

Role of diet and gut microbiota in management of inflammatory bowel disease in an Asian migrant

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Activity Objectives

1. To recognize differences in incidence of IBD in Asian immigrants.
2. To recognize the role of altered gut microbiota (dysbiosis) as one of the factors promoting IBD.
3. To recognize the potential role of diet in IBD.

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Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: E. Loftus has consultant arrangements with AbbVie, UCB, and Janssen and has received grants from AbbVie, UCB, Janssen, Amgen, Bristol Myers Squibb, Millenium Takeda, Brain-tree, Santarus, Pfizer, and Genentech. J. T. Li has consulted for Abbott. The rest of the authors declare that they have no relevant conflicts of interest.

CLINICAL VIGNETTE

A 26-year-old man who had migrated to Canada from southeast Asia at the age of 10 years was referred for management of ulcerative colitis (UC). He first noted diarrhea and hematochezia 3 years ago. Colonoscopy at the time of diagnosis revealed moderately active extensive colitis. He had no family history of inflammatory bowel disease (IBD). He was initially treated with oral mesalamine but continued to experience loose stools and hematochezia. He was offered but declined treatment with azathioprine or infliximab and instead agreed to start oral balsalazide (2.25 g three times daily); however, he reported increased stool frequency and bleeding, and the medication was discontinued. A repeat colonoscopy again confirmed moderately

active pancolitis, and results of stool studies were negative for infection. He insisted on further conservative measures before starting immunosuppressive or biologic therapy and inquired about data on the role of dietary modification in the management of the symptoms of IBD. On questioning, he believed that his diet was quite different from that of other members in his family, who were vegetarian and primarily consumed fresh vegetables and non-animal-based protein, such as lentils, whereas he consumed red meat, fried food, and refined sugars.

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Received for publication April 23, 2013; revised May 22, 2013; accepted for publication May 24, 2013.

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0091-6749/\$36.00

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<http://dx.doi.org/10.1016/j.jaci.2013.05.021>

REVIEW

Host genetic factors, gut microbiota, and environmental factors, such as geography, diet, and sanitation, appear to be interrelated and have an effect on the risk of IBD. The incidence of IBD in Asia, once thought to be low, appears to have significantly increased in recent years^{E1}; furthermore, the incidence of UC in migrants from Asia to the United States and United Kingdom (and their children) is higher than among their Western counterparts.^{E2-E4} Systematic studies of IBD in indigenous and migrant populations highlight the importance of environmental factors in the development of IBD. Dietary patterns associated with industrialized countries might, in genetically predisposed subjects, promote a pathological imbalance in the gut microbiota (“dysbiosis”) that causes or exacerbates colitis. Moreover, Western influences on dietary patterns in developing countries have been blamed for the increasing incidence of IBD in these countries.^{E5} Thus in certain host genetic contexts, both diet and the gut microbiota might be important determinants of the epidemiology and cause of IBD. In patient populations in which this is the case, dietary alteration might be a suitable approach to ameliorate the symptoms of IBD and maintain remission.

Environment and epidemiology of IBD

IBD encompasses UC and Crohn disease (CD), which are chronic conditions with distinct clinical and pathologic characteristics; however, although both are multifactorial, neither has a well-defined cause that can be generalized across patient populations. The differences in distribution of these 2 subsets of IBD along the length of the gastrointestinal tract and depth of the intestinal wall suggest that independent pathways lead to each disease phenotype; however, similar factors have been implicated in their pathogenesis, such as host genotype and immune system, as well as environment and gut microbiota. In addition, both UC and CD respond to similar modalities of treatment.

IBD can be a disabling condition and is associated with significant and increasing health care costs, especially in industrialized countries. Epidemiologic studies indicate that IBD incidence in a geographic region follows industrialization, and it has been speculated that a worldwide epidemic of IBD will emerge as developing nations diverge from agrarian lifestyles.^{E6} Remarkably, IBD was rare in North America and Europe until the latter half of the 20th century and now has a prevalence approaching approximately 1% in these regions.^{E7}

Although several genetic predispositions have been shown to influence the risk of IBD (eg, mutations in *NOD2/CARD15*, which are much less common in Asian patients with IBD than in white patients),^{E8} additional factors have also been implicated, including diet,^{E9} antibiotic use,^{E10} and microbial exposure.^{E11,E12} IBD has been shown to be associated with dysbiosis characterized by low species diversity and increased microbial densities at gut mucosal surfaces^{E13,E14}; however, it has been difficult to determine whether such changes in gut microbial communities are causative agents in the development of IBD or consequences of the disease itself. Nevertheless, the response to antibiotics in subsets of patients with IBD^{E15} and extensive data from germ-free animal studies investigating the role of gut microbes in the development of colitis highlight the importance of the microbiota in the pathogenesis of IBD.^{E6} It is possible that, through stratification of IBD-afflicted populations based on symptoms and histories,

distinct subsets of UC and CD can be identified in which modulation of the intestinal microbiota through dietary intervention, bacteriotherapy, or more targeted microbial approaches might bring about clinical remission that can be effectively maintained over time.

Gut microbiota in patients with IBD

The distal gut contains trillions of microbes that normally exist in a mutualistic relationship with the host, performing important functions, such as fermentation of certain dietary fibers and synthesis of essential vitamins. However, this beneficial relationship depends on intestinal homeostasis and a vigilant but not overactive mucosal immune system. The power of intestinal microbes to promote colitis has been convincingly demonstrated through observations that several genetically susceptible mouse and rat models that normally develop chronic colitis do not do so when reared in a completely germ-free (sterile) setting.^{E6} Evidence in human subjects is also available in 2 reports on patients who underwent ileocolonic resection for CD; it was found that recurrence of intestinal inflammation was dependent on exposure of the newly fashioned terminal ileum to fecal contents.^{E16,E17} However, we are still in the process of trying to understand how commensal and mutualistic constituents of the human gut microbiome maintain intestinal homeostasis and how deleterious microbes promote disease in different IBD variants.

It has been suggested that certain beneficial species (eg, *Faecalibacterium prausnitzii*, a normal member of the healthy gut microbiota) are associated with reduced severity of IBD symptoms, perhaps through production of secreted molecules with anti-inflammatory effects.^{E18} Reduced microbial diversity is observed in the gut microbiota of both patients with UC and those with CD compared with control subjects.^{E19,E20} In a subset of patients with IBD, the intestinal microbiota is characterized by a reduction in the relative abundance of the normally predominant phyla Firmicutes and Bacteroidetes, with a coordinate expansion of the phylum Proteobacteria^{E21}; however, there are no uniform changes characterizing specifically UC or CD. Although it is difficult to attribute microbial signatures to the subsets of IBD, species such as *F. prausnitzii* have been shown to be anti-inflammatory in patients with CD.^{E18} Interestingly, the gut microbiota of both patients with UC and those with CD exhibit significant differences in functional pathways and metabolic modules (eg, metabolism of the sulfur-containing amino acid cysteine) compared that of with healthy subjects, as imputed based on 16S rRNA-based composition and metabolic reconstruction from genomic databases.^{E22} Adherent-invasive strains of *Escherichia coli* and other members of the bacterial phylum Proteobacteria are increased in patients with ileal CD or other forms of IBD and might, in fact, be causative agents. Furthermore, adherent and invasive species within Proteobacteria, such as *Campylobacter concisus* isolated from patients with IBD, have been found to have distinctive genotypic and pathogenic characteristics, which might play a role in promoting IBD.^{E23} Additional studies are necessary to determine the relative importance of specific members of these phylogenetic clades in patients with UC and those with CD.

Diet and gut microbiota

Diet has been shown to have profound effects on the composition of the microbiota^{E24,E25} and thus might tip the balance in subjects at risk for IBD to promote the disease through the

inability to contain deleterious gut microbes (barrier function), through defective host immunoregulation, or both. It is tempting to hypothesize that the environmental factors and dietary alterations that coincide with industrialization have altered gut microbial ecology to enrich for deleterious Proteobacteria or other pathogens in a manner that might help explain the epidemiologic trends observed for IBD over the past few decades. A study of the enteric microbiota of 29 children from urban Florence (Italy) and rural Africa (Burkina Faso) found that the relative abundance of Proteobacteria was approximately 8-fold higher in Italian children compared with those from rural Africa (6.7% vs 0.8%, respectively). Of note, all 4 of the dominant bacterial phyla in the human gut were found to have significantly different abundances when comparing these urban versus rural populations.^{E26} High-fat diets enriched with omega-6 polyunsaturated fatty acids from safflower oil increase the relative abundance of Proteobacteria, Firmicutes, and Actinobacteria in the gut microbiota of rodent models, whereas the abundance of phylum Bacteroidetes is reduced.^{E27,E28} Consumption of safflower oil has been suggested to favor the growth of Deltaproteobacteria through an effect on gene expression for flagellar development and chemotaxis.^{E29} Interestingly, switching mice from a low-fat to a high-fat diet was shown to significantly increase the relative abundance of Gammaproteobacteria and Firmicutes, while decreasing the relative abundance of Bacteroidetes.^{E29}

Another diet-related environmental factor to explore in the epidemiology of IBD is antibiotic exposure, especially in developed countries. There is compelling epidemiologic evidence that antibiotic use is a risk factor for IBD.^{E30-E32} Administration of vancomycin in mice results in members of the Proteobacteria becoming much more prevalent in the gut. Furthermore, in an intensive study of a single patient who underwent a 14-day regimen of intravenous cefazolin, it was found that 40 days after the treatment, bacterial transcripts taxonomically assigned to Burkholderiaceae (another family within Proteobacteria) comprised nearly half of all fecal mRNAs detected in this subject.^{E33} It might be important to note that antibiotic sales to the meat industry in the United States are at all-time highs, with 13.7 million kg of antimicrobial agents being sold for use in food-producing animals in 2011 alone.^{E34} An interesting future study to address the effect of this on human health would be to examine the effect of antibiotic-treated meat products on gut microbiota.

Dietary factors in patients with IBD

Although anecdotal evidence suggests that consumption of specific foods can exacerbate IBD symptoms, self-reported food sensitivities can be quite variable among patients.^{E35} Enteral nutrition with elemental or defined formula diets have been found to be efficacious, primarily in patients with CD, and are associated with marked changes in the gut microbiome. Several dietary components considered part of "the Western diet" have been associated with IBD. A recent study reported that high consumption of total fat, polyunsaturated fats, omega-6 fatty acids, and meats was associated with an increased risk of both UC and CD, whereas consumption of dietary fiber and fruits was found to decrease the risk of CD, and increased vegetable consumption was associated with decreased risk of UC.^{E36} Consistent with this finding, another clinical study found that a semivegetarian diet was significantly more effective in maintaining remission from CD than an omnivorous diet.^{E37} A further study found that patients who

self-reported higher intake of meat (especially red and processed meat), eggs, protein, and alcohol were more likely to experience relapsing UC.^{E38} The authors suggested that dietary sulfur and sulfate could be important determinants of relapsing colitis. Indeed, sulfur-containing amino acids and other sulfur-containing compounds (eg, sulfate and sulfite) can shape the gut microbiota by favoring bacteria that use these compounds. Sulfur-reducing bacteria use sulfate or sulfite in anaerobic respiration and produce hydrogen sulfide, a compound that is also generated through bacterial metabolism of sulfurous amino acids. Although hydrogen sulfide concentrations have been found to be 3- to 4-fold higher in feces from patients with UC compared with those seen in control subjects,^{E39} a causative link between hydrogen sulfide and development of IBD has not been proved. Furthermore, many dietary compounds (eg, complex polysaccharides and fats) can be involved in increasing or decreasing the relative abundance of bacterial groups (including enteropathogens) in the gastrointestinal tract.

How can dietary interventions improve IBD?

Specific dietary components (milk fats) have been recently implicated in the expansion of pathogens that exacerbate colitis in mice. Devkota et al^{E40} demonstrated, in an *IL10*^{-/-} mouse model of colitis, that dietary intake of milk-derived saturated fat promoted expansion of a pathogenic, sulfite-reducing member of the Deltaproteobacteria, *Bilophila wadsworthia*, and significantly increased the severity of colitis in this model. Interestingly, when administered orally to germ-free mice, *B wadsworthia* did not colonize the gastrointestinal tract of mice unless the administered low-fat diet was supplemented with milk-derived saturated fat or taurine-conjugated bile acids, which are produced endogenously in response to consumed milk fats.^{E40} This study has provocative implications and suggests that dietary factors that differentially stimulate bile acid conjugation, secretion, or both might influence microbial community composition in a manner that observably alters colitis severity. Furthermore, it provides a logical scenario that could explain how specific dietary interventions in patients could bring about symptomatic improvement.

In migrants to Western countries it is plausible that dietary changes precipitate alteration of the gut microbiota that promotes IBD in genetically susceptible subjects. Agrarian diets common to South Asia are higher in fruits and vegetables than the Western diets commonly consumed in the United Kingdom and United States (Fig E1); however, on migration to these industrialized nations, increased meat and dairy consumption could lead to shifts in the relative abundance of microbial groups (eg, expansion of deleterious species or genera of Proteobacteria, as discussed above) that are differentially tolerated by migrant populations, depending on host genotype or other factors.

In cases of IBD in which pathogenic gut microbes might be playing a causative role, diet could affect disease onset, progression, and remission through the action of selective pressures that enable, maintain, or preclude colonization by specific microbial groups within the gut microbiome based on available nutrients and energetic substrates. It might be possible to individualize therapies for IBD based on patient genotype and gut microbial composition to lessen the severity of IBD symptoms or even to promote complete remission in certain patients.

On the basis of a recent genome-wide association study, more than 160 IBD loci meet genome-wide significance thresholds,

most of which contribute to both UC and CD.^{E41} The significant overlap between susceptibility loci for UC and CD and lack of discrete microbial signatures associated with either subset make it difficult to elucidate specific molecular pathways influenced by microbiota and diet in subsets of patients with IBD. There have been several studies identifying the role of individual genes (*NOD2* and *FUT2*) involved in IBD on the gut microbiota; however, more recently, a study of the effect of 30 different genes on gut microbial composition identified the *IRGM* autophagy gene to be associated with *Prevotella* species-dominated microbial communities.^{E42} With rapid advancement in sequencing technologies, future studies to understand diet-mediated microbial and immunologic mechanisms and their interaction with host genes involved in patients with IBD represent an important area of research and a potentially crucial aspect of future therapeutic modalities.

THE CASE REVISITED

The patient eliminated dairy, most refined sugar, pork, beef, and fried foods and restricted his diet to mostly vegetables, fruit, chicken, and fish. A year after his initial visit, he reported alleviation of most of his UC symptoms, with significant improvement in hematochezia and decrease in bowel frequency. He was having 2 to 3 semiformal bowel movements daily without blood. Colonoscopy showed mildly active pancolitis. At the next yearly follow-up, he reported having bloody stools, and colonoscopy showed moderately active pancolitis. He confessed to having reverted to red meat and dairy in his diet and believed this was a major contributor to his symptoms. Ten months later, after strict continuance of his restricted diet, he is doing well with 3 to 4 semiformal bowel movements daily and no unusual urgency, bleeding, or cramping. Although we have agreed to continue dietary restriction at this time, he understands that he might require more aggressive therapy in the future.

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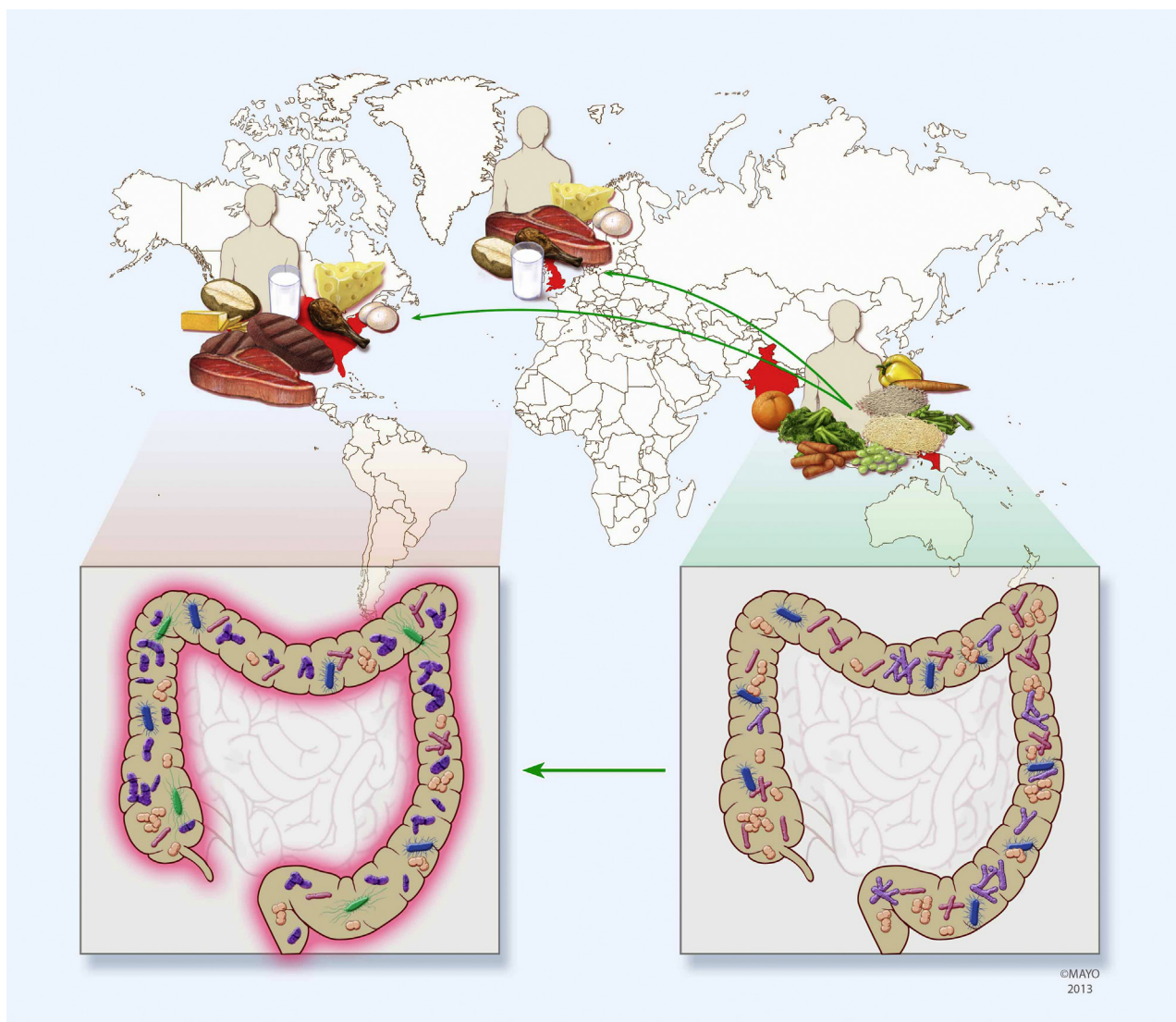


FIG E1. Change from an agrarian to a more Western diet in Asian migrants to the United Kingdom and the United States can alter the gut microbiota and in a genetically susceptible host can lead to development of IBD.