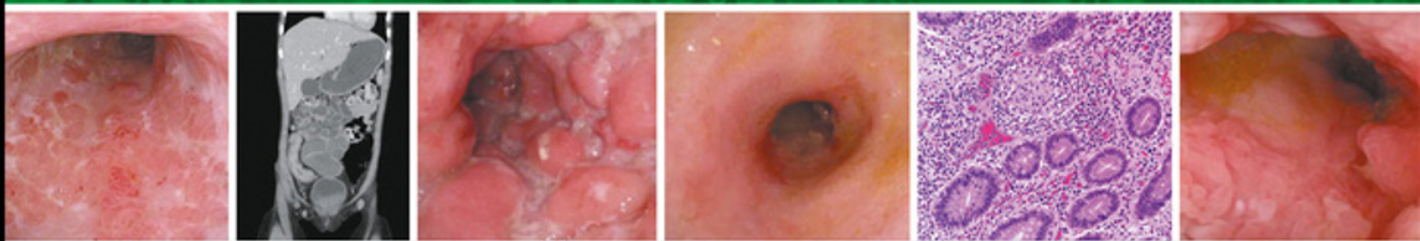


INFLAMMATORY BOWEL DISEASES

A Clinician's Guide



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Inflammatory Bowel Diseases

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Preface

Inflammatory bowel diseases (IBDs), comprising Crohn's disease (CD) and ulcerative colitis (UC), are complex diseases that often have their onset during young adulthood. They have a protracted course characterized by periods of remission and relapse, and frequently result in hospitalization, surgery, and continued morbidity. Importantly, they also exert a significant impact on the individuals' health-related quality of life and work productivity. Physicians caring for patients with IBD encounter varied and often complex challenges. The importance of optimal decision-making for the welfare of the patient cannot be overstated.

This book was developed to serve as a resource for practicing physicians, allied healthcare providers, and trainees who care for patients with Crohn's disease and ulcerative colitis. Although exhaustive textbooks are available, this new handbook aims to provide a concise understanding of these disorders and practical guidance on approaches to diagnosis and treatment. Care of patients with IBD is integral to the practice of gastroenterology and frequently also encountered by internists, surgeons, pediatricians, and other physicians, in addition to nurses and other caregivers.

The past two decades have witnessed a significant revolution both in our understanding of the pathogenesis behind these complex diseases and in the availability of therapeutic options that have enhanced the ability to achieve clinical and endoscopic

remission. Facilitated by advances in sequencing tools and analytic methods, we now recognize that these diseases arise as a result of a dysregulated immune response to intestinal microflora in a genetically susceptible individual. Over 150 genes have been identified that contribute to the pathogenesis of these disease, influencing innate and adaptive immune responses and integrity of the intestinal barrier. The intestinal microflora demonstrate a dysbiotic pattern with reduced diversity and altered abundance of pro- and anti-inflammatory bacterial species. Therapeutic paradigms have evolved with our understanding of the benefit of effective treatment early in the course of disease and the role of combination therapy to reduce immunogenicity and increase the likelihood of sustained response. Whereas therapy for IBD was initially restricted to broad, non-selective immunosuppressive therapy, emerging treatments increasingly target specific inflammatory pathways such as tumor necrosis factor α , adhesion molecules, and the IL-23 pathway. Yet this scientific and therapeutic revolution has made the management of these diseases more complex than ever before.

Part I describes the epidemiology and pathogenesis of IBD, including the role of genetics, the environment, and the gut microbiome. We discuss the clinical features and procedures that aid in establishing a diagnosis of Crohn's disease and ulcerative colitis. We also discuss the various manifestations of

IBD that occur outside the intestine and are a source of morbidity to a significant fraction of patients. We discuss the evolution of these diseases towards more complicated behavior and identify relevant risk factors.

Part II discusses each of the classes of therapeutic agents used for the management of IBD, and systematically examines the efficacy of each class in the treatment of patients with ulcerative colitis or Crohn's disease. We also discuss the safety of each category and review newer therapeutic modalities such as those aimed at the microbiome.

Part III presents practical algorithms for the medical and surgical management of ulcerative colitis and Crohn's disease, stratifying by severity and extent of involvement. We also review the disease-specific complications for

each IBD subtype and the management of these complications.

Part IV reviews some special clinical considerations in the management of these diseases, including the role of nutrition and dietary therapies, and two commonly encountered clinical scenarios – the management of IBD during pregnancy and in children – ending with a discussion of transition of care.

Throughout this book, learning is facilitated by practical take-home points in each chapter and patient-centered questions reviewing the material covered in each chapter. Overall, we hope that this guide will enable clinicians to provide the best help to their patients with IBD through the many challenges that they may face.

Section I

Pathogenesis and Clinical Features

1

Epidemiology and Pathogenesis

Clinical Take Home Messages

- Inflammatory bowel diseases (IBDs) have a peak incidence in the second through fourth decades of life but may have their onset at any age.
- Most studies have suggested comparable rates of incidence across both genders but risk of disease varies among ethnic populations, e.g., higher frequency in the Ashkenazi Jewish population.
- Family history is the strongest risk factor for development of IBD. At least 163 distinct genetic polymorphisms have been described in association with Crohn's disease (CD) or ulcerative colitis (UC) but explain less than one-quarter of the variance in risk for either disease.
- Disease risk alleles highlight the importance of various genetic pathways in the pathogenesis of these diseases, including innate immunity, adaptive immune response, intestinal barrier function, and pathogen sensing and response. However, polymorphisms at these loci have not been consistently associated with natural history and phenotype of IBD except for correlation between NOD2 polymorphisms and ileal fibrostenosing CD.
- Several environmental factors may influence risk of disease and subsequent natural history. The most robust data support an effect of cigarette smoking (increasing risk of CD and reducing risk of UC), but other factors including diet, stress and depression, antibiotic exposure, environmental hygiene, vitamin D, physical activity, and hormones may play a role.

Epidemiology

Crohn's disease (CD) and ulcerative colitis (UC) are chronic, immunologically mediated diseases. They may occur at any age but most often have an onset during young adulthood and a protracted course characterized by remissions and relapses over the course of their natural history. They affect an estimated 2.2 million individuals in Europe and 1.5 million in the United States.

The incidence and prevalence appear to be increasing in areas of the world where historically rates have been far lower than found in Northern Europe and North America, such as Asia. The peak age of onset of CD is between 20 and 30 years whereas UC has a peak incidence a decade later between the ages of 30 and 40 years. However, up to 15% of patients may have their first presentation of inflammatory bowel disease (IBD) after the age of 65 years,

and a bimodal pattern of incidence with a second smaller peak in the sixth and seventh decades of life has been described, particularly for UC. In addition, a subset of patients can manifest IBD at a very early age, less than 2 years old, termed very early-onset IBD (VEOIBD), which is characterized by distinct genetic predisposition and clinical phenotype characterized by treatment refractoriness, severe perianal disease, and response to bone marrow transplant.

The incidence of UC in several countries in the Western Hemisphere is informed by large population-based cohorts tracking secular trends. However, incidence data are lacking from other parts of the world where the emergence of these diseases has been more recent. In North America, the incidence of UC ranges from 0 to 19.2 per 100 000 persons and a similar distribution exists in Europe. CD has a similar incidence, ranging between 0.3 and 12.7 per 100 000 persons in Europe and between 0 and 20.2 per 100 000 persons in North America. Serial estimates of incidence from population-based cohorts dating back to the mid-twentieth century reveal interesting secular trends. In Olmsted County, Minnesota, the incidence of UC rose from 0.6 per 100,000 in 1940–1943 to 8.3 per 100 000 in 1990–1993, with the steepest increase in incidence in the 1970s. CD similarly rose from 1.0 per 100,000 person-years in 1940–1943 to 6.9 cases per 100 000 person-years in 1984–1993. A systematic review of all studies examining trends in disease incidence suggested that over 75% of the studies involving CD and 60% of the studies involving UC identified secular increases in disease incidence. Virtually no study has reported a consistent decrease in incidence in any population over time. Both CD (incidence 0–5.0 per 100 000) and UC (incidence 0.1–6.3 per 100 000) remain relatively uncommon in Asia compared with Western populations. However, increasing incidence, potentially paralleling westernization of life

style, has been found in several Asian countries over the past few decades, including Japan, China, Taiwan, and Korea (Figure 1.1). Interestingly, the incidence for UC generally occurs first, followed a decade later by an increase in the incidence of CD.

There are well-recognized ethnic differences in risk for CD and UC, and less consistently a difference by gender. In most studies, CD and UC occur equally frequently among men and women, although in some studies there is a slight predominance of men among patients with UC (60%) and a predominance of women among those with CD. The incidence of both diseases is more common in the Jewish population; the risk of CD is 3–8-fold that of non-Jews, with a more modest but still elevated risk of UC [1]. The incidence is lower among Sephardic than Ashkenazi Jews and in Israeli than American and European Jews. An international cohort of eight countries in the Asia–Pacific region identified higher incidences of both diseases in Australia than in Asia, but also geographic and ethnic variations within the different countries in Asia [2]. IBD is also uncommon in certain subpopulations even within a high-incidence geographic region such as the First Nations population in Canada and the Aboriginal population in Australia. Within North America, the prevalence of CD and UC was initially reported to be lower in African American and Hispanic populations, but recent data suggest a rising incidence within these populations and an incidence comparable to the lower end of that reported for Caucasians [3]. The risk of IBD varies with migration from a low- to a high-incidence area. Studies in the United Kingdom and Sweden have demonstrated that the risk, particularly of UC, in immigrants from low-incidence countries rapidly approaches the rate in the local population within one or two generations. However, this change in

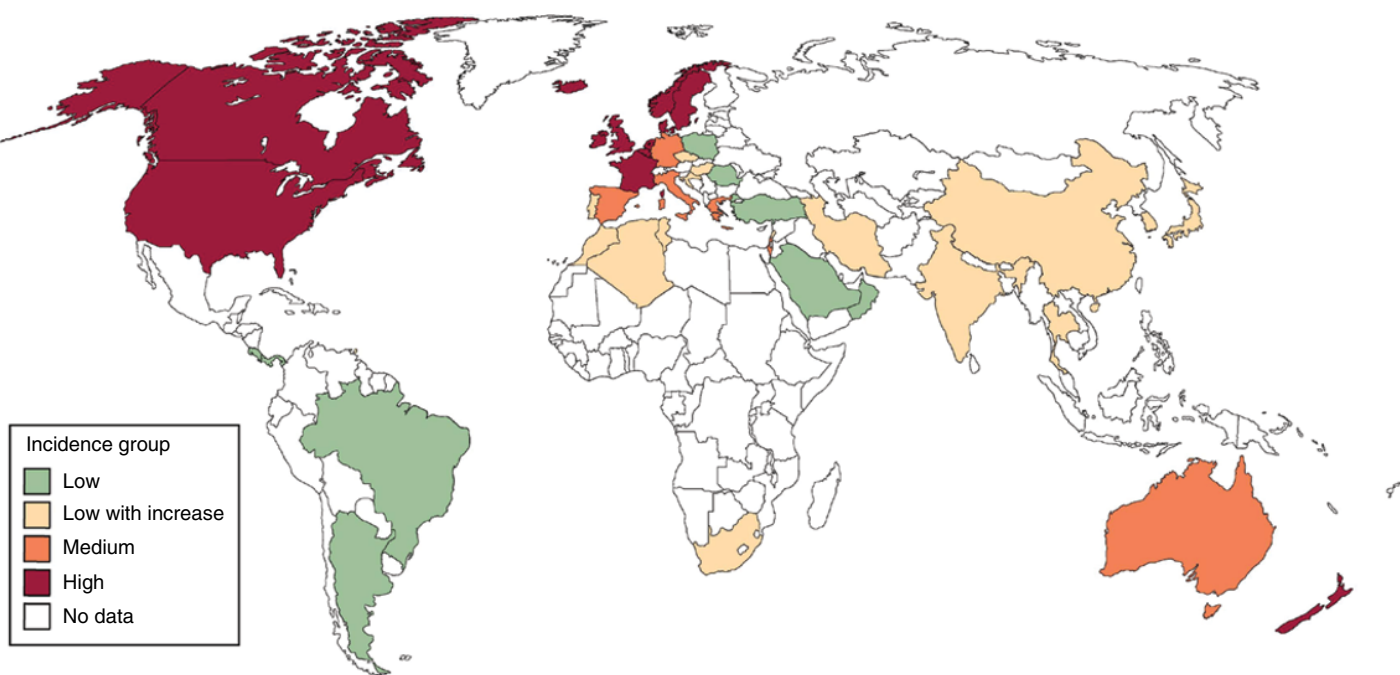


Figure 1.1 Geographic variation in incidence of Crohn's disease and ulcerative colitis. *Source:* Adapted from Cosnes *et al.* 2011 [26]. Reproduced with permission of Elsevier.

risk is dependent on the country of origin. Individuals of South Asian or West Asian origin experience a greater increase in disease risk whereas the risk in those from East Asia remains lower than in the country of residence [4].

Pathogenesis

The key mechanism underlying the development of IBD appears to be a dysregulated immune response to commensal flora in a genetically susceptible individual (Figure 1.2). Family history is one of the strongest risk factors for the development of disease. Only 10–20% of patients will have an affected first-degree relative. However, the risk of the offspring developing IBD increases 2–13-fold if one parent is affected. This absolute risk can be as high as 36% if both parents are affected. The concordance of disease is greater in

monozygotic twins (30–35%) than dizygotic twins, also supporting an important role for genetics in these diseases. However, genetic mutations alone are not sufficient for disease except in the rare VEOIBD owing to high-penetrance mutations involving the interleukin (IL)-10 receptor.

Genetics

An international consortium has identified 163 common risk loci for IBD. Most loci are shared between both diseases; 30 loci are distinctly associated with CD whereas 23 loci demonstrate genome-wide significant association with UC alone. These loci together explain only 13.6% of the variance in risk of CD and 7.5% of the variance in risk for UC. Although most common loci demonstrate an effect in the same direction, two loci demonstrate divergent effects. *NOD2* and *PTPN22* polymorphisms are associated

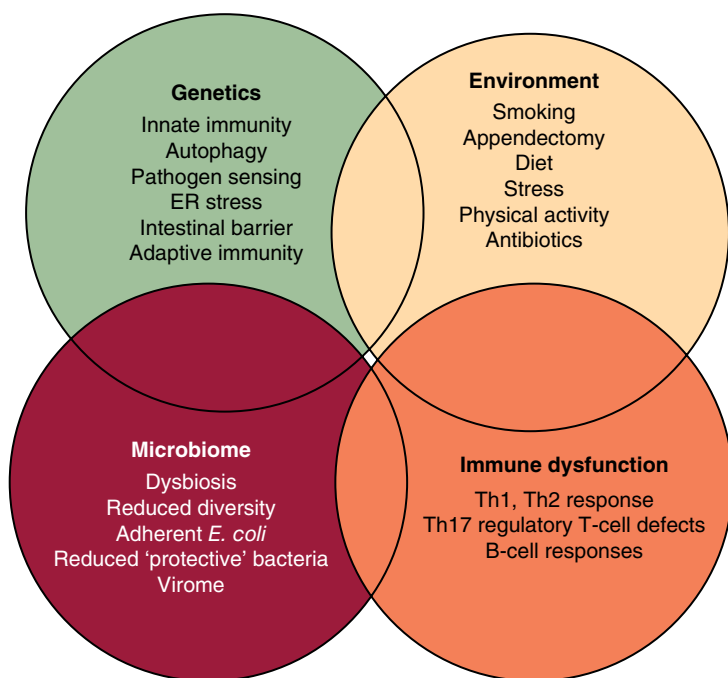


Figure 1.2 Inflammatory bowel disease develops as a result of a complex interplay between genetics, the microbiome, immunologic dysregulation, and the external environment.

with an increased risk of CD but are inversely associated with UC. Several of the loci are also implicated in other autoimmune diseases, including psoriasis and celiac disease, suggesting considerable sharing of pathogenic pathways across various autoimmune or inflammatory diseases. Although the spectrum of immunologic disruption as a consequence of these genetic polymorphisms is wide, several pathways emerge as being important in the development of IBD. These include the innate immunity, autophagy, adaptive immune responses, pathogen sensing, maintenance of the intestinal barrier through the mucous layer and epithelial integrity, and response to oxidative stress. Several genes may influence the same pathway. For example, *HNF4A*, *MUC19*, *CDH1*, and *GNA12* all influence intestinal barrier integrity whereas *NOD2*, *ATG16L1*, *IRGM*, and *LRRK2* affect autophagy. The pathways may act in isolation, in combination with each other, or in conjunction with environmental insults. For example, the functional consequences of autophagy defects on Paneth cell function are triggered by infection with the Norovirus. The identified genetic polymorphisms also highlight the substantial evolutionary conversation between pathways that are important in the development of autoimmune diseases, but also play an important role in mediating responses to infections. For example, polymorphisms in the vitamin D receptor (*VDR*) or *SLC11A1*, both linked to IBD, are also associated with increased risk of *Mycobacterium tuberculosis* infection, and *NOD2* and *LRRK2* polymorphisms are associated with leprosy. Some of the IBD risk variants (*STAT3*, *CARD9*) are also associated with primary immunodeficiency states and may predispose to recurrent bacterial or fungal infections.

NOD2 was the first genetic variant to be associated with CD [5, 6]. It functions as an intracellular sensor of the peptidoglycan muramyl dipeptide (MDP), a component of

bacterial cell walls. Stimulation of *NOD2* by MDP results in activation of a cascade of inflammatory pathways involving nuclear factor- κ B (NF- κ B) and mitogen-activated protein (MAP) kinase signaling resulting in the production of inflammatory cytokines including tumor necrosis factor alpha (TNF- α) and IL-1 β . Three common polymorphisms – Arg702Trp, Gly908Arg, and Leu1007fsX1008 – and five rare variants in *NOD2* have been identified through deep sequencing. *NOD2* also activates T-cell responses through MDP-independent mechanisms. Despite *NOD2* variants being associated with the greatest relative risk of CD, their presence alone is not sufficient for disease as up to 30% of individuals of European ancestry may carry such variants. In addition, *NOD2* has not been consistently associated with CD in non-European populations.

Variants in genes whose products contribute to autophagy, a cellular process involved in intracellular microbial clearance and degradation of cytosolic contents, have also been associated with CD, most notably variants of *ATG16L1* and *IRGM*. In addition to their independent effect, autophagy variants may influence susceptibility to environmental triggers through a “two-hit” hypothesis. This was highlighted in an elegant study in which the defects in Paneth cell structure and function in *ATG16L1* knockout mice were exaggerated in the setting of murine Norovirus infection [7].

Adaptive immune responses, through both T- and B-lymphocytes, play an important role in the pathogenesis of IBD. In the setting of active inflammation, naive T cells are activated and differentiate into Th1, Th2, or Th17 cells depending on the influence of different cytokines [8, 9]. Th1 cells, initially thought to be key in the pathogenesis of Crohn’s disease, produce TNF- α and interferon gamma (IFN- γ) along with other cytokines that activate macrophages, lead to epithelial cell apoptosis, and induce

differentiation of stromal myofibroblasts, which, through the production of matrix metalloproteinases, result in degradation of the extracellular matrix. In contrast, Th2 cells produce IL-13, which increases intestinal permeability and induces epithelial apoptosis [8, 9].

A relatively recently described class of helper T cells – Th17 cells – produce IL-17A, IL-21, and IL-22, which aid in neutrophil recruitment and inflammation through activation of NF- κ B and MAPK pathways [8, 9]. Several other cell types also appear to play important roles in the pathogenesis of IBD. The innate lymphoid cell (ILC) is a newly described effector cell subtype that makes IFN- γ (group 1 ILC), IL-5 and IL-13 (group 2 ILCs), or IL-17, IL-22, and IFN- γ (group 3 ILCs). Group 3 ILCs in particular appear to play an important role in inducing colitis through an IL-23R/IL-22-dependent mechanism. In an animal model, RAG^{-/-} mice developed colitis after injection of CD40 ligand (CD40L), but only in the presence of innate lymphoid cells [10].

Trafficking of leukocytes to the small intestine and colon, mediated through chemoattractants, chemokine receptors, and adhesion molecules, plays an important role in homing of lymphocytes into gut-associated lymphoid tissues at the site of inflammation [11]. For example, the mucosal vascular addressin cell adhesion molecule 1 (MADCAM1), expressed on the high endothelial venules of Peyer's patches and on the venules of small intestine and colon, is a receptor for the α 4 β 7 integrin and facilitates migration of leukocytes to Peyer's patches and sites of intestinal inflammation [11].

The rapid pace of discovery in the field of genetics and immunopathogenesis of these diseases has contributed to the development of existing and emerging therapeutics and highlighted novel effective modalities of action. Monoclonal antibodies to TNF- α , reviewed in detail in subsequent chapters, are among the most effective existing treatments

for both CD and UC. Recognition of the importance of the IL-17/IL-23 pathway in IBD led to the development of an antibody targeting the p40 subunit of IL-12/IL-23, ustekinumab, that is already in use for the treatment of psoriasis and shows promise in the management of CD. Leukocyte migration has been targeted by several drug categories, including monoclonal antibodies such as natalizumab and vedolizumab, and also small-molecule inhibitors. The direct implication of genotype in guiding a personalized approach to diagnosis or therapy is less well established. NOD2 mutations are associated with ileal location or fibrostenosing CD. None of the other genetic mutations have been consistently predictive of natural history or response to therapy, although panels comprising multiple genes show a modest ability to predict therapy response.

Microbiome

Several lines of evidence support an important role for the intestinal microbiome in the pathogenesis of IBD. Mice genetically predisposed to develop colitis, such as IL10^{-/-} or TCR α ^{-/-}, either do not develop colitis in germ-free conditions, or develop only attenuated inflammation (*SAMP1/yit* or IL2^{-/-} mice). Defects in pattern recognition receptors such as Toll-like receptors result in attenuation of the colitis. Several polymorphisms important in the development of IBD, for example *NOD2* and *ATG16L1*, are key for the recognition of patterns from luminal microbial antigens and activation of innate immune responses in response to such stimulation. Polymorphisms at these loci result in aberrant Paneth cell function and impaired production of antimicrobial peptides, further highlighting the importance of luminal microbial antigenic stimulation. Clinically, in patients with CD, exposure to the fecal stream is essential for the development of postoperative recurrence after intestinal resection [12, 13].

The normal adult human microbiome contains 10^{13} – 10^{14} bacterial cells and an estimated 1000 different bacterial species. The largest microbial community in the human intestine is Bacteroidetes with a smaller proportion of Firmicutes. Other important groups occurring at a lower frequency are Proteobacteria, Actinobacteria, Fusobacteria, and Verrucomicrobia. There is substantial inter-individual variation in the intestinal microbiome, which attains stability after the first 2–4 years of life. The intestinal microbiota is also susceptible to the effect of external environmental influences, most prominently diet and antibiotic exposure.

Three dominant patterns of gut microbial changes are apparent in patients with IBD. First, there is an overall reduction in diversity and abundance of gut microbiota in patients with IBD compared with controls. Mucosal biopsies in IBD demonstrate a reduced abundance of Firmicutes and Bacteroidetes and an increase in Proteobacteria and Actinobacteria [14, 15]. Second, specific subphenotypes of IBD may demonstrate an increase in some pathogenic microbes. Specifically, enteroadherent *Escherichia coli* is found at a greater frequency in ileal lesions of patients with CD than with UC or in healthy controls [16]. Third, patients with IBD may demonstrate a reduced frequency of bacteria, which may be important in conferring protection from intestinal inflammation. For example, individuals with IBD have reduced levels of short-chain fatty acids in stool, pointing to the potential role of Ruminococcaceae, which are important butyrate producers. They also have reduced abundance of *Faecalibacterium prausnitzii*, a bacterium belonging to the Clostridiales family. Furthermore, the prevalence of *F. prausnitzii* correlates inversely with likelihood of endoscopic recurrence of CD following intestinal resection and supernatants from *F. prausnitzii* cultures ameliorate colitis in

animal models [17, 18]. In addition to the above variations in composition of the gut microbiome, there are also differences in functional pathways between IBD and healthy individuals, including those mediating response to oxidative stress, and a decrease in carbohydrate and amino acid biosynthesis [19]. However, bacteria may not be the sole components of the gut microbiome influencing susceptibility to IBD. Viral infections, particularly in the context of specific genetic polymorphisms, may act as triggers for intestinal inflammation and disruption of immune function [7]. Fungal diversity may be increased in patients with IBD.

Environmental Triggers

Several environmental factors appear to influence the risk of and natural history of IBD. Harries *et al.* [20] first noted that patients with UC were less frequently smokers than healthy individuals. Several studies since have replicated this association and demonstrated an increased risk of CD among current and former smokers. In contrast to the inverse association between current smoking and UC, smoking cessation is associated with a twofold increase in risk of UC that is apparent within 2–5 years of cessation and may persist for up to 20 years. Passive smoking has a similar direction of effect. The effect of smoking is not uniform in all populations and may be dependent on ethnicity and gender. Women are more susceptible to the adverse effects of smoking on IBD whereas men have a greater magnitude of the protective effect of cigarette smoke on UC. Smoking exerts an influence on natural history of disease similar to its effect on incident disease. Current smokers have more aggressive CD with a greater need for immunosuppression, a higher likelihood of surgery, and increased risk of recurrence after resection. In contrast, in UC, smoking is associated with a milder course and reduced likelihood of surgery. It is unclear which

substance(s) within tobacco smoke are responsible for these effects. Trials with nicotine-based agents do not ameliorate disease in patients with UC. A similar interesting divergent direction of effect is seen for appendectomy. When performed before the age of 20 years and for inflammatory appendicitis, it is associated with a reduced risk of UC [21]. In contrast, it does not confer similar protection against CD and may be associated with an increased risk.

Given the central role of the microbiome in disease pathogenesis and the strong influence of long- and short-term diet on gut composition, it is plausible that diet plays a role in the predisposition to developing IBD or influences subsequent natural history. However, high-quality prospective data informing such associations are lacking. The most consistent dietary association described is an inverse relationship between fruits, vegetables, or fiber intake and risk of CD. Several plausible mechanisms support this association. Soluble fiber may prevent bacterial transmigration through the epithelium and modify the composition of gut microbiota. Specific dietary substances may be ligands for the aryl hydrocarbon receptor, which plays a role in ameliorating gut inflammation. Dietary fat may increase the risk of UC although the data are less consistent and many studies have shown no effect. However, in animal models, a high milk fat diet resulted in expansion of pathobionts in the gut and more severe colitis. n-3 polyunsaturated fatty acids such as are found in fish oil have been inversely associated with risk of UC, although therapeutic interventions modifying their intake have yielded mostly unsuccessful results in both CD and UC. Studies have also demonstrated substantial heterogeneity in

susceptibility to symptomatic exacerbations in response to the intake of specific foods. Therapeutically, elemental diet is effective in inducing remission in pediatric CD but is poorly tolerated over the long term. Several other elimination diets have been proposed but there is a lack evidence in support of efficacy.

Other environmental influences associated with risk of IBD include antibiotic exposure, low vitamin D, sleep, stress and depression, physical activity, hormone use, non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin, breastfeeding, environmental hygiene, and exposure to animals in childhood. Although offering intriguing insights into disease pathogenesis, few of these have been translated into interventions to benefit individuals with established disease. Normalization of vitamin D levels in patients with deficiency is associated with a reduction in risk of subsequent surgeries, and vitamin D supplementation may reduce the likelihood of relapses. Interventions targeting stress and depression may improve psychological quality of life but have a variable impact on actual clinical disease activity. Enteric infections, in particular *Clostridium difficile* infection, are frequent triggers of relapses in those with established IBD and should be sought for in the setting of unexplained clinical activity (Table 1.1). Although ascertaining exposure to some of these potential triggers at the time of disease exacerbation is reasonable, with the exception of smoking cessation in those with established CD, systematic efforts to modify these risk factors with the aim of influencing overall disease activity cannot be recommended due to lack of high-quality interventional studies.

Table 1.1 Effect of environmental risk factors on risk of development of Crohn's disease or ulcerative colitis.

Environmental factor	Crohn's disease	Ulcerative colitis
<i>Smoking</i>		
Current smoking	Increased risk	Decreased risk
Former smoking	Increased risk	Increased risk
Appendectomy	Equivocal	Decreased risk
<i>Diet</i>		
Dietary fiber, Fruits, vegetables	Reduces risk	No effect
Dietary fat	Equivocal	High n-3 polyunsaturated fats may reduce risk whereas n-6 fats may be associated with increased risk Saturated fat diet (particularly milk fat) may be associated with increased risk
Protein	Equivocal	Equivocal. May increase risk
Zinc	Decreased risk	No effect
Stress, depression	Increased risk	Increased risk
NSAIDs, aspirin	Increased risk	Increased risk
Low vitamin D levels	Increased risk	No effect
Antibiotic use	Increased risk	Increased risk
History of being breastfed	Decreased risk	Decreased risk

Case Studies and Multiple Choice Questions

- 1 John is a 26-year-old male who presented to his gastroenterologist with complaints of diarrhea and rectal bleeding of 4 months' duration. He has no extraintestinal symptoms. He has no family history of IBD. A colonoscopy is performed and reveals erythema, granularity, friability, and erosions consistent with left-sided ulcerative colitis. Which of the following factors if present in John's history is associated with an increased risk of ulcerative colitis?
 - A Increased intake of dietary fiber.
 - B A history of appendectomy at age 9 years for appendicitis.
 - C Current smoking of one pack per day.
 - D Smoking cessation 2 years prior to diagnosis.
- 2 The proportion of patients with IBD who will have at least one affected first-degree relative with Crohn's disease or ulcerative colitis is
 - A 0–5%.
 - B 10–20%.
 - C 50–60%.
 - D 80–90%.
- 3 Which of the following changes in the gut microbiome have *not* been described in patients with IBD?
 - A Increased frequency of enteroinvasive *Escherichia coli*.
 - B Reduced diversity of gut microbiota.
 - C Reduced abundance of bacteria belonging to the phylum Firmicutes.
 - D Greater abundance of *Faecalibacterium prausnitzii*.
- 4 The known 163 common single-nucleotide polymorphisms that modify risk of Crohn's disease or ulcerative colitis explain what proportion of the variance in risk for each disease?
 - A 8% of the variance in UC and 14% of the variance in CD.
 - B 22% of the variance in UC and 48% of the variance in CD.
 - C 60% of the variance in UC and 30% of the variance in CD.
 - D 5% of the variance in UC and 20% of the variance in CD.