

ADVANCES IN IBS

Current Developments in the Treatment of Irritable Bowel Syndrome

Section Editor: William D. Chey, MD

Allergies and Irritable Bowel Syndrome



Nicholas J. Talley, AC, MD, PhD
Laureate Professor
Pro Vice-Chancellor
University of Newcastle
Newcastle, New South Wales, Australia

G&H What is currently understood about the connection between allergies and irritable bowel syndrome?

NT Epidemiologic studies suggest an etiopathogenic link between atopic diseases, such as asthma and eczema, and functional gastrointestinal disorders, particularly irritable bowel syndrome (IBS) and functional dyspepsia. These studies build on the previously recognized relationship between asthma and gastroesophageal reflux disease, the latter of which overlaps with IBS and functional dyspepsia. Supporting an atopic disease process is emerging evidence that food antigens (eg, wheat proteins) may drive small intestinal pathologic alterations such as increased intestinal permeability and tissue eosinophilia in patients with IBS and functional dyspepsia. The immune system may play a critical role in functional gastrointestinal disorders, as further demonstrated by circulating small intestinal homing T cells and the release of cytokines in both IBS and functional dyspepsia that may influence the brain (ie, immune-driven gut-brain disorders). Interestingly, there is an increased risk of autoimmune diseases in patients with functional gastrointestinal disorders. This finding has been replicated in 2 large epidemiologic studies and further supports the concept that a subset of patients with IBS or functional dyspepsia has immune activation.

G&H What is the role of mast cells in the pathogenesis of IBS?

NT This is a controversial area. Although meta-analyses and individual studies have reported an increase in mast cells among a subset of patients with IBS (particularly diarrhea-predominant IBS [IBS-D]), a number of studies have failed to identify such an increase. It is unclear whether this difference in findings is a result of methodologic limitations, geographic distribution of disease, or varying risk factors for disease. However, it is reasonable to conclude that there are some IBS patients who have increased intestinal mast cells. My colleagues and I have demonstrated increased mast cells in the small intestine in patients with IBS, but most of the work has focused on the colon, with inconsistent findings. Of note, both mast cells and the microbiome can release histamine, and there is intriguing new evidence that blocking histamine in IBS may be an efficacious therapy for some patients. If this evidence can be replicated, it will be very important in terms of treatment options for patients in the future. Currently, more research is needed to determine whether mast cells or other producers of histamine are relevant in IBS.

G&H How common are food allergies among patients with IBS?

NT True immunoglobulin (Ig) E-mediated food allergies are rare in patients with IBS, although they can occur. However, food is implicated in inducing symptoms in patients with IBS or functional dyspepsia, as symptoms frequently occur postprandially. A group from Germany

published results of a recent study that followed up their research from 5 years ago; they found that when food antigens, such as wheat proteins, are placed onto the duodenal mucosa in patients with IBS, acute changes can often be induced with increased permeability and acute eosinophilia observed by confocal endoscopy. This finding strongly suggests that an atypical food allergy process that is not IgE-mediated may be key in a major subgroup of patients with IBS. It is an important observation because the study further demonstrates the significance of specific foods in IBS, or at least in a subset of IBS, in driving immune-activation processes.

G&H Should patients with IBS be referred to an allergist?

NT Referral to an allergist is generally not beneficial. Allergists are helpful for identifying true IgE-mediated food allergies, which patients with IBS and functional dyspepsia tend not to have. However, that does not mean that a food allergen is not driving the disease. Standard allergen skin tests or the radioallergosorbent test (RAST) are unlikely to provide useful information and may even lead to false-positive information. Therefore, I do not routinely send my patients with functional gastrointestinal symptoms to an allergist unless I suspect a true food allergy or if my patient has another disease process such as eosinophilic gastroenteritis.

G&H Which foods are most likely to induce symptoms of IBS?

NT Fermentable carbohydrates can induce symptoms; thus, a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) can help patients with IBS, particularly those with IBS-D or mixed IBS and occasionally those with constipation-predominant IBS (IBS-C). Randomized trials suggest that 50% to 70% of IBS patients benefit from a low-FODMAP diet if they are able to tolerate it. Importantly, the low-FODMAP diet is not intended for long-term management. Rather, patients should start the diet for 2 to 4 weeks, then reintroduce various food groups in order to determine which food groups are not tolerated and should be removed from the final diet. According to the aforementioned German data, wheat proteins can also potentially induce not just fermentation but pathologic processes in the small intestine. More research in this area is needed, but the results thus far appear highly relevant. In the setting of wheat intolerance, a gluten-free diet may work. Another syndrome called nonceliac wheat sensitivity overlaps with IBS and functional dyspepsia. Patients with true nonceliac wheat sensitivity may have duodenal

eosinophilia, and if wheat is eliminated from their diet, they find that their symptoms improve significantly. However, the majority of patients who believe they are

... dietary approaches, rather than pharmacologic therapy, remain the best first-line treatment to try to manage mild to moderate IBS.

wheat intolerant are not actually sensitive to wheat on objective, double-blind, food-challenge testing.

G&H Are certain subtypes of IBS more likely to be associated with specific allergies?

NT Most of the data suggest that IBS-D may be linked to food allergens, whereas IBS-C may have a different pathogenesis.

G&H How are food allergies or sensitivities diagnosed?

NT Diagnosing food allergies or sensitivities in this patient population is challenging. There are no reliable clinical tests for identifying food allergies in patients with IBS. Standard allergy tests, including the RAST and the skin antigen test, are not useful. IgG food testing panels are of very uncertain value. Experimentally, the small intestinal mucosa can be exposed to food antigens and increased permeability can be directly observed through a confocal endoscope, but that is not a clinical tool. Clinicians currently rely on patient history and food elimination diets, the latter of which are insufficient because not everybody has a food-induced syndrome or responds quickly to food elimination and rechallenge.

G&H How can IBS patients with allergies manage their symptoms?

NT There is currently a lack of established options for managing symptoms, although it may be possible to intervene pharmacologically. Prescribing an antihistamine may be helpful, but other pharmacologic methods remain experimental. The primary method is dietary therapy, which is best handled by guidance from an

expert nutritionist who understands the field. Both the low-FODMAP and gluten-free diet trials need careful interpretation because, for example, a positive response to wheat withdrawal will often occur in people who are not gluten intolerant. Regardless, dietary approaches, rather than pharmacologic therapy, remain the best first-line treatment to try to manage mild to moderate IBS.

G&H Are pediatric and adult populations affected similarly?

NT Although more pediatric studies are needed, it does appear that the same mechanisms apply to both patient populations. If the atopic theory is correct, that is, if a subset of patients with IBS or functional dyspepsia have atopy, and because atopic diseases are increasing, it is likely that the burden of illness of functional gastrointestinal disorders will also increase over time. This is an area that needs more research but represents an interesting hypothesis.

G&H What other research is needed in this area?

NT One of the major gaps in the field is the lack of reliable diagnostic tests or biomarkers that can identify which patients have a food-induced syndrome and determine which specific food elimination would be beneficial. Further studies are needed to assess the connection between food, IBS, and immune activation, which could provide insights into mechanisms and new approaches to treatment. If treatments can switch off intestinal immune activation in patients with IBS or functional dyspepsia, assuming this is a key mechanism, then a cure is possible.

Dr Talley has received personal fees from Allergan PLC, Viscera Labs, IM HealthScience, Napo Pharmaceuticals,

Outpost Medicine, Progenity, Allakos, Samsung Bioepis, Synergy Pharmaceuticals, Takeda, Theravance, GI Therapies, Cadila Pharmaceuticals, Planet Innovation, Danone, Pfizer, Dr Reddy's Laboratories, Ardelyx, and Sanofi. He has also received grants from Viscera USA, Commonwealth Diagnostics International, and GI Therapies as well as nonfinancial support from HVN National Science Challenge NZ. He is a patent holder for IBS biomarkers, licensing questionnaires (Mayo Clinic Talley Bowel Disease Questionnaire and Mayo Dysphagia Questionnaire), a Nestec European patent, and a Singapore provisional patent ("Microbiota Modulation of BDNF Tissue Repair Pathway").

Suggested Reading

Burns G, Carroll G, Mathe A, et al. Evidence for local and systemic immune activation in functional dyspepsia and the irritable bowel syndrome: a systematic review. *Am J Gastroenterol*. 2019;114(3):429-436.

De Giorgio R, Volta U, Gibson PR. Sensitivity to wheat, gluten and FODMAPs in IBS: facts or fiction? *Gut*. 2016;65(1):169-178.

Fritscher-Ravens A, Pflaum T, Mösinger M, et al. Many patients with irritable bowel syndrome have atypical food allergies not associated with immunoglobulin E. *Gastroenterology*. 2019;157(1):109-118.e5.

Halmos EP, Power VA, Shepherd SJ, Gibson PR, Muir JG. A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. *Gastroenterology*. 2014;146(1):67-75.e5.

Koloski N, Jones M, Walker MM, et al. Population based study: atopy and autoimmune diseases are associated with functional dyspepsia and irritable bowel syndrome, independent of psychological distress. *Aliment Pharmacol Ther*. 2019;49(5):546-555.

Potter MDE, Walker MM, Keely S, Talley NJ. What's in a name? 'Non-coeliac gluten or wheat sensitivity': controversies and mechanisms related to wheat and gluten causing gastrointestinal symptoms or disease. *Gut*. 2018;67(12):2073-2077.

Robles A, Perez Ingles D, Myneedu K, et al. Mast cells are increased in the small intestinal mucosa of patients with irritable bowel syndrome: a systematic review and meta-analysis [published online September 9, 2019]. *Neurogastroenterol Motil*. doi:10.1111/nmo.13718.

Wouters MM, Balemans D, Van Wanrooy S, et al. Histamine receptor H1-mediated sensitization of TRPV1 mediates visceral hypersensitivity and symptoms in patients with irritable bowel syndrome. *Gastroenterology*. 2016;150(4):875-887.e9.