curcumin in preventive mode (F), early therapeutic mode (G), or late therapeutic mode (H) (original magnification  $\times 50$ ). Reproduced with permission from reference Sugimoto *et al*<sup>[66]</sup>.

Treg suppression of responses to food antigens (regulating food tolerance) and also to commensal bacteria (in prevention of colitis)<sup>[49]</sup>.

#### Common treatments for food insensitivity and IBD

Alterations in diet have been used as a treatment for IBD. The use of enteral feeding has been shown to be beneficial, with a majority of studies showing a remission rate of over 60%<sup>[56]</sup>. Liquid feeding is thought to be helpful because it leads to more rapid transit time for feeds, induces partial bowel rest, as well as alters the fecal flora present<sup>[57]</sup>. Tube feeding with an enteral elemental liquid formula cannot be used long-term however, as most patients do not tolerate this, and IBD typically relapses after discontinuation of the diet<sup>[57]</sup>. However, the use of polymeric drinks may be better tolerated and shows similar effectiveness in this population<sup>[57]</sup>.

The use of elimination diets has also been studied. These typically involve the use of a food diary, with elimi-

nation of symptom provoking foods, or the use of a basic diet with reintroduction of potentially problematic foods one food type at a time<sup>[58]</sup>. This approach was shown to be beneficial in inducing remission in six of nine studies<sup>[58]</sup>. Referral to a nutritionist may be of significant benefit<sup>[58]</sup>.

Other potential therapies in the treatment of IBD include the use of polyunsaturated fatty acids (PUFA). These acids, including omega-3 fatty acids, decrease inflammation as their derivatives, including eicosapentaenoic acid, and leukotriene derivatives, downregulate neutrophil trafficking and thereby decrease edema formation<sup>[59-61]</sup>. Twelve studies with n-3 PUFA, mostly from fish oil, showed benefit in IBD patients, with a decreased need for steroids, diminished disease activity and a lower relapse rate<sup>[59]</sup>.

Several herbal preparations are considered useful by some in the treatment of inflammatory disorders. *Lonicera japonica* is a Korean traditional treatment, and has been shown to decrease histamine release from mast

cells and inhibit inflammatory pathways, including the NF- $\kappa$ B and AP-1 pathways<sup>[62-64]</sup>. Lonicera may be an attractive agent for future clinical trials in both IBD and allergic disease<sup>[62]</sup>. In addition, curcumin and green tea polyphenols have been shown to be potent antioxidants and have anti-inflammatory activity in mice<sup>[65-67]</sup>. In one study, 35.5% of mice treated with trinitrobenzene (TNBS) died after developing an ulcerative colitis-like disease; however, no mice died in a group preventively given a 2% curcumin solution<sup>[66]</sup>. In addition, mice given doses of curcumin after TNBS-induced colitis demonstrated histologic improvement of colonic mucosa<sup>[66]</sup> (Figure 3).

## DIFFERENCES BETWEEN EOSINOPHILIC COLITIS AND IBD

Eosinophilic gastrointestinal disorder (EGID) is marked by GI inflammation and intense infiltration of the GI tract with eosinophils seen in the absence of other identified systemic disorders such as malignancy, collagen-vascular disease, IBD, parasitic disease, and medication induced eosinophilia<sup>[68]</sup>. In 50%-70% of patients with EGID, there is a family history of allergic disorders or a personal history of atopy<sup>[48]</sup>. Symptoms vary between children and adults: in children, the common symptoms are vomiting and abdominal pain, while in adults common symptoms include food impaction, difficulty swallowing, chest pain and heartburn<sup>[68]</sup>. Symptoms mimic both irritable bowel syndrome and IBD. Histologically, EGID can be distinguished from GERD; more than 15-20 eosinophils per high power field are seen on biopsy in EGID as opposed to less than 5 in GERD<sup>[48,68]</sup>. Both elimination and elemental diets have shown promise in the treatment of patients with EGID<sup>[48,68]</sup>.

## CONCLUSION

While the immunological underpinnings of both IBD and allergic disease are complex and multifaceted, the degree of overlap between the two disorders is striking. Further studies are warranted to try to help better understand their complex basis and commonality, and there is much to be gained by studying treatments that benefit patients with these illnesses.

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