CLINICAL UPDATE

Mechanisms of Inflammatory Bowel Disease

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G&H What differentiates Crohn's disease from ulcerative colitis?

RP Crohn's disease (CD) and ulcerative colitis (UC), the most common subtypes of inflammatory bowel disease (IBD), can be differentiated based on their clinical presentation (including disease location and symptoms) as well as their histopathology. CD can affect any portion of the gastrointestinal tract, although its presentation occurs primarily in the ileum. In contrast, UC is limited to the colon and the rectum. CD is associated with full-thickness inflammation (ie, the inflammation is transmural, involving all the tissue layers of the gastrointestinal lining). The inflammation associated with UC is limited to the mucosal layer of colonic tissue.

The symptoms that arise with each form of IBD are predominantly related to the location and severity of the disease. Symptoms of CD include diarrhea, abdominal pain, weight loss, fever, rectal bleeding, perianal disease, signs of malnutrition, abdominal mass, and growth failure in children and adolescents. Potential complications of CD include bowel obstruction and interpenetrating disease (stricture), perforation, fistula, and abscess. In contrast, the hallmark symptom of UC is bloody diarrhea. The other symptoms of UC are similar to those of CD and may include abdominal pain, weight loss, fever, anemia, rectal bleeding, and signs of malnutrition. Complications that may arise from UC include perforated bowel and toxic megacolon. Both CD and UC are associated with an increased risk of colorectal cancer. In both cases, the risk of colorectal cancer is related to disease duration as well as the length of colon involved.

G&H What is the economic burden of IBD?

RP A significant financial burden is associated with both CD and UC. The direct costs related to IBD in the United States are estimated to be approximately $5.2 billion, with CD costing $3.1 billion and UC costing $2.1 billion. These direct costs are comprised of inpatient costs (including medical and surgical care), outpatient costs (such as emergency room and doctor's office visits and workup such as endoscopy and laboratory, pathology, and radiology examinations), and medication costs. Other indirect costs of IBD are estimated to add an additional $5.5 billion in the United States. In addition to these quantifiable economic costs, other costs contribute to the significant economic burden of IBD, such as short-term disability and losses in productivity due to absenteeism.

G&H What noneconomic costs are associated with IBD?

RP Numerous other clinical and social challenges arise from IBD, some of which may not be fully appreciated by all clinicians. In a recent European survey of patients with IBD, approximately 75% of respondents reported that their symptoms affected their ability to enjoy leisure activities, and 69% stated that their symptoms affected their performance at work. Results from 2 Canadian surveys showed that adult patients with IBD had higher rates of depression compared with the general public, an association not known to be related to the disease, disease-related inflammation and pain, or some other known factor. In the same survey, younger patients showed delayed puberty and body image issues.

Children and adolescents also showed social awkwardness due to disease symptoms and medication side effects.

G&H What are the therapeutic options for treatment of IBD?

RP The therapeutic armamentarium for IBD can be divided into 6 classes of drugs. Despite the fact that aminosalicylates have been used to manage IBD for decades, their mechanism of action in this setting remains unclear. Antidiarrheal therapy results in reduced gut motility. Antibiotics can be used in IBD to control luminal bacteria. Corticosteroids target glucocorticoid receptors, whereas immunomodulators target purine biosynthesis and cell proliferation. Also available for IBD treatment are a number of biologic therapies that target either the tumor necrosis factor α (TNF-α) molecule or α4 integrins.

Several of the classes of drugs used in the treatment of IBD are associated with safety profiles that must be carefully weighed by both the treating physician and the patient prior to beginning therapy. For example, both corticosteroids and immunomodulators are associated with an increased risk of infection as well as bone mass loss (corticosteroids) or reduced white blood cells (immunomodulators). Safety concerns with biologic agents include an increased risk of infection (including tuberculosis) as well as an increase in the risk of lymphoma development—a particularly concerning risk for many patients.

G&H What other management strategies can be used in patients with IBD?

RP One of the first questions that many patients with newly diagnosed IBD often ask is whether they should alter their diet. Unfortunately, the answer is not straightforward, as no single diet or eating plan works for every patient (or even large numbers of patients). Instead, patients are generally advised to follow a normal, healthy diet as tolerated. However, patients can be advised to avoid certain foods during symptom flares in order to alleviate diarrhea and cramping. These foods include fresh fruit; raw vegetables; foods high in fiber, fat, or sugar; and food or drinks containing caffeine. In addition, many patients prefer to consume smaller, more frequent meals and may benefit from a daily multivitamin/mineral complex. During flares, oral liquid supplements may be used as a nutritional supplement; in severe cases, enteral tube feeding or parenteral nutrition may become necessary.

G&H How often do patients with IBD relapse?

RP Approximately half of patients with UC experience a relapse in any year. The vast majority of patients with CD (70–80%) will go on to require surgery at some point in their lifetime. However, as a study by Olaison and colleagues demonstrated, patients typically experience recurrent inflammation even after surgery. In this study, recurrent inflammation occurred 3 months after surgery in 73% of patients, increasing to 93% of patients 1 year postsurgery.

G&H Thus far, what has been elucidated regarding the causes of IBD?

RP It has been established for many years that there is a genetic predisposition for the development of IBD. However, the role of genetics in IBD pathogenesis is highly complex, demonstrated by the fact that over 100 potential susceptibility genes have been identified thus far. Some of these genes are involved in immune system recognition of bacteria (eg, *NOD2*). Other identified genes (such as *ATG16L1*) are important in autophagy, a catabolic form of cellular degradation.

A genetic predisposition to IBD is not sufficient to explain the majority of IBD cases, leading researchers to investigate other factors that are important for disease development. Environmental triggers may act as foreign antigens, causing the body to mount an immune response resulting in an influx of inflammatory cells that damage the gastrointestinal mucosa. Once inflammation is triggered, the immune system of a patient with IBD has difficulty turning off its immune response, perhaps due to genetic aberrations.

G&H What risk factors have been identified for IBD?

RP Several risk factors have now been identified that increase an individual's likelihood of developing IBD. Age is one such risk factor, as IBD is more likely to occur in younger patients. Another risk factor is ethnicity, as IBD is more likely to present in whites, particularly Ashkenazi Jews. In addition, IBD is most common in the United States and Europe, compared with other regions of the world. Another risk factor is family history; studies have shown that the risk of IBD is increased 10–30-fold among individuals with a close relative with the disease. Smoking has also been identified as an important risk factor in IBD, with active smokers being more than twice as likely to develop CD compared with nonsmokers. Interestingly, this risk does not appear to extend to UC, as the data thus far show a decreased risk of UC in active smokers.

G&H What is the role of TNF-α in both normal and disease pathology?

RP TNF-α is a key player in the inflammatory process underlying IBD. It is a pleiotropic, proinflammatory

cytokine that regulates essential biologic functions such as cell survival, proliferation, differentiation, and apoptosis. In addition, TNF-α mediates the local inflammatory immune response as well as induces the expression of other proinflammatory cytokines and chemokines. Due to TNF-α's broad actions and important functions in the development of diseases, it has been targeted for inhibition in several diseases (ankylosing spondylitis, psoriasis, psoriatic arthritis, and rheumatoid arthritis) in addition to UC and CD.

G&H What characteristics of the gastrointestinal tract make it susceptible to the development of IBD?

RP Faced with constant exposure to foodstuffs, bacteria and other microbes, and antigens from the environment, the gastrointestinal tract encounters more antigens than any other tissue in the body. Thus, the gastrointestinal tract is a very tightly regulated environment to ensure that it reacts appropriately to these signals. When this regulation is hampered, such as in IBD, the ensuing heightened immune responses can have dramatically negative influences on the intestinal environment.

Normal gut host immune defenses begin with a mucus barrier, which serves not only as a physical barrier but also as a chemical barrier to human antigens. The gastrointestinal epithelium acts as a further structural barrier. The lamina propria is populated with nonepithelial inflammatory cells such as lymphocytes, macrophages, and dendritic cells (antigen-presenting cells); this last group of cells is becoming increasingly appreciated as having a specialized function to sense changes in the lumen and then present these changes to the lymphocytes located in the lamina propria. In IBD, for example, these dendritic cells can sample abnormal luminal bacteria and present the antigen to the lymphocytes. The resulting lymphocyte stimulation causes the release of proinflammatory cytokines, including TNF-α and interleukins. Although these cytokines have a myriad of actions, perhaps the most important one for the formation of IBD is an increase in adhesion molecule expression on the vascular endothelium, which attracts more inflammatory cells as well as increased vascular permeability.

G&H How is lymphocyte trafficking altered in IBD?

RP The accumulation of excess infiltrating lymphocytes is a hallmark of IBD pathogenesis. Lymphocyte recruitment is a typical response even in normal individuals. For example, it occurs in gastroenteritis, when patients experience symptoms of inflammation in response to a luminal pathogen. In nor-

mal individuals, this response is tightly regulated and halted naturally. However, in cases of IBD, this response is instead manifested as an inappropriate and sustained recruitment of inflammatory T cells in cases of infection or inflammation, ultimately resulting in tissue damage.

Lymphocyte infiltration and migration are made possible by the presence of tissue-specific adhesion molecules as well as integrins. Several of these adhesion molecules have now been identified, including ICAM-1, ICAM-2, VCAM-1, and MAdCAM-1.

G&H Could you describe the mechanism of lymphocyte trafficking in greater detail?

RP Lymphocytes are migratory cells that traffic to specific tissues as needed. An intricate system exists to guide lymphocytes to areas of inflammation within these tissues. As lymphocytes travel through the body, they encounter antigens in specific tissues and become activated. The activated lymphocytes then undergo a type of imprinting, which allows for preferential migration into the tissue. If this imprinting occurs in the gut, the lymphocytes will migrate into the gut.

Lymphocyte trafficking requires a multistep adhesion cascade mediated by adhesion molecules and integrin molecules. As lymphocytes encounter the endothelial surface, they become tethered, a step that is modulated by the adhesion molecules on the lymphocyte surface. The next step is rolling, which is again modulated by the adhesion molecules on the surface of the lymphocyte. This triggers the lymphocytes to express other receptors that respond to signal molecules expressed or secreted by the endothelial cells. When this happens, the signal leads to rapid activation of integrins, which allows the lymphocyte to infiltrate into the tissue to cause inflammation.

A number of molecules have been found to be involved in the multistep lymphocyte trafficking/adhesion cascade. However, only a few of these are responsible for gut specificity. Among these are the CCR9 chemokine receptor and its ligand CCL25, as well as α4β7 integrin and its ligand MAdCAM-1.

G&H What is the role of chemokines in IBD?

RP Chemokines are a family of small proteins that play an important role in the recruitment and activation of lymphocytes. The biologic effects of chemokines result from binding to the chemokine receptors. Several chemokines and their receptors play a role in the homeostasis of mucosal immunity and the pathogenesis of IBD. Some examples include the CCR6 chemokine receptor and its ligand CCL20, the CCR9 chemokine receptor and its ligand CCL25 (as described above), and the CCR10 receptor and its ligand CCL28.

G&H What is known about the role of the α4β7 integrin and its ligand MAdCAM-1 in IBD?

RP Mounting evidence continues to point to the α4β7 integrin playing an important role in IBD pathogenesis. Specifically, interactions between the α4β7 integrin and its ligand MAdCAM-1 likely mediate selective lymphocyte trafficking to normal gastrointestinal mucosa and other gut-associated tissues. In a study by Briskin and colleagues, MAdCAM-1 was shown to be expressed in the gut mucosa and gut-associated lymphoid tissue. Furthermore, MAdCAM-1 expression is increased at sites of IBD-related inflammation. Overall, it is hypothesized that the adhesion mechanism between the α4β7 integrin and MAdCAM-1 may be closely involved in lymphocyte trafficking to the site of gut inflammation.

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Suggested Reading

Olaison G, Smedh K, Sjödahl R. Natural course of Crohn's disease after ileocolic resection: endoscopically visualized ileal ulcers preceding symptoms. *Gut.* 1992;33(3):331-335.

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of infectious esophagitis in a patient with AIDS who is not on antiretroviral therapy is essentially 100%. As immunosuppressive therapy is reduced, the likelihood of infection, and thus the recurrence rate of infectious esophagitis, falls.

G&H Does the presence of infectious esophagitis increase the risk of other esophageal disorders or complications?

CMW Not specifically. If a patient has severe ulceration in the esophagus, an esophageal stricture that requires treatment may develop. However, this does not generally happen, unlike in reflux esophagitis, in which patients may be predisposed to Barrett esophagus. Once the lesions caused by infectious esophagitis are healed, there are usually no sequelae.

G&H What are the next steps in research in this area?

CMW Most of the research currently being conducted in this area is centered on determining which patients are at risk for development of infections and determining the best prophylactic antimicrobial treatments and when to apply them. There are several ongoing studies looking at cytomegalovirus and how long before or after transplantation antimicrobial therapy should be administered. There is not as much research on the pathogenesis of infectious esophagitis compared with research on antimicrobial therapy.

Dr. Wilcox has no conflicts of interest to disclose.

Suggested Reading

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