07 - 337 Inflammatory Bowel Disease

337 Inflammatory Bowel Disease

performed specifically to diagnose infection (e.g., Whipple’s disease or giardiasis). In most other instances, the infection is detected incidentally during the workup for diarrhea or other abdominal symptoms. Many of these infections occur in immunocompromised patients with diarrhea; the etiologic agents include Cryptosporidium, Isospora belli, microsporidia, Cyclospora, Toxoplasma, cytomega lovirus, adenovirus, Mycobacterium avium-intracellulare, and G. lamblia. In immunocompromised patients, when Candida, Aspergil lus, Cryptococcus, or Histoplasma organisms are seen on duodenal biopsy, their presence generally reflects systemic infection. Apart from Whipple’s disease and infections in the immunocompromised host, small-bowel biopsy is seldom used as the primary mode of diagnosis of infection. Even giardiasis is more easily diagnosed by stool antigen studies and/or duodenal aspiration than by duodenal biopsy. SUMMARY The evaluation and management of patients with disorders of absorp tion are challenging due to the complexity of the underlying patho physiology and the large number of associated diseases. A diagnostic approach based on the information summarized in Tables 336-1 and 336-5 should prove useful for guiding the care of these challenging patients. Acknowledgments Henry Binder wrote this chapter in prior editions and some material from his chapter has been retained. ■ ■FURTHER READING Bering J, DiBaise JK: Short bowel syndrome: Complications and management. Nutr Clin Pract 38:S46, 2023. Boumaza A et al: Whipple’s disease and Tropheryma whipplei infec tions: From bench to bedside. Lancet Infect Dis 22:e280, 2022. Bousaba J et al: Bile acid diarrhea: As bad as it gets? Curr Opin Gastroenterol 39:184, 2023. Cowardin CA et al: Environmental enteric dysfunction: Gut and microbiota adaptation in pregnancy and infancy. Nat Rev Gastroenterol Hepatol 20:223, 2023. Fernández-Bañares F et al: Carbohydrate maldigestion and intolerance. Nutrients 14:1923, 2022. Gregory M, Rubin DC: Small bowel disorders, in The Washington Manual Gastroenterology Subspecialty Consult, 4th ed, Gyawali CP et al (eds). Walters Kluwer, 2021, pp.142–155. Jansson-Knodell CL, Rubio-Tapia A: Gluten-related disorders from bench to bedside. Clin Gastroenterol Hepatol 22:693, 2024. Johnson LR: Digestion and absorption of nutrients, in Gastrointestinal Physiology, 9th ed. Philadelphia, Elsevier, 2019, pp 102–120. Ozen A, Lenardo MJ: Protein-losing enteropathy. N Engl J Med 389:733, 2023. Zafar H et al: Small intestinal bacterial overgrowth: current update. Curr Opin Gastroenterol 39:522, 2023. Sonia Friedman, Richard S. Blumberg

Inflammatory Bowel

Disease Inflammatory bowel disease (IBD) is a chronic idiopathic inflammatory disease of the gastrointestinal tract. Ulcerative colitis (UC) and Crohn’s disease (CD) are the two major types of

IBD.

■ ■GLOBAL CONSIDERATIONS: EPIDEMIOLOGY UC and CD have emerged as global diseases in the twenty-first century. The disease burden is high, with a prevalence of >0.3% in North America, Oceania, and most countries in Europe. In newly industrialized countries in Africa, Asia, and South America where there is increased urbanization and Westernization, the incidence of IBD has been ris ing and mirrors the prior increase of IBD in the Western world in the twentieth century. For example, in Brazil, the annual percent change is +11.1% (95% confidence interval [CI], 4.8–17.8%) for CD and +14.9% (95% CI, 10.4–19.6%) for UC, whereas in Taiwan, the annual percent change is +4.0% (95% CI, 1.0–7.1%) for CD and +4.8% (95% CI, 1.8–8.0%) for UC. In a study of newly diagnosed IBD cases between 2011 and 2013 from 13 countries or regions in the Asia Pacific, the mean annual IBD incidence per 100,000 was 1.50 (95% CI, 1.43–1.57). India (9.31; 95% CI, 8.38–10.31) and China (3.64; 95% CI, 2.97–4.42) had the highest IBD incidences in Asia. The highest reported preva lence values were in Europe (UC, 505 per 100,000 in Norway; CD, 322 per 100,000 in Germany) and North America (UC, 286 per 100,000 in the United States; CD, 319 per 100,000 in Canada). The most recent U.S. study showed that 2.39 million Americans are diagnosed with IBD. The most likely factors that explain the geographic variability of IBD rates, especially the rising incidence in developing countries and urban areas, are environmental variables including changes in diet (with downstream effects on the intestinal microbiota), exposure to sunlight or temperature differences, and socioeconomic status and hygiene (Table 337-1).

Peak incidence of UC and CD is in the second to fourth decades, with 78% of CD studies and 51% of UC studies reporting the highest incidence among those aged 20–29 years old. A second modest rise in incidence occurs between the seventh and ninth decades of life. The female-to-male ratio ranges from 0.51 to 1.58 for UC studies and 0.34 to 1.65 for CD studies, suggesting that the diagnosis of IBD is not gen der-specific. Pediatric IBD (patients <17 years old) composes ~20–25% of all IBD patients, and ~5% of all IBD patients are <10 years old. Children with IBD are also grouped as those with early-onset (EO) IBD (patients <10 years old), very-early-onset (VEO) IBD (patients <6 years old), and infantile IBD (patients <2 years old). VEOIBD and infantile IBD mainly affect the colon and are resistant to standard medications, and patients often have a strong family history of IBD, with at least one first-degree relative affected. In infantile IBD or VEOIBD, a number of rare, single genetic mutations have been identified as the basis for this susceptibility in up to 10% of patients, suggesting a simple Mendelian origin of the disease in these cases. CHAPTER 337 Inflammatory Bowel Disease Although the greatest prevalence of IBD is among Whites, the preva lence of IBD in Latinx, Black, and Asian people is increasing. Urban areas have a higher prevalence of IBD than rural areas, and high socioeconomic classes have a higher prevalence than lower socioeconomic classes. Epidemiologic studies have identified a number of potential envi ronmental factors that are associated with disease risk (Fig. 337-1). TABLE 337-1 Epidemiology of IBD ULCERATIVE COLITIS CROHN’S DISEASE Age of onset Second to fourth decades and seventh to ninth decades Second to fourth decades and seventh to ninth decades Ethnicity White > Black > Latinx > Asian Female-to-male ratio 0.51–1.58 0.34–1.65 Smoking May prevent disease (odds ratio 0.58) May cause disease (odds ratio 1.76) Oral contraceptives No increased risk Hazard ratio 2.82 Appendectomy Protective (risk reduction 13–26%) Not protective Monozygotic twins 6–18% concordance 38–58% concordance Dizygotic twins 0–2% concordance 4% concordance Infections in the first year of life 1.6 and 3 times the risk of developing IBD by age 10 and 20 years Abbreviation: IBD, inflammatory bowel disease.

Genetic susceptibility TLR4 XBP1 DLG5 ECM1 ITLN1 SLC22A5 DMBT1 PTGER4 XBP1 NOD2 ATG16L1 Microbial flora Enteropathogens Antibiotics Diet, hygiene NSAIDs, smoking PART 10 Disorders of the Gastrointestinal System Environmental factors FIGURE 337-1 Pathogenesis of inflammatory bowel disease (IBD). In IBD, the tridirectional relationship between the commensal flora (microbiota), intestinal epithelial cells (IECs), and mucosal immune system is dysregulated, leading to chronic inflammation. Each of these three factors is affected by genetic and environmental factors that determine risk for the disease. NSAIDs, nonsteroidal anti-inflammatory drugs. (Republished with permission Annual Review of Immunology from Inflammatory Bowel Disease, A Kaser et al: 28:573, 2010. Permission conveyed through Copyright Clearance Center, Inc.) Smoking is an important risk factor in IBD with opposite effects on UC (odds ratio [OR] 0.58) and CD (OR 1.76) that may be influenced by genetic risk factors and ethnic origin. Previous appendectomy with confirmed appendicitis (risk reduction of 13–26%), particularly at a young age, has a protective effect on the development of UC across dif ferent geographical regions and populations. Appendectomy is mod estly associated with the development of CD, but this may be due to diagnostic bias. Oral contraceptive use is associated with an increased risk of CD, with a reported hazard ratio as high as 2.82 among current users and 1.39 among past users. The association between oral con traceptive use and UC is limited to women with a history of smoking. Breast-feeding may protect against the development of IBD, which supports the potential importance of early-life exposures to later IBD development. Infections in the first year of life are associated with development of IBD, especially before the ages of 10 and 20 years. Infectious gastroenteritis with pathogens (e.g., Salmonella, Shigella, Campylobacter spp., Clostridioides difficile) increases IBD risk by two- to threefold. Diets high in animal protein, sugars, sweets, oils, fish and shellfish, and dietary fat, especially ω-6 fatty acids, and low in ω-3 fatty acids have been implicated in increasing the risk of IBD. A protective effect of vitamin D on the risk of CD has been reported. IBD is a familial disease in 5–10% of patients (Fig. 337-2), and the strongest risk factor for the development of IBD is a first-degree rela tive with the disease. The children of mothers and fathers with UC have an approximately fourfold increased risk of UC, and the children of mothers and fathers with CD have an almost eightfold increased risk of CD. Some of these patients may exhibit early-onset disease during the first decade of life and, in CD, a concordance of anatomic site and clini cal type within families. In twin studies, 38–58% of monozygotic twins are concordant for CD, and 6–18% are concordant for UC, whereas 4%

IL23R, IL12B, JAK2, STAT3, CCR6, NOD2, TLR4, CARD9, IRF5, ATG16L1, IRGM, LRRK2 TNFSF15, TNFRSF6B TNFAIP3, PTPN2/22 NLRP3, IL18RAP ICOSL, ARPC2, STAT3, IL10 Immune dysregulation IEC Stress Diet, hygiene of dizygotic twins are concordant for CD, and 0–2% are concordant for UC in Swedish and Danish cohorts. In the remainder of patients, IBD is observed in the absence of a family history (i.e., sporadic disease). GLOBAL CONSIDERATIONS:

IBD PHENOTYPES IBD location and behavior show racial differences that may reflect underlying genetic variations and have important implications for diagnosis and management of disease. Blacks and Latinxs tend to have an ileocolonic CD distribution. Data from East Asia show that Monogenic Oligogenic Polygenic Environment Undiagnosed infections? Early onset Genetics Familial (10%) Sporadic FIGURE 337-2 A model for the syndromic nature of inflammatory bowel disease (IBD). Genetic and environmental factors variably influence the development and phenotypic manifestations of IBD. At the one extreme, IBD is exemplified as a simple Mendelian disorder as observed in early-onset IBD due to single-gene defects such as IL10, IL10RA, and

IL10RB; and at the other extreme, it may be exemplified by as yet to be described emerging infectious diseases. (Reproduced with permission from A Kaser et al: Genes and environment: How will our concepts on the pathophysiology of IBD develop in the future? Dig Dis 28:395, 2010.)

ileocolonic CD is the most common CD phenotype (50.5–71%) and perianal disease is more common in East Asian patients (30.3–58.8%) than Whites (25.1–29.6%). Pancolonic disease is more common than left-sided colitis or proctitis among Black, Latinx, and Asian patients with UC. Older Asian patients with UC (age >60) tend to have a more aggressive disease course. Among Blacks, joint involvement is the predominant extraintestinal manifestation (EIM) reported and ranges from 15.7 to 29.6%. Ocular involvement is also common in African Americans and ranges from 7.1 to 13%. Dermatologic manifestations are the most common EIMs reported in Latinxs (10–13%). These ethnic variations indicate the importance of different genetic and/or environmental factors in the pathogenesis of this disorder. ETIOLOGY AND PATHOGENESIS Under physiologic conditions, homeostasis normally exists between the commensal microbiota, epithelial cells that line the interior of the intestines (intestinal epithelial cells [IECs]), and immune cells within the tissues (Fig. 337-1). A consensus hypothesis is that each of these three major host compartments that function together as an integrated “supraorganism” (microbiota, IECs, and immune cells) are affected by specific environmental (e.g., smoking, antibiotics, enteropatho gens) and genetic factors that, in a susceptible host, cumulatively and interactively disrupt homeostasis during the course of one’s life and, in so doing, culminate in a chronic state of dysregulated inflammation; i.e., IBD. Although chronic activation of the mucosal immune system may represent an appropriate response to an infectious agent, a search for such an agent has thus far been unrewarding in IBD. As such, IBD is currently considered an inappropriate immune response to the endog enous (autochthonous) commensal microbiota within the intestines, with or without some component of autoimmunity. Importantly, the normal, uninflamed intestines contain a large number of immune cells that are in a unique state of activation, in which the gut is restrained from full immunologic responses to the commensal microbiota and dietary antigens by very powerful regulatory pathways that function within the immune system (e.g., T regulatory cells that express the FoxP3 transcription factor and suppress inflammation). Maintenance of homeostasis also involves oversight from local parenchymal cells including nerve, endothelial, and stromal cells, as well as the com mensal microbiota that provide essential remedial factors necessary for health and serve as a target of the immune response. During the course of infections or other environmental stimuli in the normal host, full activation of the lymphoid tissues in the intestines occurs but is rapidly superseded by dampening of the immune response and tissue repair. In IBD, such processes may not be regulated normally. GENETIC CONSIDERATIONS The genetic underpinning of IBD is known from its concordance in identical twins, its occurrence in the context of several genetic syndromes, and the development of severe, refractory IBD in early life in association with single-gene defects that affect the immune system (Table 337-2). More than 60 different gene defects have been identified in patients with VEOIBD and infantile IBD by whole-exome sequencing (WES), in whom most of the monogenic mutations have been discovered. These include mutations in genes encoding, for example, interleukin (IL) 10, the IL-10 receptor (IL-10R), cytotoxic T-lymphocyte-associated protein-4 (CTLA4), neutrophil cytosolic fac tor 2 protein (NCF2), X-linked inhibitor of apoptosis protein (XIAP), lipopolysaccharide responsive and beige-like anchor protein (LRBA), and tetratricopeptide repeat domain 7A protein (TTC7), among many other genes that are involved in host-commensal interactions. A mono genic etiology may also be possible in a small subset of adult patients with IBD. In addition, IBD has a familial origin in at least 10% of afflicted adults, consistent with an

inherited basis for this disease (Fig. 337-2). However, the majority of pediatric and adult IBD cases are multigenic (or polygenic) in origin, suggesting a syndromic nature of this disease that gives rise to multiple clinical subgroups beyond the simple classification as UC and CD. The polygenic nature of the disease has been elucidated through a variety of genetic approaches, including candidate gene studies, linkage analysis, and genome-wide association

TABLE 337-2 Primary Genetic Disorders Associated with IBD NAME GENETIC ASSOCIATION PHENOTYPE Turner’s syndrome Loss of part or all of X chromosome Associated with UC and colonic CD Hermansky-Pudlak syndrome Autosomal recessive disorder genes involved in the biogenesis of lysosomerelated organelles or adaptor protein-3 complex Granulomatous colitis, oculocutaneous albinism, platelet dysfunction, and pulmonary fibrosis Wiskott-Aldrich syndrome (WAS) X-linked recessive disorder, loss of WAS protein function Colitis, immunodeficiency, severely dysfunctional platelets, and thrombocytopenia Glycogen storage disease type 1b Autosomal recessive disorder of SLC37A4 resulting in deficiency of the glucose-6-phosphate translocase Granulomatous colitis, presents in infancy with hypoglycemia, growth failure, hepatomegaly, and neutropenia Immune dysregulation polyendocrinopathy, enteropathy X-linked (IPEX) Loss of FoxP3 transcription factor and T regulatory cell function UC-like autoimmune enteropathy, with endocrinopathy (neonatal type 1 diabetes or thyroiditis), dermatitis Early-onset IBD Deficient IL-10 and IL-10 receptor function Severe, refractory IBD in early life Abbreviations: CD, Crohn’s disease; IBD, inflammatory bowel disease; IL, interleukin; UC, ulcerative colitis. CHAPTER 337 studies (GWAS) that focus on the identification of disease-associated single nucleotide polymorphisms (SNPs) within the human genome and WES and whole-genome sequencing to elucidate the specific mutations potentially involved. GWAS have identified ~240 genetic loci with multiple potential candidate genes; two-thirds of these loci are associated with both disease phenotypes, with the remainder being specific for either CD or UC (Table 337-3). These genetic similarities account for the overlapping immunopathogenesis and consequently epidemiologic observations of both diseases in the same families and similarities in response to therapies. Because the specific causal vari ants for each identified gene or locus are mostly unknown as most risk loci are contained within regulatory (noncoding) regions of the associ ated genes, it is not clear whether the similarities in the genetic risk factors associated with CD and UC are shared at a structural or func tional level. The risk conferred by each identified gene or locus is unequal and generally small, such that only ~20% of the disease risk is considered to be explained by the current genetic information. Further, many of the genetic risk factors identified are also observed to be asso ciated with risk for other immune-mediated diseases, suggesting that related immunogenetic pathways are involved in the pathogenesis of multiple different disorders, accounting for the common responsive ness to similar types of biologic therapies (e.g., anti–tumor necrosis factor [TNF] therapies) and possibly the simultaneous occurrence of these disorders. The diseases and the genetic risk factors that are shared with IBD include, for example, rheumatoid arthritis (TNFAIP3), pso riasis (IL23R, IL12B), ankylosing spondylitis (IL23R), type 1 diabetes mellitus (IL10, PTPN2), asthma (ORMDL3), and systemic lupus ery thematosus (TNFAIP3, IL10), among others. Inflammatory Bowel Disease The genetic factors that are recognized to mediate risk for IBD have highlighted the importance of shared mechanisms of disease that variably affect CD and/or UC (Table 337-3). These include the fol lowing: those genes that are associated with fundamental cell biologic processes such as the unfolded protein response due to endoplasmic reticulum stress, autophagy, and metabolism that regulate the ability of cells to manage the physiologic needs of the intestinal environment; those associated with innate immunity associated with nonlymphoid cells that function in responses to

and control of microbes; those associated with the regulation of adaptive immunity that control the balance between inflammatory and anti-inflammatory cellular path ways associated with lymphocytes; and, finally, those that are involved in the development and resolution of inflammation associated with

PART 10 Disorders of the Gastrointestinal System TABLE 337-3 Some Genetic Loci Associated with Crohn’s Disease and/or Ulcerative Colitis CHROMOSOME PUTATIVE GENE GENE NAME PROTEIN FUNCTION CD UC Unfolded Protein Response, Autophagy, and Metabolism 2q37 ATG16L1 ATG16 autophagy related 16-like 1 Autophagy + 5q31 SLC22A5 Solute carrier family 22, member 5 b-Carnitine transporter + 5q33 IRGM Immunity-related GTPase family, M Autophagy + 7p21 AGR2 Anterior gradient 2 Unfolded protein response + + 12q12 LRRK2 Leucine-rich repeat kinase 2 Autophagy + 13q14 LACC1 Laccase domain containing 1 (FAMIN) Immunometabolic regulator + 17q21 ORMDL3 Orosomucoid related member 1-like 3 Unfolded protein response and lipid synthesis + + 22q12 XBP1 X-box binding protein 1 Unfolded protein response + + Innate Immunity 1q23 ITLN1 Intelectin 1 Bacterial binding + 16q12 NOD2 Nucleotide-binding oligomerization domain containing 2 Bacterial sensing and autophagy activation + Adaptive Immunity 1p31 IL23R Interleukin 23 receptor TH17 cell stimulation + + 1q32 IL10 Interleukin 10 Treg-associated cytokine + 5q33 IL12B Interleukin 12 subunit beta IL-12 p40 chain of IL-12/IL-23 + + 18p11 PTPN2 Protein tyrosine phosphatase, nonreceptor type 2 T-cell regulation + Inflammation and Healing 3p21 MST1 Macrophage Stimulating 1 Macrophage activation + + 5p13 PTGER4 Prostaglandin E receptor 4 PGE2 receptor + + 6q23 TNFAIP3 Tumor necrosis factor, alpha-induced protein 3 (A20) Toll-like receptor regulation + 6q27 CCR6 Chemokine (C-C motif) receptor 6 Dendritic cell migration + 9p24 JAK2 Janus kinase 2 IL-6R and IL-23R signaling + + 9q32 TNFSF15 Tumor necrosis factor–like cytokine 1A (TL1A) Promotes inflammation and fibrosis + + 17q21 STAT3 Signal transducer and activator of transcription 3 IL-6R, IL-23R, and IL-10R signaling + + Abbreviations: CD, Crohn’s disease; GTPase, guanosine triphosphatase; IL, interleukin; PGE2, prostaglandin E2; Treg, T regulatory cell; UC, ulcerative colitis. Source: Adapted from A Kaser et al: Ann Rev Immunol 28:573, 2010; Graham DB, Xavier RJ: Nature 578:527, 2020. healing that control leukocyte recruitment and inflammatory media tor production or the development of fibrosis. Each of these genetic susceptibilities contributes in an incremental manner to IBD risk, variably affects the activities of virtually all subtypes of immune and nonimmune cells within the intestines, and encodes mutations (poly morphisms) that promote or protect from IBD. Some of these loci are associated with specific subtypes of disease such as the association between NOD2 polymorphisms and fibrostenosing CD or ATG16L1 and fistulizing disease, especially within the ileum. However, the clini cal utility of these genetic risk factors for the diagnosis or determina tion of prognosis and therapeutic responses remains to be defined. ■ ■COMMENSAL MICROBIOTA AND IBD The endogenous commensal microbiota within the intestines plays a central role in the pathogenesis of IBD. Humans are born with sterile guts and acquire their commensal microbiota initially from the mother during egress through the birth canal and subsequently from environ mental sources. A stable configuration of up to 1000 species of bacteria that achieves a biomass of ~1012 colony-forming units per gram of feces is achieved by 3 years of age, which likely persists into adult life, with each individual human possessing a unique combination of species. In addition, the intestines contain other microbial life forms including fungi, archaea, viruses, and protists. The microbiota is thus considered as a critical and sustaining component of the human organism. The establishment and maintenance of the intestinal microbiota compo sition and function are under the control of host (e.g., immune and epithelial responses), environmental (e.g., diet and antibiotics), and likely

genetic (e.g., NOD2) factors (Fig. 337-1). In turn, the microbiota, through its structural components and metabolic activity, has major influences on the epithelial and immune function of the host, which, through epigenetic effects, may have durable consequences. During early life when the commensal microbiota is being established, these microbial effects on the host may be particularly important in deter mining later life risk for IBD. Specific components of the microbiota can promote or protect from disease. The commensal microbiota in patients with both UC and CD is demonstrably different from that of nonafflicted individuals, a state of dysbiosis suggesting the presence of microorganisms that drive disease (e.g., Proteobacteria such as enteroinvasive and adherent Escherichia coli) and to which the immune response is directed and/or the loss of microorganisms that hinder inflammation (e.g., Firmicutes such as Faecalibacterium prausnitzii). Many of the changes in the commensal microbiota occur as a conse quence of the inflammation and are thus potential secondary drivers of disease. In addition, agents that alter the intestinal microbiota such as metronidazole, ciprofloxacin, and elemental diets, may improve CD. CD may also respond to fecal diversion, demonstrating the ability of luminal contents to exacerbate disease. ■ ■DEFECTIVE IMMUNE REGULATION IN IBD The mucosal immune system does not normally elicit an inflammatory immune response to luminal contents due to oral (mucosal) tolerance. Administration of soluble antigens orally, rather than subcutaneously or intramuscularly, leads to antigen-specific control of the response and the host's ability to tolerate the antigen. Multiple mechanisms are involved in the induction of oral tolerance and include deletion or anergy (nonresponsiveness) of antigen-reactive T cells or induction of CD4+ T cells that suppress gut inflammation (e.g., T regulatory cells expressing the FoxP3 transcription factor) and that secrete antiinflammatory cytokines such as IL-10, IL-35, and transforming growth factor β (TGF-β). Oral tolerance may be responsible for the lack of immune responsiveness to dietary antigens and the commensal micro biota in the intestinal lumen. In IBD, this suppression of inflammation is altered, leading to uncontrolled inflammation. The mechanisms of this regulated immune suppression are incompletely known.

 Gene knockout (–/–) or transgenic (Tg) mouse models of IBD, includ ing those that are directed at genes associated with risk for the human disease, have revealed that deleting specific cytokines (e.g., IL-2, IL-10, TGF-β) or their receptors, deleting molecules associated with T-cell antigen recognition (e.g., T-cell antigen receptors), or interfering with IEC barrier function and the regulation of responses to commensal bacteria (e.g., mucus glycoproteins or nuclear factor-κB [NF-κB]) leads to spontaneous colitis or enteritis. In the majority of circumstances, intestinal inflammation in these animal models requires the presence of the commensal microbiota. However, in some cases, activation of certain elements of the intestinal immune system may be exacerbated by the absence of bacteria, resulting in severe colitis and emphasizing the presence of protective properties of the commensal microbiota. Thus, a variety of specific alterations in either the microbiota or host can lead to uncontrolled immune activation and inflammation directed at the intestines in mice. How these relate to human IBD remains to be defined, but they are consistent with inappropriate responses of the genetically susceptible host to the commensal microbiota. ■ ■THE INFLAMMATORY CASCADE IN IBD In both UC and CD, inflammation likely emerges from the genetic predisposition of the host in the context of yet-to-be-defined envi ronmental factors. Once initiated in IBD by abnormal innate immune sensing of bacteria by parenchymal cells (e.g., IECs) and hematopoietic cells (e.g., macrophages, dendritic cells), the immune inflammatory response is

perpetuated by T-cell and B-cell activation when coupled together with inadequate regulatory pathways. A sequential cascade of inflammatory mediators extends the response, making each step a potential target for therapy. Inflammatory cytokines from innate immune cells such as IL-1, IL-6, IL-12, IL-23, and TNF have diverse effects on tissues. They promote fibrogenesis, collagen production, activation of tissue metalloproteinases, and/or the production of other inflammatory mediators; they also activate the coagulation cascade in local blood vessels (e.g., increased production of von Willebrand fac tor). These cytokines are normally produced in response to infection but are usually turned off or inhibited by cytokines such as IL-10 and TGF-β at the appropriate time to limit tissue damage. In IBD, their activity is not regulated, resulting in an imbalance between the proin flammatory and anti-inflammatory mediators. Some of these cytokines activate other inflammatory cells (macrophages and B cells), and others such as chemokines act indirectly to recruit other lymphocytes, inflam matory leukocytes, and mononuclear cells from the bloodstream into the gut through interactions between homing receptors on leukocytes (e.g., α4β7 integrin) and addressins on vascular endothelium (e.g., MadCAM1). Lymphocytes such as CD4+ T helper (TH) cells emerge from the lymph nodes under the influence of sphingosine-1-phosphate (S1P) gradients that act on S1P receptors (S1PR) expressed on the lym phocyte and endothelium. CD4+ TH cells that promote inflammation are of four major types, all of which may be associated with colitis in animal models and perhaps humans: TH1 cells (secrete IL-2, interferon [IFN] γ), TH2 cells (secrete IL-4, IL-5, IL-13), TH9 cells (secrete IL-9), and TH17 cells (secrete IL-17, IL-21, IL-22). TH17 cells may also provide protective functions. Innate immune-like cells (ILCs) that lack T-cell receptors are also present in intestines, polarize to the same functional fates, and may similarly participate in IBD. TH1 cells induce transmu ral granulomatous inflammation that resembles CD; TH2 cells and related natural killer T cells that secrete IL-4, IL-5, and IL-13 induce superficial mucosal inflammation resembling UC in animal models; TH9 cells promote allergic-like inflammation; and TH17 cells may be responsible for neutrophilic recruitment. Each of these T-cell subsets cross-regulates each other. The TH1 cytokine pathway is initiated by IL-12, a key cytokine in the pathogenesis of experimental models of mucosal inflammation. IL-4 and IL-23, together with IL-6 and TGF-β, induce TH2 and TH17 cells, respectively, and IL-23 inhibits the suppres sive function of regulatory T cells. Activated macrophages secrete TNF and IL-6. Cytokines produced by innate immune cells and lymphocytes exert their effects on target cells through cytokine-specific receptors, which precisely engage intracellular Janus kinases (JAK) 1, 2, and/or 3 for transmission of intracellular activating signals. These characteristics of the immune response in IBD explain the beneficial therapeutic effects of antibodies to block proinflammatory cytokines or the signaling by their receptors (e.g., anti-TNF, anti-IL-12, anti-IL-23, JAK inhibitors), molecules that antagonize the activity of S1PR-induced emigration of lymphocytes from the lymph nodes (ozanimod), or antibodies that impede leukocyte recruitment into the intestines (e.g., anti-α4β7). They also highlight the potential usefulness of cytokines that inhibit inflammation and promote regulatory T cells or promote intestinal barrier function (e.g., IL-10) in the treatment of IBD. Therapies such as the 5-aminosalicylic acid (5-ASA) compounds and glucocorticoids are also potent inhibitors of these inflammatory mediators through inhibition of transcription factors such as NF-κB that regulate their expression. PATHOLOGY ■ ■ULCERATIVE COLITIS: MACROSCOPIC FEATURES UC is a mucosal disease that usually involves the rectum and extends proximally to involve all or part of the colon. About 40–50% of patients have disease limited to the rectum and rectosigmoid, 30–40% have dis ease extending beyond the sigmoid but not involving the whole colon, and 20% have a pancolitis. Proximal spread occurs in continuity with out areas of uninvolved mucosa. When the whole colon is involved, the

inflammation extends 2–3 cm into the terminal ileum in 10–20% of patients. The endoscopic changes of backwash ileitis are superficial and mild and are of little clinical significance. Although variations in macroscopic activity may suggest skip areas, biopsies from normalappearing mucosa are usually abnormal. Thus, it is important to obtain multiple biopsies from apparently uninvolved mucosa, whether proxi mal or distal, during endoscopy. One caveat is that effective medical therapy can change the appearance of the mucosa such that either skip areas or the entire colon can be microscopically normal. With mild inflammation, the mucosa is erythematous and has a fine granular surface that resembles sandpaper. In more severe disease, the mucosa is hemorrhagic, edematous, and ulcerated (Fig. 337-3). In long-standing disease, inflammatory polyps (pseudopolyps) may be present as a result of epithelial regeneration. The mucosa may appear normal in remission, but in patients with many years of disease, it appears atrophic and featureless, and the entire colon becomes nar rowed and shortened. Patients with fulminant disease can develop a toxic colitis or megacolon where the bowel wall becomes thin and the mucosa is severely ulcerated; this may lead to perforation. ■ ■ULCERATIVE COLITIS: MICROSCOPIC FEATURES Histologic findings correlate well with the endoscopic appearance and clinical course of UC. The process is limited to the mucosa and FIGURE 337-3 Ulcerative colitis. Diffuse (nonsegmental) mucosal disease, with broad areas of ulceration. The bowel wall is not thickened, and there is no cobblestoning. (Courtesy of Dr. R. Odze, Division of Gastrointestinal Pathology, Department of Pathology, Brigham and Women’s Hospital, Boston, Massachusetts; with permission.)

FIGURE 337-4 Medium-power view of colonic mucosa in ulcerative colitis showing diffuse mixed inflammation, basal lymphoplasmacytosis, crypt atrophy and irregularity, and superficial erosion. These features are typical of chronic active ulcerative colitis. (Courtesy of Dr. R. Odze, Division of Gastrointestinal Pathology, Department of Pathology, Brigham and Women’s Hospital, Boston, Massachusetts; with permission.) superficial submucosa, with deeper layers unaffected except in fulmi nant disease. In UC, two major histologic features suggest chronicity and help distinguish it from infectious or acute self-limited colitis. First, the crypt architecture of the colon is distorted; crypts may be bifid and reduced in number, often with a gap between the crypt bases and the muscularis mucosae. Second, some patients have basal plasma cells and multiple basal lymphoid aggregates. Mucosal vascular con gestion, with edema and focal hemorrhage, and an inflammatory cell infiltrate of neutrophils, lymphocytes, plasma cells, and macrophages may be present. The neutrophils invade the epithelium, usually in the crypts, giving rise to cryptitis and, ultimately, to crypt abscesses (Fig. 337-4). Ileal changes in patients with backwash ileitis include villous atrophy and crypt regeneration with increased inflammation, increased neutrophil and mononuclear inflammation in the lamina propria, and patchy cryptitis and crypt abscesses. PART 10 Disorders of the Gastrointestinal System ■ ■CROHN’S DISEASE: MACROSCOPIC FEATURES CD can affect any part of the gastrointestinal (GI) tract from the mouth to the anus. Some 30–40% of patients have small-bowel disease alone, 40–55% have disease involving both the small and large intestines, and 15–25% have colitis alone. In the 75% of patients with small-intestinal disease, the terminal ileum is involved in 90%. Unlike UC, which almost always involves the rectum, the rectum is often spared in CD. CD is often segmental with skip areas throughout the diseased intes tine (Fig. 337-5). Perianal disease, manifesting as perirectal fistulas, fissures, abscesses, and anal stenosis, is present in one-third of patients with CD, particularly those with colonic involvement. Rarely, CD may also involve the liver and the pancreas. Unlike UC, CD is a transmural process. Endoscopically, aphthous or small superficial ulcerations characterize mild disease; in more active dis ease, stellate

ulcerations fuse longitudinally and transversely to demarcate islands of mucosa that frequently are histologically normal. This “cobble stone” appearance is characteristic of CD, both endoscopically and by barium radiography. As in UC, pseudopolyps can form in CD. Active CD is characterized by focal inflammation and formation of fistula tracts, which resolve by fibrosis and stricturing of the bowel. The bowel wall thickens and becomes narrowed and fibrotic, leading to chronic, recurrent bowel obstructions. Projections of thickened mesentery known as “creeping fat” encase the bowel, and serosal and mesenteric inflammation promotes adhesions and fistula formation. ■ ■CROHN’S DISEASE: MICROSCOPIC FEATURES The earliest lesions are aphthoid ulcerations and focal crypt abscesses with loose aggregations of macrophages, which form noncaseating

FIGURE 337-5 Crohn’s disease of the colon showing thickening of the wall, with stenosis, linear serpiginous ulcers, and cobblestoning of the mucosa. (Courtesy of Dr. R. Odze, Division of Gastrointestinal Pathology, Department of Pathology, Brigham and Women’s Hospital, Boston, Massachusetts; with permission.) granulomas in all layers of the bowel wall (Fig. 337-6). Granulomas are a characteristic feature of CD and are less commonly found on muco sal biopsies than on surgical resection specimens. Other histologic features of CD include submucosal or subserosal lymphoid aggregates, particularly away from areas of ulceration, gross and microscopic skip areas, and transmural inflammation that is accompanied by fissures that penetrate deeply into the bowel wall and sometimes form fistulous tracts or local abscesses. CLINICAL PRESENTATION ■ ■ULCERATIVE COLITIS Signs and Symptoms The major symptoms of UC are diarrhea, rectal bleeding, tenesmus, passage of mucus, and crampy abdominal pain. The severity of symptoms correlates with the extent of disease. Although UC can present acutely, symptoms usually have been present for weeks to months. Patients with proctitis usually pass fresh blood or blood-stained mucus, either mixed with stool or streaked onto the surface of a normal or hard stool. They also have tenesmus, or urgency with a feeling of incomplete evacuation, but rarely have abdominal pain. With proctitis FIGURE 337-6 Medium-power view of Crohn’s colitis showing mixed acute and chronic inflammation, crypt atrophy, and multiple small epithelioid granulomas in the mucosa. (Courtesy of Dr. R. Odze, Division of Gastrointestinal Pathology, Department of Pathology, Brigham and Women’s Hospital, Boston, Massachusetts; with permission.)

TABLE 337-4 Montreal Classification of Extent and Severity of Ulcerative Colitis (UC) EXTENT ANATOMY E1: Ulcerative proctitis Involvement limited to the rectum E2: Left-sided UC (distal UC) Involvement limited to the colorectum distal to the splenic flexure E3: Extensive UC (pancolitis) Involvement extends proximal to the splenic flexure SEVERITY DEFINITION S0: Clinical remission Absence of symptoms S1: Mild disease activity ≤4 stools/d (with or without blood), absence of systemic illness, normal inflammatory markers (ESR) S2: Moderate disease activity ≥4 stools/d but minimal signs of systemic toxicity S3: Severe disease activity ≥6 bloody stools/d, pulse ≥90 beats/min, temperature ≥37.5°C, hemoglobin <10.5 g/100 mL, and ESR ≥30 mm/h Abbreviation: ESR, erythrocyte sedimentation rate. Source: C Gasche et al: A simple classification of Crohn’s disease: Report of the Working Party for the World Congresses of Gastroenterology, Vienna 1998. Inflamm Bowel Dis 6:8, 2000; and J Satsangi et al: The Montreal classification of inflammatory bowel disease: Controversies, consensus, and implications. Gut 55:749, 2006. or proctosigmoiditis, proximal transit slows, which may account for the constipation commonly seen in patients with distal disease. When the disease extends beyond the rectum, blood is usually mixed with stool or grossly bloody diarrhea may be noted. Colonic motility is altered by inflammation with rapid transit through the inflamed intestine. When the disease is severe, patients pass a liquid stool containing

blood, pus, and fecal matter. Diarrhea is often noc turnal and/or postprandial. Although severe pain is not a prominent symptom, some patients with active disease may experience lower abdominal discomfort or mild central abdominal cramping. Severe cramping and abdominal pain can occur with severe attacks of the dis ease. Other symptoms in moderate to severe disease include anorexia, nausea, vomiting, fever, and weight loss. Physical signs of proctitis include a tender anal canal and blood on rectal examination. With more extensive disease, patients have tenderness to palpation directly over the colon. Patients with a toxic colitis have severe pain and bleeding, and those with megacolon have hepatic tympany. Both may have signs of peritonitis if a perforation has occurred. The classification of disease activity is shown in Table 337-4. Laboratory, Endoscopic, and Radiographic Features Active disease can be associated with a rise in acute-phase reactants (C-reactive protein [CRP]), platelet count, and erythrocyte sedimentation rate (ESR) and a decrease in hemoglobin. Fecal lactoferrin, a glycoprotein present in activated neutrophils, is a highly sensitive and specific marker for detecting intestinal inflammation. Fecal calprotectin is present in neutrophils and monocytes, and the levels correlate well with histologic inflammation, predict relapses, and detect pouchitis. Both fecal lactoferrin and calprotectin are an integral part of IBD management and are used frequently to rule out active inflammation versus symptoms of irritable bowel or bacterial overgrowth. In severely ill patients, the serum albumin level will fall rather quickly. Leukocy tosis may be present but is not a specific indicator of disease activity. Diagnosis relies on the patient’s history, clinical symptoms, negative stool and/or tissue examination for bacteria, C. difficile toxin, ova and parasites, and viruses depending on epidemiologic considerations and clinical presentation; sigmoidoscopic appearance (see Fig. 333-4A); and histology of rectal or colonic biopsy specimens. Sigmoidoscopy is used to assess disease activity and is usually per formed before treatment. If the patient is not having an acute flare, colonoscopy is used to assess disease extent and activity (Fig. 337-7). Endoscopically mild disease is characterized by erythema, decreased vascular pattern, and mild friability. Moderate disease is characterized by marked erythema, absent vascular pattern, friability, and erosions,

FIGURE 337-7 Colonoscopy with acute ulcerative colitis: severe colon inflammation with erythema, friability, and exudates. (Courtesy of Dr. M. Hamilton, Gastroenterology Division, Department of Medicine, Brigham and Women’s Hospital, Boston, Massachusetts; with permission.) and severe disease is characterized by spontaneous bleeding and ulcer ations. Histologic features change more slowly than clinical features but can also be used to grade disease activity. Intestinal ultrasound is a newer tool to assess UC activity and mucosal healing and correlates well with endoscopy and inflammatory markers. CHAPTER 337 Complications Only 15% of patients with UC present initially with severe disease. Massive hemorrhage occurs in 1% of patients, and treatment for the disease usually stops the bleeding. Toxic megacolon is defined as a transverse or right colon with a diameter of >6 cm, with loss of haustration in patients with severe attacks of UC. It occurs rarely and can be triggered by electrolyte abnormalities and narcotics. About 50% of acute dilations will resolve with conservative management alone, but urgent colectomy is required for those who do not improve. Perforation is the most dangerous of the local complications, and the physical signs of peritonitis may not be obvious, especially if the patient is receiving glucocorticoids. Although perforation is rare, the mortality rate for perforation complicating a toxic megacolon is ~15%. In addi tion, patients can develop a toxic colitis and such severe ulcerations that the bowel may perforate without first dilating. Inflammatory Bowel Disease Strictures occur in ~5% of patients and are always a concern in UC because of the possibility of underlying neoplasia. Although benign strictures can form from the inflammation and fibrosis of UC, stric tures that are

impassable with the colonoscope should be presumed malignant until proven otherwise. A stricture that prevents passage of the colonoscope is an indication for surgery. UC patients occasion ally develop anal fissures, perianal abscesses, or hemorrhoids, but the occurrence of extensive perianal lesions should suggest CD. ■ ■CROHN'S DISEASE Signs and Symptoms Although CD usually presents as acute or chronic bowel inflammation, the inflammatory process evolves toward one of two patterns of disease: a fibrostenotic obstructing pattern or a penetrating fistulous pattern, each with different treatments and prognoses. The site of disease influences the clinical manifestations (Table 337-5). ILEOCOLITIS Because the most common site of inflammation is the terminal ileum, the usual presentation of ileocolitis is a chronic his tory of recurrent episodes of right lower quadrant pain and diarrhea. Sometimes the initial presentation mimics acute appendicitis with pronounced right lower quadrant pain, a palpable mass, fever, and leukocytosis. Pain is usually colicky; it precedes and is relieved by def ecation. A low-grade fever is usually noted. High-spiking fever suggests intraabdominal abscess formation. Weight loss is common—typically

TABLE 337-5 Vienna and Montreal Classifications of Crohn's Disease VIENNA MONTREAL Age at diagnosis A1: <40 years A2: >40 years A1: <16 years A2: Between 17 and 40 years A3: >40 years Location L1: Ileal L2: Colonic L3: Ileocolonic L4: Upper L1: Ileal L2: Colonic L3: Ileocolonic L4: Isolated upper diseasea Behavior B1: Nonstricturing, nonpenetrating B2: Stricturing B3: Penetrating B1: Nonstricturing, nonpenetrating B2: Stricturing B3: Penetrating p: Perianal disease modifierb aL4 is a modifier and can be added to L1–L3 when there is concomitant foregut disease. bp is added to B1–B3 when there is concomitant perianal disease. 10–20% of body weight—and develops as a consequence of diarrhea, anorexia, and fear of eating. An inflammatory mass may be palpated in the right lower quadrant of the abdomen. The mass is composed of inflamed bowel, induration of the mesentery, and enlarged abdominal lymph nodes. The "string sign" on radiographic studies results from a severely narrowed loop of bowel, which makes the lumen resemble a frayed cotton string. It is caused by incomplete filling of the lumen as the result of edema, irritability, and spasms associated with inflammation and ulcerations. The sign may be seen in both nonstenotic and stenotic phases of the disease. PART 10 Disorders of the Gastrointestinal System Bowel obstruction may take several forms. In the early stages of disease, bowel wall edema and spasm produce intermittent obstructive manifestations and increasing symptoms of postprandial pain. Over several years, persistent inflammation gradually progresses to fibroste notic narrowing and stricture. Diarrhea will decrease and be replaced by chronic bowel obstruction. Acute episodes of obstruction occur as well, precipitated by bowel inflammation and spasm or sometimes by impaction of undigested food or medication. These episodes usually resolve with intravenous fluids and gastric decompression. Severe inflammation of the ileocecal region may lead to localized wall thinning, with microperforation and fistula formation to the adjacent bowel, the skin, or the urinary bladder, or to an abscess cav ity in the mesentery. Enterovesical fistulas typically present as dysuria or recurrent bladder infections or, less commonly, as pneumaturia or fecaluria. Enterocutaneous fistulas follow tissue planes of least resistance, usually draining through abdominal surgical scars. Entero vaginal fistulas are rare and present as dyspareunia or as a feculent or foul-smelling, often painful vaginal discharge. They are unlikely to develop without a prior hysterectomy. JEJUNOILEITIS Extensive inflammatory disease is associated with a loss of digestive and absorptive surface, resulting in malabsorption and steatorrhea. Nutritional deficiencies can also result from poor intake and enteric losses of protein and other nutrients. Intestinal malab sorption can cause anemia, hypoalbuminemia, hypocalcemia, hypo magnesemia, coagulopathy, and hyperoxaluria with nephrolithiasis in patients with an intact colon. Many patients

need to take intravenous iron since oral iron is poorly tolerated and often ineffective. Verte bral fractures are caused by a combination of vitamin D deficiency, hypocalcemia, and prolonged glucocorticoid use. Pellagra from niacin deficiency can occur in extensive small-bowel disease, and malabsorp tion of vitamin B12 can lead to megaloblastic anemia and neurologic symptoms. Other important nutrients to measure and replete if low are folate and vitamins A, E, and K. Levels of minerals such as zinc, sele nium, copper, and magnesium are often low in patients with extensive small-bowel inflammation or resections, and these should be repleted as well. Most patients should take daily multivitamin, calcium, and vitamin D supplements. Diarrhea is characteristic of active disease; its causes include (1) bacterial overgrowth in obstructive stasis or fistulization, (2) bile acid

malabsorption due to a diseased or resected terminal ileum, (3) intes tinal inflammation with decreased water absorption and increased secretion of electrolytes, and (4) enteroenteric fistula(e). COLITIS AND PERIANAL DISEASE Patients with colitis present with low-grade fevers, malaise, diarrhea, crampy abdominal pain, and sometimes hematochezia. Gross bleeding is not as common as in UC and appears in about one-half of patients with exclusively colonic dis ease. Only 1–2% exhibit massive bleeding. Pain is caused by passage of fecal material through narrowed and inflamed segments of the large bowel. Decreased rectal compliance is another cause for diarrhea in Crohn’s colitis patients. Stricturing can occur in the colon in 4–16% of patients and produce symptoms of bowel obstruction. If the endoscopist is unable to traverse a stricture in Crohn’s colitis, surgical resection should be considered, especially if the patient has symptoms of chronic obstruction. Colonic disease may fistulize into the stomach or duodenum, causing feculent vomiting, or to the proximal or mid-small bowel, causing malab sorption by “short circuiting” the absorptive surface and bacterial overgrowth. Ten percent of women with Crohn’s colitis will develop a rectovaginal fistula. Perianal disease affects about one-third of patients with Crohn’s colitis and is manifested by incontinence, large hemorrhoidal tags, anal stric tures, anorectal fistulas, and perirectal abscesses. Not all patients with perianal fistula will have endoscopic evidence of colonic inflammation. GASTRODUODENAL DISEASE Symptoms and signs of upper GI tract disease include nausea, vomiting, and epigastric pain. Patients usually have a Helicobacter pylori–negative gastritis. The second portion of the duodenum is more commonly involved than the bulb. Fistulas involv ing the stomach or duodenum arise from the small or large bowel and do not necessarily signify the presence of upper GI tract involvement. Patients with advanced gastroduodenal CD may develop a chronic gas tric outlet obstruction. About 30% of children diagnosed with CD have esophagogastroduodenal involvement. The classification of disease activity is shown in Table 337-5. Laboratory, Endoscopic, and Radiographic Features Laboratory abnormalities include elevated ESR and CRP. In more severe disease, find ings include hypoalbuminemia, anemia, and leukocytosis. Fecal calprotec tin and lactoferrin levels have been used to distinguish IBD from irritable bowel syndrome (IBS), to assess whether CD is active, and to detect post operative recurrence of CD. Fecal calprotectin is a more sensitive marker of ileocolonic or colonic inflammation rather than isolated ileal inflammation. Endoscopic features of CD include rectal sparing, aphthous ulcer ations, fistulas, and skip lesions. Colonoscopy allows examination and biopsy of mass lesions or strictures and biopsy of the terminal ileum. Upper endoscopy is useful in diagnosing gastroduodenal involvement in patients with upper tract symptoms. An ileal or colonic stricture may be dilated with a balloon introduced through the colonoscope. Strictures ≤4 cm in length and those at anastomotic sites respond better to endo scopic dilation. The perforation rate is as high as 10%. Most endoscopists dilate only fibrotic strictures and not those associated with active inflam mation. Wireless capsule endoscopy (WCE) allows direct visualization of the

entire small-bowel mucosa (Fig. 337-8). The diagnostic yield of detecting lesions suggestive of active CD is higher with WCE than computed tomography (CT) or magnetic resonance (MR) enterography. WCE should not be used in the setting of a small-bowel stricture. Cap sule retention occurs in <1% of patients with suspected CD, but retention rates of 4–6% are seen in patients with established CD. It is helpful to give the patient with CD a patency capsule, which is made of barium and starts to dissolve 30 h after ingestion. An abdominal x-ray can be taken at around 30 h after ingestion to see if the capsule is still present in the small bowel, which would indicate a stricture. In CD, early radiographic findings in the small bowel include thickened folds and aphthous ulcerations. “Cobblestoning” from lon gitudinal and transverse ulcerations most frequently involves the small bowel. In more advanced disease, strictures, fistulas, inflammatory masses, and abscesses may be detected. The earliest macroscopic find ings of colonic CD are aphthous ulcers. These small ulcers are often

FIGURE 337-8 Wireless capsule endoscopy image in a patient with Crohn’s disease of the ileum shows ulcerations and narrowing of the intestinal lumen. (Courtesy of Dr. S. Reddy, Gastroenterology Division, Department of Medicine, Brigham and Women’s Hospital, Boston, Massachusetts; with permission.) multiple and separated by normal intervening mucosa. As the disease progresses, aphthous ulcers become enlarged, deeper, and occasionally connected to one another, forming longitudinal stellate, serpiginous, and linear ulcers (see Fig. 333-4B). The transmural inflammation of CD leads to decreased luminal diameter and limited distensibility. As ulcers progress deeper, they can lead to fistula formation. The segmental nature of CD results in wide gaps of normal or dilated bowel between involved segments. CT enterography and MR enterography have been shown to be equally accurate in the identification of active small-bowel inflamma tion. MRI is thought to offer superior soft tissue contrast and has the added advantage of avoiding radiation exposure changes (Figs. 337-9 and 337-10). The lack of ionizing radiation is particularly appealing in younger patients and when monitoring response to therapy where serial images will be obtained. Pelvic MRI is superior to pelvic CT for demonstrating pelvic lesions such as ischiorectal abscesses and perianal fistulas (Fig. 337-11). An underutilized resource for assessing small-bowel CD is small-bowel ultrasound (SBUS). SBUS is at least as sensitive as MR enterography and CT enterography for detecting small-bowel CD, with a sensitivity of 94%, specificity of 97%, positive predictive value of 97%, and negative predictive value of 94%. Use of oral contrast medium can increase the sensitivity and specificity to detect small-bowel lesions to 100%. SBUS is best suited for distal smallbowel assessment, as the sensitivity of detecting lesions within the duo denum and proximal jejunum may be lower due to anatomic position. The limitations of SBUS include availability and operator dependence. Complications Because CD is a transmural process, serosal adhe sions develop that provide direct pathways for fistula formation and reduce the incidence of free perforation. Perforation occurs in 1–2% of patients, usually in the ileum but occasionally in the jejunum or as a complication of toxic megacolon. The peritonitis of free perfo ration, especially colonic, may be fatal. Intraabdominal and pelvic abscesses occur in 10–30% of patients with CD at some time in the course of their illness. CT-guided percutaneous drainage of the abscess is standard therapy. Despite adequate drainage, most patients need resection of the offending bowel segment. Percutaneous drainage has an especially high failure rate in abdominal wall abscesses. Systemic glucocorticoid therapy increases the risk of intraabdominal and pelvic

FIGURE 337-9 A coronal magnetic resonance image was obtained using a half Fourier single-shot T2-weighted acquisition with fat saturation in a 27-year-old pregnant (23 weeks’ gestation) woman.

The patient had Crohn’s disease and was maintained on mercaptopurine and prednisone. She presented with abdominal pain, distension, vomiting, and small-bowel obstruction. The image reveals a 7- to 10-cm long stricture at the terminal ileum (white arrows) causing obstruction and significant dilatation of the proximal small bowel (white asterisk). A fetus is seen in the uterus (dashed white arrows). (Courtesy of Drs. J. F. B. Chick and P. B. Shyn, Abdominal Imaging and Intervention, Department of Radiology, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts; with permission.) CHAPTER 337 Inflammatory Bowel Disease abscesses in CD patients who have never had an operation. Other com plications include intestinal obstruction in 40%, massive hemorrhage, malabsorption, and severe perianal disease. Serologic Markers Clinical factors described at diagnosis are more helpful than serologies at predicting the natural history of IBD. The positive and negative predictive values of serologic tests such as anti-Saccharomyces cerevisiae antibody (ASCA) and perinuclear antineutrophil cytoplasmic antibody (pANCA) vary depending on the prevalence of IBD in different populations, such that their clinical usefulness is unclear. DIFFERENTIAL DIAGNOSIS OF UC AND CD Once a diagnosis of IBD is made, distinguishing between UC and CD is impossible initially in up to 15% of cases. These are termed indeterminate colitis. Fortunately, in most cases, the true nature of the underlying colitis becomes evident later in the course of the patient’s disease. Approximately 5% of colon resection specimens are difficult to classify as either UC or CD because they exhibit overlapping histologic features. ■ ■INFECTIOUS DISEASES Infections of the small intestines and colon can mimic CD or UC. They may be bacterial, fungal, viral, or protozoal in origin (Table 337-6). Campylobacter colitis can mimic the endoscopic appearance of severe UC and can cause a relapse of established UC. Salmonella can cause watery or bloody diarrhea, nausea, and vomiting. Shigellosis causes watery diarrhea, abdominal pain, and fever followed by rectal tenesmus and by the passage of blood and mucus per rectum. All three are usu ally self-limited, but 1% of patients infected with Salmonella become asymptomatic carriers. Yersinia enterocolitica infection occurs mainly in the terminal ileum and causes mucosal ulceration, neutrophil

FIGURE 337-10 A coronal balanced, steady-state, free precession, T2-weighted image with fat saturation was obtained in a 32-year-old man with Crohn’s disease and prior episodes of bowel obstruction, fistulas, and abscesses. He was being treated with mercaptopurine and presented with abdominal distention and diarrhea. The image demonstrates a new gastrocolic fistula (solid white arrows). Multifocal involvement of the small bowel and terminal ileum is also present (dashed white arrows). (Courtesy of Drs. J. F. B. Chick and P. B. Shyn, Abdominal Imaging and Intervention, Department of Radiology, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts; with permission.) PART 10 Disorders of the Gastrointestinal System FIGURE 337-11 Axial T2-weighted fat-saturated image obtained in a 39-year-old male with Crohn’s disease shows a defect in the internal sphincter at the 6 o’clock position of the mid anal canal (open white arrow) communicating with a 1.1-cm intersphincteric collection (black arrow). Wide defect in the external sphincter at the 7 o’clock position (solid white arrow) leads to a moderate-sized perianal abscess in the ischioanal fossa (asterisk). (Courtesy of Drs. J.S. Quon and P.B. Shyn, Abdominal Imaging and Intervention, Department of Radiology, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts; with permission.)

TABLE 337-6 Diseases That Mimic IBD Infectious Etiologies Bacterial Mycobacterial Viral Salmonella Tuberculosis Cytomegalovirus Shigella Mycobacterium avium Herpes simplex Toxigenic Parasitic HIV Escherichia coli Amebiasis Fungal Campylobacter Isospora Histoplasmosis Yersinia Trichuris

trichiura Candida Clostridioides difficile Hookworm Aspergillus Gonorrhea Strongyloides Chlamydia trachomatis Noninfectious Etiologies Inflammatory Neoplastic Drugs and Chemicals Appendicitis Lymphoma NSAIDs Diverticulitis Metastatic Phosphosoda Diversion colitis Carcinoma Cathartic colon Collagenous/lymphocytic Carcinoma of the ileum Carcinoid Familial polyposis Gold Oral contraceptives Cocaine Immune checkpoint colitis Ischemic colitis Radiation colitis/enteritis inhibitor colitis Mycophenolate Solitary rectal ulcer syndrome mofetil Eosinophilic gastroenteritis Neutropenic colitis Behçet's syndrome Graft-versus-host disease Abbreviations: IBD, inflammatory bowel disease; NSAIDs, nonsteroidal antiinflammatory drugs. invasion, and thickening of the ileal wall. Other bacterial infections that may mimic IBD include C. difficile, which presents with watery diarrhea, tenesmus, nausea, and vomiting; and E. coli, three categories of which can cause colitis. These are enterohemorrhagic, enteroinva sive, and enteroadherent E. coli, all of which can cause bloody diarrhea and abdominal tenderness. Gonorrhea, Chlamydia, and syphilis can also cause proctitis. GI involvement with mycobacterial infection occurs primarily in the immunosuppressed patient but may occur in patients with nor mal immunity. Distal ileal and cecal involvement predominates, and patients present with symptoms of small-bowel obstruction and a ten der abdominal mass. The diagnosis is made most directly by colonos copy with biopsy and culture. Although most of the patients with viral colitis are immunosuppressed, cytomegalovirus (CMV) and herpes simplex proctitis may occur in immunocompetent individuals. CMV occurs most commonly in the esophagus, colon, and rectum but may also involve the small intestine. Symptoms include abdominal pain, bloody diarrhea, fever, and weight loss. With severe disease, necrosis and perforation can occur. Diagnosis is made by identification of char acteristic intranuclear inclusions in mucosal cells on biopsy. Herpes simplex infection of the GI tract is limited to the oropharynx, anorec tum, and perianal areas. Symptoms include anorectal pain, tenesmus, constipation, inguinal adenopathy, difficulty with urinary voiding, and sacral paresthesias. Diagnosis is made by rectal biopsy with identifica tion of characteristic cellular inclusions and viral culture. HIV itself can cause diarrhea, nausea, vomiting, and anorexia. Small-intestinal biopsies show partial villous atrophy; small-bowel bacterial overgrowth and fat malabsorption may also be noted. Protozoan parasites include Isospora belli, which can cause a selflimited infection in healthy hosts but causes a chronic profuse, watery diarrhea and weight loss in AIDS patients. Entamoeba histolytica or related species infect ~10% of the world's population; symptoms include abdominal pain, tenesmus, frequent loose stools containing

blood and mucus, and abdominal tenderness. Colonoscopy reveals focal punctate ulcers with normal intervening mucosa; diagnosis is made by biopsy or serum amebic antibodies. Fulminant amebic colitis is rare but has a mortality rate of >50%. Other parasitic infections that may mimic IBD include hookworm (Necator americanus), whipworm (Trichuris trichiura), and Strongyloi des stercoralis. In severely immunocompromised patients, Candida or Aspergillus can be identified in the submucosa. Disseminated histoplas mosis can involve the ileocecal area. ■ ■NONINFECTIOUS DISEASES Diverticulitis can be confused with CD clinically and radiographically. Both diseases cause fever, abdominal pain, tender abdominal mass, leu kocytosis, elevated ESR, partial obstruction, and fistulas. Perianal disease or ileitis on small-bowel series favors the diagnosis of CD. Significant endoscopic mucosal abnormalities are more likely in CD than in diver ticulitis. Endoscopic or clinical recurrence following segmental resection favors CD. Diverticular-associated colitis is similar to CD, but mucosal abnormalities are limited to the sigmoid and descending colon. Ischemic colitis is commonly confused with IBD. The ischemic process can be chronic and diffuse, as in UC, or segmental, as in CD. Colonic inflammation due to ischemia may resolve quickly or may

per sist and result in transmural scarring and stricture formation. Ischemic bowel disease should be considered in the elderly following abdominal aortic aneurysm repair or when a patient has a hypercoagulable state or a severe cardiac or peripheral vascular disorder. Patients usually present with sudden onset of left lower quadrant pain, urgency to defecate, and the passage of bright red blood per rectum. Endoscopic examination often demonstrates a normal-appearing rectum and a sharp transition to an area of inflammation in the descending colon and splenic flexure. The effects of radiotherapy on the GI tract can be difficult to distin guish from IBD. Acute symptoms can occur within 1–2 weeks of start ing radiotherapy. When the rectum and sigmoid are irradiated, patients develop bloody, mucoid diarrhea and tenesmus, as in distal UC. With small-bowel involvement, diarrhea is common. Late symptoms include malabsorption and weight loss. Stricturing with obstruction and bacte rial overgrowth may occur. Fistulas can penetrate the bladder, vagina, or abdominal wall. Flexible sigmoidoscopy reveals mucosal granularity, friability, numerous telangiectasias, and occasionally discrete ulcer ations. Biopsy can be diagnostic. Solitary rectal ulcer syndrome is uncommon and can be con fused with IBD. It occurs in persons of all ages and may be caused by impaired evacuation and failure of relaxation of the puborectalis muscle. Single or multiple ulcerations may arise from anal sphincter overactivity, higher intrarectal pressures during defecation, and digital removal of stool. Patients complain of constipation with straining and pass blood and mucus per rectum. Other symptoms include abdominal pain, diarrhea, tenesmus, and perineal pain. Ulceration, which may be as large as 5 cm in diameter, is usually observed anteriorly or anterolat erally 3–15 cm from the anal verge. Biopsies can be diagnostic. Several types of colitis are associated with nonsteroidal antiinflammatory drugs (NSAIDs), including de novo colitis, reactivation of IBD, and proctitis caused by use of suppositories. Most patients with NSAID-related colitis present with diarrhea and abdominal pain, and complications include stricture, bleeding, obstruction, perforation, and fistulization. Withdrawal of these agents is crucial, and in cases of reactivated IBD, standard therapies are indicated. Colitis secondary to immune checkpoint inhibitors (ICIs), termed ICI-related colitis, has emerged as these agents have found use in a wide variety of cancers. Immune checkpoint proteins such as CTLA-4 and programmed cell death protein 1 (PD-1) are receptors expressed on the surface of effector T cells that interact with their ligands CD80/ CD86 (CTLA-4) and programmed death ligand 1 (PD-L1) on antigenpresenting cells and normally function as inhibitors of immune responses. ICIs block these inhibitory pathways and promote the acti vation and proliferation of the native adaptive T-cell response against malignant cells as their mechanism of antitumor activity. While very effective at enhancing antitumor T-cell activity, ICIs also activate global T-cell responses that induce several autoimmune-related adverse

events. Although immune-related adverse events of ICIs occur in mul tiple organ systems, the GI tract is affected in 21–44% of patients. The most common clinical presentation is self-limited diarrhea that can be associated with frank colitis and can lead to significant morbidity and mortality if not managed appropriately. Treatment is generally based on symptom severity. Moderate to severe symptoms usually require glucocorticoids, whereas biologics such as anti-TNF agents and integ rin inhibitors are used in steroid-refractory cases.

■ ■THE ATYPICAL COLITIDES Two atypical colitides—collagenous colitis and lymphocytic colitis—have normal endoscopic appearances. Collagenous colitis has two main histologic components: increased subepithelial collagen deposition and colitis with increased intraepithelial lymphocytes. The female-to-male ratio is 9:1, and most patients present in the sixth or seventh decade of life. The main symptom is chronic watery diarrhea. Risk factors include smoking; use of NSAIDs, proton

pump inhibitors, or beta blockers; and a history of autoimmune disease. Lymphocytic colitis has features similar to collagenous colitis, includ ing age at onset and clinical presentation, but it has almost equal inci dence in men and women and no subepithelial collagen deposition on pathologic section. However, intraepithelial lymphocytes are increased. Use of sertraline (but not beta blockers) is an additional risk factor. The frequency of celiac disease is increased in lymphocytic colitis and ranges from 9 to 27%. Celiac disease should be excluded in all patients with lymphocytic colitis, particularly if diarrhea does not respond to conven tional therapy. Treatments for both microscopic colitides vary depending on symptom severity and include, antidiarrheals (e.g., loperamide and diphenoxylate), bismuth, aminosalicylates, budesonide, systemic gluco corticoids, and biologics for refractory disease. CHAPTER 337 Diversion colitis is an inflammatory process that arises in segments of the large intestine that are not continuous with the fecal stream. It usually occurs in patients with ileostomy or colostomy when a mucus fistula or a Hartmann's pouch has been created. Clinically, patients have mucus or bloody discharge from the rectum. Erythema, granu larity, friability, and, in more severe cases, ulceration can be seen on endoscopy. Histopathology shows areas of active inflammation with foci of cryptitis and crypt abscesses. Crypt architecture is normal, which differentiates it from UC but not necessarily CD. Short-chain fatty acid enemas may help in diversion colitis, but the definitive therapy is surgical reanastomosis. Inflammatory Bowel Disease EXTRAINTESTINAL MANIFESTATIONS Up to one-third of IBD patients have at least one extraintestinal disease manifestation. Please see Table 337-7 for a summary of IBD EIMs. ■ ■DERMATOLOGIC Erythema nodosum (EN) occurs in up to 15% of CD patients and 10% of UC patients. Attacks usually correlate with bowel activity; skin lesions develop after the onset of bowel symptoms, and patients frequently have concomitant active peripheral arthritis. The lesions of EN are hot, red, tender nodules measuring 1–5 cm in diameter and are found on the anterior surface of the lower legs, ankles, calves, thighs, and arms. Therapy is directed toward the underlying bowel disease. Pyoderma gangrenosum (PG) is seen in 1–12% of UC patients and less commonly in Crohn's colitis. Although it usually presents after the diagnosis of IBD, PG may occur years before the onset of bowel symptoms, run a course independent of the bowel disease, respond poorly to colectomy, and even develop years after proctocolectomy. It is usually associated with severe disease. Lesions are commonly found on the dorsal surface of the feet and legs but may occur on the arms, chest, stoma, and even the face. PG usually begins as a pustule and then spreads concentrically to rapidly undermine healthy skin. Lesions then ulcerate, with violaceous edges surrounded by a margin of ery thema. Centrally, they contain necrotic tissue with blood and exudates. Lesions may be single or multiple and grow as large as 30 cm. They are sometimes very difficult to treat and often require IV antibiotics, IV glucocorticoids, dapsone, azathioprine, thalidomide, IV cyclosporine (CSA), infliximab, or adalimumab.

TABLE 337-7 Extraintestinal Manifestations CATEGORY CLINICAL COURSE TREATMENT Rheumatologic Disorders (5–20%) Peripheral arthritis Asymmetric, migratory Parallels bowel activity Sacroiliitis Symmetric: spine and hip joints Independent of bowel activity Ankylosing spondylitis Gradual fusion of spine Independent of bowel activity Two-thirds have HLA-B27 antigen Metabolic Bone Disorders (up to 40% of patients) Osteoporosis Risk increased by glucocorticoids, cyclosporine, methotrexate, total parenteral nutrition, malabsorption, and inflammation Fracture rates highest in the elderly (age >60) Osteonecrosis Death of osteocytes and adipocytes and eventual bone collapse; affects hips more than knees or shoulders; risk factor is steroid use Dermatologic Disorders (10–20%) Erythema nodosum Hot, red, tender, nodules/extremities Parallels bowel activity Pyoderma gangrenosum Ulcerating, necrotic lesions on extremities, trunk,

face, stoma Independent of bowel activity Psoriasis Unrelated to bowel activity Topical steroids, light therapy, methotrexate, infliximab, adalimumab, ustekinumab, risankizumab, JAK inhibitors Pyoderma vegetans Intertriginous areas Parallels bowel activity PART 10 Disorders of the Gastrointestinal System Pyostomatitis vegetans Mucous membranes Parallels bowel activity Metastatic Crohn's disease (CD) CD of the skin Parallels bowel activity Sweet syndrome Neutrophilic dermatosis Parallels bowel activity Aphthous stomatitis Oral ulcerations Parallels bowel activity Ocular Disorders (1–11%) Uveitis Ocular pain, photophobia, blurred vision, headache Independent of bowel activity Episcleritis Mild ocular burning Parallels bowel activity Hepatobiliary Disorders (10–35%) Fatty liver Secondary to chronic illness, malnutrition, steroid therapy Improve nutrition, reduce steroids Cholelithiasis Patients with ileitis or ileal resection Malabsorption of bile acids, depletion of bile salt pool, secretion of lithogenic bile Primary sclerosing cholangitis (PSC) Intrahepatic and extrahepatic Inflammation and fibrosis leading to biliary cirrhosis and hepatic failure 7–10% cholangiocarcinoma Small-duct PSC involves small-caliber bile ducts and has a better prognosis Urologic Nephrolithiasis (10–20%) CD patients following small-bowel resection; calcium oxalate stones most common Less Common Extraintestinal Manifestations Thromboembolic disorders Increased risk of venous and arterial thrombosis; factors responsible include abnormalities of the platelet-endothelial interaction, hyperhomocysteinemia, alterations in the coagulation cascade, impaired fibrinolysis, involvement of tissue factor–bearing microvesicles, disruption of the normal coagulation system by autoantibodies, and a genetic predisposition Cardiopulmonary Endocarditis, myocarditis, pleuropericarditis, interstitial lung disease Treatment is varied; stop 5-ASA agents as they can rarely cause interstitial lung disease Systemic amyloidosis Secondary (reactive) in long-standing IBD, especially CD Colchicine and referral to specialty center Pancreatitis Duodenal fistulas, ampullary CD, gallstones, PSC, drugs (MP, azathioprine, 5-ASAs), autoimmune, primary CD of the pancreas Abbreviations: 5-ASA, 5-aminosalicylic acid; DEXA, dual-energy x-ray absorptiometry; ERCP, endoscopic retrograde cholangiopancreatography; IBD, inflammatory bowel disease; IL, interleukin; MP, mercaptopurine; TNF, tumor necrosis factor.

Reduce bowel inflammation Steroids, injections, methotrexate, anti-TNF Physical therapy, steroids, injections, methotrexate, antiTNF, IL-17 inhibitors, JAK inhibitors Screening with DEXA scan, check vitamin D levels, treat if osteoporosis or osteopenia on long-term corticosteroids Pain control, injections, joint replacement Reduce bowel inflammation Antibiotics, steroids, cyclosporine, infliximab, dapsone, azathioprine, intralesional steroids; not debridement or colectomy Evanescent; resolves without progression Evanescent; resolves without progression Reduce bowel inflammation Reduce bowel inflammation Reduce bowel inflammation/topical therapy Topical or systemic steroids Topical corticosteroids Reduce bowel inflammation; cholecystectomy in symptomatic patients Cholecystectomy in patients with gallbladder polyps due to the high incidence of malignancy Low-oxalate diet; control of bowel inflammation; surgical intervention Anticoagulation; control of inflammation Treatment is varied; stop offending medication; diagnose and treat with ERCP and/or cholecystectomy

Other dermatologic manifestations include pyoderma vegetans, which occurs in intertriginous areas; pyostomatitis vegetans, which involves the mucous membranes; Sweet syndrome, a neutrophilic dermatosis; and metastatic CD, a rare disorder defined by cutaneous granuloma formation. Psoriasis affects 5–10% of patients with IBD and is unrelated to bowel activity, consistent with the potential shared immunogenetic basis of these diseases. Perianal skin tags are found in 75–80% of patients with CD, especially those with colon involvement. Oral mucosal

lesions, seen often in CD and rarely in UC, include aph thous stomatitis and “cobblestone” lesions of the buccal mucosa. ■ ■RHEUMATOLOGIC Peripheral arthritis develops in 15–20% of IBD patients, is more common in CD, and worsens with exacerbations of bowel activity. It is asymmetric, polyarticular, and migratory and most often affects large joints of the upper and lower extremities. Treatment is directed at reducing bowel inflammation. In severe UC, colectomy frequently cures the arthritis. Ankylosing spondylitis (AS) occurs in ~10% of IBD patients and is more common in CD than UC. About two-thirds of IBD patients with AS express the HLA-B27 antigen. The AS activity is not related to bowel activity and does not remit with glucocorticoids or colectomy. It most often affects the spine and pelvis, producing symptoms of dif fuse low-back pain, buttock pain, and morning stiffness. The course is continuous and progressive, leading to permanent skeletal damage and deformity. Anti-TNF therapy reduces spinal inflammation and improves functional status and quality of life. Sacroiliitis is symmetric, occurs equally in UC and CD, is often asymptomatic, does not correlate with bowel activity, and does not always progress to AS. Other rheumatic manifestations include hyper trophic osteoarthropathy, pelvic/femoral osteomyelitis, and relapsing polychondritis. ■ ■OCULAR The incidence of ocular complications in IBD patients is 1–10%. The most common are conjunctivitis, anterior uveitis/iritis, and episcleritis. Uveitis is associated with both UC and Crohn’s colitis, may be found during periods of remission, and may develop in patients following bowel resection. Symptoms include ocular pain, photophobia, blurred vision, and headache. Prompt intervention, sometimes with systemic glucocorticoids, is required to prevent scarring and visual impairment. Episcleritis is a benign disorder that presents with symptoms of mild ocular burning. It occurs in 3–4% of IBD patients, more commonly in Crohn’s colitis, and is treated with topical glucocorticoids. ■ ■HEPATOBILIARY Hepatic steatosis is detectable in about one-half of the abnormal liver biopsies from patients with CD and UC; patients usually present with hepatomegaly. Fatty liver usually results from a combination of chronic debilitating illness, malnutrition, and glucocorticoid therapy. Cholelithiasis occurs in 10–35% of CD patients with ileitis or ileal resection. Gallstone formation is caused by malabsorption of bile acids, resulting in depletion of the bile salt pool and the secretion of lithogenic bile. Primary sclerosing cholangitis (PSC) is a disorder characterized by both intrahepatic and extrahepatic bile duct inflammation and fibro sis, frequently leading to biliary cirrhosis and hepatic failure; ~5% of patients with UC have PSC, but 50–75% of patients with PSC have IBD. PSC occurs less often in patients with CD. Although it can be recog nized after the diagnosis of IBD, PSC can be detected earlier or even years after proctocolectomy. Consistent with this, the immunogenetic basis for PSC appears to be overlapping but distinct from UC based on GWAS, although both IBD and PSC are commonly pANCA positive. Most patients have no symptoms at the time of diagnosis; when symp toms are present, they consist of fatigue, jaundice, abdominal pain, fever, anorexia, and malaise. The traditional gold standard diagnostic test is endoscopic retrograde cholangiopancreatography (ERCP), but magnetic resonance cholangiopancreatography (MRCP) is sensitive, specific, and safer. MRCP is reasonable as an initial diagnostic test in

children and adults and can visualize irregularities, multifocal stric tures, and dilatations of all levels of the biliary tree. In patients with PSC, both ERCP and MRCP demonstrate multiple bile duct strictures alternating with relatively normal segments.

Gallbladder polyps in patients with PSC have a high incidence of malignancy, and cholecystectomy is recommended, even if a mass lesion is <1 cm in diameter. Gallbladder surveillance with ultrasound should be performed annually. Endoscopic stenting may be palliative for cholestasis

secondary to bile duct obstruction. Patients with symp tomatic disease develop cirrhosis and liver failure over 5–10 years and eventually require liver transplantation. PSC patients have a 10–15% lifetime risk of developing cholangiocarcinoma and then cannot be transplanted. Patients with IBD and PSC are at increased risk of colon cancer and should be surveyed yearly by colonoscopy and biopsy. In addition, cholangiography is normal in a small percentage of patients who have a variant of PSC known as small duct primary scle rosing cholangitis. This variant (sometimes referred to as "pericholan gitis") is probably a form of PSC involving small-caliber bile ducts. It has similar biochemical and histologic features to classic PSC. It has a significantly better prognosis than classic PSC, although it may evolve into classic PSC. Granulomatous hepatitis and hepatic amyloidosis are much rarer EIMs of IBD. ■ ■UROLOGIC The most frequent genitourinary complications are calculi, ureteral obstruction, and ileal bladder fistulas. The highest frequency of neph rolithiasis (10–20%) occurs in patients with CD following small-bowel resection. Calcium oxalate stones develop secondary to hyperoxaluria, which results from increased absorption of dietary oxalate. Normally, dietary calcium combines with luminal oxalate to form insoluble cal cium oxalate, which is eliminated in the stool. In patients with ileal dysfunction, however, nonabsorbed fatty acids bind calcium and leave oxalate unbound. The unbound oxalate is then delivered to the colon, where it is readily absorbed, especially in the presence of inflammation. CHAPTER 337 Inflammatory Bowel Disease ■ ■METABOLIC BONE DISORDERS Low bone mass occurs in 14–42% of IBD patients. The risk is increased by glucocorticoids, CSA, methotrexate (MTX), and total parenteral nutrition (TPN). Malabsorption and inflammation mediated by IL-1, IL-6, TNF, and other inflammatory mediators also contribute to low bone density. An increased incidence of hip, spine, wrist, and rib fractures has been noted: 36% in CD and 45% in UC. The absolute risk of an osteoporotic fracture is ~1% per person per year. Fracture rates, particularly in the spine and hip, are highest among the elderly (age >60). One study noted an OR of 1.72 for vertebral fracture and an OR of 1.59 for hip fracture. The disease severity predicted the risk of a fracture. Only 13% of IBD patients who had a fracture were on any kind of antifracture treatment. Up to 20% of bone mass can be lost per year with chronic glucocorticoid use. The effect is dose-dependent. Budesonide may also suppress the pituitary-adrenal axis and thus car ries a risk of causing osteoporosis. Osteonecrosis is characterized by death of osteocytes and adipocytes and eventual bone collapse. The pain is aggravated by motion and swelling of the joints. It affects the hips more often than knees and shoulders, and in one series, 4.3% of patients developed osteonecrosis within 6 months of starting glucocorticoids. Diagnosis is made by bone scan or magnetic resonance imaging (MRI), and treatment consists of pain control, cord decompression, osteotomy, and joint replacement. ■ ■THROMBOEMBOLIC DISORDERS Patients with IBD have an increased risk of both venous and arterial thrombosis even if the disease is not active. Factors responsible for the hypercoagulable state have included abnormalities of the plateletendothelial interaction, hyperhomocysteinemia, alterations in the coagulation cascade, impaired fibrinolysis, involvement of tissue factor–bearing microvesicles, disruption of the normal coagulation system by autoantibodies, and a genetic predisposition. A spectrum of vasculitides involving small, medium, and large vessels has also been observed.

■ ■OTHER DISORDERS More common cardiopulmonary manifestations include endocarditis, myocarditis, pleuropericarditis, and interstitial lung disease. A second ary or reactive amyloidosis can occur in patients with long-standing IBD, especially in patients with CD. Amyloid material is deposited sys temically and can cause diarrhea, constipation, and renal failure. The renal disease can be successfully treated with colchicine. Pancreatitis is a rare EIM of IBD and results from

duodenal fistulas; ampullary CD; gallstones; PSC; drugs such as mercaptopurine, azathioprine, or, very rarely, 5-ASA agents; autoimmune pancreatitis; and primary CD of the pancreas.

TREATMENT Inflammatory Bowel Disease 5-ASA AGENTS These agents are effective at inducing and maintaining remission in UC. Peroxisome proliferator–activated receptor γ (PPAR-γ) may mediate 5-ASA therapeutic action by decreasing nuclear localiza tion of NF-κB. Sulfa-free aminosalicylate formulations include alternative azo-bonded carriers, 5-ASA dimers, and delayed-release and controlled-release preparations. Each has the same efficacy as sulfasalazine when equimolar concentrations are used. Sulfasalazine is effective treatment for mild to moderate UC, but its high rate of side effects limits its use. Although sulfasalazine is more effective at higher doses, at 6 or 8 g/d, up to 30% of patients experience allergic reactions or intolerable side effects such as headache, anorexia, nausea, and vomiting that are attributable to the sulfapyridine moiety that is attached to 5-ASA. Hypersensitivity reactions, independent of sulfapyridine levels, include rash, fever, hepatitis, agranulocytosis, hypersensitivity pneumonitis, pancre atitis, worsening of colitis, and reversible sperm abnormalities. Sulfasalazine can also impair folate absorption, and patients should be given folic acid supplements. PART 10 Disorders of the Gastrointestinal System Balsalazide contains an azo bond binding mesalamine to the car rier molecule 4-aminobenzoyl-β-alanine; it is effective in the colon. Delzicol and Asacol HD (high dose) are enteric-coated forms of mesalamine with the 5-ASA being released at pH >7. They dis integrate with complete breakup of the tablet occurring in many different parts of the gut ranging from the small intestine to the splenic flexure; they have increased gastric residence when taken with a meal. Lialda is a once-a-day formulation of mesalamine (Multi-Matrix System [MMX]) designed to release mesalamine in the colon. The MMX technology incorporates mesalamine into a lipophilic matrix within a hydrophilic matrix encapsulated in a polymer resistant to degradation at a low pH (<7) to delay release TABLE 337-8 Oral 5-Aminosalicylic Acid (5-ASA) Preparations PREPARATION FORMULATION DELIVERY DOSING PER DAY Azo-Bond Sulfasalazine (500 mg) (Azulfidine) Sulfapyridine-5-ASA Balsalazide (750 mg) (Colazal) Aminobenzoyl-alanine–5-ASA Delayed-Release Mesalamine (400, 800 mg) (Delzicol, Asacol HD) Mesalamine (1.2 g) (Lialda) Eudragit S (pH 7) MMX mesalamine (SPD476) Controlled-Release Mesalamine (250, 500, 1000 mg) (Pentasa) Ethylcellulose microgranules Stomach-colon 2–4 g (acute) 1.5–4 g (maintenance) Delayed- and Extended-Release Mesalamine (0.375 g) (Apriso) Intellicor extended-release mechanism Ileum-colon 1.5 g (maintenance) Abbreviation: MMX, Multi-Matrix System.

throughout the colon. The safety profile appears to be comparable to other 5-ASA formulations. Apriso is a formulation containing encapsulated mesalamine gran ules that delivers mesalamine to the terminal ileum and colon via a proprietary extended-release mechanism (Intellicor). The outer coat ing of this agent (Eudragit L) dissolves at a pH >6. In addition, there is a polymer matrix core that aids in sustained release throughout the colon. Because Lialda and Apriso are given once daily, an anticipated benefit is improved compliance compared with two to four daily doses required for other mesalamine preparations. Pentasa is another mesalamine formulation that uses an ethylcel lulose coating to allow water absorption into small beads containing the mesalamine. Water dissolves the 5-ASA, which then diffuses out of the bead into the lumen. Disintegration of the capsule occurs in the stomach. The microspheres then disperse throughout the entire GI tract from the small intestine through the distal colon in both fasted and fed conditions. Salofalk Granu-Stix, an unencapsulated version of mesalamine, has been in use in Europe for induction and maintenance of remis sion for several years. Appropriate doses of the 5-ASA compounds are shown

in Table 337-8. Some 50–75% of patients with mild to moderate UC improve when treated with 5-ASA doses equivalent to 2 g/d of mesalamine; the dose response continues up to at least 4.8 g/d. More common side effects of the 5-ASA medications include headaches, nausea, hair loss, and abdominal pain. Rare side effects of the 5-ASA medications include renal impairment, hematuria, pancreatitis, and paradoxical worsening of colitis. Renal function tests and urinalysis should be checked yearly. Topical Rowasa enemas are composed of mesalamine and are effective in mild-to-moderate distal UC. Combination therapy with mesalamine in both oral and enema form is more effective than either treatment alone for both distal and extensive UC. Canasa suppositories composed of mesalamine are effective in treating proctitis. GLUCOCORTICOIDS The majority of patients with moderate to severe UC benefit from oral or parenteral glucocorticoids. Prednisone is usually started at doses of 40–60 mg/d for active UC that is unresponsive to 5-ASA therapy. Parenteral glucocorticoids may be administered as hydro cortisone, 300 mg/d, or methylprednisolone, 40–60 mg/d. A newer glucocorticoid for UC, budesonide (Uceris), is released entirely in the colon and has minimal to no glucocorticoid side effects. The dose is 9 mg/d for 8 weeks, and no taper is required. Topically applied glucocorticoids (hydrocortisone enemas or budesonide foam) are also beneficial for distal colitis and may serve as an adjunct in those who have rectal involvement plus more proximal Colon 3–6 g (acute) 2–4 g (maintenance) 6.75–9 g Colon Distal ileum-colon 2.4–4.8 g (acute) 1.6–4.8 g (maintenance) 2.4–4.8 g Ileum-colon

disease. Hydrocortisone enemas are significantly absorbed from the rectum and can lead to adrenal suppression with prolonged administration. Topical 5-ASA therapy is more effective than topi cal steroid therapy in the treatment of distal UC. Glucocorticoids are also effective for treatment of moderate to severe CD. Controlled-ileal-release budesonide has been nearly equal to prednisone for ileocolonic CD with fewer glucocorticoid side effects. Budesonide is used for 2–3 months at a dose of 9 mg/d and then tapered. Glucocorticoids play no role in maintenance therapy in either UC or CD. Once clinical remission has been induced, they should be tapered according to the clinical activity, normally at a rate of no more than 5–10 mg/week. The side effects are numerous, including fluid retention, abdominal striae, fat redis tribution, hyperglycemia, subcapsular cataracts, osteonecrosis, osteoporosis, myopathy, emotional disturbances, and withdrawal symptoms. Most of these side effects, aside from osteonecrosis, are related to the dose and duration of therapy. ANTIBIOTICS Antibiotics have no role in the treatment of active or quiescent UC. However, pouchitis, which occurs in ~30–50% of UC patients after colectomy and ileal pouch anal anastomosis (IPAA), usu ally responds to treatment with a variety of antibiotics including metronidazole and ciprofloxacin. Some patients require long-term treatment with antibiotics for chronic pouchitis. AZATHIOPRINE AND MERCAPTOPURINE Azathioprine and mercaptopurine (MP) are purine analogues used concomitantly with biologic therapy or, much less often, as the sole immunosuppressants. Azathioprine is rapidly absorbed and con verted to MP, which is then metabolized to the active end product, thioinosinic acid, an inhibitor of purine ribonucleotide synthesis and cell proliferation. Efficacy can be seen as early as 3–4 weeks but can take up to 4–6 months. Adherence can be monitored by mea suring the levels of 6-thioguanine and 6-methylmercaptopurine, end products of MP metabolism. The doses used range from 2 to 3 mg/kg per day for azathioprine and 1 to 1.5 mg/kg per day for MP. Although azathioprine and MP are usually safe, pancreatitis occurs in 3–4% of patients, typically presents within the first few weeks of therapy, and is completely reversible when the drug is stopped. Other side effects include nausea, fever, rash, and hepatitis. Bone marrow suppression (particularly leukopenia) is dose-related and often delayed, necessitating regular monitoring of the complete blood cell count (CBC).

Additionally, 1 in 300 individuals lacks thiopurine methyltransferase, the enzyme responsible for drug metabolism to inactive end products (6-methylmercaptopurine); an additional 11% of the population are heterozygotes with intermediate enzyme activ ity. Both are at increased risk of toxicity because of increased accumu lation of active 6-thioguanine metabolites. Although 6-thioguanine and 6-methylmercaptopurine levels can be followed to determine correct drug dosing and reduce toxicity, weight-based dosing is an acceptable alternative. CBCs and liver function tests should be moni tored frequently regardless of dosing strategy. One meta-analysis demonstrated a fourfold risk of lymphoma in IBD patients on azathioprine and MP. The highest risk for thio purine-associated lymphoma is in patients >65 years old actively using thiopurines (yearly incidence rate per 1000 patient-years of 5.41), with a moderate risk in those between the ages of 50 and 65 (incidence rate of 2.58 compared to an incidence rate of 0.37 in patients <50 years old). Patients using thiopurines also have a two- to threefold increased risk of nonmelanoma skin cancers. METHOTREXATE MTX inhibits dihydrofolate reductase, resulting in impaired DNA synthesis. Additional anti-inflammatory properties may be related to decreases in the production of IL-1. It is used most often con comitantly with biologic therapy to decrease antibody formation and improve disease response. Intramuscular (IM) or subcutane ous (SC) doses range from 15 to 25 mg/week. Potential toxici ties include leukopenia and hepatic fibrosis, necessitating periodic

evaluation of CBCs and liver enzymes. The role of liver biopsy in patients on long-term MTX is uncertain but is probably limited to those with increased liver enzymes. Hypersensitivity pneumonitis is a rare but serious complication of therapy.

CYCLOSPORINE CSA is a lipophilic peptide with inhibitory effects on both the cel lular and humoral immune systems. CSA blocks the production of IL-2 by T helper lymphocytes. CSA binds to cyclophilin, and this complex inhibits calcineurin, a cytoplasmic phosphatase enzyme involved in the activation of T cells. CSA also indirectly inhibits B-cell function by blocking helper T cells. CSA has a more rapid onset of action than MP and azathioprine. CSA is most effective when given at 2–4 mg/kg per day IV in severe UC that is refractory to IV glucocorticoids, with 82% of patients responding. CSA can be an alternative to infliximab for steroid-refractory UC before colectomy. Levels as measured by monoclonal radioimmunoassay or by the high-performance liquid chromatography assay should be maintained between 150 and 350 ng/mL. CSA may cause significant toxicity; renal function should be monitored frequently. Hypertension, gingival hyperplasia, hyper trichosis, paresthesias, tremors, headaches, and electrolyte abnor malities are common side effects. Creatinine elevation calls for dose reduction or discontinuation. Seizures may also complicate therapy, especially if the patient is hypomagnesemic or if serum cholesterol levels are <3.1 mmol/L (<120 mg/dL). Opportunistic infections, most notably Pneumocystis jirovecii pneumonia, may occur with combination immunosuppressive treatment; antibiotic prophylaxis with trimethoprim-sulfamethoxazole should be given. CHAPTER 337 TACROLIMUS Tacrolimus is a macrolide antibiotic with immunomodulatory prop erties similar to CSA but 100 times as potent and not dependent on bile or mucosal integrity for absorption. Thus, tacrolimus has good oral absorption despite proximal small-bowel Crohn’s involvement. Tacrolimus is effective in children with refractory IBD and in adults with extensive involvement of the small bowel. Tacrolimus use is decreasing due to side effects and the expanding choice of biologic and small-molecule therapies. Inflammatory Bowel Disease BIOLOGIC THERAPIES Biologic therapy is now commonly given as an initial therapy for patients with moderate to severe CD and UC to prevent future complications of IBD. High-risk patients with UC who are more likely to require biologics include those with

moderate to severe disease, steroid-dependent or steroid-refractory disease, and refrac tory pouchitis. High-risk patients with CD who are more likely to require biologics include those who are <30 years old, with exten sive disease, perianal or severe rectal disease and/or deep ulcer ations in the colon, and stricturing or penetrating disease behavior. The current goal of IBD treatment with biologics is to treat early in the disease course, treat aggressively with appropriate therapies, check drug and drug metabolite levels, administer dual therapy with immunomodulators and biologics in appropriate patients, and aim for deep remission (endoscopic and histologic remission). Patients who respond to biologic therapies enjoy an improvement in clinical symptoms; a better quality of life; less disability, fatigue, and depression; and fewer surgeries and hospitalizations. Anti-TNF Therapies TNF is a proinflammatory cytokine that regulates immune cells to coordinate a systemic immune response. Dysregulation of TNF production has been associated with immune-mediated disorders including IBD, and inhibition of TNF signaling is used in the treatment of IBD. Four TNF inhibi tors are currently approved for the treatment of IBD: infliximab, adalimumab, certolizumab pegol, and golimumab. Infliximab, a chimeric IgG1 antibody against TNF-α, was the first biologic therapy approved for moderately to severely active inflammatory and fistulizing CD and UC.

Randomized trials support combination therapy with infliximab and azathioprine for moderate to severe CD and UC. For moder ate to severe CD, combination therapy has been shown to be more effective than either infliximab or azathioprine alone. Similarly, combination therapy has been shown to be more effective for mod erate to severe UC than either infliximab or azathioprine alone.

Hospitalized patients with acute severe glucocorticoid-refractory UC have a high inflammatory burden and may develop a proteinlosing enteropathy, leading to an accelerated consumption, exces sive fecal wasting, and low serum concentrations of infliximab. Given a clear exposure–response relationship for infliximab in patients with IBD, intensive infliximab dosing regimens have been used in these patients. Adalimumab (ADA) is a recombinant human monoclonal IgG1 antibody containing only human peptide sequences and is injected subcutaneously. ADA binds TNF and neutralizes its function by blocking the interaction between TNF and its cell-surface receptor. Therefore, it seems to have a similar mechanism of action to inflix imab but with less immunogenicity. ADA is approved for treatment of moderate to severe CD and UC. For CD and UC, results with ADA are better in patients who are naïve to anti-TNF than in patients who have previously been treated with infliximab. In clinical practice, the remission rate in both CD and UC patients taking ADA increases with a dose increase to 40 mg weekly instead of every other week. Certolizumab pegol is a pegylated form of an anti-TNF Fab portion of an antibody administered SC once monthly. SC cer tolizumab pegol is effective for induction of clinical response in patients with active inflammatory CD. Golimumab is another fully human IgG1 antibody against TNF-α and is currently approved for the treatment of moderately to severely active UC. Like ADA and certolizumab, golimumab is injected SC. PART 10 Disorders of the Gastrointestinal System Side Effects of Anti-TNF Therapies
Development of Antibodies and Drug Levels The develop ment of antibodies to infliximab is associated with an increased risk of infusion reactions and a decreased response to treatment. Cur rent practice does not include giving on-demand or episodic infu sions in contrast to scheduled periodic infusions because patients are most likely to develop antibodies. Anti-infliximab antibodies are generally present when the quality of response or the response duration to infliximab infusion decreases. Commercial assays can detect both infliximab and ADA antibodies and measure trough

levels to determine optimal dosing. If a patient has high antiinfliximab antibodies and a low trough level of infliximab, it is best to switch to another anti-TNF therapy. If a patient has a therapeutic anti-TNF level and active inflammatory symptoms, the drug should be switched to a different class of biologic. Most acute infusion reac tions and serum sickness can be managed with glucocorticoids and antihistamines. Some reactions can be serious and would neces sitate a change in therapy, especially if a patient has anti-infliximab antibodies. It is now common practice to add an immunomodula tor such as azathioprine, MP, or MTX to anti-TNF therapy to help prevent antibody formation. Non-Hodgkin's Lymphoma (NHL) The baseline risk of NHL in CD patients is 2 in 10,000, slightly higher than in the general popu lation. Azathioprine and/or MP therapy increases the risk to ~4 in 10,000. It is difficult to assess whether anti-TNF medications are associated with lymphoma because many patients are also receiving thiopurines. After adjustment for co-treatments, no excess risk of lymphoma was found in a Danish study of a cohort of IBD patients exposed to anti-TNF medications. Hepatosplenic T-Cell Lymphoma (HSTCL) HSTCL is a nearly universally fatal lymphoma in patients with or without CD. In patients with CD, a total of 37 unique cases have been reported. Eighty-six percent of the patients were male, and the median age was 26 years. Patients had CD for a mean of 10 years before the diagnosis of HSTCL. Thirty-six patients had used either MP or azathioprine, and 28 patients had used infliximab.

Skin Lesions New-onset psoriasiform skin lesions develop in nearly 5% of IBD patients treated with anti-TNF therapy. Most often, these can be treated topically, and occasionally, anti-TNF therapy must be decreased, switched, or stopped. Patients with IBD may have a slight, unexplained, intrinsic higher risk of developing melanoma. The risk of melanoma is increased almost twofold with anti-TNF and not thiopurine use. The risk of nonmelanoma skin cancer is increased with thiopurines and biologics, especially with ≥1 year of follow-up. Patients on these medications should have a skin check at least once a year. Infections All of the anti-TNF drugs are associated with an increased risk of infections, particularly reactivation of latent tuber culosis and opportunistic fungal infections including disseminated histoplasmosis and coccidioidomycosis. Patients should have a purified protein derivative (PPD) or a QuantiFERON-TB Gold test before initiation of anti-TNF therapy. Patients >65 years old have a higher rate of infections and death on infliximab or ADA than those <65 years old. Other Acute liver injury due to reactivation of hepatitis B virus and to autoimmune effects and cholestasis has been reported. Rarely, infliximab and the other anti-TNF drugs have been associ ated with optic neuritis, seizures, new onset or exacerbation of clini cal symptoms, and radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis. They may exacerbate symptoms in patients with New York Heart Association functional class III/IV heart failure. ANTI-INTEGRINS Integrins are expressed on the cell surface of leukocytes and serve as mediators of leukocyte adhesion to vascular endothelium and entry into the intestines. α4-Integrin along with its β1 or β7 subunit inter act with endothelial ligands termed adhesion molecules. Interaction between α4β7 and mucosal addressin cellular adhesion molecule (MAdCAM-1) is important in lymphocyte trafficking to gut mucosa. Natalizumab is a recombinant humanized IgG4 antibody against α4-integrin and is effective in induction and maintenance of patients with CD. However, natalizumab is no longer used for CD due to the risk of progressive multifocal leukoencephalopathy (PML) and the development of alternative biologic and small-molecule therapies. Vedolizumab (VDZ), another leukocyte trafficking inhibitor, is a monoclonal antibody directed against α4β7-integrin specifically and has the ability to convey gut-selective immunosuppression. Unlike natalizumab, it inhibits adhesion of a discrete gut-homing subset of T lymphocytes to MAdCAM-1, but not to vascular adhe sion molecule 1. VDZ decreases GI

inflammation without inhibit ing systemic immune responses or affecting T-cell trafficking to the central nervous system. It may be prescribed as a first-line biologic or after failure of a TNF antagonist in patients with CD or UC. Vedolizumab is more effective than adalimumab for first-line biologic therapy in moderate to severe UC. Ustekinumab, a fully human IgG1 monoclonal antibody, blocks the biologic activity of IL-12 and IL-23 through their common p40 subunit by inhibiting the interaction of these cytokines with their receptors on T cells, natural killer cells, and antigen-presenting cells. It is as equally effective as adalimumab for first-line biologic therapy for moderate to severe CD and is another option for treat ment of moderate to severe UC. It is particularly appealing for use in patients with concomitant psoriatic arthritis. Risankizumab is a monoclonal antibody that selectively binds to the IL-23 p19 subunit, inhibiting its interaction with the IL-23R complex It is the first selective IL-23 inhibitor approved for moder ate to severe CD and provides an additional therapeutic option for patients, particularly those who have been previously treated with other advanced IBD therapies. SMALL MOLECULES Small molecules (drugs with molecular weight <1 kDa) are a new class of orally administered medications developed for IBD that lack the immunogenicity associated with monoclonal antibodies. The

advantage of small molecules is their ability to diffuse through cell membranes into the intracellular space and inhibit cytokine signaling pathways. This mechanism of action may be more efficacious com pared to monoclonal antibodies that inhibit specific targets because several cytokine pathways are involved in IBD pathogenesis and inhibiting numerous cytokines may be synergistic. A key regulatory pathway of many cytokines associated with IBD is the JAK/STAT pathway that activates transcription and translation of proteins that mediate the immune response. Janus kinase (JAK) is a family of intra cellular, nonreceptor tyrosine kinases that regulate cytokine signal ing via the JAK/STAT pathway, ultimately suppressing the immune response and inflammation. The JAK family members include JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). Tofacitinib is a reversible and competitive JAK inhibitor used for the treatment of moderate to severe UC refractory to conventional therapy. It competes with ATP to bind to the ATP-docking site of the kinase domain of JAK. By competing with ATP, tofacitinib inhibits phosphorylation and activation of JAK, leading to downstream reduction of cytokine production and alteration of the immune response. Although tofacitinib is a pan-JAK inhibitor, it has higher specificity for JAK1 and JAK3 than for JAK2 and TYK2. The panJAK inhibition is concerning for adverse events and overall safety. Upadacitinib is an oral, selective, and reversible JAK inhibitor that is approved for both UC and CD. It potently inhibits JAK1 and is less potent against the other isoforms, JAK2, JAK3, and TYK2. Upadacitinib demonstrates rapid clinical and endoscopic improve ment at the end of induction, which is sustained to the end of main tenance, with a positive benefit/risk profile. The FDA review concluded that there is an increased risk of serious adverse events including heart attack, stroke, cancer, blood clots, and death in patients who are prescribed JAK inhibitors. Patients who are at risk for cardiovascular disease, have a history of blood clots, are current or past smokers, and/or are over the age of 50 should consider alternative therapies. The risk of herpes zoster is higher with JAK inhibitors, and patients should receive the shingles vaccine (Shingrix). Tofacitinib and upadacitinib are FDA approved for use as second-line agents after failure of anti-TNF therapy. Ozanimod is a potent sphingosine-1-phosphate (S1P1) receptor modulator that binds selectively with high affinity to the S1P recep tor subtypes S1P1 and S1P5, both of which are involved in immune regulation. By preventing trafficking of disease-exacerbating lym phocytes from the lymph nodes to the gut, ozanimod may provide immunomodulatory effects and moderate disease processes. Ozanimod is approved for the treatment of moderate to severe ulcerative colitis. It is

administered as a daily capsule. The biologic and small-molecule therapies used in daily practice are detailed in Table 337-9. NUTRITIONAL THERAPIES Diet has long been thought to contribute to the pathogenesis of IBD and may also be an avenue for managing disease activity. Diet plays a significant role in shaping the gut microbiome, and dietary com ponents may interact with the microbiome and stimulate a mucosal immune response. In fact, active CD responds to exclusive enteral nutrition (EEN) or bowel rest with TPN, interventions as effective as glucocorticoids in inducing remission but not as effective for maintenance therapy. In contrast to CD, active UC is not effectively treated by elemental diets or TPN. Dietary approaches to maintenance therapy in CD have largely been adapted from epidemiologic studies; however, significant heterogeneity is noted among research study outcomes. In general, low fiber, refined carbohydrates (especially sweetened beverages), animal fats, red meat, and processed meat have been associated with onset of IBD. Therefore, the overall dietary approach is to maximize fiber intake, particularly from fruits and vegetables, and to limit consumption of higher-risk foods. Several defined diets adhere to these principles with some variation, including the Mediterra nean diet pattern, specific carbohydrate diet, semi-vegetarian diet, and IBD anti-inflammatory diet (IBD-AID). However, it remains

unclear whether diet studies will eventually lead to evidence-based nutrition guidelines.

Standard medical management of UC and CD is shown in Fig. 337-12. SURGICAL THERAPY Ulcerative Colitis Nearly one-half of patients with extensive chronic UC undergo surgery within the first 10 years of their illness. The indications for surgery are listed in Table 337-10. Morbidity is ~20% for elective, 30% for urgent, and 40% for emergency procto colectomy. The risks are primarily hemorrhage, contamination and sepsis, and neural injury. The operation of choice is an IPAA. Because UC is a mucosal disease, the rectal mucosa can be dis sected and removed down to the dentate line of the anus or ~2 cm proximal to this landmark. The ileum is fashioned into a pouch that serves as a neorectum. This ileal pouch is then sutured cir cumferentially to the anus in an end-to-end fashion. If performed carefully, this operation preserves the anal sphincter and maintains continence. The overall operative morbidity is 10%, with the major complication being bowel obstruction. Pouch failure necessitating conversion to permanent ileostomy occurs in 5–10% of patients. Some inflamed rectal mucosa is usually left behind, and thus, endoscopic surveillance is necessary. Primary dysplasia of the ileal mucosa of the pouch has occurred rarely. Patients with IPAA usually have ~6–10 bowel movements a day. On validated quality-of-life indices, they report better per formance in sports and sexual activities than ileostomy patients. The most frequent complication of IPAA is pouchitis in ~30–50% of patients with UC. This syndrome consists of increased stool frequency, watery stools, cramping, urgency, nocturnal leakage of stool, arthralgias, malaise, and fever. Pouch biopsies may distin guish true pouchitis from underlying CD. Although pouchitis usu ally responds to antibiotics, 3–5% of patients remain refractory and may require chronic antibiotic therapy, biologics, or even pouch removal. CHAPTER 337 Inflammatory Bowel Disease Crohn’s Disease The majority of patients with CD will require at least one operation in their lifetime. The need for surgery is related to duration of disease and the site of involvement. Patients with small-bowel disease have an 80% chance of requiring surgery. Those with colitis alone have a 50% chance. Surgery is an option only when medical treatment has failed or complications dictate its necessity. The indications for surgery are shown in Table 337-10. Small-Intestinal Disease Because CD is chronic and recur rent, with no clear surgical cure, as little intestine as possible is resected. Current surgical alternatives for treatment of obstructing CD

include resection of the diseased segment and strictureplasty. Surgical resection of the diseased segment is the most frequently performed operation, and in most cases, primary anastomosis can be done to restore continuity. An end-to-end anastomosis may provide the best opportunity for an optimal functional outcome, compared to an antiperistaltic side-to-side anastomosis, which cre ates a functional block to motility leading to distention and pain at the anastomotic site in a subgroup of patients. If much of the small bowel has already been resected and the strictures are short, with intervening areas of normal mucosa, strictureplasties should be done to avoid a functionally insufficient length of bowel. The strictured area of intestine is incised longitudinally and the incision sutured transversely, thus widening the narrowed area. Complica tions of strictureplasty include prolonged ileus, hemorrhage, fistula, abscess, leak, and restricture. Risk factors for early recurrence of disease include cigarette smoking, penetrating disease (internal fistulas, abscesses, or other evidence of penetration through the wall of the bowel), early recur rence since a previous surgery, multiple surgeries, and a young age at the time of the first surgery. Aggressive postoperative treatment with biologics should be considered for this group of patients. It is also recommended to evaluate for endoscopic recurrence of CD via a colonoscopy, if possible, 3–6 months after surgery.

TABLE 337-9 Biologic and Small-Molecule Agents in the Treatment of Inflammatory Bowel Disease MEDICATION DOSAGE INDICATION SERIOUS TOXICITIES Infliximab 5 mg/kg at 0, 2, and 6 weeks, then every 8 weeks; may increase dose to 10 mg/kg every 4 weeks depending on trough levels Intensive dosing for hospitalized corticosteroidrefractory patients Moderate to severe Crohn’s disease and ulcerative colitis Fistulizing Crohn’s disease Increased risk of infections (bacterial and fungal), tuberculosis (TB) reactivation, hepatitis B reactivation, lymphoma (controversial), psoriasis, melanoma and nonmelanoma skin cancers, drug-induced lupus Contraindicated in multiple sclerosis, class III/IV congestive heart failure Adalimumab 160 mg day 0, 80 mg day 14 and then 40 mg every 14 days; may increase to 40 mg every 7 days depending on trough levels Moderate to severe Crohn’s disease and ulcerative colitis Fistulizing Crohn’s disease As above Injection site reactions (better with citrate-free preparation) Certolizumab 400 mg on days 0 and 14, then 400 mg every 28 days Moderate to severe Crohn’s disease As above As above As above Golimumab 200 mg on day 0, 100 mg on day 14, then 100 mg every 28 days Moderate to severe ulcerative colitis As above As above As above Vedolizumab 300 mg at 0, 2, and 6 weeks, then every 8 weeks; may increase dose to 300 mg every 4 weeks Moderate to severe ulcerative colitis (more effective than adalimumab as firstline therapy in one study) Moderate to severe Crohn’s disease. No increased risk of serious systemic or opportunistic infections No increased risk of malignancy PART 10 Disorders of the Gastrointestinal System Ustekinumab 6 mg/kg IV, then 90 mg every 8 weeks; may increase dose to 90 mg every 4 weeks Moderate to severe Crohn’s disease and ulcerative colitis Reversible posterior leukoencephalopathy syndrome (presents with headaches, seizures, confusion, and visual disturbances), anaphylaxis, and angioedema Risankizumab 600 mg IV every 4 weeks × 3 doses then 180 mg or 360 mg SC every 8 weeks Moderate to severe Crohn’s disease Reversible posterior leukoencephalopathy syndrome (presents with headaches, seizures, confusion, and visual disturbances), anaphylaxis, and angioedema Tofacitinib 10 mg bid; can decrease to 5 mg bid when patient in remission Moderate to severe ulcerative colitis Increased risk of heart attack, stroke, cancer, blood clots, and death. Patients who are at risk for cardiovascular disease, are current or past smokers, and/or are over the age of 50 should consider alternative therapies. Increased risk of viral infections, including herpes zoster, and bacterial and invasive fungal infections Upadacitinib 45 mg PO qd × 8 weeks for ulcerative colitis; 45 mg PO qd × 12

weeks for Crohn’s disease, then 15 or 30 mg qd Moderate to severe ulcerative colitis or Crohn’s disease Increased risk of heart attack, stroke, cancer, blood clots, and death. Patients who are at risk for cardiovascular disease, are current or past smokers, and/or are over the age of 50 should consider alternative therapies. Increased risk of viral infections, including herpes zoster, and bacterial and invasive fungal infections Ozanimod 0.23 mg PO days 1–4, 0.46 mg PO days 5–7, 0.92 mg PO thereafter Moderate to severe UC Bradycardia, atrioventricular conduction delay, increased blood pressure, macular edema, posterior reversible encephalopathy syndrome

OTHER COMMON SIDE EFFECTS TESTING Infusion reactions Prior to infusion: TB testing Hepatitis B testing (HBsAb, HBsAg, HBcAb) Maintenance: Skin check yearly Influenza, pneumococcal vaccinations Hepatitis B vaccine if not immune As above Nasopharyngitis, headache, arthralgias, nausea Prior to infusion: TB testing Hepatitis B testing (HBsAb, HBsAg, HBcAb) Maintenance: Influenza, pneumococcal vaccinations Hepatitis B vaccine if not immune Nasopharyngitis, upper respiratory tract infection, fatigue, headache Prior to infusion: TB testing Hepatitis B testing (HBsAb, HBsAg, HBcAb) Maintenance: Influenza, pneumococcal vaccinations Hepatitis B vaccine if not immune Nasopharyngitis, upper respiratory tract infection, fatigue, headache TB testing Hepatitis B testing (HBsAb, HBsAg, HBcAb) Maintenance: Influenza, pneumococcal vaccinations Hepatitis B vaccine if not immune Elevated lipids, neutropenia, anemia, elevated liver enzymes Prior to infusion: First dose of Shingrix recommended, TB testing Hepatitis B testing (HBsAb, HBsAg, HBcAb) Maintenance: Influenza, pneumococcal vaccinations Hepatitis B vaccine if not immune Elevated lipids, neutropenia, anemia, elevated liver enzymes Prior to infusion: First dose of Shingrix recommended, TB testing Hepatitis B testing (HBsAb, HBsAg, HBcAb) Maintenance: Influenza, pneumococcal vaccinations Hepatitis B vaccine if not immune Infections, elevated liver enzymes Prior to infusion: First dose of Shingrix recommended, TB testing Hepatitis B testing (HBsAb, HBsAg, HBcAb) Maintenance: Influenza, pneumococcal vaccinations Hepatitis B vaccine if not immune

Tofacitinib/ upadacitinib Biologic +/– MP/AZA/ MTX or ozanimod Prednisone oral (induction of remission only) Hydrocortisone rectal Budesonide oral and/or rectal 5-ASA oral and/or rectal Mild to Moderate Ulcerative Colitis Moderate to Severe Ulcerative Colitis Prednisone oral (induction of remission only) Total parenteral or exclusive enteral nutrition and bowel rest Mild to Moderate Crohn’s Disease Upadacitinib Biologic +/– MP/AZA/MTX Hydrocortisone or solumedrol IV (induction of remission only) Prednisone oral (induction of remission only) Moderate to Severe Crohn’s Disease Fistulizing Crohn’s Disease FIGURE 337-12 Medical management of inflammatory bowel disease. 5-ASA, 5-aminosalicylic acid; AZA, azathioprine; MP, mercaptopurine; MTX, methotrexate. Colorectal Disease A greater percentage of patients with Crohn’s colitis require surgery for intractability, fulminant disease, and anorectal disease. Several alternatives are available, ranging from the use of a temporary loop ileostomy to resection of segments of diseased colon or even the entire colon and rectum. For patients with segmental involvement, segmental colon resection with pri mary anastomosis can be performed. In 20–25% of patients with extensive colitis, the rectum is spared sufficiently to consider rectal preservation. Most surgeons believe that an IPAA is contraindicated in CD due to the high incidence of pouch failure. A diverting colos tomy may help heal severe perianal disease or rectovaginal fistulas, but disease almost always recurs with reanastomosis. These patients often require a total proctocolectomy and ileostomy. TABLE 337-10 Indications for Surgery ULCERATIVE COLITIS CROHN’S DISEASE Intractable disease Small Intestine Fulminant disease Stricture and obstruction Toxic megacolon unresponsive to medical therapy

Colonic perforation Massive hemorrhage Massive colonic hemorrhage Refractory fistula Extracolonic disease Abscess Colonic obstruction Colon and rectum Colon cancer prophylaxis Intractable disease Colon dysplasia or cancer Fulminant disease Perianal disease unresponsive to medical therapy Refractory fistula Colonic obstruction Cancer prophylaxis Colon dysplasia or cancer

Cyclosporine IV Tofacitinib/upadacitinib Biologic +/– MP/AZA/MTX Hydrocortisone or solumedrol IV (induction of remission only) Upadacitinib Prednisone oral (induction of remission only) Biologic +/– MP/AZA/MTX Total parenteral nutrition and bowel rest Budesonide oral Biologic +/– MP/AZA/MTX Abscess drainage and antibiotics CHAPTER 337 Inflammatory Bowel Disease ■ ■IBD AND PREGNANCY Patients with quiescent UC and CD have normal fertility rates; the fallopian tubes can be scarred by the inflammatory process of CD, especially on the right side because of the proximity of the terminal ileum. In addition, perirectal, perineal, and rectovaginal abscesses and fistulas as well as pelvic surgery can result in dyspareunia. Infertility in men can be caused by sulfasalazine but reverses when treatment is stopped. Women with an IPAA have decreased fertility due to scarring or occlusion of the fallopian tubes secondary to pelvic inflammation and adhesions, although studies have shown that fertility is improved with laparoscopic versus open IPAA. Mild or quiescent UC or CD has no effect on birth outcomes. The courses of CD and UC during pregnancy mostly correlate with disease activity at the time of conception. Patients should be in remission for 3–6 months before conceiving. Most CD patients can deliver vagi nally, but cesarean delivery may be the preferred route of delivery for patients with anorectal and perirectal abscesses and fistulas to reduce the likelihood of fistulas developing or extending into the episiotomy scar. Unless they desire multiple children, UC patients with an IPAA may consider a cesarean delivery due to an increased risk of future fecal incontinence. Sulfasalazine and all mesalamines are safe for use in pregnancy and nursing with the caveat that additional folate supplementation must be given with sulfasalazine. Topical 5-ASA agents are safe during pregnancy and nursing. Glucocorticoids are generally safe for use during pregnancy and are indicated for patients with moderate to severe disease activity. The amount of glucocorticoids received by the nursing infant is minimal. The safest antibiotics to use for CD in pregnancy for short periods of time (weeks, not months) are ampicillin and cephalosporins. Metroni dazole can be used in the second or third trimester. Ciprofloxacin causes cartilage lesions in immature animals and should be avoided because of the absence of data on its effects on growth and development in humans. MP and azathioprine pose minimal or no risk during pregnancy. Breast milk has been shown to contain negligible levels of MP/azathio prine when measured in a limited number of patients.

MTX is teratogenic and should be discontinued at least 3 months before conception.

In a large prospective and multiple retrospective studies, no increased risk of stillbirths, miscarriages, or spontaneous abortions was seen with infliximab, ADA, certolizumab, vedolizumab, or ustekinumab. These biologics, with the exception of certolizumab, are IgG1 antibodies and are actively transported across the placenta in the late second and third trimesters. Infants can have serum levels of infliximab, ADA, vedoli zumab, and ustekinumab well into the first year of life, and live vac cines should be avoided until 12 months of age. Certolizumab crosses the placenta by passive diffusion, and infant serum and cord blood levels are minimal. The biologics are safe in nursing. Miniscule levels of infliximab, ADA, certolizumab, vedolizumab, and ustekinumab have been reported in breast milk. These levels are of no clinical sig nificance. It is recommended that

drugs should not be switched during pregnancy unless necessitated by the medical condition of the IBD. Tofacitinib and upadacitinib should not be used during pregnancy. Animal studies show teratogenic effects with both of these drugs, and data in humans are limited. A washout period of at least 4 weeks is recommended before conception. Surgery in UC should be performed only for emergency indications, including severe hemorrhage, perfora tion, and megacolon refractory to medical therapy. Total colectomy and ileostomy carry a 50% risk of postoperative spontaneous abortion. The best time to perform surgery is in the second trimester if necessary. Patients with IPAAs have increased nighttime stool frequency during pregnancy that resolves postpartum. Transient small-bowel obstruc tion or ileus has been noted in up to 8% of patients with ileostomies. CANCER IN IBD PART 10 Disorders of the Gastrointestinal System ■ ■ULCERATIVE COLITIS Patients with long-standing UC are at increased risk for developing colonic epithelial dysplasia and carcinoma (Fig. 337-13). The risk of neoplasia in chronic UC increases with duration and extent of disease. In contrast to the relatively high risk in one large meta-analysis (2% after 10 years, 8% after 20 years, and 18% after 30 years of disease), a decrease in the risk of colorectal cancer has been noted over time potentially due to better control of inflammation and better colonoscopic surveillance. The rates of colon cancer are still about 1.5–2 times higher than in the general population, and colonoscopic surveillance is the standard of care. Annual or biennial colonoscopy with multiple biopsies is recom mended for patients with >8–10 years of extensive colitis (greater than one-third of the colon involved) or 12–15 years of proctosig moiditis (less than one-third but more than just the rectum) and has been widely used to screen and survey for subsequent dysplasia and carcinoma. International guideline societies have recommended chro moendoscopy for dysplasia surveillance in IBD. Chromoendoscopy enhances the visualization of the surface and pit pattern of the mucosa, FIGURE 337-13 Medium-power view of low-grade dysplasia in a patient with chronic ulcerative colitis. Low-grade dysplastic crypts are interspersed among regenerating crypts. (Courtesy of Dr. R. Odze, Division of Gastrointestinal Pathology, Department of Pathology, Brigham and Women’s Hospital, Boston, Massachusetts; with permission.)

as well as borders of lesions, in order to better define areas of dysplasia compared to standard-definition white light endoscopy. In real-life settings, the practice has been to use standard-definition white light endoscopy with surveillance biopsies in patients with chronic colitis at average risk and chromoendoscopy in higher-risk patients including those with a history of dysplasia, PSC, or family history of colorectal cancer. Risk factors for cancer in UC include long-duration disease, exten sive disease, family history of colon cancer, PSC, a colon stricture, and the presence of postinflammatory pseudopolyps on colonoscopy. ■ ■CROHN’S DISEASE Risk factors for developing cancer in Crohn’s colitis are long-duration and extensive disease, bypassed colon segments, colon strictures, PSC, and family history of colon cancer. The cancer risks in CD and UC are probably equivalent for similar extent and duration of disease. In the CESAME study, a prospective observational cohort of IBD patients in France, the standardized incidence ratios of colorectal cancer were 2.2 for all IBD patients (95% CI, 1.5–3.0; $p < .001$) and 7.0 for patients with long-standing extensive colitis (both Crohn’s and UC) (95% CI, 4.4–10.5; $p < .001$). Thus, the same endoscopic surveillance strategy used for UC is recommended for patients with chronic Crohn’s colitis. A pediatric colonoscope can be used to pass narrow strictures in CD patients, but surgery should be considered in symptomatic patients with impassable strictures. ■ ■MANAGEMENT OF DYSPLASIA AND CANCER Dysplasia can be flat or polypoid. If flat high-grade dysplasia is encountered on colonoscopic surveillance, the usual treatment is colectomy for UC and either colectomy or segmental resection for CD. If flat low-grade dysplasia is found (Fig. 337-13), most inves tigators recommend immediate colectomy. Adenomas may occur coincidently in UC and CD

patients with chronic colitis and can be removed endoscopically provided that biopsies of the surrounding mucosa are free of dysplasia. IBD patients are also at greater risk for other malignancies. Patients with CD may have an increased risk of NHL, leukemia, and myelodys plastic syndromes. Severe, chronic, complicated perianal disease in CD patients may be associated with an increased risk of cancer in the lower rectum and anal canal (squamous cell cancers). Although the absolute risk of small-bowel adenocarcinoma in CD is low (2.2% at 25 years in one study), patients with long-standing, extensive, small-bowel disease should be considered for screening. COVID-19 AND IBD COVID-19, caused by SARS-CoV-2, was first reported in December 2019 and has rapidly spread throughout the world, leading to an inter national pandemic. Glucocorticoids, immunomodulators (thiopurines, MTX), biologics, and JAK inhibitors, commonly used to treat IBD, are associated with higher rates of serious viral and bacterial infec tions, and patients with IBD using these medications are potentially at increased risk of a serious COVID-19 infection. Yet, it is also pos sible that some forms of immune suppression may blunt the excessive immune response/cytokine storm characteristic of severe COVID-19 infection and consequently reduce mortality. Using data from the Sur veillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease, it was found that increasing age (adjusted OR 1.04; 95% CI, 1.01–1.02), two or more comorbidities (adjusted OR 2.9; 95% CI, 1.1–7.8), and systemic glucocorticoids (adjusted OR 6.9; 95% CI, 2.3–20.5) are associated with severe COVID-19 in IBD patients. Anti-TNF treatment was not associated with severe COVID-19 (adjusted OR 0.9; 95% CI, 0.4–2.2). ■ ■FURTHER READING Barberio B et al: Efficacy of biological therapies and small molecules in induction and maintenance of remission in luminal Crohn’s dis ease: Systematic review and network meta-analysis. Gut 72:264, 2023. Chang JT: Pathophysiology of inflammatory bowel disease. N Eng J Med 383:2652, 2020.

Revision #1
Created 2026-01-06 16:34:33 UTC by Omar Ayman
Updated 2026-01-06 16:34:34 UTC by Omar Ayman