

Current perspectives

Prototypic disorders of gastrointestinal mucosal immune function: Celiac disease and Crohn's disease

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Celiac disease is a disorder of the small intestine characterized by chronic inflammation of the mucosa and protean clinical manifestations caused by loss of tolerance to dietary antigens. Two strongly associated cofactors have been identified: the presence of HLA-DQ2 or HLA-DQ8 in the host and specific antigenic peptides in the diet that are present in wheat, rye, and barley. Most patients have complete remission after dietary elimination of these foods. Crohn's disease is characterized by chronic, relapsing, recurrent, focal, transmural inflammation of the gastrointestinal tract that can lead to multiple serious problems requiring chronic medical and surgical therapy. Crohn's disease is associated with multiple genetic mutations, at least one of which has been clearly implicated in innate immunity. Multiple lines of evidence suggest that the disease involves abnormal immune responses to gut microbial flora. (J Allergy Clin Immunol 2005;115:25-30.)

Key words: Celiac disease, Crohn's disease, mucosal immunity, tolerance

OVERVIEW

The mucosal immune system of the gastrointestinal tract provides the host with mechanisms to protect itself against invasion by potential pathogens and at the same time permits tolerance for potentially immunogenic products of digestion and the resident normal intestinal microbial flora. A number of important disorders of the gastrointestinal mucosa involve disturbances of these fundamental immunologic mechanisms. This article will describe 2 diseases for which there has been significant research progress in understanding pathogenic mechanisms: celiac disease, which is characterized by loss of tolerance to specific dietary peptides, and Crohn's disease,

Abbreviation used

NF- κ B: Nuclear factor κ B

which might represent a complex disorder of innate immunity involving abnormal immune responses to gut microflora.

CELIAC DISEASE

Background

Celiac disease is a disorder of the small intestine characterized by chronic inflammation of the mucosa, which leads to atrophy of the intestinal villi, malabsorption, and protean clinical manifestations.¹ It is also strongly associated with the skin disorder dermatitis herpetiformis. Both the major host genetic and immunologic risk factor, the presence of HLA-DQ2 and HLA-DQ8, and the necessary environmental factors, peptides in the diet that are present in wheat, rye, and barley, have been identified. Most patients have complete remission after dietary elimination of these foods.

The disease is restricted to populations having HLA-DQ2 or HLA-DQ8 phenotypes, which are commonly found in white European subjects and in North African, Indian, North American, and admixed populations, such as African Americans, but not in Asian populations. The estimated prevalence is approximately 1% of the population of Europe and North America,^{2,3} but the majority of cases are undiagnosed at the present time. The onset of disease varies from early childhood through old age. The classical sprue syndrome, consisting of vomiting, steatorrhea, and failure to thrive in infants and young children, is now uncommon for unknown reasons, and increasingly, patients are given diagnoses in adult life with diarrhea, weight loss, abdominal discomfort, and symptoms compatible with functional bowel disease, fatigue, nutritional deficiencies, anemia, osteoporosis, or other less common manifestations, such as infertility, psychiatric syndromes, and neurologic disorders. Virtually all patients with the skin disease dermatitis herpetiformis have celiac disease, although the bowel disease is often mild or asymptomatic. The prevalence of autoimmune disorders, particularly

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type 1 diabetes, is increased in patients with celiac disease. Approximately 3% to 8% of patients with type 1 diabetes have celiac disease. The frequency of IgA deficiency is also increased in patients with celiac disease, which occasionally might decrease the utility of IgA-based diagnostic tests. Patients with long-standing untreated celiac disease have a significantly increased relative risk of non-Hodgkins lymphoma of the gastrointestinal tract.

Pathogenesis

Celiac disease is a highly genetically determined disease, with the major genetic factor being the expression of specific HLA-DQ alleles.⁴ About 95% of patients have HLA-DQ2, which might be encoded by DQA1*0501 and DQB1*0201 in cis in patients with the DR3-DQ2 haplotype or in trans by DQA1*0501 and DQB1*0202 in patients with the DR5-DQ7/DR7-DQ2 haplotype. A small percentage of patients have DQA1*0301 and DQB1*0302 in the HLA-DQ8 haplotype. These specific HLA-DQ heterodimers have the capacity to bind the specific gliadin peptides that have been implicated in celiac disease.^{5,6} Less than 1% of patients with celiac disease do not have one of these HLA phenotypes. These haplotypes are common in white European populations, but less than 1% of patients with these haplotypes have celiac disease. Thus other unidentified genetic and environmental factors are critical for expression of the disease.

The major site of tissue injury in celiac disease is the proximal small intestine (Fig 1). The gross appearance of the small bowel is normal in most cases. Small bowel biopsy is the gold standard for diagnosis. The mucosa is expanded by increased numbers of lymphoid cells both in the intraepithelial compartment, in which there is an increase in $\gamma\delta$ T cells, and in the lamina propria, which is expanded by lymphocytes and plasma cells. The intestinal crypts are elongated because of an increase in dividing epithelial cells, and villi are shortened or even completely absent because of rapid loss of mature epithelial cells from the villus tip. The cytokine profile of T cells is characterized by a strong T_H1 bias. Intestinal epithelial cells have increased expression of IL-15, which might serve as a trophic factor for intraepithelial lymphocytes and play a role in the development of intestinal lymphoma.

Unlike many immunologically mediated diseases, the critical environmental antigens that cause celiac disease have been identified, namely specific peptide sequences present in proteins found in wheat, rye, and barley grains.⁷ Molecular modeling indicates that dominant antigenic gluten peptides bind HLA-DQA1*0501/B1*0201, and *in vitro* these peptides stimulate T cells from patients with celiac disease.^{8,9} In addition, patients with celiac disease commonly have serum IgG and IgA anti-gliadin antibodies. Thus the disease is characterized by a loss of oral tolerance. Despite the presence of both T-cell and antibody reactivity to dietary peptides, it is unclear whether this immunologic reactivity directly causes injury to the mucosa or whether the injury is a bystander event caused

by this reactivity. Anti-gliadin antibodies are not necessary for disease pathogenesis because some patients with well-defined celiac disease do not have these antibodies. Patients with celiac disease usually have tissue autoantibodies. The best characterized autoantibody detected by means of tissue immunofluorescence, anti-endomyseal antibody, is directed against a specific antigen identified as tissue transglutaminase. This ubiquitous enzyme is of uncertain significance in the disease pathogenesis, other than the interesting observation that gliadin peptides can be a substrate for the enzyme, and interestingly, deglutamination of gliadin by tissue transglutaminase increases its antigenicity by increasing the binding avidity for HLA-DQ2.¹⁰

Diagnosis

The diagnosis of celiac disease is established by means of serologic screening tests accompanied by biopsy of the small intestine and confirmation of a clinical response to gluten elimination from the diet (Table I).¹¹ Tests for the HLA-DQ alleles potentially serve an adjunctive role. The best single measure for screening is IgA anti-recombinant human tissue transglutaminase, measured by means of ELISA, which has high sensitivity and specificity for celiac disease. As indicated above, the concurrent presence of IgA deficiency might lead to false-negative IgA-based serologic test results for celiac disease. Serologic screening for this disease in the asymptomatic general population is not recommended in the United States because of the low prevalence of the disease.¹¹ Anti-gliadin antibodies are present in 80% to 90% of patients but should not be used for screening in adults because of a high false-positive rate. Because of the lifelong treatment requirement for significant dietary restrictions, the diagnosis should always be confirmed by means of biopsy of the small intestine, the gold standard for diagnosis. Although previously a follow-up small biopsy demonstrating resolution of histologic abnormalities was required for diagnosis, this is no longer recommended when all features are typical of the disease and there is clinical resolution of any abnormalities with a gluten-free diet. A clinical trial of a gluten-free diet as an alternative to small bowel biopsy is not recommended because improvement in symptoms is not specific, and the requirement for therapy is life long. Because the histologic abnormalities of celiac disease might resolve completely with a long-standing gluten-free diet, biopsy might not be diagnostic in patients who have already been treated with a gluten-free diet. In addition, autoantibody titers decrease and might become negative with prolonged treatment. Some patients have wheat allergy without other features of celiac disease, and this condition is distinctly different from celiac disease. HLA testing might have utility in screening family members of patients with celiac disease because the absence of HLA-DQ2/8 largely excludes the possibility of celiac disease. Patients with celiac disease might have multiple nutritional deficiencies; nutritional testing does

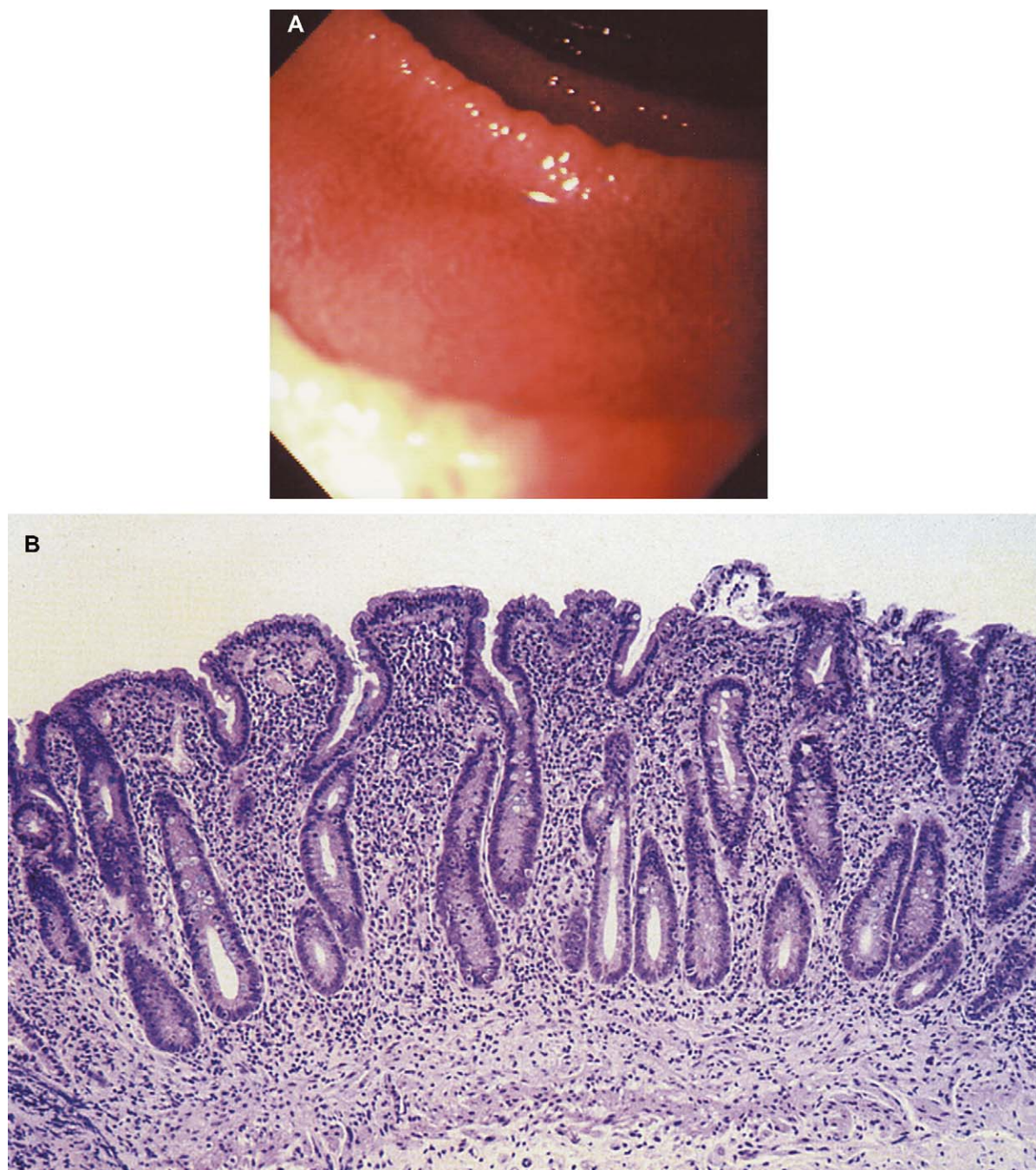


FIG 1. **A**, The endoscopic appearance of scalloped folds in celiac disease. Reprinted with permission from: Dickey W. Serology and endoscopy in coeliac disease: applications and limitations [thesis]. Londonderry, Northern Ireland: Altnagelvin Area Hospital, 2000. **B**, A small bowel biopsy specimen of subtotal villous atrophy in celiac disease. Reprinted with permission from: Wahab PJ. Celiac disease: more than villous atrophy [thesis]. Arnhem, The Netherlands: Rijnstate Hospital; 2002.

not have diagnostic specificity but might be important for clinical monitoring and replacement therapy.

Treatment

The treatment for celiac disease is life-long elimination of wheat, rye, and barley from the diet. Oats appear to be

safe. Maintenance of this diet can be difficult in Western societies, where use of gluten in processed foods is common. Assistance in maintaining a gluten-free diet and in obtaining gluten-free foods can be obtained from multiple patient-oriented organizations. Because of the significant association of non-Hodgkins lymphoma with

TABLE I. Salient features of celiac disease and Crohn's disease

	Celiac disease	Crohn's disease
Clinical features	• Asymptomatic most common • Gastrointestinal symptoms less common • Symptoms of nutritional deficiencies • Dermatitis herpetiformis • Growth retardation in children • Numerous associated conditions	• Focal, transmural granulomatous inflammation of any site in the gastrointestinal tract • Symptoms depend on location: nausea, vomiting, abdominal pain, diarrhea, bleeding • Physical findings: abdominal mass or tenderness, fistulae, growth retardation in children
Cause	• Immune-mediated small bowel damage in HLA-DQ2 or HLA-DQ8 individuals caused by specific peptides in dietary wheat, rye, and barley	• <i>Card15</i> mutations in some patients • Multiple hypotheses, including immune hyperreactivity to microbial flora
Diagnosis	• IgA anti-tissue transglutaminase • Confirmatory small bowel biopsy required	• Typical endoscopic or radiographic appearance • Compatible endoscopic biopsy • Exclusion of conditions that mimic (eg, infection, neoplasm, ulcerative colitis)
Management	• Life-long gluten-free diet • Repletion of nutritional deficiencies	• ASA preparations • Corticosteroids • Azathioprine, 6-mercaptopurine, or methotrexate • Infliximab • Surgical resection

ASA, Aminosalicilic acid.

untreated celiac disease, the addition of occasional amounts of gluten to the diet or after a long period of remission cannot be safely recommended. There are no clear treatment recommendations for patients with some features of celiac disease, such as tissue transglutaminase seropositivity with minimal histologic abnormalities. Additional nutritional supplementation might be required initially for specific deficiencies, such as iron or vitamin deficiency. In relatively uncommon refractory cases, other treatment approaches have been used, such as parenteral nutritional support, corticosteroids, and use of immunosuppressive agents, such as azathioprine, 6-mercaptopurine, or infliximab.

CROHN'S DISEASE

Background

Crohn's disease is a syndrome of unknown cause characterized by chronic, recurrent, focal, transmural inflammation of the gastrointestinal tract in any location but most typically in the terminal ileum, colon, and small intestine. The disease typically has a relapsing and remitting course that could lead to multiple serious symptoms and complications, including strictures, perforation, and fistulae, which frequently require surgical therapy in addition to medical management.¹²

The disease is found most commonly in developed countries, where there were rapid increases in prevalence during the 20th century. The estimated prevalence is 20 to 40 per 100,000. The relative risk of Crohn's disease is higher in smokers, and the incidence is higher in women who use oral contraceptives, but other specific environmental risk factors have not been identified. There is a

strong familial tendency, multiple genetic loci have been identified by means of linkage analysis of familial Crohn's disease, and the disease is more prevalent in certain ethnic groups, particularly Ashkenazi Jews. The onset typically begins in teenagers and young adults, but onset at any age can occur. The sex ratio is nearly equal.

Typical symptoms of Crohn's disease include diarrhea, abdominal pain, fatigue, weight loss, rectal pain, hematochezia, fever, growth failure in children, nausea, vomiting, dyspepsia, arthralgias, skin lesions (pyoderma gangrenosum), aphthous mouth ulcers, visual changes (iritis), and, rarely, jaundice. The physical findings in milder forms of Crohn's disease might be normal, but with more severe disease, there might be abdominal tenderness, abdominal masses, perianal or abdominal fistulae, or mouth ulcers. Common extraintestinal manifestations include iritis and uveitis, erythema nodosum, and swelling and tenderness of joints; many other manifestations are observed less frequently. Routine laboratory studies might show nonspecific abnormalities, such as anemia, a high sedimentation rate, or abnormalities of hepatic function, suggesting the possibility of associated liver disease. The characteristic features of the disease are best visualized by means of endoscopy or radiographic imaging studies.

Pathogenesis

Multiple lines of evidence suggest that the disease is the result of an abnormal interaction between multiple host susceptibility genes, the mucosal immune system, and the gastrointestinal epithelium with the environment, particularly the microbial environment in the gut. Although there is no animal model that faithfully replicates all features of the human condition, a great deal has been

learned from animal models.¹³ Remarkably, multiple murine genetic knockout strains, such as IL-2-, IL-10-, or T-cell receptor-deficient animals, spontaneously experience chronic intestinal inflammation and wasting syndromes. In other models immune imbalance caused by transfer of naive T cells into mice with severe combined immunodeficiency leads to disease. In most models the disease is dominated by a T_H1 cytokine profile. In a number of models, the disease might be modulated or prevented by the presence of circulating CD4⁺CD25⁺ regulatory T cells. Interestingly, manipulations that increase T_H2 cytokines, such as intestinal parasite infection, ameliorate inflammation in some models. This latter observation is consistent with the thesis that one of the contributing factors of modern industrialized life that has led to the emergence of Crohn's disease is a high level of sanitation, with resultant low levels of chronic gastrointestinal infection. The disease in many of these animal models requires the presence of a gastrointestinal microbial flora. These observations in animal models suggest that perturbation of the mucosal host defense system in many different ways could lead to chronic gastrointestinal disease in the presence of gut microflora, as seen in the human condition.

The characteristic early gastrointestinal lesions of Crohn's disease consist of aphthous ulcer-like lesions that occur in a focal fashion in the gut. As these enlarge and ulcerate, they are associated with a transmural inflammation characterized by CD4 T cells and macrophages, which can aggregate into noncaseating granulomas, although these are frequently not seen in endoscopic mucosal biopsy specimens. Another characteristic feature of Crohn's disease is fissuring ulceration that extends from the intestinal lumen into the deeper layers of the gut wall. The transmural nature of the inflammation is associated in some cases with the formation of strictures, fistulae, or perforations of the bowel wall. Immunologically, the lesions are characterized by a T_H1 cytokine pattern.

There is evidence suggesting a role for gut flora in the pathogenesis of human Crohn's disease. Patients with Crohn's disease have increased titers of anti-bacterial antibodies, particularly to gut flora. In addition, they commonly have antibodies against *Saccharomyces cerevisiae*. These observations support the notion that one of the pathologic steps in Crohn's disease is loss of oral tolerance to gut flora. The lesions of Crohn's disease most typically are found in locations with high bacterial counts, namely the cecum and terminal ileum. Surgical diversion of the fecal stream typically leads to amelioration of active inflammation. Many patients have at least temporary responses to antibiotic therapy. These features suggest that the gut microbial flora provide an important contribution to disease pathogenesis. A number of studies suggest a potential causative role for specific pathogens, such as *Mycobacterium avium* paratuberculosis¹⁴ or adherent *Escherichia coli*¹⁵; however, their role remains a subject of investigation.

Another interesting feature of Crohn's disease is the presence of increased gut permeability to macromole-

cules. Although the pathophysiologic basis for this observation is unknown, it could potentially represent a genetic abnormality and result in increased influx of potentially immunostimulatory molecules into the gastrointestinal tract.

Important recent clues to the pathogenesis of Crohn's disease have emerged from genetic research. Genome-wide scans of familial Crohn's disease demonstrated linkage to a number of regions, including a locus on chromosome 16 (*IBD1*), now identified as the *nod2/card15* gene.¹⁶ As many as 50% of patients with Crohn's disease have mutations in this gene, which appears to play a role in innate immunity and, specifically, in signaling mediated by bacterial peptidoglycans. The reported *nod2/card15* mutations cause loss of function in *in vitro* assays of nuclear factor κ B (NF- κ B) activation. However, these *in vitro* observations are discordant with findings in the disease, which is characterized by increased NF- κ B activation and a marked increase in T_H1 cytokine profile in the mucosa. Recent studies of lymphoid cells from *card15*^{-/-} mice demonstrate increased toll-like receptor 2-mediated activation of NF- κ B and T_H1 cytokines, suggesting that the gene product plays a complex role in negative regulation of signaling by microbial products.¹⁷ Interestingly, other mutations in this gene in human subjects are associated with the Blau syndrome, a chronic granulomatous disease that has extraintestinal features similar to those of Crohn's disease. Interestingly, the gene mutated in another chronic and relapsing inflammatory syndrome, familial Mediterranean fever, has some homology to the *nod2/card15* gene. *Nod2/card15* mutations alone are not sufficient to explain the disease because some individuals with Crohn's disease lack mutations, and there are individuals who have mutations but no evidence of disease. Multiple other genetic linkages have been reported, including linkage to the 5q31 cytokine gene cluster.¹⁸ Other gene mutations have also recently been reported to be associated with Crohn's disease.^{19,20} Further definition of syntenic regions in mice and human subjects and further studies of animal models of inflammatory bowel disease might lead to further definition of the genetic basis of Crohn's disease.

Diagnosis

The diagnosis of Crohn's disease is based on the finding of typical clinical and pathologic features and the absence of evidence of other conditions that mimic the disease (Table I). The diagnostic tests with highest specificity are gastrointestinal endoscopy with biopsy and imaging studies, such as computed tomography and barium contrast studies. Differentiation of Crohn's disease from other inflammatory conditions, such as infection or ulcerative colitis, often cannot be made on the basis of biopsy. The gross appearance of lesions and their location and distribution is often more helpful in differentiating Crohn's disease from other conditions. Serologic testing for both perinuclear anti-neutrophilic cytoplasmic antibody and anti-*Saccharomyces cerevisiae* antibodies has been suggested to be helpful in distinguishing Crohn's disease

from ulcerative colitis,²¹ but the utility of these tests is unproved. At the present time, there is no accepted clinical role for genetic testing.

Treatment

The detailed treatment options for Crohn's disease are complex and beyond the scope of this text. Oral or topical aminosalicylic acid preparations have efficacy in mild Crohn's disease but might have limited efficacy compared with ulcerative colitis because of the transmural nature of the inflammation in Crohn's disease. Corticosteroids, usually administered orally, are the initial choice for rapid resolution of symptoms, but many patients experience corticosteroid dependence or resistance with time or have significant side effects. Azathioprine or 6-mercaptopurine have demonstrated efficacy in multiple randomized controlled trials, and there might be a role for measuring metabolite levels for optimal management. Methotrexate also has efficacy. Cyclosporine might have utility in some cases. More recently, infliximab (anti-TNF mAb) has been shown in randomized controlled trials to improve remission for active disease and to heal fistulae.²² Interestingly, etanercept, another agent interfering with TNF- α signaling, does not seem to be effective, suggesting different modes of action of these agents. Recent clinical trials suggest that antibodies directed against integrins involved in leukocyte migration (anti α -4 integrin mAb) have efficacy.²³ Another different recent approach has been the investigational use of GM-CSF as an immunostimulant²⁴ on the basis of the discovery of *nod2/card15* gene defects and the possibility that Crohn's disease is a deficiency disorder of innate immunity. Antibiotics, particularly metronidazole and fluoroquinolones, are frequently used and appear to have efficacy, although there are fewer data to support their use. The use of probiotics is investigational. Nutritional support, either enteral nutrition or parenteral nutrition, might be required in some patients. Vitamin B12 might be required in patients with extensive ileal damage or loss caused by surgery. Surgery is commonly required for the management of Crohn's disease, despite optimal medical management. Common indications for surgery are refractory disease, perforation, fistulae, or obstruction caused by stricture or gastrointestinal adenocarcinoma, which has an increased incidence in Crohn's disease.

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