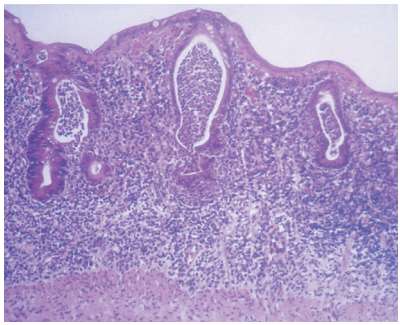
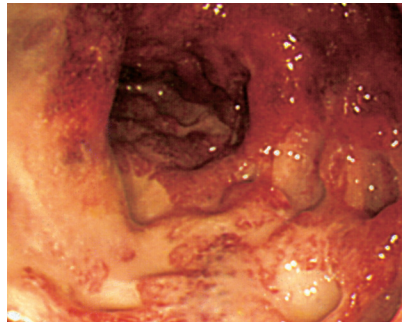
Fast Facts

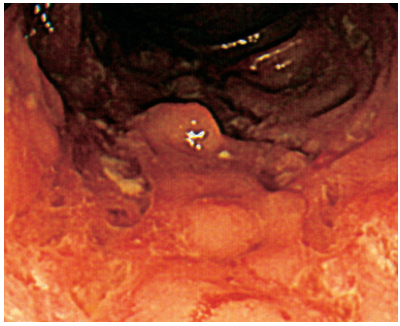
Fast Facts: Inflammatory Bowel Disease

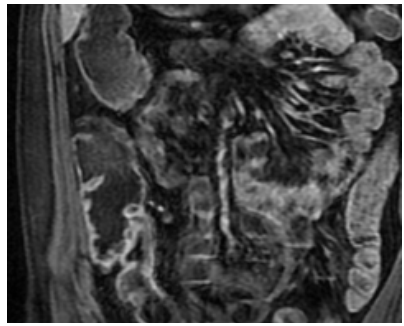
David S Rampton and Fergus Shanahan

Fifth edition









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List of abbreviations

5-ASA: 5-aminosalicylate

AS: ankylosing spondylitis

ASCA: anti-*Saccharomyces cerevisiae* antibody

ATI: antibodies to infliximab

***ATLG 16L1*:** autophagy-related 16-like 1 gene

BMI: body mass index

***CARD15*:** caspase-activating recruitment domain, member 15 (also known as *NOD2*)

CDAI: Crohn's Disease Activity Index

CMV: cytomegalovirus

COX: cyclo-oxygenase

CRP: C-reactive protein

CT: computed tomography

CUTE: colitis of uncertain type or etiology

ERCP: endoscopic retrograde cholangiopancreatography

GWAS: genome-wide association scan

HACA: human antichimeric antibodies, now known as ATI

HLA: human leukocyte antigen

IBD: inflammatory bowel disease

IFN: interferon

Ig: immunoglobulin

IL: interleukin

***IRGM*:** immunity-related GTPase family, M gene

JAK: Janus kinase

MAP: mitogen-activated protein

MP: mercaptopurine

MRCP: magnetic resonance cholangiopancreatography

MRI: magnetic resonance imaging

NF-κB: nuclear [transcription] factor κB

***NOD2*:** nucleotide-binding oligomerization domain containing 2; other name for *CARD15*

NSAIDs: non-steroidal anti-inflammatory drugs

pANCA: perinuclear antineutrophil cytoplasmic antibody

PPAR: peroxisome proliferator-activated receptor

SeHCAT: ^{75}selenium-labeled homocholic acid taurine

TB: tuberculosis

^{99}Tc-HMPAO: ^{99}technetium-labeled hexamethylpropyleneamine oxime

TGF: transforming growth factor

TGN: thioguanine nucleotide

Th: T helper cell

TNF: tumor necrosis factor

TPMT: thiopurine methyltransferase

Treg: regulatory T cells

Introduction

Inflammatory bowel disease (IBD) comprises two idiopathic chronic relapsing and remitting inflammatory disorders of the gastrointestinal tract: ulcerative colitis and Crohn's disease. The swift pace of advances in knowledge, understanding and innovation in the treatment of IBD has driven the need for this new edition.

Here, we continue to emphasize the disturbances of host immune and environmental interactions in the etiopathogenesis of these disorders, in particular the genetically determined disturbances of host–microbe interactions. We also highlight recent improvements in our understanding of how best to use immunomodulatory and biological drugs, alone and in combination, and include the most recent innovations in this area.

In the future, increasing efforts will be made to offer personalized treatment to each patient. The selection of specific drugs only after detailed assessment of the genotype and other features of the individual will help us to identify who will respond well and who will respond badly, and thus enable us to use therapeutic agents more appositely.

We must also continue to embrace the holistic approach to management of these chronic diseases. Doctors often used to overlook problems such as anemia, mood disturbance, fatigue and osteoporosis, yet each of these is a common if not always easily reversible cause of impaired quality of life for patients with IBD. In this time of increasing specialization, high technology diagnostics, molecular therapeutics and evidence-based everything, the doctor–patient relationship will come under increasing scrutiny and change. Technology helps to clarify the objective aspects of the disease but not the subjective experience – the illness – which is unique to each patient.

Health professionals who care for patients with IBD need to care about patients with IBD. This requires an interest in the condition, a commitment to long-term follow-up and more than a little compassion. This book is aimed at non-specialist doctors (particularly primary care providers and hospital doctors in training), nurses, stoma therapists, dieticians, psychologists, counselors, social workers and other professionals involved in the care of patients with IBD. Medical students should also find it helpful. We hope too that patients with IBD may benefit from reading this overview of their illness.

1 Etiopathogenesis

Overview

Heterogeneous disorders. The collective term inflammatory bowel disease (IBD) obscures the distinctive nature of Crohn's disease and ulcerative colitis. These are separate conditions, with some overlapping and several distinct features. Crohn's disease in particular, and ulcerative colitis to a lesser degree, are heterogeneous, with more than one underlying defect or mechanism leading to a similar clinical outcome. In addition, different mechanisms may account for different subsets of disease. Like many other chronic inflammatory disorders, tissue damage is immune-mediated and arises from a variable interaction between genetic susceptibility factors and environmental triggers or modifiers.

Genetic versus environmental factors. Genetic factors are more important in Crohn's disease than in ulcerative colitis. This is evident from studies of genetically identical (monozygotic) twins, which show that the concordance rate for Crohn's disease (risk of second twin developing disease if one is affected) is 40–50%, whereas that for ulcerative colitis is about 10%. These figures also reflect the importance of environmental or lifestyle factors in both conditions, as indicated by the marked rise in the frequency of both forms of IBD in recent decades, particularly in countries undergoing socioeconomic development. The increased incidence and prevalence of these conditions over a relatively short period of time, within one to two generations, can not be accounted for by genetic changes alone.

The indigenous microbiota colonizing the gut from birth is the most immediate environmental modifier of mucosal and systemic immune development, and hence is a pivotal influence on the pathogenesis of IBD. Disturbances in the microbiota, particularly in early life, may affect immune maturation and predispose to microbe-induced immunopathology later in life. Most of the elements of a modern lifestyle and putative risk factors for developing IBD within the wider environment influence the composition of the indigenous microbiota. Furthermore, many of the genetic risk factors for Crohn's disease and ulcerative colitis either code for sensors of the microbial

environment or regulate host responses to that environment or, in the case of ulcerative colitis, influence barrier function at the interface with the intestinal microenvironment. Whether tissue damage results from an abnormal immune reaction to a normal microbiota or from a normal immune response to an abnormal microbiota has been much debated (Figure 1.1). Animal models support both possibilities. Animal models have also shown that while genetic susceptibility and the presence of the microbiota are required for the pathogenesis of chronic inflammation, the timing of onset may be determined by environmental triggers such as chemical injury or viral infection.

Epidemiology

The epidemiological features of Crohn's disease and ulcerative colitis are similar in most respects (Table 1.1), the most striking exception being tobacco smoking.

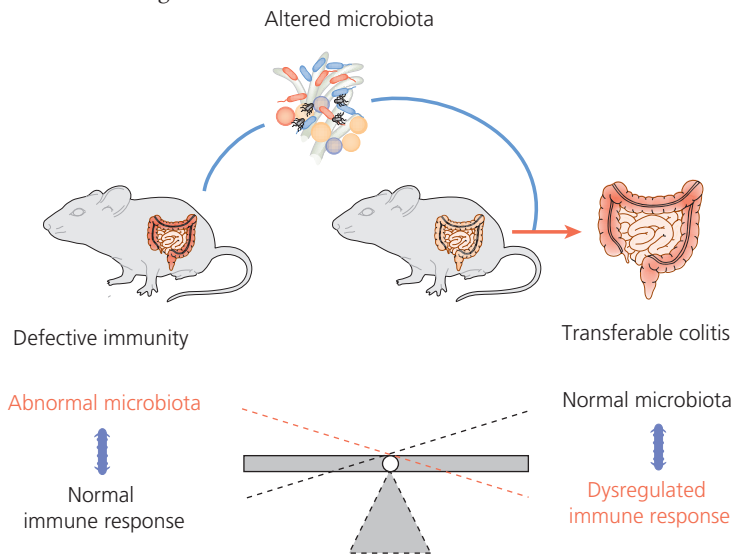

Figure 1.1 The complexity of host–microbe interactions in IBD. Animal models have shown that the immune system conditions the composition of the microbiota. In a host with defective innate immunity, the immune system may change the microbiota toward one with colitogenic potential with capacity to transfer colitis to a normal host. Thus, disease may arise either from a normal immune response to an abnormal microbiota or from an abnormal immune response to a normal microbiota.

TABLE 1.1

Epidemiological features of Crohn's disease and ulcerative colitis

	Crohn's disease	Ulcerative colitis
Incidence*	~5–10	~5–10
Prevalence†	100–200	100–200
Male/female ratio	~1:1	~1:1
Age of onset	All ages	All ages
	Peak at 20–40‡	Peak at 20–40‡
Smoking	Risk factor	Linked with cessation of smoking
	Aggravates	Modest beneficial effect
Appendectomy (appendicitis)	No effect	Protective
Geographic/ socioeconomic§	Common in developed countries	Common in developed countries
Ethnicity	All ethnic groups affected	All ethnic groups affected
	More common in Ashkenazi than Sephardic Jews	More common in Ashkenazi than Sephardic Jews
Infections	Adverse	Adverse
Psychological stress	Perceived stress aggravates disease	Perceived stress aggravates disease
Adverse effect of drugs		
Antibiotics	Risk factor in early life	Probable but unproven
Oral contraceptives	Unproven	Unproven
NSAIDs	Yes, in high doses	Yes, in high doses

*New cases/10^5 population/year. †cases/10^5 population. ‡Some but not all studies report a bimodal age distribution with a later, lesser peak at 60–80 years. In a rare subset of patients who present in very early childhood, a distinct monogenic pattern of inheritance may be involved. §As with other immunoallergic disorders, IBD is more common in urban than in rural areas. Endemic parasitism with helminths and unsanitary conditions seem to be protective.
NSAIDs, non-steroidal anti-inflammatory drugs

Smoking is more common among patients with Crohn's disease, aggravates the clinical course of the disease and antagonizes the efficacy of immune-modulatory drug therapy. In contrast, the cessation of smoking is often linked with the onset or relapse of ulcerative colitis, and nicotine has a modest beneficial effect on the condition. The mechanisms underlying these opposing effects are unclear, but smoking impairs autophagy and influences many aspects of mucosal homeostasis including immune and barrier function, blood flow and the composition of the microbiota.

Appendectomy, particularly when performed early in life, is associated with a reduced risk of developing ulcerative colitis but not Crohn's disease. It seems that appendicitis and mesenteric lymphadenitis, rather than appendectomy per se, during childhood or adolescence confers protection against subsequent development of ulcerative colitis.

Socioeconomic development. The most consistent epidemiological feature of both Crohn's disease and ulcerative colitis is the increase in incidence and prevalence of both conditions in societies undergoing socioeconomic development. This probably accounts for epidemiological observations in the past, including notional east–west and north–south geographic gradients. The emergence of IBD with socioeconomic development follows a consistent pattern, first with the appearance of ulcerative colitis, followed by Crohn's disease. Incidence and prevalence has already peaked in some but not all Western countries, is rising rapidly in developing areas of the globe, and can be predicted to appear in others. This should be seen not only as an epidemiological lesson but also as an opportunity – an imperative for the developed world to try to prevent. Studies of migrant populations moving from low- to high-prevalence areas confirm the influence of modern environmental and lifestyle factors, and suggest that their effect is greatest at the earliest stages of life when the indigenous microbiota is becoming established and the immune system is still developing.

Epidemiological clues to the role of gut microbiota. The possibility that IBD or a subset thereof might be caused by a pathogen waiting to be discovered cannot be fully discounted. However, the involvement of a transmissible agent is at variance with the population distribution of these diseases:

overcrowding, large family size and poor sanitary conditions seem to be protective. Therefore, many researchers have moved from a 'one microbe, one disease' model toward a more complex concept of mixed microbial patterns or populations within the indigenous microbiota becoming risk factors for disease depending on host susceptibility. Most elements of a modern lifestyle have been shown to influence the composition of the indigenous microbiota (Table 1.2). The link between lifestyle factors, particularly diet, and the risk of developing IBD, is complex and may be indirect, mediated by an influence on the microbiota in early life.

Diet. Dietary changes associated with socioeconomic development have been implicated in the changing epidemiology of IBD. Animal models have demonstrated the influence of specific food ingredients, in particular a high-fat diet, on the composition of the microbiota. A diet high in milk-derived fat but not polyunsaturated fat has been linked with expansion of the pathobiont *Bilophila wadsworthia* and colitis in interleukin (IL)-$10^{-/-}$-deficient mice. Whether similar gene–diet–microbe interactions occur in humans is less clear,

TABLE 1.2

Elements of a modern lifestyle in socioeconomically developed countries with potential to modify host–microbe gut interactions*

Improved sanitation and hygiene
Refrigeration
Living on concrete (urbanization)
Smoking
Decline in ancestral microbes (e.g. *Helicobacter pylori*, endemic parasitism with helminths)
Increased antibiotic usage
Vaccinations
Smaller family size
Delayed exposure to mucosal infections
Sedentary lifestyle – obesity
Increased likelihood of birth delivery by Cesarean section
Diet, including greater use of processed foods with higher fat content

*In animal models, stress may alter the composition of the microbiota, providing evidence for a microbe–gut-brain axis.

but it is noteworthy that the increased incidence of IBD over recent decades in Japan correlates closely with changes in dietary fat, particularly animal fat. In addition, it has recently been shown that dietary diversity is positively correlated with fecal microbial diversity, both of which are linked with reduced levels of pro-inflammatory markers in healthy adults.

Antibiotic exposure, particularly in the first year of life, has been linked with up to an eightfold increased risk for development of Crohn's disease in childhood.

The gut microbiota

Animal models have shown the complexity and heterogeneity of the role of gut microbes in the pathogenesis of IBD.

- The microbiota is necessary for full development and maturation of the immune system, without which an inflammatory response to any cause would not be possible.
- While some microbial products are protective against inflammation, others are pro-inflammatory in susceptible individuals.
- A defect in host immunity may change the composition of the indigenous microbiota toward one with colitogenic properties.
- Gut microbiota and their products may play a role not only in the onset and pathogenesis of IBD, but also in its progression and complications such as stricture formation and adhesions. They may also contribute to the risk of colitis-associated carcinogenesis.
- The microbiota has direct involvement in translocation, sepsis and, as a competitive influence, in the risk of complicating infections such as *Clostridium difficile*-associated disease.
- Mucosal infections may determine both the onset and subsequent relapses of IBD. Mucosal infection temporarily disrupts barrier function and generates immune responses not only against the pathogen but also against commensal species. Repeated infections may lead to accumulation of commensal-reactive T cells, which eventually shift mucosal homeostasis from controlled or physiological inflammation toward chronic inflammatory disease.

Microbial alterations. The more consistently observed microbial alterations are summarized in Table 1.3. Reduced microbial biodiversity is

consistently found but is non-specific. While reduced biodiversity in the gut may have arisen because of reduced acquisition of environmental microbes (the so-called hygiene hypothesis), it is more likely that it reflects progressive loss of ancestral microorganisms, for example helminths and *Helicobacter pylori* (which was in decline in the Western world long before its discovery in the 1980s).

Increased numbers of mucosal adherent and intramucosal bacteria are found in Crohn's disease and may reflect defective clearance of bacteria. This may also account for increased rates of detection of *Mycobacterium avium paratuberculosis* and enteroadherent *Escherichia coli* in patients with Crohn's disease. While such co-infections may not cause Crohn's disease, they may influence its clinical progression. Other organisms such as *Faecalibacterium prausnitzii*, which has anti-inflammatory properties, are reduced in many patients with IBD, whereas other microbial disturbances may contribute to tissue injury because of their mucolytic or proteolytic properties. It is likely that improvements in traditional culture-based techniques, combined with modern molecular non-culture-dependent strategies such as high-throughput sequencing and metagenomic compositional analysis will provide new microbial biomarkers of risk and IBD subsets in the future. As with animal models, heterogeneity of responses to therapeutic manipulation of the

TABLE 1.3

Examples of the microbiota in inflammatory bowel disease*

Increased	Reduced
Mucosal bacterial numbers (CD)	Bacterial diversity (CD, UC)
Mycobacterium avium paratuberculosis (CD)	Clostridium groups IV, XIVa (*Faecalibacterium prausnitzii*) (CD, UC)
Clostridium difficile (CD, UC)	Bifidobacteria and lactobacilli (CD, UC)
Ruminococcus gnavus (CD)	Akkermansia (UC, CD)
Enterobacteriaceae e.g. adherent invasive *Escherichia coli* (CD)	

*Examples of consistently detected changes in the intestinal microbiota in patients with Crohn's disease (CD) and ulcerative colitis (UC)

microbiota can be anticipated in patients with IBD. For example, antibiotics have efficacy in colonic Crohn's disease but not in small-bowel disease (see Chapters 5 and 8), and are the treatment of first choice in pouchitis (Chapter 9) but not in uncomplicated ulcerative colitis.

In summary, the microbiota is protective for most individuals, may be a permissive bystander in some cases of IBD, or may have a more direct contributory role in others, depending on genetic–microbial–environmental interactions, particularly in early life.

Genetics

The identification of the first susceptibility gene for Crohn's disease in 2001, nucleotide-binding oligomerization domain containing 2 (*NOD2*), also known as *CARD15* (caspase-activating recruitment domain family, member 15), prompted an intense search for additional genes. This has been facilitated by several technological advances, particularly genome-wide association scans (GWAS). Meta-analysis of GWAS of large cohorts of patients with IBD has identified over 160 disease-related genetic loci. Although these loci account for only a small amount of total variance in disease risk for Crohn's disease and ulcerative colitis, IBD-associated genes have provided important and sometimes unexpected insights into disease biology. In particular, they have highlighted the importance of innate immunity to microbiota, mucosal barrier function, autophagy and T helper cell (Th) 17-driven immune responses.

Additional insights into disease mechanisms arising from different underlying genetic defects have been acquired from various genetically engineered mouse models, most of which involve defective mucosal barrier function or immune regulation. From human and animal studies, the following generalizations may be made:

- No single susceptibility gene is necessary or sufficient to lead to disease.
- Multiple genes are involved, leading to extensive disease heterogeneity.
- A subset of patients presenting with very early onset intestinal disease may have monogenic disease. Rare monogenic disorders, including homozygous recessive mutations in the IL-10 receptor, have been linked with very early onset. Most of the affected children have diffuse colonic disease but don't fit easily into a Crohn's/ulcerative colitis classification.
- The genetic contribution of most genetic loci to explained heritability is low.

- Different mechanisms may lead to similar phenotypes.
- Gene–gene interactions modify the severity of disease. For example, susceptibility to inflammatory disease caused by a single genetic defect in mice varies depending on the background strain.
- Gene–environment interactions are confirmed by the requirement for enteric bacteria for full development of disease.
- Genetic factors are more important in Crohn's disease than in ulcerative colitis.
- Distinct genetic susceptibility factors may underlie Crohn's disease confined to the colon (distinct from susceptibility factors that underlie small-bowel Crohn's disease).
- Most GWAS have been conducted in populations of European ancestry, but some loci are not associated with Crohn's disease in Japanese people, suggesting that the genetics of Crohn's disease varies across populations.
- Some genetic risk factors are common to ulcerative colitis and Crohn's disease, whereas others are disease specific (Figure 1.2).

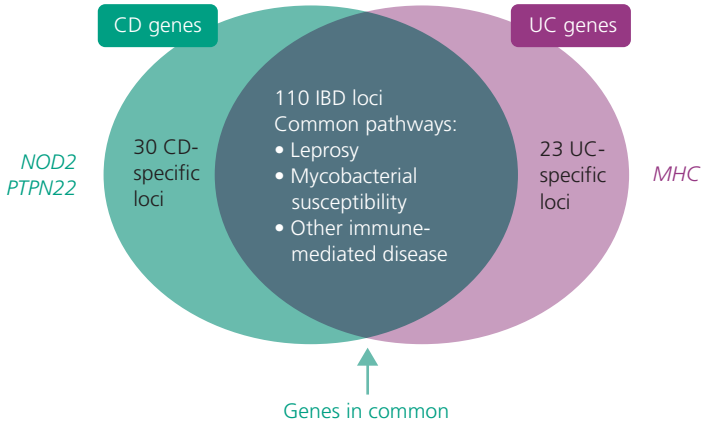

Figure 1.2 Meta-analysis of Crohn's disease (CD) and ulcerative colitis (UC) genome-wide association scans. Of 163 loci, 110 are associated with both disease phenotypes; 30 are classified as CD specific and 23 as UC specific. Two Crohn's disease loci, *PTPN22* and *NOD2*, show significant protective effects in ulcerative colitis, reflecting the biological distinctiveness of the two diseases. Many of the susceptibility loci for IBD overlap with those involved in other immune-mediated disorders such as ankylosing spondylitis and psoriasis, and in resistance/susceptibility to mycobacterial infections. Based on data from Jostins L et al. 2012.

Details of the mechanisms by which each genetic locus contributes to the risk and pathogenesis of IBD are uncertain. However, some of the better known loci illustrate how GWAS discoveries have provided important insights into disease pathways, some of which are summarized here.

NOD2. Two single-nucleotide polymorphisms and one frame-shift mutation in the *NOD2* gene at the IBD1 locus on chromosome 16 are associated with a greater than fortyfold increased risk of Crohn's disease for individuals who are homozygous for all three. About 40% of European patients with familial Crohn's disease carry one of the three *NOD2* mutations. *NOD2* mutations predispose in particular to fibrostenosing small-bowel and right-sided colonic Crohn's disease. The protein encoded by *NOD2* is an intracellular pattern recognition receptor, a sensor for bacterial peptidoglycan that can be activated by a component of peptidoglycan, muramyl dipeptide.

The polymorphisms identified may confer susceptibility to Crohn's disease by altering immunorecognition of the constituents of bacterial flora and by modifying activation of the nuclear [transcription] factor (NF)-κB. However, because *NOD2* mutations account for only 20–30% of cases and are not linked with Crohn's disease in Japanese individuals and others of Oriental descent, this genetic risk factor, like others, is neither necessary nor sufficient for the development of Crohn's disease.

Autophagy-related gene defects. Autophagy (self-eating) is a normal cellular event in the homeostatic control of growth and development by which cellular components are degraded or recycled. It is also central to the processing of intracellular pathogens. Variants in the autophagy-related 16-like 1 gene (*ATLG 16L1*) and the immunity-related GTPase family, M *IRGM* gene have been confirmed as genetic susceptibility factors for Crohn's disease but not ulcerative colitis. The resulting increase in intracellular bacterial load may lead to the secondary Th1 activity within the mucosa that characterizes Crohn's disease.

Interleukin-23 receptor (IL-23R). Several polymorphisms of the gene encoding IL-23R have been linked with Crohn's disease (conferring protection or risk), and also contribute to the risk of ulcerative colitis.

IL-23 is a pivotal cytokine in the generation of Th17 effector cells and interleukin-17 (IL-17), which contribute to chronic mucosal inflammatory disease, particularly Crohn's disease.

The ECM locus (extracellular matrix protein 1) has recently been identified as a susceptibility locus for ulcerative colitis. The extracellular matrix protein 1 encoded here is a glycoprotein expressed in the small and large bowel that interacts with the basement membrane, inhibits matrix metalloproteinase 9, and can activate NF-κB.

Genetic and immunoinflammatory markers. With the exception of rare monogenic subsets of early-onset disease, the detection of single or combined genetic risk factors has not yet been translated into useful diagnostic tools or predictive markers of therapeutic response and prognosis. Similarly, immunologic markers such as autoantibodies that are under genetic influence have limited value (Table 1.4 and Chapter 4).

Pathogenesis

The initiating factor or factors in IBD are unknown, but there is good understanding of the amplification phase and final common pathway of tissue injury in both forms of the disease.

Upregulation of the expression of nuclear transcription factors, such as NF-κB, underlies the subsequent excessive local release of cytokines, growth factors, reactive oxygen metabolites, nitric oxide, eicosanoids (leukotrienes, thromboxanes and prostaglandins), platelet-activating factor, proteases, neuropeptides and other mediators (Figure 1.3).

Differences in cytokine profile. While there is considerable overlap between the two forms of IBD, the cytokine profile in ulcerative colitis has traditionally and simplistically been described as a non-Th1 pattern, whereas that of Crohn's disease is considered to be a typical Th1 pattern (Table 1.5). More recently, the Th17 effector cell and associated cytokine profile have been linked with several immune-mediated disorders, including Crohn's disease. This $CD4^+$ T-cell lineage is generated by IL-23, produces IL-17 and is counterregulated in a complex manner by the Th1 and Th2 pathways.

TABLE 1.4

Utility of genetic and immune-inflammatory markers in diagnosing and managing inflammatory bowel disease

Test	Crohn's disease	Ulcerative colitis	Comment
Serology			
pANCA	No	Yes	Insufficient specificity for diagnostic use
ASCA	Yes	No	
Genetics	No role except in rare monogenic disease	No role except in rare monogenic disease	
Level of CRP	A marker of disease activity not disease risk	A marker of disease activity	Useful in following disease response to therapy
Stool studies e.g. calprotectin	Useful, especially in distinguishing active IBD from comorbid irritable bowel syndrome	Useful in children	Good for colonic disease; less for ileal disease

ASCA, anti-*Saccharomyces cerevisiae* antibodies; CRP, C-reactive protein; pANCA, perinuclear antineutrophil cytoplasmic antibodies.

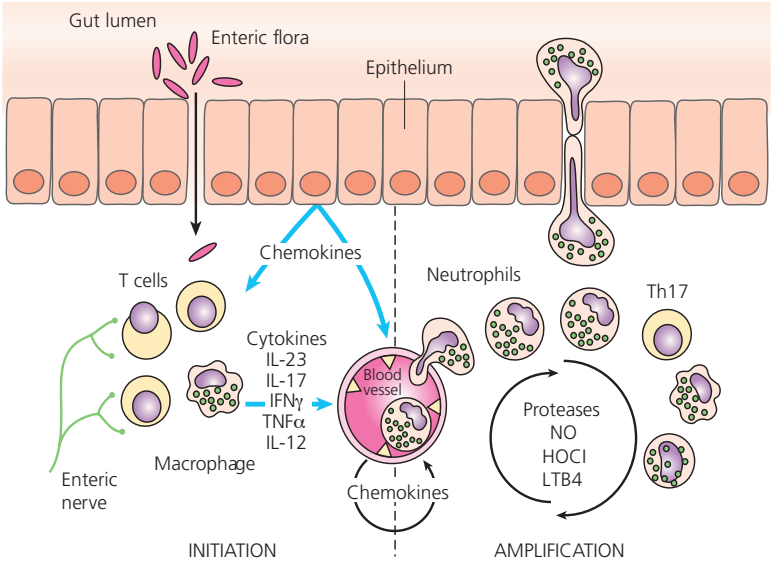

Figure 1.3 Mediators and mechanisms involved in the pathogenesis of IBD. The initiating factors are uncertain, but may include a breakdown in tolerance to enteric flora. T-cell and macrophage activation leads to production of cytokines, which act at several levels, including the local microvasculature. The chemokine gradient generated causes transmigration of neutrophils, leading to tissue damage by metalloproteases and other reactive substances, augmentation of the inflammatory response and disruption of the epithelial barrier, itself causing further ingress of enteric flora and their products. The inflammatory response may be modulated by activation of lymphocytes by enteric nerve endings. HOCl, hypochlorite; IFN, interferon; IL, interleukin; LTB4, leukotriene B4; NO, nitric oxide; Th17, T helper cell 17; TNF, tumor necrosis factor.

The balance of effector cells in the mucosa is subject to several regulatory constraints, including regulatory T cells (Treg). In the absence of inflammatory signals, transforming growth factor (TGF)-β tends to promote the development of Tregs which suppress inflammatory responses, whereas in the presence of inflammatory cytokines such as IL-6, TGF-β induces the differentiation of Th17 cells.

Possible immune regulatory disorder. The immunologic disturbances in ulcerative colitis include prominent autoimmune responsiveness, whereas

TABLE 1.5

Immune and inflammatory response in IBD

	Ulcerative colitis	Crohn's disease
Humoral immunity		
Association with autoimmune disease (e.g. Hashimoto's thyroiditis, SLE)	Strong	Weak
Autoantibody production (e.g. anticolon antibody, pANCA)	Common	Rare
Cell-mediated immunity		
Mucosal infiltrate	Non-granulomatous Neutrophils prominent	Granulomatous T cells prominent
T-cell reactivity	Normal/decreased	Increased
Cytokine profile		
Th response	Non-Th1 (IL-10, IL-5, IL-13)	Th17 (IL-23, IL-17, IL-2, IFN, IL-12, TNFα)
Other cytokines	IL-1, IL-6, IL-8	IL-1, IL-6
Innate immunity	–	Altered processing of intracellular bacteria
	–	Reduced defensins

IFN, interferon; IL, interleukin; pANCA; perinuclear antineutrophil cytoplasmic antibody; SLE, systemic lupus erythematosus; Th, T helper cell; TNFα, tumor necrosis factor α.

those in Crohn's disease appear to be primarily directed against components of the gut microbiota. In both disorders, this might suggest an underlying defect in immune regulation, but this has not yet been confirmed.

Possible immune deficiency. In contrast, there is compelling evidence for a deficiency in innate immunity, particularly in some patients with Crohn's disease. As indicated above, there is an increased bacterial load in the mucosa of patients with Crohn's disease. This may be secondary

to defective processing of intracellular bacteria, related to variant genes such as *NOD2* or autophagy genes. Furthermore, deficiency of the transcription factor T-bet in the innate immune system of mice has been shown to lead to an alteration in the microbiota, which predisposes them to colitis and can transfer the disease to susceptible hosts (see Figure 1.1). Reduced production of defensins, antimicrobial peptides secreted into the lumen by Paneth cells in the small-bowel epithelium, has also been linked with Crohn's disease and may be a contributory factor. In addition, defective phagocyte function, unrelated to *NOD2* function, has been described in patients with Crohn's disease, lending further support for the concept of an immune deficiency state rather than an immunoregulatory disorder.

Other possible factors. Defective colonic mucus (in ulcerative colitis) and abnormal intestinal epithelial permeability (in both forms of IBD) may increase the access of luminal dietary and bacterial products to the mucosa. Impaired availability and metabolism of bacterially derived luminal short-chain fatty acids may adversely affect colonic epithelial function in ulcerative colitis.

Pathology

The macroscopic and microscopic appearances of the bowel play a key role in the diagnosis of ulcerative colitis and Crohn's disease. Despite their names, ulceration is an early event in Crohn's disease even when mild; it is a late event and related to severe disease activity in ulcerative colitis.

Ulcerative colitis usually begins in the rectum, and either remains there or spreads proximally (Figure 1.4a). In severe total ulcerative colitis, the distal ileum ('backwash ileitis') is occasionally involved, but this is not clinically important. Diffuse mucosal inflammation in the colon, with hyperemia, granularity, surface pus and blood leads, in severe cases, to extensive ulceration (Figure 1.4b). This heals by granulation to form multiple pseudopolyps.

Microscopically, acute and chronic inflammatory cells infiltrate the lamina propria and crypts (producing crypt abscesses). Crypt architecture is distorted and goblet cells lose their mucin (goblet-cell

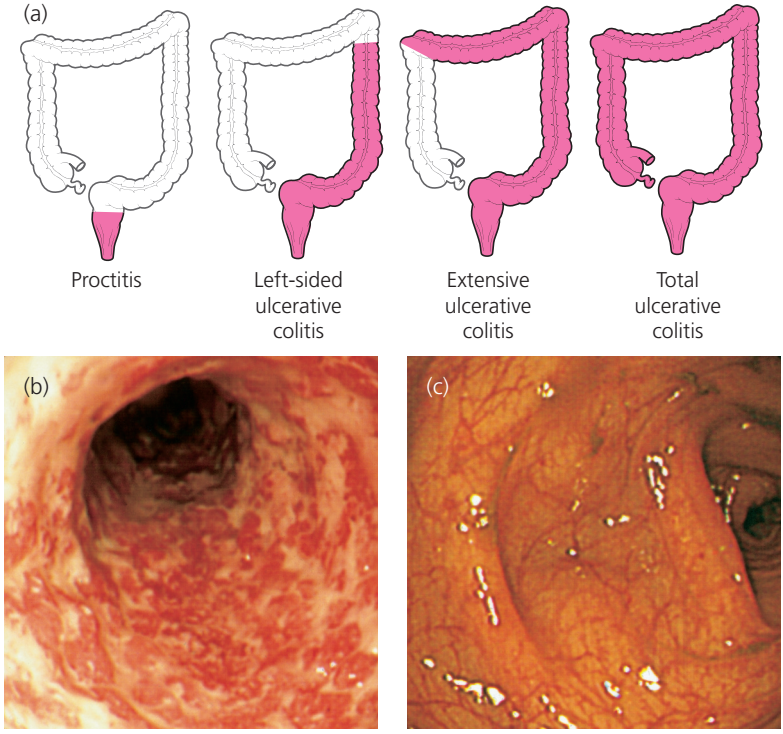

Figure 1.4 (a) Distribution of ulcerative colitis; (b) colonoscopic appearance of active ulcerative colitis – mucopurulent exudate, erythema, granularity and superficial ulceration; (c) normal colonic mucosa for comparison.

depletion) (Table 1.6, Figure 1.5); Paneth cell hyperplasia at the base of crypts is common. The mucosa is edematous with epithelial ulceration. Biopsies in long-standing total colitis may show dysplasia, in which epithelial cell nuclei are enlarged and crowded and lose their polarity: carcinoma may supervene.

Crohn's disease can affect any part of the gut (Table 1.7). Typically, there are discontinuously affected gut segments (skip lesions). The first visible abnormality is lymphoid follicular enlargement with a surrounding ring of erythema (the 'red-ring' sign); this leads to aphthoid ulceration which, in turn, progresses to deep fissuring ulcers with cobblestoning, fibrosis, stricturing and fistulation (Figure 1.6). Inflammation and fibrosis

TABLE 1.6

Histology of inflammatory bowel disease

Feature	Ulcerative colitis	Crohn's disease
Lamina propria cell infiltrate	Diffuse, superficial Neutrophils prominent	Discontinuous Deep lymphocytes
Cryptitis, crypt abscesses	Prominent	Focal
Crypt distortion and loss	Widespread	Patchy
Goblet cell mucin depletion	Marked	Rare
Paneth cell hyperplasia	Common	Rare
Ulceration	Superficial In severe disease only	Superficial (aphthoid) in early disease; deep in later disease
Epithelioid granulomas	None	Occasional

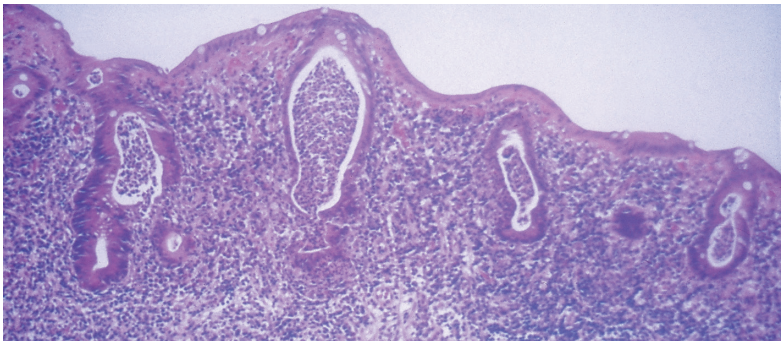

Figure 1.5 Microscopic appearance of ulcerative colitis – intense inflammatory cell infiltration of the lamina propria, goblet-cell depletion and crypt abscesses. Photomicrograph reproduced courtesy of Professor RM Feakins, Barts and The London School of Medicine and Dentistry, London, UK.

predispose to intestinal strictures, presenting with obstructing symptoms, and to local perforation of the gut wall, leading to abscess formation.

TABLE 1.7

Sites of Crohn's disease

Site	Proportion of cases (%)
Ileocecal	45
Colitis only	25
Terminal ileum only	20
Extensive small bowel	5
Other (anorectal, gastroduodenal, oral only)	5

Histologically, there is transmural chronic inflammatory cell infiltration with ulceration and formation of microabscesses. Non-caseating epithelioid granulomas, sometimes containing multinucleate giant cells, are found in about 25% of patients investigated with colonoscopic biopsies, and in 60% of those examined after surgical resection of the bowel (see Table 1.6, Figure 1.7. There is an increased risk of cancer in chronically inflamed areas of small intestinal, anorectal and, particularly, colorectal mucosa.

Colitis of uncertain type or etiology. In some patients with chronic colitis, the pathological features are not typical of either ulcerative colitis or Crohn's disease. In these people, the term 'colitis of uncertain type or etiology' (CUTE) is preferable to the previously favored 'indeterminate' colitis'. 'IBD unclassified' is an alternative term that may be useful in this setting, particularly for those in whom the small bowel has not yet been imaged.

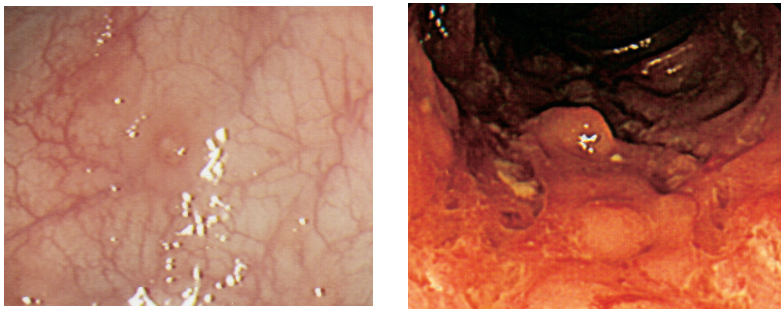

Figure 1.6 Colonoscopic appearances of Crohn's disease: (a) aphthous erosion in early disease; (b) ulceration and 'cobblestoning' in well-established chronic disease.

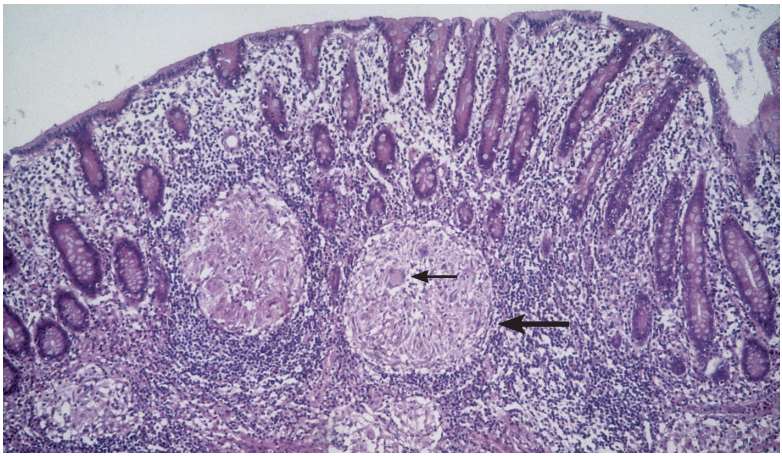

Figure 1.7 Microscopic appearance of colonic Crohn's disease. Three large epithelioid granulomas with multinucleate giant cells are visible; the large arrow shows a granuloma and the small arrow shows a giant cell. Photomicrograph reproduced courtesy of Professor RM Feakins, Barts and The London School of Medicine and Dentistry, London, UK.

Key points – etiopathogenesis

- Epidemiological studies of populations migrating from less to more developed countries suggest that the risk of IBD may be related to lifestyle or environmental exposure during early life.
- Genome wide association scans have identified over 160 genetic loci linked with IBD, although these account for only a small amount of the total variance in disease risk.
- Clarification of the human and gut microbial genome is increasing our understanding of the etiopathogenesis of IBD and highlights the importance of abnormal host–microbe interactions.
- Some genetic and environmental risk factors are common to ulcerative colitis and Crohn's disease while others are disease specific.
- Smoking exacerbates small-bowel Crohn's disease, but has a protective effect in ulcerative colitis.
- The histology of affected gut mucosa provides essential clues to the diagnosis of IBD.

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2 Clinical features and intestinal complications

Clinical features of ulcerative colitis

The onset of ulcerative colitis is usually gradual, and its natural history chronic, with relapses and remissions over many years. Between attacks, patients are usually free of symptoms. The features of active disease depend on the extent as well as the activity of disease. Although for formal epidemiological and clinical trial purposes various classifications of ulcerative colitis have been proposed (see Key references), they are rarely used in routine clinical practice. The main features of the disease are as described below.

Acute severe ulcerative colitis most commonly occurs in patients with extensive colonic involvement and causes profuse frequent diarrhea (six or more loose stools per day) with blood and mucopus, peridefecatory abdominal pain, fever, malaise, anorexia and weight loss. On external examination the patient is thin, anemic, fluid-depleted, febrile and tachycardic. In the few (now very rare) patients who develop acute colonic dilatation (previously called toxic megacolon) and/or perforation, further deterioration is usually obvious, with sudden worsening of abdominal pain, distension, fever, tachycardia, sepsis and shock.

Moderately active ulcerative colitis is commonly left-sided, causes rectal bleeding and discharge of mucopus accompanied by diarrhea (fewer than six loose stools daily), urgency and abdominal pain. Patients may experience malaise, but examination is usually normal.

Active proctitis causes rectal bleeding and mucous discharge, often with tenesmus and pruritus ani. Patients may have diarrhea, but often well-formed stools. Indeed, many patients with refractory proctitis are constipated (see Chapter 7). Patients usually maintain general health.

Clinical features of Crohn's disease

The symptoms and signs of Crohn's disease depend on the affected site and the predominant pathological process in each patient. As for

ulcerative colitis, a consensus meeting held in Montreal in 2005 proposed a classification based on disease site and behavior, but this is rarely used for routine clinical purposes. However, the classification does take into account an important feature of the natural history of Crohn's, which is its tendency to progress from an inflammatory phenotype in most patients at diagnosis, to intestinal stricturing and then fistula and/or abscess formation (so-called 'penetrating' disease) as the years go by. Fistulation most commonly occurs between loops of bowel (entero-enteric), bowel and skin (enterocutaneous), and bowel and urogenital tract (e.g. enterovesical, rectovaginal). Fistulation and abscess are particularly common in patients with perianal disease (see below).

Patients likely to have a poor prognosis tend to demonstrate the following clinical features at diagnosis:

- age, younger than 40 years
- ileocolonic disease
- early treatment with corticosteroids
- cigarette smoking
- weight loss of more than 5 kg
- perianal disease.

Active ileocecal and terminal ileal Crohn's disease patients usually present with pain and/or a tender mass in the right iliac fossa, with or without diarrhea and weight loss. Common mechanisms of diarrhea include mucosal inflammation, bile-salt malabsorption (see pages 31 and 136) and bacterial overgrowth proximal to a stricture (Table 2.1). In patients with symptoms predominantly due to inflammation or abscess, the pain tends to be constant, often with fever. In those with small-bowel obstruction, whether due to active inflammation or to fibrosis and stricture formation in the healing phase, the pain is more generalized, intermittent and colicky, and associated with loud borborygmi (abdominal gurgling sounds), abdominal distension, vomiting and eventually absolute constipation. Enterocutaneous fistulas are clinically obvious, but direct questions about pneumaturia, fecaluria and feculent vaginal discharge may be necessary to identify enterovesical or enterovaginal fistulas. Presentation as an acute abdomen, with peritonitis due to free perforation, is rare.

TABLE 2.1

Mechanisms of diarrhea in Crohn's disease

Mechanism	Treatment
Inflammation	Anti-inflammatory drugs
Small-bowel bacterial overgrowth	Antibiotics
Bile-salt diarrhea	Colestyramine (cholestyramine), colesevalam, low fat diet
Lactase deficiency	Avoid lactose
Short-bowel syndrome	See Table 2.2
Internal fistula	Surgery
Antibiotic-related	Stop antibiotics
Intercurrent infection (e.g. *Clostridium difficile*)	Appropriate antibiotic
Coincident disorders (e.g. irritable bowel syndrome, celiac disease)	As appropriate

Active Crohn's colitis causes symptoms similar to those of active ulcerative colitis, although frank bleeding is less common. Extraintestinal manifestations (see Chapter 3) are more common in Crohn's disease of the large bowel than of the small bowel.

Extensive small-bowel Crohn's disease may have features of malabsorption, with steatorrhea, anemia and weight loss, as well as the above symptoms.

Perianal Crohn's disease is due to fissure, fistula (Figure 2.1) or abscess, and is suggested by perianal pain and/or discharge. It can be quickly confirmed in most patients by perineal inspection. Although perianal Crohn's disease is often much less uncomfortable than it looks, sigmoidoscopy (see Chapter 4) may be too painful to undertake without sedation or even anesthesia.

Gastroduodenal and oral Crohn's disease are both common in children (Chapter 10) but rare in adults. The former presents with upper abdominal pain or dyspepsia, often with anorexia, nausea, vomiting and weight loss, while the latter causes chronic oral ulceration and/or induration.

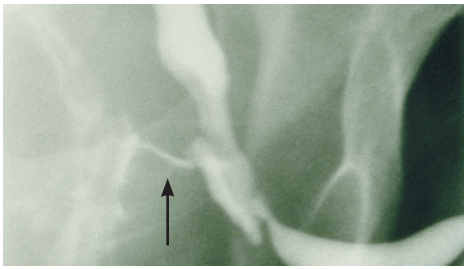

Figure 2.1 Micturating cystogram showing rectourethral fistula in Crohn's disease. The arrow indicates the fistula between the urethra and the rectum.

Intestinal complications of IBD

The main intestinal complications of IBD (other than the stricturing, fistulation and abscess formation characteristic of Crohn's disease [see above]), are undernutrition, short-bowel syndrome and cancer.

Nutritional deficiency is particularly common in Crohn's disease. Causes include reduced food intake, malabsorption in those with extensive small-bowel disease, increased loss of protein from an inflamed bowel, and increased metabolic requirements in sick patients, including the catabolic effects of cytokines and other inflammatory mediators. Those at particular risk should be monitored carefully for evidence of undernutrition by measurement of weight, at least, and blood tests such as blood count, albumin, folate, vitamin B_{12} (cobalamin), ferritin, calcium and magnesium. Management options include supplemental sip feeding with appropriate replacement of specific deficiencies, and enteral and parenteral nutrition.

Short-bowel syndrome develops when extensive bowel resection leads to excessive malabsorption of fluids, electrolytes and nutrients. The most common cause is Crohn's disease but it can also occur in patients without IBD, for example in mesenteric vascular occlusion, trauma and neoplasia.

Pathogenesis. Factors influencing symptoms include the extent of resection(s), the presence of residual Crohn's disease and the absence of the ileocecal valve, which normally slows small-bowel transit and inhibits colonization of the distal small bowel by colonic flora. Furthermore, the site of resection is important: terminal ileal resection causes bile-salt malabsorption, vitamin B_{12} deficiency, gallstones and hyperoxaluria (see page 40), while removal of the colon with part of the small bowel causes severe diarrhea owing to loss of colonic absorptive capacity.

Presentation. Patients present with watery diarrhea and increasingly severe fluid, electrolyte and nutritional depletion immediately after resection. This tends to improve as the intestine adapts, or it may progress to steatorrhea as bile-salt deficiency develops. Later complications include urinary stones and gallstones.

Investigation. Fluid, electrolyte and nutritional deficiencies, stool output, bile-salt malabsorption, vitamin B_{12} absorption and urinary oxalate excretion should be quantified.

Bile-salt malabsorption, which causes diarrhea only if the colon is still present, can be confirmed by means of SeHCAT scanning; SeHCAT (the taurine conjugate of 23-[^{75}Se]-25-homocholic acid) is a synthetic bile salt that emits gamma rays. After an oral dose it is absorbed in the terminal ileum, and the amount retained after 7 days can be estimated by whole-body scanning. In patients with extensive ileal disease causing bile-salt malabsorption, retention is usually less than 10%. Alternatively, and more cheaply, a therapeutic trial with a bile-salt binding drug such as colestyramine (cholestyramine) can be tried.

Management. Intravenous restoration of fluid and electrolytes and total parenteral nutrition may be necessary at first. Enteral feeding should be started early, to promote gut adaptation, using lactose-free iso-osmolar solutions (Table 2.2). Small frequent meals are introduced later, a low-fat diet being helpful for those with marked steatorrhea. Excessive dietary oxalate should be avoided: this entails avoidance of, for example, spinach, beetroot, strawberries, chocolate, coffee, tea and cola drinks. Loperamide and codeine phosphate may reduce stool output by slowing transit and increasing mucosal absorption.

Further treatment options after extensive small-bowel resections include:

- dietary calorie supplements with medium-chain triglycerides (which are directly absorbed without having to be digested)
- proton-pump inhibitors (to reduce gastric hypersecretion)
- octreotide (to reduce gastric, biliary and pancreatic secretions)
- antibiotics (if there is small-bowel overgrowth).

Patients with massive resections who are unable to cope on exclusively oral nutrition need referral to specialist centers. They may need regular parenteral supplements of calcium, magnesium, trace elements (particularly zinc), essential fatty acids and vitamins, or total parenteral nutrition administered at home. Rarely, referral for small-bowel transplantation may be required.

TABLE 2.2

Management of short-bowel syndrome

Supportive treatment

- Intravenous fluids and nutrition initially
- Enteral nutrition next
- Small frequent low-fat meals later
- Minimize dietary oxalate
- Specific nutritional supplements as necessary (calcium, magnesium, folate, vitamins, trace elements [incl. zinc], essential fatty acids)
- Loperamide, codeine phosphate

Specific measures in severe cases

- Calorie supplementation with medium-chain triglycerides
- Gastric acid inhibition (e.g. omeprazole, 80 mg twice daily)
- Octreotide
- Antibiotics for small-bowel overgrowth
- Home total parenteral nutrition (refer to specialist center)
- Small-bowel transplant (rarely)

Colorectal carcinoma. Patients with chronic extensive ulcerative colitis and Crohn's colitis have an increased risk of colorectal carcinoma; in ulcerative colitis this amounts to a cumulative risk of 5–10% after 30 years of disease. Factors increasing the risk of colorectal cancer in both diseases include:

- chronicity of disease
- chronically inflamed mucosa
- coexistent primary sclerosing cholangitis
- family history of colorectal cancer
- adenomatous polyp(s) sited in inflamed mucosa
- failure to use aminosalicylate drugs (perhaps) and folate deficiency.

In both ulcerative colitis and Crohn's disease, most authorities advocate regular colonoscopic screening (see Chapter 7) to detect epithelial dysplasia and/or early cancer, with a view to prompt surgical treatment. However, this approach has not yet been shown unequivocally to reduce mortality from colorectal cancer in IBD.

Small intestinal and anal carcinoma. There is a small but finite risk of these otherwise rare cancers in patients with Crohn's disease: in particular, they occur at sites of very prolonged and severe inflammation.

Key points – clinical features and intestinal complications

- The presentation of ulcerative colitis depends on its activity and extent, while that of Crohn's disease depends also on the underlying pathological process (inflammation, stricturing or penetrating disease).
- Intestinal complications of IBD include undernutrition, short-bowel syndrome (in Crohn's disease only) and colorectal cancer.
- The risk of colorectal cancer complicating extensive ulcerative colitis or Crohn's colitis is less than previously feared – 5–10% rather than 20–30% at 30 years after diagnosis.

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3 Extraintestinal manifestations and complications

The many systemic associations and complications of IBD affect 6–50% of patients with the disease; most affect the liver/biliary tree, joints, skin and eyes (Table 3.1). Most occur in patients with colitis and some largely in those with active disease. In some instances (ankylosing spondylitis [AS], uveitis, arthropathy), there seems to be a genetic and/or immunologic association with IBD: these associations are often termed extraintestinal manifestations. Others are complications of IBD; for example, anemia and metabolic problems (gallstones and urinary stones).

Hepatobiliary manifestations

Sclerosing cholangitis occurs in about 5% of patients with ulcerative colitis and a smaller proportion of those with Crohn's disease. The pathogenesis is unknown, but the condition may occur years before the onset of overt colitis; 80% of patients have perinuclear antineutrophil cytoplasmic antibodies (pANCAs) in their serum. The condition is characterized by the gradual progression of an inflammatory obliterative fibrosis of the extra- and intrahepatic biliary tree (Figure 3.1), and is sometimes complicated by cholangiocarcinoma. The risk of colorectal cancer in patients with ulcerative colitis and sclerosing cholangitis exceeds that associated with ulcerative colitis alone.

Patients usually present with complications of biliary stricturing, such as obstructive jaundice, cholangitis or abnormal liver-function tests (raised alkaline phosphatase and γ-glutamyltranspeptidase) at routine screening. The diagnosis may be suggested by ultrasound and is usually confirmed by magnetic resonance cholangiopancreatography (MRCP) and/or liver biopsy; use of endoscopic retrograde cholangiopancreatography (ERCP) (see Figure 3.1) is now largely confined to the stenting of dominant strictures.

The course of sclerosing cholangitis is steadily progressive. Oral ursodeoxycholic acid in standard doses (10–15 mg/kg/day) improves pruritus and jaundice, but, paradoxically, high doses (25–30 mg/kg/day) may worsen outcome; its previously suspected beneficial effect on the incidence of

TABLE 3.1

Extraintestinal manifestations and complications of IBD

Organ	Complication
Joints/bones	Enteropathic arthropathy*
	Sacroiliitis
	Ankylosing spondylitis
	Clubbing (CD only)
	Osteoporosis†
Eyes	Episcleritis*
	Uveitis*
Skin	Erythema nodosum*
	Pyoderma gangrenosum
Mouth	Aphthous ulceration
Liver	Fatty change
	Chronic active hepatitis
	Granulomatous hepatitis (CD only)
	Amyloid (CD only)†
Biliary tract	Cholesterol gallstones (terminal ileal CD or resection)†
	Sclerosing cholangitis
	Cholangiocarcinoma
	Autoimmune pancreatitis
Kidneys	Uric acid stones (total colitis, ileostomy)†
	Oxalate stones (terminal ileal CD/resection)†
Lungs	Fibrosing alveolitis
Blood	Anemia*† (iron, B_{12}, folate deficiency)
	Arterial and venous thrombosis†
Constitutional	Weight loss*†
	Growth retardation (children)*†

*Worse when IBD is active. †Complication rather than manifestation.
CD, Crohn's disease.

colorectal cancer in patients with ulcerative colitis and sclerosing cholangitis has recently been called into question. Liver transplant is the only hope of long-term survival in those who do not develop cholangiocarcinoma; otherwise, median survival for symptomatic patients is about 15 years.

Patients with sclerosing cholangitis should be screened annually by colonoscopy and MRCP for colorectal and bile duct cancer, respectively.

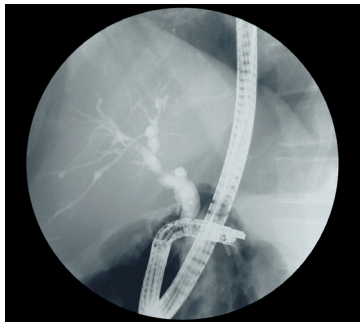

Figure 3.1 Primary sclerosing cholangitis on endoscopic retrograde cholangiopancreatography (ERCP). Multiple strictures, particularly in the intrahepatic biliary tree, give a beaded appearance.

Autoimmune pancreatitis is a rare association with ulcerative colitis. It is characterized by irregular narrowing of the pancreatic duct and swelling of the gland itself. There are often biliary changes resembling those found in sclerosing cholangitis. The condition is diagnosed using CT, MRCP and/or ERCP; the serum immunoglobulin (Ig)G_4 level is also usually raised. The condition responds quickly to prednisolone, but may recur on withdrawal.

Joint manifestations

IBD-related arthropathy occurs in up to 10% of patients with IBD. The type of arthritis is linked to human leukocyte antigen (HLA) genotype. IBD-related arthropathy should not be confused with other musculoskeletal pains associated with IBD and its treatment, which include arthralgia related to steroid withdrawal, azathioprine-induced arthralgia and steroid-induced myopathy.

Pauciarticular disease involves fewer than five joints; characteristically, it affects one large joint, for example the knee, and is most common in women. Attacks usually coincide with relapse of colitis; sometimes there is simultaneous erythema nodosum or iritis (see below). Its pathogenesis may involve deposition of gut-derived immune complexes in the affected joint in genetically predisposed individuals. Although the attacks of arthritis may come and go over many years, the disease is neither progressive nor deforming. In most people, the joint symptoms resolve on treatment of the active colitis. Sulfasalazine may be more effective for the joints than other aminosalicylates. Acetylsalicylic acid (ASA; aspirin) and other non-steroidal anti-inflammatory drugs (NSAIDs) may exacerbate IBD (see Table 1.1, page 9) and therefore should be avoided if possible. Alternatives include paracetamol (acetaminophen) and joint aspiration with steroid instillation.

Polyarticular IBD-related arthropathy affects more than five joints, particularly small joints such as the metacarpophalangeals, and can often be symmetrical. Symptoms are more common in women, are chronic and are not clearly related to activity of the associated IBD. It may sometimes be misdiagnosed as rheumatoid arthritis. Management resembles that of pauciarticular disease, except that response of the arthropathy to treatment of the IBD itself is poor.

Ankylosing spondylitis and sacroiliitis. While about 95% of patients without IBD who have AS are HLA-B27 positive, this is true of only 50–80% of those with both diseases. AS affects about 5% of patients with ulcerative or Crohn's colitis and, like enteropathic arthritis, it is probably immunologically mediated. The patient presents with back pain, stiffness and, in the later stages of the disease, kyphosis (Figure 3.2); diagnosis is confirmed by radiography. The course of AS is independent of the activity of IBD, and it may present years before the bowel disease manifests. Treatment consists of vigorous physiotherapy, sulfasalazine and, if tolerated, NSAIDs. Anti-tumor necrosis factor (TNF)α agents (see Chapter 5) are effective in refractory AS.

Sacroiliitis can be an early symptom of AS or can occur in isolation. It presents with low backache and morning stiffness, although it can also be asymptomatic. In contrast to mechanical back pain, it is insidious in onset, occurring in younger people. MRI is more sensitive than plain X-ray for diagnosis. Treatment follows the same principles as for AS.

Figure 3.2 Ankylosing spondylitis, showing marked kyphosis. Reproduced courtesy of Professor DP D'Cruz, Guy's, King's and St Thomas' Hospital Medical School, London, UK.

Skin manifestations

Erythema nodosum occurs in about 8% of patients with ulcerative and Crohn's colitis, usually when the disease is active. Hot red tender nodules appear, usually on extensor surfaces of the lower legs and arms (Figure 3.3); they gradually subside after a few days to leave brownish skin discoloration. There may be an associated pauciarticular arthropathy. The diagnosis is clinical and biopsy is not necessary. Histology, if performed, shows vasculitis. Treatment is of the active associated IBD.

Pyoderma gangrenosum occurs during the course of IBD in about 2% of patients. There is no clear association with disease activity. Pyoderma presents initially as a discrete pustule with surrounding erythema; this develops into an indolent painful enlarging ulcer. The most common site is the leg (Figure 3.4).

Lesions are occasionally multiple and may occur at sites of recent trauma, for example operation scars. Histology shows lymphocytic vasculitis with dense secondary neutrophilic infiltration. Pyoderma is often refractory to treatment: options include intralesional, topical and systemic corticosteroids, dapsone, heparin and immunosuppressive drugs such as ciclosporin (cyclosporine), but the most effective is infliximab. Colectomy does not reliably induce healing of the skin lesion.

Other dermatological associations of IBD include side effects of drugs (e.g. thiopurine-induced skin cancer and anti-TNF-related psoriasis) (see Chapter 5), and hidradenitis suppurativa, a chronic painful condition

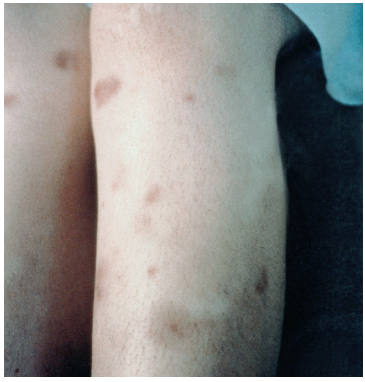

Figure 3.3 Erythema nodosum.

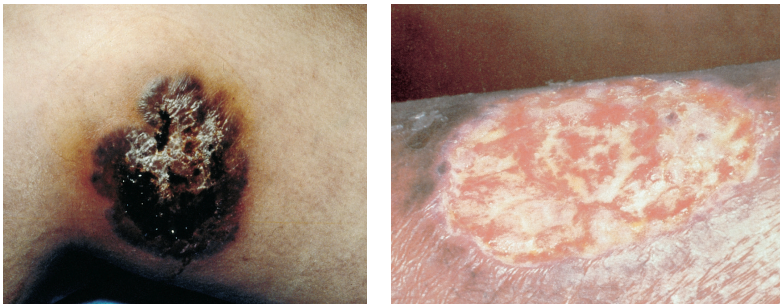

Figure 3.4 Pyoderma gangrenosum: (a) at presentation; (b) in the healing phase.

affecting sweat glands, which occurs more often in people with Crohn's disease than in the general population.

Ocular manifestations

The most common ocular associations of IBD are episcleritis and uveitis. Together they occur in fewer than 5% of patients, usually when bowel disease is active.

Episcleritis presents with burning and itching, accompanied by a localized area of dilated blood vessels at the site of scleral inflammation (Figure 3.5). Topical steroids and treatment of the active IBD usually produce a satisfactory response. Uveitis is a more serious and often recurrent problem, presenting with headache, red eye and blurred vision; slit-lamp examination shows pus in the anterior chamber (hypopyon). Treatment includes topical steroids, cycloplegics and therapy of the active IBD.

Patients with IBD complicated by ocular symptoms should be promptly referred to an ophthalmologist.

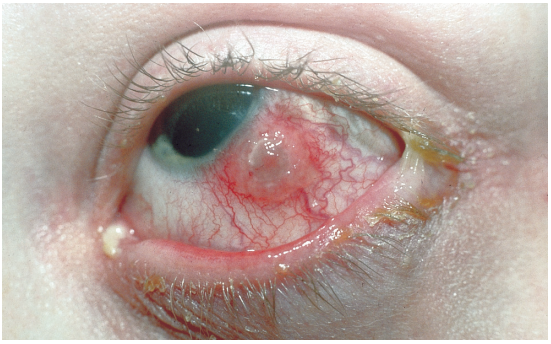

Figure 3.5 Episcleritis in a patient with active ulcerative colitis.

Extraintestinal complications

Osteoporosis is a common consequence of chronic intestinal inflammation, malabsorption and treatment with corticosteroids, particularly a cumulative dose of more than 10 g prednisolone. Its exact prevalence is unclear. The disease is asymptomatic for many years, presenting eventually with vertebral collapse or long bone fractures. To prevent osteoporosis, everyone with IBD should be advised to eat a diet containing adequate calcium and vitamin D, supplemented if necessary by vitamin D tablets. They should avoid becoming either undernourished or obese, stop smoking and take regular exercise.

Patients at risk of osteoporosis should undergo bone densitometry. Those with established osteoporosis, or needing long-term therapy with prednisolone, should receive cyclic bisphosphonate therapy (e.g. etidronate). The efficacy of oral budesonide (see Chapter 5) in reducing the risk of osteoporosis in steroid-dependent patients with Crohn's disease is not proven.

Hormone replacement therapy is associated with an increased risk of breast and gynecologic cancer and thromboembolic disease. Its use in the management of osteoporosis in postmenopausal women with IBD should be restricted to those in whom other treatments are ineffective or contraindicated.

Gallstones. There is an increased risk of cholesterol gallstones in patients with bile-salt malabsorption as a result of terminal ileal Crohn's disease or resection: interruption of the enterohepatic circulation of bile salts results in insufficient bile-salt concentrations in gall-bladder bile to solubilize cholesterol. Treatment of symptomatic patients is usually by laparoscopic cholecystectomy, although patients with terminal ileal Crohn's disease or resection are at increased risk of post-cholecystectomy bile-salt-induced diarrhea than those with an intact ileum.

Urinary tract stones. Patients with bile-salt or fat malabsorption due to small-bowel Crohn's disease are at increased risk of forming calcium oxalate urinary stones as a result of increased absorption of dietary oxalate ('enteric hyperoxaluria'). Uric acid stones are more common in patients with an ileostomy for ulcerative colitis or Crohn's disease than in those without, as a result of increased acidification of urine. Oxalate and uric acid stones are treated by conventional urological methods. Patients with enteric hyperoxaluria are advised to avoid oxalate-containing foods

and drinks (see page 31) and may also benefit from oral calcium supplements to reduce oxalate absorption by increasing its intestinal luminal precipitation as insoluble calcium oxalate.

Anemia is common in people with IBD, affecting around 50% of the IBD population at any one time.

Causes. The commonest cause is iron deficiency due to intestinal blood loss (often occult), poor iron intake and/or reduced mucosal absorption and cellular utilization of iron as a result of an inflammation-induced increase in serum hepcidin, a peptide hormone produced by the liver which regulates iron transport.

Anemia of chronic disease, in which a range of inflammatory mediators alter iron metabolism, erythropoiesis and red cell survival, can occur in IBD as in any chronic inflammatory illness.

Other causes of anemia in IBD include vitamin B_{12} malabsorption in patients with Crohn's disease who have had a terminal ileal resection or have extensive ileal involvement, and folate deficiency.

Monitoring. Although anemia may seem to be asymptomatic, and indeed is often ignored by doctors, it causes fatigue and impairs quality of life and cognitive function; when severe it can cause shortness of breath and reduce exercise tolerance. Patients with IBD, particularly if the disease is active, need regular checks of their blood count and hematinics, and the results should be acted upon. Because serum ferritin concentration rises in the presence of inflammation, the simplest marker of iron deficiency in patients with IBD is a transferrin saturation of less than 20%.

Management. Iron should be replaced initially with low-dose oral iron (no more than 100 mg of elemental iron daily) to minimize the risk of intestinal side effects, which are dose-related and include abdominal pain, constipation and diarrhea. In more anemic patients (Hb < 6.2 mmol/L [10 g/dL]) or in those (up to 20%) who do not tolerate or fail to respond to oral iron, intravenous iron should be given (e.g. ferric carboxymaltose (Ferinject), sodium ferric gluconate (Ferrlecit), iron isomaltoside (Monofer), iron sucrose (Venofer) or iron hydroxide dextran complex (Cosmofer); these preparations are less frequently complicated by acute infusion reactions than their predecessors. Vitamin B_{12} and folate deficiencies should be replaced with intramuscular vitamin B_{12} and oral folate, respectively.

Arterial and venous thrombosis. People with IBD are at increased risk of arterial and, more commonly, venous thrombosis, particularly when the disease is active. In sick patients with IBD, the risk factors for thrombosis include inflammation, fluid depletion and immobility, together with enhanced clotting, thrombocythemia and platelet activation. All patients admitted to hospital, whether as emergencies or for elective surgery, should be kept as mobile as possible and given prophylactic heparin (see Chapter 6).

Psychological distress. Mood disturbances and stress are common in people with IBD, particularly when the disease is active. Furthermore, stress, for example from major life events, can trigger relapse of IBD (Chapter 1). Patients attending IBD clinics should be asked how they feel: patients who are anxious, depressed or stressed should be offered psychological support. Unfortunately, it is not yet clear which interventions targeted at mood and stress work best in patients with IBD: while there is some evidence that cognitive behavioral therapy may improve both psychological status and disease course, more trials are needed, particularly with antidepressants.

Fatigue is a persistent and overwhelming sense of tiredness, weakness or exhaustion that reduces the capacity for physical and/or mental work and is characteristically unrelieved by sleep or rest. It is common in both the general population and people with IBD, particularly those with active disease, in whom it is probably due to circulating pro-inflammatory cytokines (see Chapter 1). Like anemia and psychological disturbances, fatigue is a symptom that is all too often neglected by those providing IBD care.

The causes of fatigue include not only active disease but also drugs (e.g. sulfasalazine, azathioprine, methotrexate), steroid withdrawal, anemia, iron deficiency, nutrient deficiencies (folate, vitamin B_{12}, vitamin D, zinc), poor sleep (due to nocturnal abdominal pain and/or diarrhea), and stress and depression. Causes unrelated to IBD (e.g. hypothyoidism) should also be considered.

In some patients, one or other of these causes can be identified and treated specifically, but in many their fatigue has no clear explanation. In other contexts such as chronic fatigue syndrome, graded exercise therapy can be helpful, and this approach may be worth trying in fatigued patients with IBD in whom there is no clear cause.

Key points – extraintestinal manifestations and complications

- The skin, joint, ocular and hepatobiliary associations of IBD are most common in patients with colonic disease.
- The course of sclerosing cholangitis and ankylosing spondylitis is unrelated to the activity of the associated IBD.
- Anemia, mood disturbance and fatigue are often overlooked and should be sought and treated in patients with IBD.

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4 Diagnosis

The differential diagnosis of common presentations of IBD is shown in Tables 4.1–4.4. In younger patients (under 50 years) the main differential diagnoses, depending on presentation, include infection and irritable bowel syndrome. In older people (over 50 years), neoplasia, diverticular disease and ischemia require special consideration. The aims of investigation (Tables 4.5, 4.6) are to establish the diagnosis, its site, extent and activity, and to check for complications of the disease (Chapter 3) and its treatment (Chapters 5–7).

Blood tests

Hematology. In patients presenting with abdominal pain and/or diarrhea, test results revealing anemia and raised platelet count may suggest active IBD but are not diagnostic. Those with extensive chronic terminal ileal Crohn's disease may have low serum B_{12}, while a low red-cell folate may indicate active chronic inflammation, reduced intake or malabsorption. Iron deficiency is common, although not necessarily diagnostic of IBD.

TABLE 4.1

Causes of bloody diarrhea

Cause	Disease		
Inflammatory	Ulcerative colitis	Crohn's colitis	Behçet's colitis
Infective colitis	Campylobacter Salmonella Shigella *Clostridium difficile* Yersinia Tuberculosis	Enterohemorrhagic *Escherichia coli* (VTEC/0157:H7) Amebiasis Schistosomiasis Cytomegalovirus* Herpes simplex*	
Neoplastic	Colorectal cancer		
Vascular	Ischemia		
Iatrogenic	NSAIDs	Antibiotics	Irradiation

*Particularly in immunocompromised patients.
NSAIDs, non-steroidal anti-inflammatory drugs.

TABLE 4.2

Causes of rectal bleeding

Cause	Disease	
Inflammatory	Proctitis	Crohn's disease
Sexually transmitted	Gonococcus Cytomegalovirus Herpes simplex	Atypical mycobacterium Chlamydia Kaposi's sarcoma
Neoplasia	Colorectal polyps Colorectal cancer	Anal cancer
Vascular	Ischemia	Angiodysplasia
Iatrogenic	NSAIDs (oral or suppositories)	Irradiation
Other	Benign solitary rectal ulcer Diverticulosis (acute bleeds only)	Severe upper gastrointestinal bleeding

NSAIDs, non-steroidal anti-inflammatory drugs.

Biochemistry. Raised C-reactive protein (CRP) and low serum albumin levels suggest active disease in patients with established ulcerative colitis or Crohn's disease; they are also suggestive, although not diagnostic, of IBD in those in whom the diagnosis has not yet been made. Low serum albumin, calcium, magnesium, vitamin D, zinc and essential fatty acid concentrations may be found in Crohn's disease patients, while abnormal liver function tests may be found in those with hepatobiliary complications of IBD.

Serology. In patients presenting for the first time with diarrhea, a negative test for endomysial or transglutaminase antibodies usually excludes celiac disease. Most patients with ulcerative colitis and a minority with Crohn's disease have circulating perinuclear antineutrophil cytoplasmic antibodies (pANCAs), but this test is not sufficiently sensitive or specific to be of diagnostic value. Antibodies to *Saccharomyces cerevisiae* (ASCA) are present in most patients with small-intestinal Crohn's disease. Profiles of these and other antibodies, including those against bacterial antigens such as *Escherichia coli* outer membrane porin protein C (OmpC), *Pseudomonas*

TABLE 4.3

Causes of abdominal pain, diarrhea and weight loss

Cause	Disease	
Inflammatory	Crohn's disease Ulcerative colitis Behçet's colitis	Microscopic/ lymphocytic/ collagenous colitis*
Infections	See Table 4.1	
Neoplasia	Colorectal cancer Pancreatic cancer Small-bowel lymphoma	Endocrine tumors (carcinoid, gastrinoma, VIPoma)
Endocrine	Thyrotoxicosis Diabetic autonomic neuropathy	Hypoadrenalism
Vascular	Ischemia	
Iatrogenic	NSAIDs Antibiotics Laxative abuse	Irradiation Gut resections
Malabsorption	Celiac disease Bacterial overgrowth	Lactose intolerance†
Other	Irritable bowel syndrome†	

*Pain and weight loss unusual. †Weight loss unusual.
NSAIDs, non-steroidal anti-inflammatory drugs. VIPoma, vasoactive intestinal peptide-producing tumor.

fluorescens (I2) and flagellin (CBir1), are being used in some countries (e.g. USA) as diagnostic aids in patients with IBD of uncertain type.

For patients who have recently traveled to endemic areas, serology (as well as stool samples) should be checked for amebiasis, strongyloidiasis and schistosomiasis. The use of corticosteroids in such patients, in the mistaken belief that they have active IBD, can have fatal consequences. HIV testing should be done for those who have watery diarrhea.

Finally, in patients with newly diagnosed IBD, a panel of serological tests is requested to establish previous exposure to infections that could recrudesce during any future use of immunosuppressive medications (see Chapter 6).

TABLE 4.4

Causes of abdominal pain and mass in the right iliac fossa

Cause	Disease	
Ileocecal		
Inflammatory	Crohn's disease	Appendiceal mass
Infective	Tuberculosis Ameboma	Actinomycosis
Neoplastic	Cecal carcinoma Lymphoma	Carcinoid tumor
Other	Fecal loading	
Renal	Hydronephrosis Cysts	Neoplasia Transplant
Gynecologic	Ovarian cyst Neoplasia	Tubal mass, including ectopic pregnancy Endometriosis

Stool tests

Microscopy. Fresh stools often show red and white blood cells in people with active colitis, whether due to IBD or infection. Hot fresh samples are essential in recent travelers to look for amebic trophozoites.

Culture and toxin assay. Regardless of IBD diagnosis, patients presenting with diarrhea should always have stool samples sent for culture to check for *Clostridium difficile* toxin. In recent years, as in people without IBD, the incidence of *C. difficile* infection has increased in patients presenting with relapse of their IBD, with a consequent increase in hospitalization rates and deterioration in outcome.

Fecal calprotectin. The transmigration of neutrophils through the mucosa into the lumen is responsible for crypt abscesses and exudate formation. Fecal levels of calprotectin, a neutrophil-derived cytosolic protein that is resistant to bacterial degradation, provide an accurate index of intestinal inflammatory activity. A simple fecal calprotectin assay, deployed rapidly at the point of care, can help to monitor disease activity in patients with known IBD;

TABLE 4.5

Laboratory investigation of IBD

Sample	Test	
Blood		
Hematology	Hemoglobin White blood cells Platelets Ferritin, transferrin saturation	Vitamin B_{12} (Crohn's disease) Red-cell folate
Biochemistry	C-reactive protein Liver function tests Albumin	Calcium, magnesium Vitamin D
Serology (selected patients – see text)	Endomysial or transglutaminase antibody* Amebiasis Strongyloidiasis	Schistosomiasis HIV Hepatitis B Hepatitis C Varicella zoster Human papilloma virus
Stools	Microscopy Culture	*Clostridium difficile* toxin Calprotectin

*To exclude celiac disease. HIV, human immunodeficiency virus.

conversely, a normal fecal calprotectin result excludes IBD in new patients presenting with diarrhea.

Sigmoidoscopy and rectal biopsy

Ulcerative colitis. In patients presenting with diarrhea with or without rectal bleeding, rigid or flexible sigmoidoscopy without preparation and without excessive air insufflation can provide immediate confirmation of colitis and its activity (Figure 4.1). Sigmoidoscopy also allows biopsy for histology. To minimize the risks of bleeding and perforation, a small superficial biopsy should be taken from the posterior rectal wall less than 10 cm from the anal margin using small-cupped forceps. Rectal biopsy is not routinely necessary for those with established ulcerative colitis. However, in those presenting for the first time, infective colitis as opposed to chronic ulcerative colitis may be suggested by histology showing an

TABLE 4.6

Endoscopy, histopathology and imaging for IBD

Modality	Test
Endoscopy with biopsy	Sigmoidoscopy (outpatient department) Ileocolonoscopy Gastroscopy (CD, rarely) Enteroscopy (CD, rarely) Wireless capsule endoscopy (CD, rarely)
Conventional radiology	Chest X-ray (selected patients) Abdominal X-ray Barium follow-through or small-bowel enema (Crohn's disease only) Fistulography (rarely)
Isotope scanning	^{99}Tc-HMPAO-labeled leukocyte scan
Other imaging (mainly for CD)	Ultrasound (transabdominal endoscopic) MRI CT scan

CD, Crohn's disease; CT, computed tomography; MRI, magnetic resonance imaging; ^{99}Tc-HMPAO, ^{99}technetium hexamethylpropyleneamine oxime.

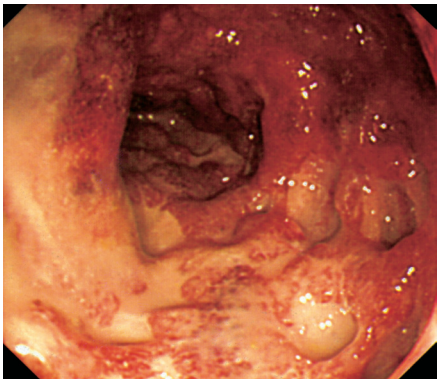

Figure 4.1 Colonoscopic view of acute severe ulcerative colitis, showing deep ulcers with epithelial denudation adjacent to erythematosus edematous mucosa.

acute, focal and superficial infiltrate with minimal goblet-cell depletion and preservation of crypt architecture. Colitis due to *C. difficile*, cytomegalovirus, amebiasis or Crohn's disease sometimes has a characteristic macroscopic appearance, but histology, like microbiology, can be used to confirm these diagnoses.

Crohn's disease. Rectal sparing is common in Crohn's colitis. Sometimes, however, rectal induration or ulceration, or the presence of perianal disease, points to the diagnosis. Furthermore, in a minority of patients with macroscopically normal rectal mucosa but Crohn's disease proximal to this site, histology of rectal biopsies shows epithelioid granulomas (see Figure 1.7).

Colonoscopy and biopsy

Ulcerative colitis. In patients who are not severely ill, colonoscopy with biopsies is the most useful test for confirming the diagnosis of ulcerative colitis and assessing disease extent and activity. Macroscopically, inactive ulcerative colitis is characterized by mucosal edema with loss of the normal vascular pattern, erythema and granularity, while in those with active disease there is, additionally, contact or spontaneous bleeding, excessive mucopus and surface ulceration (see Figure 4.1). In chronic cases, pseudopolyps and loss of the normal haustral pattern with apparent shortening of the colon are common. In very long-standing disease, the mucosa becomes atrophic.

In patients with acute severe ulcerative colitis, colonoscopy may cause perforation and dilation, and most sick patients can be managed satisfactorily without it. However, colonoscopy plays a major role in cancer surveillance in those with chronic extensive ulcerative colitis (see Chapter 7).

Crohn's disease. Colonoscopy with terminal ileoscopy and biopsy is central to the diagnosis of Crohn's disease. It can also be used to balloon-dilate short strictures. In early Crohn's disease, prominent lymphoid follicles (the red-ring sign) are followed by aphthoid ulceration (see Figure 1.6a). Later, larger pleomorphic deep ulcers develop, separated by relatively normal-looking mucosa. A cobblestone appearance of the mucosa is a late sign (see Figure 1.6b). Changes in the colon are often segmentally distributed (skip lesions).

Wireless capsule endoscopy. The advent of wireless capsule endoscopy enables non-invasive visualization of small bowel that is inaccessible to the conventional endoscope. Although enthusiasts correctly point to its usefulness in specific indications, such as occult bleeding, the place of this procedure in IBD is limited and its use is compromised by the inability of the capsule, at present, to take biopsies. It may have a role in looking for superficial small-bowel mucosal disease suggestive of Crohn's disease (Figure 4.2) in patients

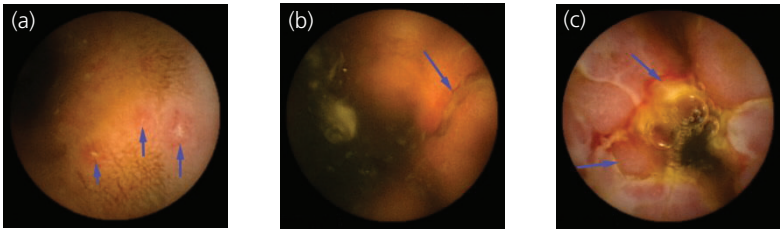

Figure 4.2 Wireless capsule endoscopy images of the small bowel in patients with Crohn's disease: (a) aphthoid ulcers; (b) linear ulcer; (c) more extensive ulceration, mucosal denudation and stricturing. Reproduced courtesy of Dr D Marcos, Barts Health NHS Trust, London, UK.

with colitis of uncertain type or etiology (CUTE) (see page 24) who have had a normal barium follow-through meal or small-bowel MRI. To minimize the risk of obstruction by previously undiagnosed small-bowel strictures, a 'patency' capsule can be given before diagnostic wireless capsule endoscopy; if a patency capsule is held up proximal to a stricture, unlike a wireless capsule it will dissolve and not cause intestinal obstruction.

Radiology

Plain abdominal radiography

Ulcerative colitis. In patients presenting with active disease, a plain film is useful to assess the extent of disease, since fecal residue on a radiograph usually indicates sites of uninflamed colonic mucosa. Plain abdominal radiography is also used to exclude colonic dilatation in those with acute severe ulcerative colitis (Figure 4.3). In this setting, severe disease is also indicated by deep ulceration and coarse nodularity of the mucosa, or 'mucosal islands', and linear gas-tracking in the gut wall.

Crohn's disease. A plain film (preferably with the individual both supine and erect) is essential if small-bowel obstruction is suspected. It may also hint at a mass in the right iliac fossa and is helpful, as in ulcerative colitis, in estimating disease extent or severity in active Crohn's colitis. Classically, but exceptionally, complicating radio-opaque urinary stones or gallstones are seen (see Table 3.1; also Chapter 8).

Barium enemas. Conventional double-contrast barium enema (Figure 4.4) has been superseded almost everywhere by colonoscopy, since the latter

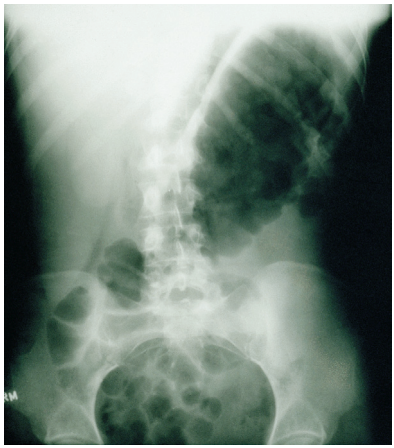

Figure 4.3 Acute colonic dilatation affecting the transverse colon.

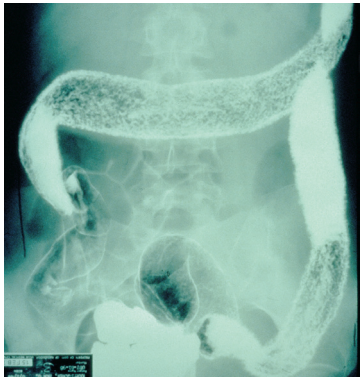

Figure 4.4 Barium enema showing superficial ulceration in active total ulcerative colitis. This test has now been largely superseded by colonoscopy in ulcerative colitis; both tests are potentially dangerous in active disease.

allows biopsy, avoids radiation exposure and is safe when undertaken by experienced operators (see above).

Small-bowel radiology. Until recently, contrast examination of the small bowel was of central importance in the diagnosis of Crohn's disease proximal to the terminal ileum, showing strictures, ulceration and fistulation (Figure 4.5). However, small-bowel MRI is now usually preferred, since it avoids radiation and also gives information about extraintestinal structures. Contrast fistulography is a useful way of clarifying anatomic connections in patients with abdominal sinuses or fistulas.

Radiolabeled leukocyte scans. The intensity and extent of colonic uptake 1 hour after injection of autologous leukocytes radiolabeled with ^{99}Tc-hexamethylpropyleneamine oxime (^{99}Tc-HMPAO) can provide information, non-invasively, about disease activity, particularly the extent and site, where doubt exists in patients with ulcerative colitis or Crohn's disease (Figure 4.6).

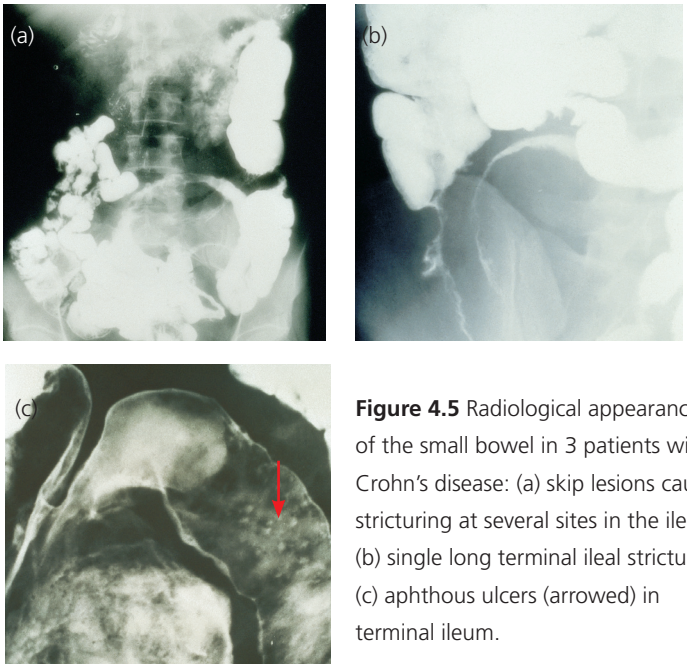

Figure 4.5 Radiological appearance of the small bowel in 3 patients with Crohn's disease: (a) skip lesions causing stricturing at several sites in the ileum; (b) single long terminal ileal stricture; (c) aphthous ulcers (arrowed) in terminal ileum.

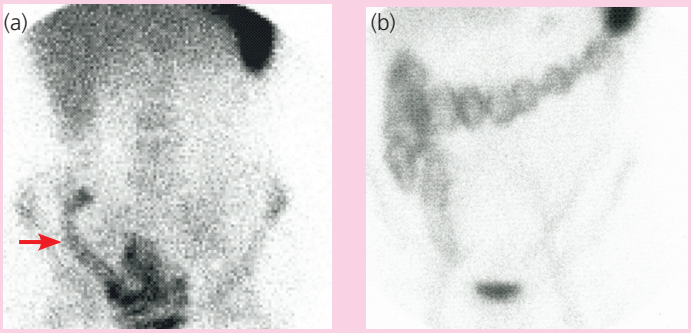

Figure 4.6 Radiolabeled leukocyte scans in 2 patients with Crohn's disease showing inflammation in: (a) the distal ileum (arrowed); (b) the terminal ileum, cecum and ascending and transverse colon.

Increased isotopic activity on such scans is not, of course, specific for IBD, since positive results are obtained in other inflammatory gut diseases. Delayed scanning can be helpful in identifying an intra-abdominal abscess, for example in patients with Crohn's disease. Many centers now perform

these scans only rarely, however, since the required diagnostic information is more easily obtained by ileocolonoscopy, MRI or CT scanning.

Cross-sectional imaging. As mentioned above, small-bowel MRI, because of its sensitivity, ability to show extraintestinal structures and safety (in particular its freedom from ionizing radiation), is now the favored method for visualizing the small bowel in most centers; for example, it can clearly show areas of mucosal thickening, stricturing, increased vascularity and fistulation in patients with active Crohn's disease (Figure 4.7). Ultrasound and CT scanning can be very useful for the evaluation and percutaneous drainage of localized collections (see Figure 8.5). While CT and MRI will precisely define the anatomy of fistulas and sinuses in Crohn's disease, endoluminal ultrasound and MRI (see Figure 8.1) provide the most accurate delineation of perianal abscesses and fistulas.

Increasing awareness of the lifetime radiation exposure of patients with Crohn's disease, together with greater expertise in their application, is leading many centers to increase the use of ultrasound and MRI at the expense of contrast radiology and CT scanning.

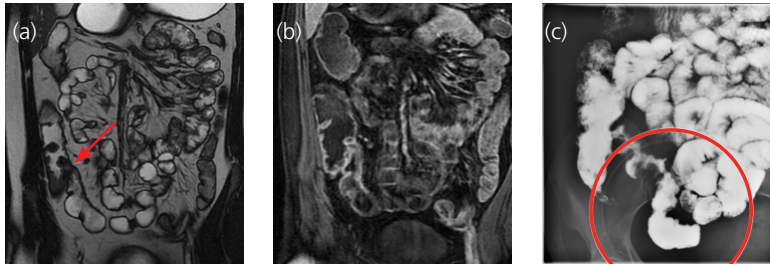

Figure 4.7 MRI enterography and barium follow-through in a patient with active ileocecal Crohn's disease: (a) T2-weighted sequence: 'white lumen' (after patient has ingested fluid) showing thickening of the wall of the terminal ileum, ileocecal valve (arrowed) and cecum with asymmetric scarring and pseudosacculation; (b) T1-weighted sequence with intravenous contrast: 'black lumen' showing enhancement of actively inflamed mucosa and bowel wall of involved segments; (c) corresponding image from barium study showing fold thickening and irregularity in the terminal ileum with mucosal ulceration consistent with active Crohn's disease. Reproduced courtesy of Dr A McLean, Barts Health NHS Trust, London, UK.

Key points – diagnosis

- The aims of investigation are to diagnose IBD, distinguish between ulcerative colitis and Crohn's disease, establish its site, extent and activity, and check for complications of the disease and its treatment.
- Laboratory, endoscopic, histological and imaging tests should be regarded as complementary, but should be undertaken selectively according to individual presentation.
- In part to reduce the lifetime radiation exposure of individuals with Crohn's disease, ultrasound and MRI scans are increasingly used in preference to X-rays and CT scanning.

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5 Drugs used to treat inflammatory bowel disease

This chapter outlines the pharmacology, mechanism of action, indications, side effects, monitoring and contraindications of drugs currently used as specific anti-inflammatory agents in ulcerative colitis and Crohn's disease. Imminent and future developments in medical therapy are also briefly described.

Corticosteroids

The corticosteroids used in IBD, their indications and their side effects are listed in Table 5.1.

Pharmacology. Corticosteroids can be given intravenously, orally or topically (as a suppository or an enema), the route selected depending on the severity and site of disease. The most widely used oral preparation is prednisolone. Intravenous alternatives are hydrocortisone and methylprednisolone.

The systemic side effects of conventional steroids (see Table 5.1) have prompted a search for safer formulations. For topical therapy of distal ulcerative colitis, several enema preparations containing steroids that are poorly absorbed and/or undergo rapid first-pass intestinal mucosal and hepatic metabolism are available (e.g. prednisolone metasulfobenzoate and budesonide). These preparations produce fewer systemic side effects and less adrenocortical suppression than hydrocortisone and prednisolone sodium phosphate enemas. A more important advance has been the introduction of an oral controlled ileal-release formulation of budesonide for the treatment of active ileocecal Crohn's disease. This drug approaches oral prednisolone in efficacy but, because of its rapid first-pass metabolism, causes less adrenocortical suppression as assessed by plasma cortisol levels. However, it is more expensive than prednisolone. A controlled colonic-release formulation of budesonide for use in ulcerative colitis (budesonide MMX) is licensed in the USA and elsewhere; it may represent a safer option for some patients.

TABLE 5.1

Corticosteroids indicated for IBD

Indications	
Active ulcerative colitis and Crohn's disease	
Formulations	
Intravenous	Hydrocortisone (300–400 mg/day) Methylprednisolone (40–60 mg/day)
Oral	Prednisolone, prednisolone enteric-coated, prednisone (up to 60 mg/day) Budesonide (up to 9 mg/day), ileal release (for ileal CD) or MMX (for UC)
Enemas	Liquid: prednisolone metasulfobenzoate, prednisolone sodium phosphate, budesonide Foam: prednisolone metasulfobenzoate (Predfoam), hydrocortisone (Colifoam), budesonide (Budenofalk foam)
Suppositories	Hydrocortisone, prednisolone sodium phosphate (Predsol)
Side effects	
General	Cushingoid facies ('moon face'), weight gain, dysphoria
Metabolic	Adrenocortical suppression, hyperglycemia, hypokalemia
Cardiovascular	Hypertension, fluid retention
Infection	Intra-abdominal sepsis (in CD), opportunistic infections, reactivation of tuberculosis, severe chickenpox
Skin	Acne, bruising, striae, hirsuties, delayed wound healing
Eyes	Cataracts, glaucoma
Musculoskeletal	Osteoporosis, avascular osteonecrosis, myopathy
Children	Growth retardation
Monitoring	
Blood pressure	
Blood sugar/potassium	

(CONTINUED)

TABLE 5.1 (CONTINUED)

Contraindications (all relative)	
Penetrating Crohn's disease (including perianal disease)	
Poorly controlled diabetes or hypertension	
Osteoporosis	
Active peptic ulcer	
Concurrent serious infections	
Mechanisms of action	
Leukocytes	Reduced migration, activation, survival Reduced activation of NF-κB Phospholipase A2 inhibition Reduced induction of COX-2 and inducible NOS Reduced production of cytokines and lipid mediators Increased kinin degradation
Endothelial cells	Reduced expression of adhesion molecules Reduced capillary permeability

CD, Crohn's disease; COX, cyclo-oxygenase; NF-κB, nuclear [transcription] factor κB; NOS, nitric oxide synthase; UC, ulcerative colitis.

Mechanism of action. By combining with intracellular glucocorticoid receptors, corticosteroids have many potentially beneficial actions on the inflammatory process (see Table 5.1), but which of these is, or are, of predominant importance in IBD is unclear.

Indications. The use of corticosteroids in IBD should be restricted to the treatment of patients with active disease, as there is no evidence that they are able to maintain remission. Corticosteroids continue to have a major role in active ulcerative colitis, but their therapeutic value in Crohn's disease is limited because of their failure to induce mucosal healing and their side effects (see below). Further details are given in Chapters 7 and 8.

Side effects. The principal side effects of corticosteroids are listed in Table 5.1. They relate to both dose and duration, except for avascular osteonecrosis,

which is unpredictable and may occur after only short courses of treatment. In patients with penetrating Crohn's disease, corticosteroids increase the risk of intra-abdominal and pelvic sepsis and delayed postoperative recovery.

Monitoring treatment. The tiny proportion of patients with IBD who require long-term treatment with oral corticosteroids should have regular checks of their blood pressure and blood sugar and potassium concentrations. Those who exceed a cumulative dose of about 10 g of prednisolone should be assessed for osteoporosis by bone densitometry and treated accordingly (see Chapter 3).

Contraindications. In patients with poorly controlled diabetes mellitus or hypertension, and in those with established osteoporosis or peptic ulceration, alternative pharmacological treatments should be used when possible. As indicated above, steroids should be avoided in patients with penetrating Crohn's disease. If steroid therapy is unavoidable, topical therapy or oral budesonide in those with ileocecal Crohn's disease is preferable to oral prednisolone.

Aminosalicylates

Pharmacology. 5-Aminosalicylates (5-ASAs) are available in oral formulations (Table 5.2) and as enemas and suppositories (Table 5.3). The original compound, sulfasalazine, consists of 5-aminosalicylic acid linked by an azo bond to sulfapyridine (Figure 5.1; see Table 5.2). The sulfonamide moiety acts as a carrier to deliver 5-ASA, the active component, to the colon, where it is released by bacterial action. About 20% of patients cannot tolerate sulfasalazine because of side effects, most of which are due to sulfapyridine (see Table 5.3).

The newer oral 5-ASA formulations are better tolerated than sulfasalazine. The pH-dependent, delayed-release and, particularly, slow-release mesalazine (mesalamine) preparations release 5-ASA more proximally in the gut (Figure 5.2). In contrast, olsalazine and balsalazide, like sulfasalazine, release 5-ASA by bacterial azo reduction in the colon and are indicated for use only in colitis. It is now known that once-daily administration of 5-ASA drugs is as effective in ulcerative colitis as twice daily or three times daily regimens: the increased convenience of once-daily regimens increases treatment adherence.

TABLE 5.2

Examples of oral formulations of aminosalicylates (5-ASAs) in IBD

Drug	Formulation	Dose range (maintenance–conventional maximum)
Prodrugs (5-ASA azo-linked to carrier)		
Sulfasalazine	5-ASA–sulfapyridine	1 g bd–2 g td
Olsalazine	5-ASA–5-ASA	500 mg bd–1 g td
Balsalazide	5-ASA–aminobenzoylalanine	1.5 g bd–2.25 g td
Mesalazine (mesalamine) (5-ASA alone) (max. dose 4.8 g daily)		
Delayed-release		
Asacol MR,* Lialda	Eudragit S coating dissolves at pH > 7	2–4.8 g od
Delzicol		1.2–2.4 g/day (0.8 g td)
Salofalk, Claversal	Eudragit L coating dissolves at pH > 6	2–4 g od
Apriso		1.5 g od
Slow-release		
Pentasa (tablet or sachet)	Ethylcellulose microspheres	2–4 g od
Salofalk	Granules	2–4 g od
Multimatrix		
Mezavant XL (UK) Lialda	Multimatrix	2.4–4.8 g od

Sites to which 5-ASAs are delivered from these formulations are shown in Figure 5.2.
Note: trade names vary in different countries. *No longer distributed in the USA.
bd, twice daily; od, once daily, td, three times daily.

Mechanism of action. Like corticosteroids, aminosalicylates have a wide variety of anti-inflammatory effects (see Table 5.3). However, it is not known which of these explains their efficacy.

Indications and choice of preparation. 5-ASA compounds have a therapeutic role in moderately active (although not acute severe) ulcerative colitis and, particularly, in the prevention of relapse in those with inactive disease. 5-ASA agents given by mouth and rectally ('top and tail') are more effective, although more expensive, in active ulcerative colitis than when given by either route alone.

TABLE 5.3

Aminosalicylates in inflammatory bowel disease

Indications	
Active and inactive ulcerative colitis	
Mildly active Crohn's disease (see Chapter 8)	
Preparations	
Oral	See Table 5.2
Enemas	Liquid: Pentasa, Salofalk, Rowasa, sulfasalazine
	Foam: Asacolfoam, Salofalk, Claversal
Suppositories	Asacol, Pentasa, Salofalk, Canasa, sulfasalazine
Side effects	
General	Headache,* fever*
Gut	Nausea,* vomiting,* diarrhea, exacerbation of ulcerative colitis
Blood	Hemolysis,* folate deficiency,* agranulocytosis,* thrombocytopenia,* aplastic anemia,* methemoglobinemia*
Renal	Orange urine,* interstitial nephritis
Skin	Rashes,* toxic epidermal necrolysis,* Stevens–Johnson syndrome,* hair loss
Other	Oligospermia,* acute pancreatitis, hepatitis, lupus syndrome, myocarditis, pulmonary fibrosis
Monitoring	
Sulfasalazine	Every 3 months: blood count, red-cell folate, serum urea/creatinine, liver function tests
Mesalazine (mesalamine)	Every 6–9 months: serum urea/creatinine
Contraindications	
Sulfasalazine	Known salicylate or sulfonamide sensitivity, G6PDH deficiency, porphyria
Mesalazine (mesalamine)	Salicylate sensitivity, renal failure

(CONTINUED)

TABLE 5.3 (CONTINUED)

Mechanisms of action	
Leukocytes	Reduced migration, cytotoxicity
	Reduced activation of NF-κB
	Reduced synthesis of IL-1 and lipid mediators
	Reduced degradation of prostaglandins
	Antioxidant
	TNF antagonist
	Activation of PPAR-γ
Epithelium	Reduced MHC class II expression
	Induction of heat shock proteins
	Reduced apoptosis

*Side effects usually due to sulfonamide component of sulfasalazine.
G6PDH, glucose-6-phosphate dehydrogenase; IL, interleukin; MHC, major histocompatibility complex; NF-κB, nuclear [transcription] factor κB; PPAR-γ, peroxisome proliferator-activated receptor-γ; TNF, tumor necrosis factor.

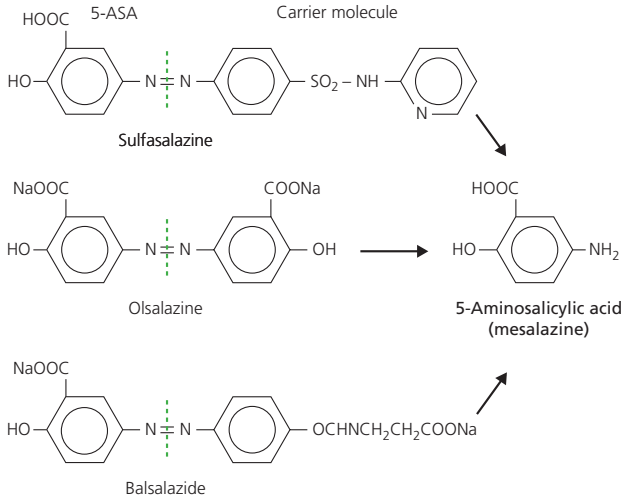

Figure 5.1 Chemistry of 5-aminosalicylate (5-ASA) preparations. The green dotted lines indicate cleavage of the azo-bond by colonic bacterial flora to release the active moiety, 5-ASA, of each drug from the carrier molecule. In the case of olsalazine, the 5-ASA serves both as active component and carrier molecule.

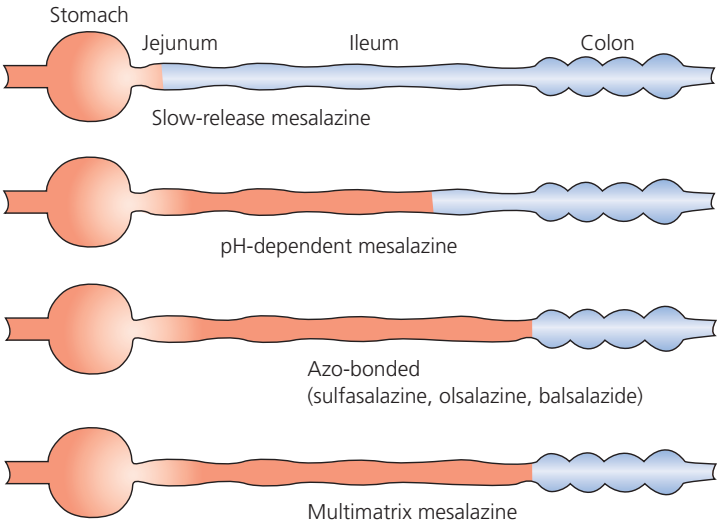

Figure 5.2 Intestinal release profiles of 5-aminosalicylate (5-ASA) formulations (see Table 5.2). There is some variability in the site of release of the various formulations (as indicated by the blue-colored areas above), depending on, for example, the precise pH at which 5-ASA is released from different pH-dependent preparations, intestinal intraluminal pH and intestinal transit rate. The multimatrix mesalazine (mesalamine) preparation has a pH-dependent coating, while hydrophilic and lipophilic excipients prolong the release of 5-ASA throughout the colon.

Taken long term, 5-ASA drugs may reduce the risk of development of colorectal cancer in patients with extensive ulcerative colitis, but current data are conflicting. Patients using sulfasalazine in the long term should also be prescribed folic acid to prevent folate deficiency: this may also help to reduce the risk of colonic cancer in chronic extensive ulcerative colitis.

Recent data suggest that although mesalazine preparations are of minor benefit in mildly active Crohn's disease, they have little or no other role in patients with this condition (see Chapter 8).

Side effects. Although better tolerated than sulfasalazine, the newer 5-ASA formulations may cause rash, headache, nausea, diarrhea, exacerbation of ulcerative colitis, pancreatitis and/or blood dyscrasias in up to 5% of patients (see Table 5.3). Interstitial nephritis has been associated very rarely

(about 1 in 500 patients) with mesalazine, while watery diarrhea due to active small-intestinal secretion occurs in about 5% of patients given olsalazine. The latter can usually be avoided by taking the drug with meals.

Monitoring treatment. Patients taking sulfasalazine require regular (every 3–6 months) blood counts, and serum folate and liver function tests. Those receiving any 5-ASA preparation should have occasional (e.g. every 6–9 months) checks of their serum urea and creatinine concentrations.

Contraindications. All 5-ASAs should be avoided in individuals with a history of hypersensitivity to salicylates, including acetylsalicylic acid (aspirin), or those with serious renal impairment. In addition, sulfasalazine should not be given to patients with sulfonamide sensitivity, porphyria or glucose-6-phosphate dehydrogenase deficiency.

Antibiotics

Metronidazole is a nitroimidazole compound with antimicrobial actions against gut anaerobes and protozoa. It also has immunomodulatory effects in vitro. The oral preparation is the most widely used in IBD.

Indications and side effects. Metronidazole, 10 mg/kg/day orally, has moderate benefit in ileocolonic, but not small-bowel, Crohn's disease and in preventing recurrence when given for 3 months after ileal resection. Despite the lack of data from controlled trials, it is commonly used in perianal Crohn's disease too. It is also sometimes given in combination with ciprofloxacin in refractory Crohn's disease. Metronidazole has no primary therapeutic role in ulcerative colitis other than in patients with pouchitis following formation of an ileoanal pouch after colectomy (see Chapter 9). Treatment must be given for up to 3 months, but it may be confounded by nausea, vomiting, an unpleasant taste in the mouth and/or an individual's unwillingness to abstain from alcohol during this time. The most serious side effect is peripheral neuropathy. This is dose related and is not always reversible when treatment ends.

Other antibiotics. Limited data suggest that oral tobramycin and trimethoprim–sulfamethoxazole could improve outcome in acute severe ulcerative colitis. However, most gastroenterologists restrict the use of

broad-spectrum antibiotics to prophylaxis against bacteremia and endotoxic shock in severely ill patients with acute severe colitis.

Ciprofloxacin has a moderately beneficial effect in Crohn's disease, particularly in perianal disease; it can also ameliorate pouchitis alone or in combination with metronidazole. Clarithromycin (sometimes in combination with rifabutin) is reported to have benefit in Crohn's disease and, like metronidazole, has some immunomodulatory effects in vitro.

Antibiotics such as amoxicillin, trimethoprim, ciprofloxacin and metronidazole are sometimes useful for the treatment of diarrhea or steatorrhea due to bacterial overgrowth in patients with small-bowel Crohn's disease, while broad-spectrum and often intravenous antibiotics may be needed, together with drainage, in the management of those with intra-abdominal or perianal abscesses complicating Crohn's disease (see Chapter 8).

Probiotics

Probiotics are defined as live microorganisms which, when given orally in sufficient quantity, confer a health benefit on the host. Given the importance of intestinal bacterial flora in driving the mucosal inflammation characteristic of IBD (see Chapter 1), it is unsurprising that a range of probiotic organisms have been assessed for its treatment (listed in Table 5.8). To date, evidence of efficacy relates only to use of *E. coli* Nissle to prevent relapse of ulcerative colitis, and of VSL3, which contains a mixture of bifidobacteria, lactobacilli and streptococci, in pouchitis.

Despite the paucity of data confirming the benefits of probiotics and prebiotics in IBD, they are widely used by patients adopting a complementary or alternative medical approach to their illness (see pages 82–3): they are probably safe.

Immunomodulatory drugs

Immunomodulatory agents currently used in the treatment of IBD include azathioprine and its metabolite mercaptopurine (MP) and, less often, methotrexate, ciclosporin (cyclosporine) and tacrolimus.

Azathioprine and mercaptopurine. Azathioprine is a prodrug that undergoes rapid conversion to MP; both are purine analogs (thiopurines). The doses most commonly used in IBD are 2.0 and 1.0 mg/kg/day, respectively (Table 5.4).

TABLE 5.4

Azathioprine and mercaptopurine in inflammatory bowel disease

Indications	
Steroid-dependent or -refractory ulcerative colitis and Crohn's disease	
Fistulating and perianal Crohn's disease	
Formulations	
Oral	Azathioprine (2.0–2.5 mg/kg/day)
	MP (1.0–1.5 mg/kg/day)
Side effects	
General	Nausea, vomiting, headache, arthralgia, fever, rash, abdominal pain
Blood	Agranulocytosis, thrombocytopenia, macrocytosis
Infections	Opportunistic including cytomegalovirus, herpes zoster
Hepatobiliary	Cholestatic hepatitis, acute pancreatitis, nodular regenerative hyperplasia
Malignancy	Lymphoma, skin
Preparatory screening	Serology and vaccinations (see Chapter 6)
	Measure TPMT before starting thiopurine
Monitoring	Blood count, liver function tests every 2 weeks for the first 2 months, then every 2–3 months
	TGN and MMP – see text
Contraindications	Pregnancy (relative contraindication)
	Homozygous TPMT deficiency
Mechanism of action	Inhibition of DNA synthesis and induction of apoptosis in T cells

MP, mercaptopurine; MMP, methylmercaptopurine; TGN, thioguanine nucleotides; TPMT, thiopurine methyltransferase.

Both drugs are currently used only in oral formulations and take up to 4 months to exert their clinical benefit.

Homozygous deficiency of thiopurine methyltransferase (TPMT), an enzyme responsible for the metabolism of azathioprine and MP (Figure 5.3),

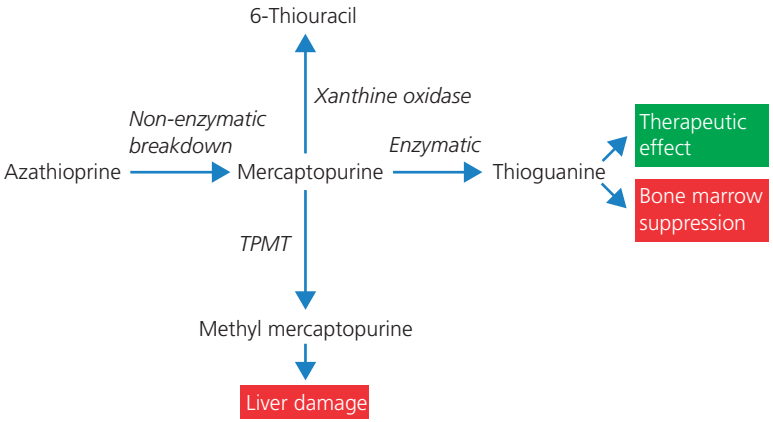

Figure 5.3 Simplified diagram of metabolism of azathioprine and mercaptopurine. TPMT, thiopurine methyltransferase.

occurs in about 0.2% of the population. This enzyme deficiency is likely to account for some of the serious untoward effects that can occur with thiopurines. TPMT assay should be undertaken before thiopurine treatment is initiated, primarily to reduce the chance of severe thiopurine-induced bone marrow suppression in those with homozygous enzyme deficiency. In the 10% of people with heterozygotic expression of the enzyme, TPMT is in the intermediate range; therefore, weight-based thiopurine doses should start at half the standard dose. Measurement of blood levels of thioguanine nucleotide (TGN), the active metabolite of thiopurines (see Figure 5.3), can help to ensure appropriate dosing.

Mechanism of action. The precise mechanism of action of azathioprine and MP is not known, but they appear to modify the immune response by inhibiting DNA synthesis in, and inducing apoptosis of, T cells. Azathioprine has anti-inflammatory and antibacterial as well as immunomodulatory effects.

Indications. Azathioprine and MP are used predominantly as steroid-sparing agents in those with steroid-dependent or steroid-refractory IBD. They may also have special roles in accelerating remission and healing ileal lesions when given in combination with prednisolone to patients with active Crohn's disease, and in fistulating Crohn's disease, particularly perianal disease.

Side effects. Up to 20% of patients cannot tolerate azathioprine because of side effects (see Table 5.4). A switch to MP may avert these problems in about half. More seriously, both drugs cause acute

pancreatitis in about 3% of people. Other potentially serious side effects of dose-dependent bone marrow depression (particularly in the first few weeks of treatment: 2% of patients) and cholestatic hepatitis necessitate regular blood monitoring. There is an increased risk of infections, particularly a serious form of glandular fever. To reduce the risk of infections, relevant serology should be tested and vaccinations given if necessary before thiopurines are started (see Chapter 6). Very long-term use, as in transplant patients, slightly increases the risk of malignancy, including lymphoma. White patients taking azathioprine or MP should avoid excessive exposure to sunlight because of an increased risk of skin cancer.

Monitoring treatment. Whatever their TPMT level, patients started on azathioprine or MP should have blood counts every 2 weeks for the first 2 months of therapy to check for incipient bone marrow depression. Thereafter, white cell count, platelet count and liver function tests should be performed every 2–3 months.

Blood TGN assays have been used increasingly in recent years to monitor patients on thiopurines. In patients failing to respond, a very low level of TGN can indicate non-adherence to treatment rather than a need to escalate therapy, for example to an anti-tumor necrosis factor (TNF) agent (see below and Figure 8.2). Conversely, high TGN concentrations increase the risk of thiopurine side effects, especially bone marrow suppression, and indicate that the dose should be reduced. Note, however, that severe bone marrow suppression can occur in patients with TGN concentrations in the therapeutic range, so routine blood count monitoring must always be undertaken.

Lastly, high concentrations of methyl mercaptopurine (MMP, see Figure 5.3) increase the risk of thiopurine-induced liver damage. Under these circumstances, patients can be given a combination of low-dose thiopurine (e.g. azathioprine, 25 mg) and allopurinol, 100 mg, daily. The latter inhibits both the xanthine oxidase and methylation pathways, thereby raising TGN levels (which should be carefully monitored) and reducing MMP.

Contraindications. Several series have allayed previous fears about the safety of thiopurines in pregnancy (see Chapter 10): flare of disease activity induced by stopping azathioprine or MP in pregnancy is more dangerous to the fetus than continuing with these drugs. Thiopurines may substantially

increase the dose of warfarin needed to achieve anticoagulation in patients with, for example, atrial fibrillation: scrupulous anticoagulation monitoring is needed when introducing or withdrawing a thiopurine from patients on warfarin.

Methotrexate acts predominantly by inhibiting the enzymes that metabolize folic acid. At high doses, the main enzyme affected is dihydrofolate reductase, with consequent inhibition of RNA, DNA and protein synthesis. At the lower doses used to treat Crohn's disease, the anti-inflammatory and immunomodulatory effects of methotrexate are likely to result from inhibition of other folate-dependent enzymes.

Indications. A once-weekly 25-mg intramuscular injection of methotrexate improves symptoms and reduces steroid requirements in patients with chronically active steroid-dependent Crohn's disease. An intramuscular dose of 15 mg/week maintains remission in such patients. Most gastroenterologists resort first to a thiopurine rather than to methotrexate in steroid-resistant or steroid-dependent patients with Crohn's disease; many prescribe it orally rather than by injection. Although not yet proven to be effective in ulcerative colitis in formal clinical trials, methotrexate is used in many centers for patients with colitis who are intolerant of or refractory to thiopurines.

Side effects necessitate discontinuation of methotrexate in up to 20% of people. Nausea, vomiting, stomatitis and diarrhea are the most common. As with other immunosuppressive agents, there is an increase in opportunistic infections and bone marrow depression. These side effects are reduced by coadministration of folic acid, which does not compromise the therapeutic effectiveness of methotrexate. Hepatic fibrosis and pneumonitis are the most serious side effects of long-term therapy with methotrexate in patients with psoriasis and rheumatoid arthritis, but these adverse effects appear to be less common in individuals with IBD.

Monitoring treatment. As with thiopurines, the risk of bone marrow depression necessitates twice-weekly blood counts for the first 2 months, and thereafter every 3 months. Folic acid should also be coadministered at a dose of 1–5 mg/day, except on the day when methotrexate is taken.

Liver function tests should be monitored every 1–2 months. Liver biopsy is probably unnecessary, except in those with persistently abnormal

liver function tests. Unexplained shortness of breath or coughing necessitates a chest X-ray, blood gas and lung function tests, particularly measurement of carbon monoxide diffusing capacity.

Contraindications. Pregnancy and conception should be avoided within 6 months of the treatment of either partner, because methotrexate is teratogenic. Breastfeeding is also contraindicated. Coadministration of other antifolate agents, such as trimethoprim–sulfamethoxazole, may increase the toxic effects of methotrexate on the bone marrow, as may non-steroidal anti-inflammatory drugs, penicillin, old age and renal impairment.

To reduce the risk of hepatotoxicity, methotrexate should not be prescribed to patients who drink more than seven units of alcohol per week, are substantially overweight or have diabetes mellitus.

Ciclosporin (cyclosporine) is a fungus-derived cyclic undecapeptide useful in steroid-refractory acute severe ulcerative colitis. Intravenous therapy is usually given initially, and replaced after a few days with the oral preparation (Neoral). Close monitoring of whole blood concentrations is used to adjust ciclosporin dosage. The target levels depend on the method used for analysis and on the route of administration (Table 5.5). Because ciclosporin is metabolized via the cytochrome P450 enzyme system, grapefruit juice and drugs that inhibit this enzyme system should be taken with caution. However, drugs that induce the cytochrome P450 system decrease blood levels of ciclosporin (see Table 5.5).

Mechanism of action. Ciclosporin reduces helper and cytotoxic T-cell function and proliferation by inhibiting interleukin (IL)-2 gene transcription.

Indications. Initial enthusiasm for intravenous ciclosporin in active Crohn's disease was not justified by later reports. The only current indication for ciclosporin in IBD is therefore as an adjunctive treatment in steroid-refractory acute severe ulcerative colitis (see Chapter 7).

Side effects and monitoring. The most serious side effects are:

- opportunistic infections (in 20% of patients) such as *Pneumocystis carinii* pneumonia, for which coadministration of prophylactic trimethoprim–sulfamethoxazole may be advisable
- renal impairment, including a 20% reduction in glomerular filtration rate in most patients and, in 25%, an interstitial nephritis that is not always reversible when treatment stops

TABLE 5.5

Ciclosporin (cyclosporine) in inflammatory bowel disease

Indications	
Steroid-refractory acute severe ulcerative colitis (intravenous then oral)	
Formulations	
Oral	Neoral, 5 mg/kg/day in divided doses
Intravenous	2 mg/kg/day by continuous infusion
Side effects	
General	Nausea, vomiting, headache
Renal	Interstitial nephritis
Infection	Opportunistic, including *Pneumocystis carinii* pneumonia
Neurological	Epileptic seizures, paresthesias, myopathy
Cardiovascular	Hypertension
Skin	Hypertrichosis, gingival hypertrophy
Metabolic	Hyperkalemia, hypomagnesemia, hyperuricemia
Liver	Cholestatic hepatitis
Malignancy	Lymphoma
Monitoring	
Pre-treatment	Serum urea and creatinine, potassium, magnesium, cholesterol, urate, liver function
On treatment	Aim for blood ciclosporin concentrations: • 250–400 ng/mL for intravenous • trough 150–300 ng/mL for oral Serum urea and creatinine, potassium, magnesium, urate, liver function Blood pressure
Contraindications	
Pregnancy, lactation	Renal impairment, hypertension, infection, epilepsy, malignancy
Disease	Low serum cholesterol or magnesium, high potassium
Biochemical	Coadministration of cytochrome P450 inhibitors (grapefruit juice, erythromycin, oral contraceptives, fluconazole, calcium-channel and proton-pump inhibitors)

(CONTINUED)

TABLE 5.5 (CONTINUED)

Drugs	Coadministration of cytochrome P450 inducers (phenytoin, barbiturates, rifampicin, carbamazepine)
Mechanism of action	
Inhibition of IL-2 gene transcription leading to inhibition of helper and cytotoxic T-cell function and proliferation	

IL-2, interleukin-2.

- hypertension (in 30% of patients)
- hepatotoxicity (in up to 20% of patients)
- epileptic seizures (in 3% of patients) due to penetration of the blood–brain barrier by cremophor, a lipid-soluble vehicle for intravenous ciclosporin; the seizures are confined to those with low serum cholesterol and/or magnesium concentrations, and do not occur with oral ciclosporin.

Long-term oral use of ciclosporin, for which there is no clear indication in IBD, may predispose to lymphoma. The side effects of the drug will prevent it ever becoming widely used for IBD. Its use demands frequent monitoring of ciclosporin blood levels and serum biochemistry.

Tacrolimus is another oral macrolide immunosuppressant derived originally from a bacterium and widely used in transplant medicine. Its side effects, which resemble those of ciclosporin, include induction of diabetes mellitus. Use of tacrolimus requires careful monitoring of drug levels, blood sugar and renal function. In IBD, the drug is restricted to those with very refractory disease, particularly ulcerative colitis.

Modulation of cytokine activity

Our increased understanding in recent years of the etiopathogenesis of IBD (see Chapter 1) has prompted trials using a wide range of antibodies and other agents specifically targeting abnormal cytokine expression. Of these, only antibodies to TNFα and vedolizumab, an antibody against the α4β7 integrin, have reached clinical use. Ustekinumab, an antibody against IL-12/23, is likely to be introduced very soon. In the long term, it is likely

that a range of other cytokine-based therapies will enter clinical practice, at least for patients with refractory IBD. These may include gene transfer techniques to induce intestinal mucosal production of anti-inflammatory cytokines, such as IL-4 and IL-10.

Anti-TNFα agents. Several anti-TNFα agents are available (Table 5.6). Infliximab (Remicade), a mouse–human chimeric anti-TNFα drug, was launched for the treatment of Crohn's disease in the late 1990s. The use of antibodies to TNFα has revolutionized the management of other chronic inflammatory diseases such as rheumatoid arthritis, and has proven a major advance for patients with refractory or fistulous Crohn's disease and, to a lesser extent, ulcerative colitis. Adalimumab (Humira), which was introduced more recently, is a fully humanized anti-TNFα drug. Initially, it was mostly used for those who lost response to, or who were intolerant of, infliximab, since these problems are usually due to formation

TABLE 5.6

Anti-TNFα agents, infliximab, adalimumab, certolizumab pegol and golimumab (ulcerative colitis only) in IBD

Indications	
Steroid-dependent or -refractory active Crohn's disease	
Fistulating Crohn's disease	
Steroid-dependent/-refractory ulcerative colitis	
Pyoderma gangrenosum	
Ankylosing spondylitis	
Preparations	
Intravenous	Infliximab, 5 (rarely 10) mg/kg at 0, 2, 6 and (usually) every 8 weeks
Subcutaneous	Adalimumab, 160 and 80 mg at 0 and 2 weeks, then 40 mg every other week or weekly
	Certolizumab pegol, 400 mg at 0, 2 and 4 weeks; then 400 mg every 4 weeks
	Golimumab, 200 and 100 mg at 0 and 4 weeks, then 100 mg (if weight > 80 kg) or 50 mg (weight < 80 kg) every 4 weeks

(CONTINUED)

TABLE 5.6 (CONTINUED)

Side effects	
Serious infections	Tuberculosis, salmonella, cellulitis, pneumonia
Infusion reactions	Headache, rash, nausea, fever
Autoantibodies	Infliximab only: ATI (delayed hypersensitivity), antibodies to DNA and cardiolipin (lupus syndrome)
Skin	Psoriatiform eruptions, infections
Malignancy	Lymphoma, including hepatosplenic T-cell lymphoma in young patients also on azathioprine
Neurological	Aseptic meningitis, demyelination
Cardiac	Congestive cardiac failure
Preparatory screening	Serology and vaccinations (see Chapter 6). TB exclusion: check TB history, chest X-ray; IGRA
Monitoring	During and 1 hour after infusions: • pulse • respiration • blood pressure • temperature
Contraindications	
Third trimester of pregnancy (see text)	
Active infection	
Current or previous malignancy	
Previous TB, multiple sclerosis, heart failure	
Hypersensitivity to murine proteins (infliximab)	
Mechanism of action	
Binding of surface-bound T-cell TNF and free TNF	

ATI, antibodies to infliximab; IGRA, interferon gamma release assay; TB, tuberculosis; TNF, tumor necrosis factor.

of antibodies to the murine component of infliximab (antibodies to infliximab; ATI). However, because it is administered as a subcutaneous injection rather than intravenous infusion (see below), and is slightly less expensive, adalimumab is often now the anti-TNFα drug of first choice. In the USA and some other countries, two other anti-TNFα agents, certolizumab pegol (Cimzia) and golimumab (Simponi), are also available.

It is noteworthy that etanercept (Embrel), a fusion protein consisting of the TNF receptor and the constant end of IgG1, which inhibits TNFα and is effective in rheumatoid and other chronic arthritides, has *not* been shown to be effective in the treatment of IBD.

Reassurance is still needed that the clear therapeutic benefits produced by anti-TNFα drugs in some patients will not, in the very long term, be outweighed by serious adverse effects, in particular infection and/or malignancy. In the future, it is possible that anti-TNFα drugs will be replaced by non-protein small-molecule drugs that prevent the production or actions of TNFα: an existing example is thalidomide, the possible benefits of which are confounded by its side effects, especially in relation to pregnancy.

Pharmacology. Infliximab is usually administered using an induction regimen of infusions at 0, 2 and 6 weeks, followed by regular infusions at intervals of 8 weeks, each infusion being given over 1–2 hours. The standard dose is 5 mg/kg per infusion, and the cost is about $2400/£1200/€2000 per infusion, depending on body weight. Some patients losing response need 10 mg/kg, or more frequent infusions.

Adalimumab is given by subcutaneous injection at induction doses of 160 and 80 mg every 2 weeks; subsequent injections of 40 mg are given every other week, although patients who lose their initial response need to increase to 40 mg every week.

Certolizumab pegol, which is a pegylated humanized anti-TNFα agent, is given subcutaneously as a 400-mg dose at 0, 2 and 4 weeks, then every 4 weeks.

The licence for golimumab is currently restricted to ulcerative colitis. Dosing is weight dependent: for patients over 80 kg, 200 mg is given at 0 weeks, 100 mg at 2 and 4 weeks, followed by 100 mg every 4 weeks; for patients less than 80 kg, the loading dose is the same, followed by a maintenance dose of 50 mg every 4 weeks.

Mechanism of action. The antibodies appear to act by binding not only to free TNFα but also to surface-bound TNFα on activated T cells, leading to their apoptosis. The net result is downregulation of the cytokine cascade (see Chapter 1).

Indications. Anti-TNFα drugs often induce remission in active and otherwise refractory Crohn's disease, and heal perianal and other fistulas in Crohn's disease (see Chapter 8). In general, 30% of patients with

previously refractory Crohn's disease achieve remission, 30% improve substantially, while the rest do not improve (primary non-responders). When patients lose their response to (secondary non-responders), or are intolerant of, one anti-TNFα drug (e.g. infliximab), they may be switched to another (e.g. adalimumab) (see Chapter 8). These agents are of moderate efficacy in refractory outpatient ulcerative colitis, and infliximab has been shown to halve the colectomy rate in inpatients with steroid-refractory acute severe colitis (see Chapter 7). Anti-TNFα agents are useful in minimizing steroid usage and in preventing growth retardation in children with active Crohn's disease.

The effects of anti-TNFα drugs in adults with severe complicated Crohn's disease are impressive: mucosal lesions sometimes heal completely. Co-prescription of azathioprine, MP or methotrexate appears to prolong the response to infliximab, probably by reducing the development of ATI and subsequent hypersensitivity reactions. Such concurrent immunosuppression may, however, increase the risks of opportunistic infection and lymphoma, and for this reason some gastroenterologists discontinue thiopurines or methotrexate after 6 months of treatment with anti-TNFα drugs. In the future, the selection of patients for treatment with anti-TNFα agents may depend not only on their disease phenotype (e.g. fistulating disease), but also on their genotype. For example, evidence suggests that patients with Crohn's disease who are positive for perinuclear antineutrophil cytoplasmic antibodies (pANCA) and have particular TNFα microsatellite haplotypes show a poor response to infliximab.

Side effects. Common side effects associated with the infusion of infliximab include headache, rash, nausea and fever (see Table 5.6). These are usually mild and respond to antihistamines. However, antihistamines, adrenaline and corticosteroids should be on hand when infusions are given in case of anaphylaxis. Infusions should therefore be carried out in hospitals with full resuscitation facilities available, although they are routinely performed on an outpatient basis.

Repeat infusions of infliximab after an interval of more than 20 weeks increase the risk of developing ATI. These may reduce the efficacy of infliximab and can cause a delayed serum-sickness-like reaction, characterized by myalgia, arthralgia, rash and fever. This reaction responds to prednisolone and analgesics but may contraindicate further

treatment. Intravenous hydrocortisone given prior to infliximab may reduce the formation of ATI. Adalimumab injections can be painful.

Several infections have been described in patients receiving anti-TNFα drugs, the most serious being tuberculosis (TB). Over 50% of cases of TB are disseminated and about 25% are extrapulmonary. To minimize the risk of reactivated disseminated TB, a careful history for previous TB should be elicited, along with a chest X-ray, before prescription of anti-TNFα drugs; in most countries an IGRA (interferon gamma release assay) to test for latent TB is also recommended.

Anti-TNFα drugs can also cause psoriasis-like skin eruptions and exacerbate congestive cardiac failure. Neurological complications include aseptic meningitis and irreversible demyelination.

There are isolated reports of lymphoma in those receiving anti-TNFα drugs for Crohn's disease or rheumatoid arthritis. Hepatosplenic T-cell lymphoma is an extremely rare but invariably lethal complication which appears mainly in young patients with Crohn's disease who are being concurrently treated with infliximab or adalimumab and a thiopurine.

The outcome of unintended pregnancies in women receiving anti-TNFα agents for rheumatoid arthritis and IBD has been reassuring, although infliximab and adalimumab should be discontinued at the start of the third trimester to prevent their passage through the placenta into the fetus. Antibodies to double-stranded DNA and to cardiolipin have been observed in up to 15% of patients who receive infliximab for Crohn's disease, and a transient lupus syndrome has been reported in those with rheumatoid arthritis.

Contraindications to the use of anti-TNFα agents are shown in Table 5.6. Most of these relate to the potential side effects of the treatment described above.

Monitoring. Patients on anti-TNFα drugs need careful assessment of their progress, and for the possible side effects listed above. In addition, in most countries, annual re-evaluation of patients' disease status enables withdrawal of the anti-TNFα treatment for those in deep clinical and endoscopic remission. In patients losing response to these drugs, many centers now offer tests that measure drug levels and antibodies to them, which can help to guide decisions about further treatment (see pages 125–6).

Vedolizumab (Entyvio) was licensed for use in IBD in Europe and the USA in 2014. It has shown good efficacy in ulcerative colitis but appears to be slightly less potent in Crohn's disease.

Mechanism of action. Unlike the anti-TNFα drugs, vedolizumab acts by blocking the α4β7 integrin on the surface of circulating lymphocytes. Normally, the α4β7 integrin binds to the mucosal vascular addressin cell adhesion molecule (MAdCAM-1), which is expressed on the endothelium of intestinal blood vessels, to facilitate egression of lymphocytes from the vasculature. By blocking this interaction, vedolizumab reduces migration of pro-inflammatory lymphocytes into the gut mucosa.

Dosage. Vedolizumab is given as 300-mg 30-minute intravenous infusions at 0, 2 and 6 weeks and then every 8 weeks thereafter. In patients losing response, administration can be increased to every 4 weeks.

Indications. Vedolizumab is primarily indicated for the induction and maintenance of remission in adults with moderately active to acute severe ulcerative colitis and Crohn's disease who have had a poor response, have lost response, or have shown intolerance to conventional therapy and/or an anti-TNFα drug. It has been shown to produce mucosal healing in ulcerative colitis. However, it may take a little longer to induce remission than infliximab in both types of IBD.

Side effects. Like infliximab, vedolizumab can occasionally induce acute infusion reactions and should therefore be given in healthcare settings where full resuscitation facilities are available; reactions should be treated as for infliximab reactions (see pages 76–7). The commonest side effects of vedolizumab are nasopharyngitis, headache and arthralgia. Pretreatment screening of patients currently resembles that for anti-TNFα therapy. However, clinical experience over the 5 years since it was first used in patients suggests that vedolizumab may be a safer option, probably because its mechanism of action is focused on the gut through its antagonism of the α4β7 integrin.

The inhibitory specificity of vedolizumab against the α4β7 integrin means that it is less likely than the non-gut-specific α4 integrin antagonist natalizumab to be linked with the rare but lethal JC virus-induced brain disease progressive multifocal leukoencephalopathy (PML). To date, no cases of PML have been reported in patients given vedolizumab. Natalizumab was effective in Crohn's disease, but it is no longer used for this indication because of the risk of PML, which is probably due to its lack of tissue specificity, inhibiting

TABLE 5.7

Vedolizumab in inflammatory bowel disease

Indications	
Induction and maintenance of remission in adults with moderately to severely active and refractory ulcerative colitis and Crohn's disease	
Preparation	
Intravenous	300 mg at 0, 2, 6 and (usually) every 8 weeks
Side effects	
Infusion reactions	Headache, rash, nausea, fever
Other	Nasopharyngitis, arthralgia
Infections	Rare to date
Preparatory screening and monitoring of infusions	
As for anti-TNFα drugs (see Table 5.6)	
Mechanism of action	Blocks α4β7 integrin on circulating lymphocytes and prevents their migration into gut lamina propria

egress of effector lymphocytes not only to the gut but also to the brain, thereby enabling unchecked intracerebral replication of the JC virus.

Contraindications and monitoring resemble those described in Table 5.6 and on page 77 for anti-TNFα drugs. However, a test to measure drug levels or antibodies in patients who lose response to vedolizumab is not yet available.

Biosimilars

Biosimilars, sometimes known as 'follow-on' or 'subsequent entry' biologics, are biological drugs that are similar to an existing authorized biological agent (such as infliximab). Like the authorized agents, biosimilars are derived from living organisms such as bacteria or yeasts; they can be introduced only after the expiry of the patent on the 'parent' drug. Because of the complexity of their manufacture, biosimilars are not structurally identical to the product that they imitate (although they are similar): neither their efficacy nor their safety is necessarily the same as that of the parent molecule.

Biosimilars to infliximab (e.g. Remsima, Inflectra) are now being introduced in many parts of the world, and this usage, because of its cost

advantage, is likely to be extended. It will be important, however, that in IBD, as in other diseases, biosimilars are assessed formally to confirm that they are as safe and effective as their innovator parents. A further consequence of the emergence of biosimilars is that all biological drugs will need to be identified by their proprietary (brand) names rather than their generic names (e.g. Remicade rather than infliximab).

New therapeutic approaches

The trend toward an increasing repertoire of immunomodulatory agents is set to continue. Progressive elucidation of the pathogenesis of IBD (Chapter 1) has led to the evaluation, in experimental animal models of IBD and to a lesser extent in humans, of a number of further therapeutic approaches aimed at specific pathophysiological targets (Figure 5.4, Table 5.8). Heterogeneity of therapeutic response is likely to match the underlying

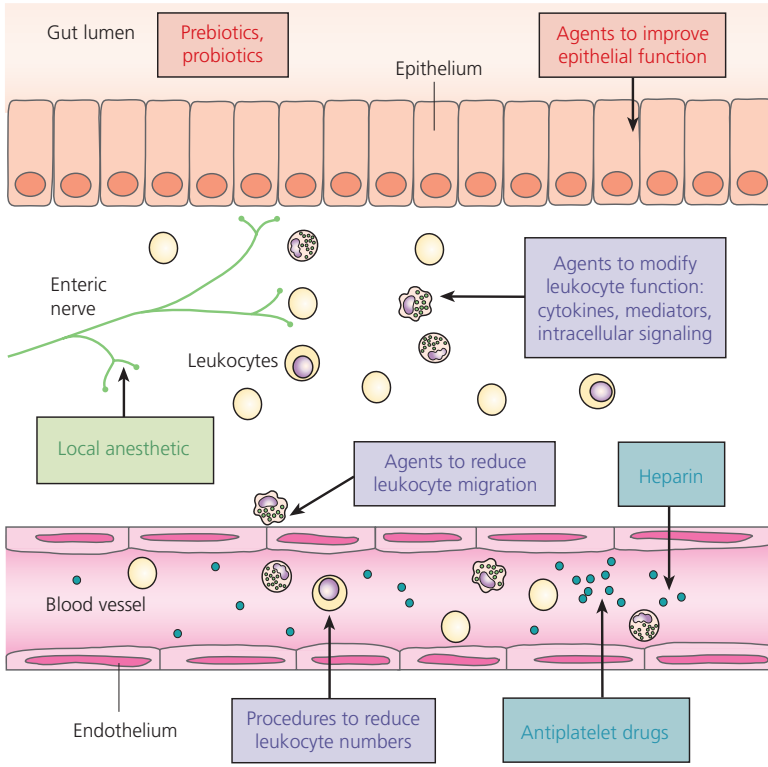

Figure 5.4 Specific pathophysiological targets of new therapeutic approaches.

TABLE 5.8
Proposed treatments for IBD for specific pathophysiological targets

Target	Agent
Colonic flora	Probiotics (bifidobacteria, *Lactobacillus* spp., non-pathogenic *Escherichia coli* including *E. coli* Nissle)* Porcine whipworm (*Trichuris suis*) or other worm eggs Fecal transplantation (from healthy person, given by nasojejunal tube or colonoscopically)
Mucus layer and epithelium	Phosphatidylcholine Epidermal growth factor enemas Trefoil peptides Growth hormone
Leukocytes	
Reduce or increase numbers	Leukocytapheresis (Adacolumn, Cellsorba)* Stem-cell transplant* Granulocyte colony-stimulating factor
Reduce migration	Adhesion-molecule antibodies (etrolizumab) ICAM-1 (Alicaforsen,* an antisense oligonucleotide)
Modify intracellular signaling	PPAR-γ agonist MAP kinase inhibitor JAK3 inhibitor (tofacitinib)* SMAD7 (mongersen,* an antisense oligonucleotide)
Cytokines	
Reduce proinflammatory cytokines	NF-κB antisense oligonucleotide
Antagonize inflammatory cytokines	Anti-IL-12/23 (ustekinumab)* Anti-IL-6, anti-IL-6 receptor (tocilizumab) IL-1 receptor antagonist
Increase anti-inflammatory cytokines	IL-10, interferon-α or -β, IL-11, TGF-β, IL-4 gene therapy
Unknown targets	Nicotine (UC)**, stopping smoking (CD)** Appendicectomy

*Current or imminent option. **The role of nicotine-producing electronic cigarettes is not yet known. CD, Crohn's disease; ICAM-1, intercellular adhesion molecule; IL, interleukin; JAK, Janus kinase; MAP, mitogen-activated protein; NF-κB, nuclear [transcription] factor κB; PPAR-γ, peroxisome proliferator-activated receptor-γ; TGF, transforming growth factor; UC, ulcerative colitis.

heterogeneity of the host genome and microbiome, and is likely to result in a new era of personalized or tailored therapeutics.

Over the next few years, several options are likely to reach the bedside, particularly for patients with disease refractory to current treatments. The most likely candidates are ustekinumab (as mentioned above), tofacitinib and mongersen (each an oral intracellular messenger inhibitor), and stem cell transplantation. The last of these is a major and invasive treatment with a substantial risk of serious side effects, and will inevitably be restricted to treatment of patients with severe and otherwise untreatable complex Crohn's disease in highly specialist centers.

Bispecific antibodies. The complexity and multifactorial nature of IBD creates heterogeneity of clinical responses. In addition, several factors conspire to limit the long-term efficacy of a single therapeutic agent and create a risk of inflammatory escape with disease relapse. Such factors include the redundancy or synergistic action of inflammatory mediators, the up-regulation of various receptors in inflamed tissue, and cross-talk among different signaling cascades. This has prompted the clinical development of bispecific antibodies, which combine the specificities of two antibodies for simultaneous activity at two therapeutic targets.

Modifying the biome. The emphasis on suppressing or modifying the host response may shift toward modifying the microbiome. Although this will prompt greater use of fecal microbial transplantation, considerations of safety and disease heterogeneity are likely to mandate an understanding of the minimal microbiota required for transplantation, which may vary according to the disease subset.

Complementary and alternative therapy

The terms 'complementary' and 'alternative' medicine denote theories and practices in medicine that deviate from conventional ones. The former applies to adjunctive therapies, while the latter applies to treatments that are used instead of standard management.

The combined term comprises a heterogeneous range of diagnostic and therapeutic procedures, ranging from traditional practices such as acupuncture, traditional Chinese medicine, homeopathy and herbal

medicine, to more modern complementary practices such as aromatherapy and reflexology. Indeed, we suggest that the term 'comprehensive' therapy might be more appropriate than 'alternative' or 'complementary' therapy.

Current usage. Recent surveys have shown that up to 50% of people in the Western world use complementary therapies, most commonly herbal remedies. The widespread use of such therapies in IBD is likely to be related to the chronic and refractory nature of the disease, and has been linked with poor quality of life in terms of psychosocial functioning.

Effectiveness. The quality of clinical trials in this area is generally poor, but limited data suggest that aloe vera, *Boswellia serrata*, wheat grass juice, curcumin (the yellow pigment of the widely used spice, turmeric), *Andrographis paniculate* extract, *Plantago ovata* and some traditional Chinese medicines may be effective in ulcerative colitis; wormwood and *Tripterygium wilfordii* are reported to induce remission in Crohn's disease. In addition, acupuncture appears to benefit some individuals with IBD.

Side effects. While it is unlikely that therapies such as reflexology will have direct adverse effects, the same cannot be said of herbal therapies: adverse effects have included fatal liver toxicity as well as irreversible renal failure. The interaction of herbal therapies with conventional drugs needs further clarification. In the context of IBD, however, St John's wort reduces blood levels of ciclosporin by enhancing the activity of cytochrome P450 enzymes, while gingko and ginger reduce absorption of oral iron.

Perhaps more importantly, complementary and alternative therapies may be associated with indirect adverse effects. For example, patients who initially consult an alternative practitioner may suffer from misdiagnosis, while others may delay or forego appropriate conventional options in favor of ineffective unconventional ones.

There is an urgent need for further scientific assessment of the benefits and dangers of complementary therapies. Herbal preparations, in particular, should require licensing by an independent national body in order to improve their quality and safety, while claims of effect should be validated by controlled trials. The general public, pharmacists and doctors need to be aware of the direct and indirect risks associated with the use of complementary therapies.

Key points – drugs used to treat inflammatory bowel disease

- Treatment for IBD has improved substantially, owing to new formulations and better use of conventional drugs, including corticosteroids, aminosalicylates, antibiotics and immunomodulatory agents.
- Anti-TNFα agents are an important advance for patients with refractory or fistulous Crohn's disease and refractory acute severe ulcerative colitis. The possibility of serious side effects, including infection and malignancy, needs to be borne in mind for all patients on these treatments.
- Vedolizumab has recently been introduced as a further biological treatment for refractory IBD. It acts by reducing the recruitment of pro-inflammatory lymphocytes to the gut mucosa.
- Treatment of IBD is likely to improve further with the advent of new biological therapies arising from improved understanding of the pathogenesis of the disease.
- Complementary and alternative therapies are widely used by patients with IBD, but there are insufficient data on their effectiveness and safety.

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6 Principles of management

The management of patients with ulcerative colitis and Crohn's disease comprises general measures, supportive treatment and specific pharmacological and surgical therapies (Table 6.1). The aims of the anti-inflammatory and immunomodulatory treatments used are to induce and then maintain full clinical and endoscopic remission (Table 6.2).

General considerations

IBD care must be patient centered. It should be high quality, safe, given as close as possible to where patients live and responsive to their needs. As with all types of chronic disease, the patient with IBD must be looked upon as a person rather than a case; the importance of a holistic approach to the patient and their family and carers is clear. Indeed, an integrated service, in which the patient is assessed and supported psychosocially as well as medically from diagnosis, is increasingly advocated.

Explanation. Patients with newly diagnosed IBD need a full explanation from their doctor and/or specialist IBD nurse about their disease and its implications in order to share control of therapeutic decisions with their multidisciplinary IBD team. They also need advice as to how best to help themselves (Table 6.3).

The process of learning about IBD can be facilitated by written information and other services provided by patient support groups (see Useful resources, page 148). The services offered by such groups include:

- educational literature, websites and helplines
- lecture and discussion meetings at which patients and their families can share their problems
- general advice for individuals with particular difficulties relating to their illness
- direction to appropriate social agencies to help with employment problems, and to insurance companies for life, travel and motor insurance
- political pressure to maximize accessibility of healthcare services to patients with IBD
- raising funds for research.

TABLE 6.1

Principles of management of inflammatory bowel disease

General measures

Explanation

- physicians, specialist nurses, pharmacist
- patient support groups

Specialist multidisciplinary hospital care

- monitoring disease activity, nutrition, therapy
- checking for extraintestinal complications
- colonoscopic cancer surveillance
- vaccination as necessary

Self-help (see Table 6.3)

Supportive treatment

Dietary and nutritional advice

Psychological support

Drugs

- antidiarrheal agents (not in active colitis)
- colestyramine or colesevalam for bile salt diarrhea (ileal Crohn's disease or resection)
- hematinics (iron, folate, vitamin B_{12})
- vitamins, electrolytes
- osteoporosis prophylaxis and treatment
- heparin, administered subcutaneously (inpatients with active IBD)

Drugs to avoid

- antidiarrheal drugs (in active colitis)
- non-essential NSAIDs, antibiotics, delayed-release drugs

Specific treatment (according to presentation)

Drugs

- corticosteroids
- aminosalicylates
- immunomodulatory drugs (azathioprine/MP, ciclosporin [cyclosporine], methotrexate)
- antibiotics
- anti-TNFα therapy

Nutritional therapy (Crohn's disease only)

- liquid formula diet

Surgery

MP, mercaptopurine; NSAID, non-steroidal anti-inflammatory drug; TNF, tumor necrosis factor.

TABLE 6.2

Goals of remission maintenance in IBD

- Keep patient asymptomatic and maintain quality of life
- Keep patient steroid free
- Prevent relapse and surgery
- Prevent disease progression and complications
  - intestinal: stricture/penetrating disease (Crohn's), colorectal cancer
  - extraintestinal: growth failure, anemia, osteoporosis
- Maintain mucosal healing
  - improve disease natural history: reduce relapse rate, hospitalizations, operations

Hospital care. Patients with IBD are best managed, whether as outpatients or during admission to hospital, by multidisciplinary teams comprising specialist gastroenterological, surgical, nursing, dietetic and pharmacy staff, with ready access to stoma therapists and a trained counselor. Specialist outpatient IBD clinics are the best way of providing patients with the necessary clinical expertise for optimal care. They should offer:

- continuity of care
- appropriate clinical, endoscopic and laboratory monitoring of the disease and its treatment
- rapid access for patients in relapse
- psychological assessment and support
- a computerized patient database providing opportunities for clinical audit and research
- training for doctors and nurses.

Partly because of financial restraints, some IBD teams have developed telephone-, email-, web- or app-based follow-up for patients in stable remission. Such systems maintain links between patients and specialist IBD services, reduce routine outpatient attendances, accelerate patients' access to clinics in the event of relapse and empower patients to play a greater part in their care.

Most primary care providers have very few patients with IBD under their care; this limited experience of the disease means that they should

TABLE 6.3

Advice to help optimize self-management

Learn about IBD from:

- patient support groups
- books for patients about IBD
- websites and newspapers (use internet resources listed on page 148 and beware unreliable information sources)
- IBD specialist nurse or hospital doctor

Look after yourself at home:

- stop smoking (especially if you have Crohn's disease)
- eat a balanced diet; follow special dietary advice when recommended
- stick rigorously to prescribed treatments; don't stop maintenance treatment because you feel well
- self-medicate for minor relapses using guidelines issued by hospital IBD team (especially ulcerative colitis)
- stop drug immediately and inform the hospital doctor or IBD nurse if a side effect is suspected
- avoid drugs which may worsen IBD (e.g. NSAIDs, antibiotics) (unless essential)
- discuss complementary or alternative therapy with hospital IBD team if considering it, and don't stop conventional treatment
- join a patient support group and attend local meetings

Make the most of hospital care:

- insist on care by a specialist IBD team
- ensure the hospital has an IBD nurse and don't hesitate to contact him/her when necessary (telephone or email)
- don't hesitate to ask IBD team if uncertain about any aspect of illness, tests or treatment
- tell your IBD team if you feel low, depressed, stressed or anxious
- fix *urgent* outpatient appointment if IBD is causing problems
- attend scheduled outpatient appointments
- have blood and other investigations done when/as necessary
- press for adequate local IBD service (e.g. through patient panel)

NSAID, non-steroidal anti-inflammatory drug.

not generally be expected to take primary responsibility for its long-term management. However, some patients with stable, inactive and limited IBD can be followed safely by their family doctor. This arrangement is

dependent on appropriate shared-care guidelines and prompt open access to the hospital IBD clinic when necessary.

Dietary advice and nutritional support. Patients with ulcerative colitis do not usually need specific dietary advice, although a few (< 5%) may find their condition improves if they avoid cows' milk, and some with proctitis and proximal constipation may benefit from fiber supplementation. Dietary and nutritional management has a much more important role for patients with Crohn's disease (see Chapter 8).

Specific nutritional deficiencies are less common in ulcerative colitis than in Crohn's disease but should be corrected as necessary with appropriate supplements. Sick inpatients who are malnourished often need enteral and occasionally total parenteral nutrition. However, while enteral feeding is effective primary therapy in active small-bowel Crohn's disease (see Chapter 8), it has no such role in ulcerative colitis.

Drugs. Iron and folic acid supplements are often needed, as are appropriate drugs for incipient or established osteoporosis (see Chapter 3). Subcutaneous heparin is recommended for patients admitted with active IBD to reduce the risk of arterial and venous thrombosis.

Drugs to avoid. Antidiarrheal (loperamide, codeine phosphate, diphenoxylate), opioid analgesic, antispasmodic and anticholinergic drugs should be avoided in active colitis as they may provoke acute colonic dilation. Non-steroidal anti-inflammatory drugs (NSAIDs) may provoke relapse of IBD and should not be used unless essential.

Preparation for possible immunomodulatory or biological therapy. As soon as it is suspected that a patient may need immunomodulatory or biological therapy, their serology for previous infections should be checked (see Table 4.5, page 48). Patients who are serologically negative for hepatitis B or varicella zoster (chicken pox), or at risk of human papilloma virus (HPV) infection, should be vaccinated promptly to minimize the risk of serious infection when they are subsequently immunosuppressed.

All patients with IBD should have annual influenza and anti-pneumococcal vaccination.

Key points – principles of management

- Management of patients with IBD should focus not only on pharmacological and surgical treatment, but also on explanation and education about their illness and its treatment, and psychological and nutritional support.
- IBD services should be multidisciplinary and offer holistic care, with readily available routes by which the patient can contact specialist nurses, dietitians, counselors and pharmacists, as well as doctors.
- Patients with IBD can take steps themselves to improve their quality of life: these include learning about their illness, utilizing fully and appropriately the multidisciplinary facilities available to them, adhering to agreed treatments and stopping smoking.

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7 Medical management of ulcerative colitis

Treatment of active ulcerative colitis

Treatment is determined by:

- the extent of disease
- the severity of the attack.

Knowledge of the extent of disease is particularly important in relation to the feasibility of effective topical therapy, while the severity of the attack defines not only the optimal type and route of therapy, but also whether the patient can be safely treated as an outpatient or needs urgent hospital admission.

Who needs hospital admission? Immediate admission is required for those with acute severe attacks of ulcerative colitis, defined primarily by clinical features (see Chapter 2). These include six or more bloody diarrheal stools daily, pyrexia and tachycardia (more than 90 beats/minute). Such patients will usually be systemically unwell, may be anemic and may have lost weight; very ill patients may have abdominal tenderness and/or distension.

The decision to admit does not usually depend on the results of blood or other tests of disease severity, though these will often be abnormal (see 'Blood tests', pages 44–6).

It is also advisable to admit less sick patients who have not responded as outpatients to 2 weeks' treatment with oral prednisolone (see 'Active left-sided or extensive ulcerative colitis', pages 99–100). Since the initial attack of ulcerative colitis is more dangerous than subsequent ones, the threshold for admission should be lowered in those presenting for the first time with bloody diarrhea.

Inpatient management of acute severe ulcerative colitis

General measures. These patients should be admitted immediately to a gastroenterology ward for close joint medical, surgical and nursing care (Table 7.1). Early involvement of the nutrition team and of a stoma therapist in those who may need surgery is important. All patients

TABLE 7.1

Principles of inpatient management of acute severe ulcerative colitis

General measures
Explanation, psychosocial support
• physicians, specialist nurses
• patient support groups
Specialist multidisciplinary care
• physicians, surgeons, nutrition team, nurses, stoma therapist, counselor
Establishing the diagnosis, extent and severity
Clinical evaluation
Complete blood cell count, C-reactive protein, albumin, liver function tests, magnesium, cholesterol, amebic serology, CMV IgG
Stool microscopy, culture, *Clostridium difficile* toxin
Flexible sigmoidoscopy and biopsy
Plain abdominal X-ray
Monitoring progress
Daily clinical assessment
• abdominal examination (twice daily)
• stool chart
• 4-hourly temperature, pulse
Daily complete blood cell count, C-reactive protein, urea and electrolytes, albumin
Daily plain abdominal X-ray
Supportive treatment
Intravenous fluids, electrolytes, blood transfusion
Nutritional supplementation
Subcutaneous heparin
Avoid antidiarrheals (codeine, loperamide, diphenoxylate), opiates, NSAIDs

(CONTINUED)

TABLE 7.1 (CONTINUED)

Specific treatments

Medical

- intravenous (hydrocortisone or methylprednisolone) then oral corticosteroids (prednisolone)
- continue with oral 5-ASA in patients already taking it; otherwise start when improvement begins
- antibiotics for very sick febrile patients, or when infection is suspected
- for patients not responding to steroids at 4–7 days, consider:
  - intravenous then oral ciclosporin (cyclosporine) (with trimethoprim–sulfamethoxazole prophylaxis) *or*
  - infliximab

Surgical (for non-responders at 5–7 days, acute colonic dilatation, perforation, massive hemorrhage)

- panproctocolectomy with ileoanal pouch or permanent ileostomy
- subtotal colectomy with ileorectal anastomosis (rarely)

5-ASA, 5-aminosalicylate; CMV, cytomegalovirus; Ig, immunoglobulin; NSAIDs, non-steroidal anti-inflammatory drugs.

undergoing a severe attack of ulcerative colitis need to be kept fully informed of their treatment and its likely outcome; they need to be aware from the outset that they have a 1 in 4 chance of needing an urgent colectomy during their admission.

Establishing the diagnosis, extent of disease and its severity requires a carefully targeted history and appropriate investigations (see Chapter 4) in those presenting for the first time. In patients with established ulcerative colitis, these procedures are required to exclude infection and to assess disease extent (if not already known) and severity.

Clinical evaluation. In patients with established ulcerative colitis, direct questions about stool frequency, consistency and urgency, overt blood content, abdominal pain, malaise, fever and weight loss indicate the severity of the attack. External examination should include assessment of

general health, pulse rate and temperature, as well as a check for anemia, fluid depletion, weight loss, and abdominal tenderness or distension.

The differential diagnosis may also need evaluation in those presenting with bloody diarrhea for the first time (see Table 4.1). Abrupt onset with fever, vomiting, epidemic or contact history and/or recent foreign travel suggests infective colitis, even in those with pre-existing ulcerative colitis. Cytomegalovirus (CMV) should be considered, particularly in patients known to be immunosuppressed. *Clostridium difficile* infection is a mimic as well as a common concomitant of attacks of ulcerative colitis, with or without previous antibiotic exposure, while non-steroidal anti-inflammatory drugs (NSAIDs) may cause either a relapse of established IBD or de novo colitis (which usually remits rapidly on NSAID withdrawal).

In patients presenting for the first time, non-smoking or recent cessation of smoking increases the likelihood of ulcerative colitis, while previous abdominal or pelvic irradiation make radiation colitis a strong possibility. Ischemic colitis usually shows sudden onset in older people with other features of vascular disease, and often causes marked abdominal pain as well as bloody diarrhea. The very rare Behçet's enterocolitis may be suggested by a history of cyclic oral and genital ulceration, uveitis, erythema nodosum, pathergy (the formation of pustules at the site of minor trauma, such as venepuncture) and/or arthropathy.

Blood tests are better for establishing the activity of ulcerative colitis than for making the diagnosis or identifying its extent (see Chapter 4). The best laboratory measures of disease activity in ulcerative colitis are hemoglobin, platelet count, C-reactive protein and serum albumin. For recent travellers, serology as well as stool samples should be requested (for amebiasis, strongyloidiasis and schistosomiasis). It is helpful to check CMV (immunoglobulin [Ig]G) serology on admission: if this is negative, CMV-induced colitis need not be considered if the patient fails to respond to steroid therapy. Serum magnesium and cholesterol should be checked in case ciclosporin (cyclosporine) is needed (see Chapter 5).

Sigmoidoscopy and rectal biopsy. Cautious rigid or flexible sigmoidoscopy and biopsy in the unprepared patient, and without excessive air insufflation, provides immediate confirmation of active colitis. Full colonoscopy may cause colonic perforation and dilation and should be avoided in acute severe ulcerative colitis.

Plain abdominal X-ray at presentation is used to assess disease extent and activity and to look for dilatation. In patients with suspected colonic perforation, diagnosis can be confirmed by erect chest X-ray or a lateral decubitus abdominal film.

Monitoring progress. Progress is monitored by twice-daily clinical assessment, including:

- abdominal examination, particularly by percussion, for gaseous distension, loss of hepatic dullness (which may indicate free gas in the peritoneal cavity) and peritoneal irritation
- stool chart (recording frequency, consistency, presence of overt blood and urgency)
- 4-hourly measurement of temperature and pulse.

Blood count, C-reactive protein, routine biochemistry and plain abdominal X-ray should be undertaken daily in sick patients (see Table 7.1).

Intravenous fluids and blood. Most patients require intravenous fluids and electrolytes, particularly potassium, to replace diarrheal losses. The serum potassium concentration should be maintained at or above 4 mmol/L (4 mEq/L), since hypokalemia may predispose to colonic dilatation. Blood transfusion is usually recommended if the hemoglobin level falls below 6.2 mmol/L (10 g/dL).

Nutritional support. Patients can usually eat normally, with liquid protein and calorie supplements if necessary. Very sick patients, many of whom will undergo surgery, may need enteral or parenteral nutrition.

Anticoagulation. Because active ulcerative colitis is associated with a high risk of venous and arterial thromboembolism, patients should be given prophylactic subcutaneous heparin (e.g. low-molecular-weight heparin, 3000–5000 units daily). Heparin does not appear to increase rectal blood loss, even when given intravenously.

Drugs to avoid are antidiarrheal (codeine phosphate, loperamide, diphenoxylate), opioid analgesic, antispasmodic and anticholinergic drugs, as well as NSAIDs. If mild pain relief is needed, oral paracetamol (acetaminophen) appears to be well tolerated, while severe pain suggests colonic dilatation or perforation needing urgent evaluation and/or intervention.

Drug therapy. A possible management pathway is shown in Figure 7.1. Corticosteroids remain the cornerstone of specific medical treatment for acute severe ulcerative colitis. Aminosalicylates and antibiotics have minor roles. Ciclosporin or infliximab are useful in steroid-refractory patients. However, oral azathioprine and mercaptopurine (MP) are too slow to work in those with severe steroid-refractory attacks.

Corticosteroids. Hydrocortisone, 300–400 mg/day, or methylprednisolone, 40–60 mg/day, are given intravenously. There is no advantage in giving higher doses, although continuous infusion may be more effective than once- or twice-daily boluses. Corticosteroid drip enemas (e.g. prednisolone, 20 mg, or hydrocortisone, 100 mg in 100–200 mL water given rectally via a soft catheter twice daily with the patient in the left lateral position) are sometimes given in addition to intravenous steroids, but their value is unproven.

Every patient's progress needs careful daily evaluation by an experienced clinician able to institute any necessary management changes promptly. About 70% of patients who receive corticosteroids improve substantially in 5–7 days.

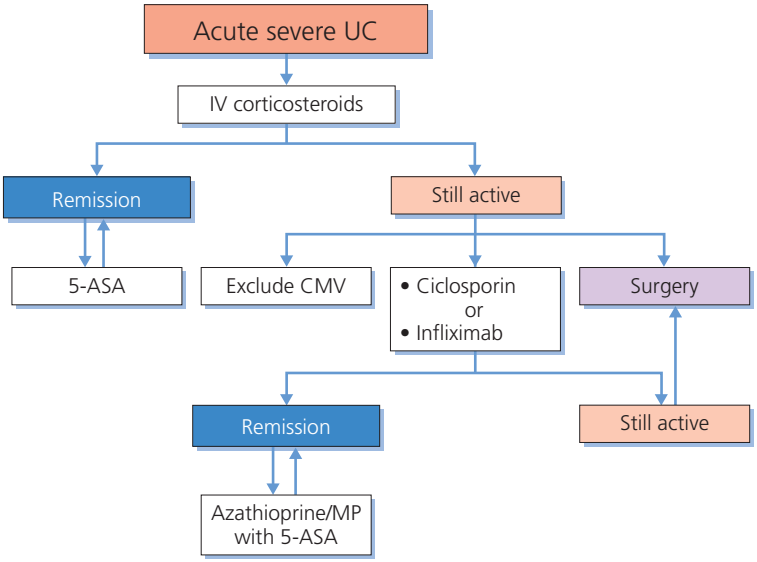

Figure 7.1 General principles of managing acute severe ulcerative colitis. In practice, each step will depend on detailed daily evaluation of the patient (see text) and discussion of the options under consideration. 5-ASA, 5-aminosalicylate; CMV, cytomegalovirus; IV, intravenous; MP, mercaptopurine; UC, ulcerative colitis.

They are then switched to oral prednisolone, 40–60 mg/day, the dose being tapered to zero over 2–3 months. However, those patients not showing a clear reduction in stool frequency and C-reactive protein after 3 days of intravenous corticosteroids need rescue therapy with ciclosporin or infliximab (see below) or urgent colectomy (see Chapter 9).

Aminosalicylates at full dose should be continued in those already taking them at the time of admission and who are well enough to take oral medication, but these drugs do not have a major therapeutic effect in acute severe ulcerative colitis. In case patients given aminosalicylates for the first time prove to be allergic to, or intolerant of, them, initiation of this therapy is best delayed until the patient has improved sufficiently while receiving intravenous steroids to switch to oral treatment (see Tables 5.2 and 5.3).

Antibiotics are usually restricted to very sick febrile patients or to those in whom an infective component is strongly suspected. A combination of antibiotics is often given (e.g. ciprofloxacin with metronidazole) to such patients.

Ciclosporin (cyclosporine). Intravenous ciclosporin, 2 mg/kg/day for 5 days, followed by oral ciclosporin (Neoral), 5 mg/kg/day in divided doses, given with tapering corticosteroids, averts colectomy in the acute phase in 60–80% of patients who do not respond to intravenous steroids given alone for 5–7 days. Oral trimethoprim–sulfamethoxazole may be coprescribed as prophylaxis against *Pneumocystis carinii* infection. Enthusiasm for this treatment has to be tempered both by the frequency of relapse necessitating colectomy (up to 50%) that follows withdrawal of ciclosporin and by its serious adverse effects (see Table 5.5), which, in turn, demand frequent monitoring of ciclosporin blood levels and serum biochemistry.

Infliximab. Controlled data indicate that after a single infusion of infliximab, 5 mg/kg, the need for colectomy can be reduced from 70% to 30% in patients who have not improved with intravenous steroids alone. This response rate closely resembles that with ciclosporin (see above). It may be possible to improve responses in acute severe colitis by using higher or more frequent doses of infliximab than are conventionally used, perhaps because a proportion of the drug is lost through inflamed colonic mucosa. Although it remains difficult to decide whether to recommend ciclosporin or infliximab for patients with steroid-refractory acute severe ulcerative colitis who are reluctant to have, or are unfit for, prompt surgery, the risk–benefit ratio may lie in favor of infliximab.

Vedolizumab. To date, no studies have evaluated the effects of vedolizumab as rescue therapy in inpatients with acute severe ulcerative colitis, and its use in this setting cannot be recommended at present.

Acute colonic dilatation. If colonic dilatation develops and does not respond within 24 hours to the intensive treatment outlined in Table 7.1 (including intravenous antibiotics and a nasogastric tube to aspirate bowel gas and fluids), immediate surgery (Chapter 9) is indicated.

Colonic perforation and massive hemorrhage are rare complications that require emergency surgery after appropriate urgent resuscitation, including intravenous antibiotics and blood transfusion, respectively (see Chapter 9). Even with immediate surgical intervention, the mortality of colonic perforation, which can occasionally also occur in patients without colonic dilatation, is up to 30%.

Outcome. About 80% of patients with severe ulcerative colitis avoid colectomy in the acute phase when treated with intravenous corticosteroids (and ciclosporin or infliximab additionally if necessary). Of these, however, over 50% will have had a colectomy for recurrent episodes of active disease before 5 years have elapsed. Mortality of acute severe ulcerative colitis should now be under 1%.

Active left-sided or extensive ulcerative colitis (mild-to-moderate attack)

The principles of evaluation and management of mild-to-moderate attacks of ulcerative colitis (when the patient is systemically well, with fewer than six stools daily) resemble those described above for inpatients (see Table 7.1); management is outlined in Figure 7.2. These patients, however, can usually be managed as outpatients. Stools should be sent to be checked for infection. In mild attacks of left-sided disease, an oral aminosalicylate (5-ASA) in a dose up to 4.8 g daily (see Table 5.2), with daily 5-ASA or steroid enemas, may suffice. Often, however, oral prednisolone, 20–60 mg/day (the dose depending on the severity of the attack), is also needed for 2–3 weeks. The dose is then tapered by 5 mg every 5–10 days. Oral iron and/or folate may also be necessary.

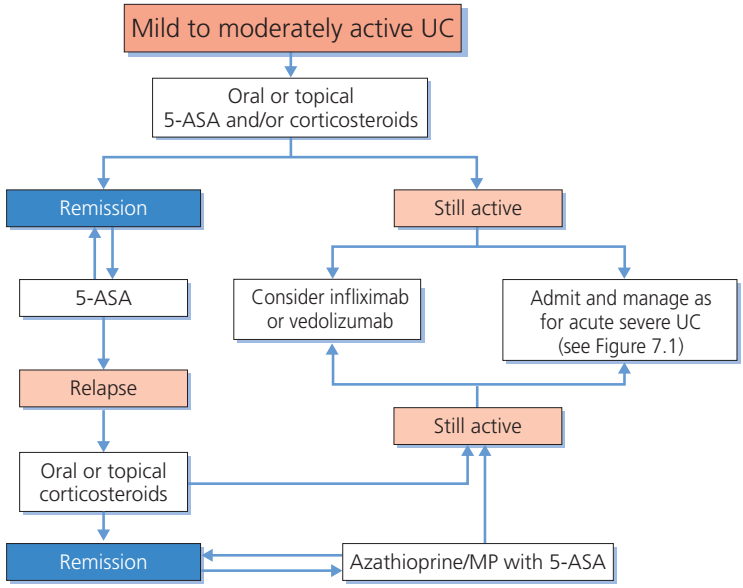

Figure 7.2 General principles of managing mild to moderately active ulcerative colitis. The route of administration of 5-ASA drugs and corticosteroids will depend on the extent of the colitis (see Table 7.1). In practice, each step will depend on detailed evaluation of the patient (see Table 7.1) and discussion of the options under consideration. 5-ASA, 5-aminosalicylate; MP, mercaptopurine; UC, ulcerative colitis.

Patients who do not begin to respond to these measures within 2 weeks (10–40%) or those who deteriorate need prompt hospital admission for more intensive management, including intravenous steroids (see above and Table 7.1). An alternative approach in steroid-refractory patients who are not so acutely ill as to require hospital admission, and in whom a response to treatment taking up to 4 months is acceptable, is to introduce oral azathioprine, 2.0–2.5 mg/kg/day, or MP, 1.0–1.5 mg/kg/day, with appropriate laboratory monitoring (see Table 5.4). Patients who do not respond to, or who are intolerant of, thiopurines and who are unwilling to have a colectomy can be offered methotrexate (see page 69) or tacrolimus (see page 72), but a better alternative is one of the anti-TNFα agents (see Table 5.6). Vedolizumab (see page 78) is a useful option in patients with no previous exposure to anti-TNFα drugs or in those who are unresponsive to or intolerant of them.

Active proctitis

The principles of management of proctitis resemble those described for more extensive ulcerative colitis. Management aspects specific to distal disease are outlined here and in Table 7.2.

Establishing the diagnosis. The diagnosis of proctitis, together with its extent and severity, can usually be quickly confirmed by rigid or flexible sigmoidoscopy and biopsy. However, care needs to be taken not to mistake rectal Crohn's disease, cancer, polyps, benign solitary ulcer, hemorrhoids, anal fissure or sexually transmitted diseases for proctitis (see Table 4.2). In patients who prove difficult to treat, and depending on the clinical picture, other diagnoses such as irritable bowel syndrome (which may coexist with proctitis), celiac disease, collagenous colitis, NSAID-induced colitis and 5-ASA intolerance should also be considered.

TABLE 7.2

Principles of the treatment of active proctitis

Supportive treatment
Treat proximal constipation with fiber and/or a laxative (e.g. macrogol)
Avoid cows' milk or other specific food (rarely)
Specific treatment
Topical 5-ASA or, as second line, steroids (suppository, liquid or foam enema)
Oral 5-ASA
Refractory proctitis
Oral or intravenous steroids
Oral azathioprine or MP
Oral ciclosporin or tacrolimus
Anti-TNFα agent
Acetarsol suppositories
Surgery: total proctocolectomy

5-ASA, 5-aminosalicylate; MP, mercaptopurine.

Supportive treatment. Rarely, patients benefit from avoiding cows' milk or other food components that they have noticed provoke attacks. In those with proximal constipation, oral fiber supplements or a stool-softening laxative such as macrogol may be helpful. It is conceivable that alleviation of constipation may improve the symptoms of proctitis, at least in part, by increasing the delivery of orally administered 5-ASA to the rectum.

Specific medical treatment. Depending on disease extent, suppositories or enemas of 5-ASA (see Table 5.3) or corticosteroids (see Table 5.1) are inserted once or twice daily until about 2 weeks after bleeding subsides. Suppositories reach about 10 cm from the anal margin, foam enemas 20 cm and liquid enemas, with optimal patient positioning, the splenic flexure. Topical treatment with 5-ASA preparations is more effective than with corticosteroids. Although prednisolone metasulfobenzoate and budesonide enemas suppress adrenal function to a lesser extent than other topical steroids, the choice of product for routine use depends on patient preference in relation to ease of insertion and retention, foam often being favored on both counts.

In patients with recurrent attacks, an oral aminosalicylate (see Table 5.2) should be added, in part to initiate subsequent remission maintenance in those who prefer long-term oral to rectal treatment. Balsalazide, olsalazine and Mezavant XL/Lialda, which deliver 5-ASA exclusively to the colon, may be preferable to slow-release or pH-dependent delayed-release aminosalicylates, which release 5-ASA more proximally (see Figure 5.2).

Refractory proctitis

Up to 80% of patients respond in 2–4 weeks to the measures described for treating active proctitis. In those who do not respond, the diagnosis needs careful confirmation. Alternative approaches in refractory proctitis, which can sometimes be very difficult to treat, include full-dose oral or even intravenous corticosteroids, oral azathioprine, 2.0–2.5 mg/kg/day, or MP, 1.0–1.5 mg/kg/day, oral ciclosporin or tacrolimus or even anti-TNFα therapy (see Table 5.6). Suppositories containing arsenic may induce remission in distal disease but, because of the risk of systemic arsenic toxicity, should only be used for short-term management (up to 4 weeks).

Many patients will feel angry about their disease and their doctor's failure to rectify their symptoms; some may need counseling. In exceptional cases, all medical treatments fail, and patients require panproctocolectomy (see Chapter 9). Left-sided colonic resections in ulcerative colitis are too frequently followed by recurrence in the residual colon to be a practical option.

Maintaining remission

5-Aminosalicylates. Patients with disease of limited extent, relapsing less than once a year may decline maintenance therapy. However, most require an oral 5-ASA for life (see Table 5.2) with appropriate blood checks every 6–12 months (see Table 5.3). Such therapy reduces the annual relapse rate to 20–30% from 70–80% with no treatment. To minimize possible systemic side effects, some patients with recurrent attacks of distal disease may prefer topical prophylactic 5-ASA therapy, with enemas or suppositories between once daily and three times weekly.

Azathioprine and mercaptopurine. In those who relapse repeatedly despite a 5-ASA in adequate dosage, and/or whenever steroid therapy after acute episodes is withdrawn, oral azathioprine, 2.0–2.5 mg/kg/day, or MP, 1.0–1.5 mg/kg/day, carefully monitored (see Table 5.4) and given for at least 2 years, is of proven benefit. It is unclear how long thiopurines should be continued for in patients with ulcerative colitis but it is reasonable to attempt to withdraw them after 4–5 years without relapse.

Biological therapy. Recent trials suggest that anti-TNFα agents may be useful in maintaining remission in some patients with ulcerative colitis that is poorly controlled by steroids and/or thiopurines. The same is true of the recently licensed vedolizumab. Whether the benefit obtained with these drugs in this context outweighs their side effects and justifies their cost is not yet clear.

Surgery. Occasionally, patients continue to have active ulcerative colitis despite all the measures described above. These, particularly if steroid-dependent, require proctocolectomy (Chapter 9).

Follow-up

Patients with well-controlled ulcerative colitis can be followed routinely by the primary care provider, subject to blood counts, urea and electrolytes and liver function tests every 6–9 months to monitor the disease and its treatment, and with referral for colonoscopy at 8–10 years to reassess disease extent in relation to the possible need for cancer surveillance (see below). Patients should be referred promptly to a gastroenterologist if they do not respond to treatment for relapse.

All other patients require periodic review (every 6–12 months if in remission) in a specialized hospital clinic offering immediate open access in the event of relapse. Such arrangements ensure continuity of care and optimal monitoring of the disease, its complications and its treatment. At routine outpatient appointments, disease activity should be assessed with questions about bowel habit; quality of life, mood and time off work should also be discussed. Blood tests, and in some centers fecal calprotectin, should be arranged, with sigmoidoscopy reserved for those in whom the history suggests active disease.

Surveillance for colorectal cancer. The increased risk of colorectal cancer in chronic extensive ulcerative colitis (see Chapter 2) has led to the introduction of colonoscopic surveillance programs. Until recently, at least 30 biopsies from randomly selected sites throughout the colon, and from any raised lesions, were recommended every 1–3 years, depending on the duration of the disease, and starting 8–10 years after onset.

It is now considered, however, that careful inspection is more important than the total number of blind biopsies taken. The earlier recommendation is time-consuming and tedious not only for the patient and colonoscopist, but particularly for the pathologist examining the multiple biopsies. New colonoscopic techniques include high-definition and magnifying colonoscopy, and narrow-band imaging, autofluorescence or, most commonly, chromo-endoscopy using dye-spray (Figure 7.3). All these methods provide improved identification and definition of tiny mucosal abnormalities, so that biopsies can be targeted directly at lesions previously easily missed: such techniques give a much higher ‘hit rate’ for dysplasia, obviate the need for multiple random biopsies and thereby substantially reduce the pathologist’s workload.

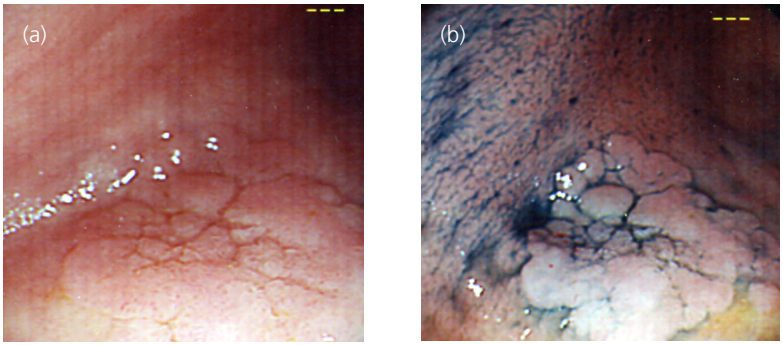

Figure 7.3 Colonoscopic views of mucosal dysplastic lesion seen: (a) before; and (b) after spraying the mucosa with indigo carmine. Reproduced courtesy of Dr M Rutter, University Hospital of North Tees, Stockton-on-Tees, UK.

Lastly, a few centers are assessing confocal endomicroscopy, in which microscopic images of suspicious areas of gut mucosa are obtained during the colonoscopy, thereby potentially diagnosing dysplasia or cancer during the test itself.

If biopsies show the premalignant changes of high-grade epithelial dysplasia (Figure 7.4), colectomy is indicated (Chapter 9). In those with confirmed low-grade dysplasia, colectomy or, for those reluctant to have surgery, more frequent colonoscopic surveillance is recommended, because the incidence of cancer in this situation is about 50% in 5 years. Unfortunately, surveillance programs have not been shown to reduce mortality from colonic cancer in ulcerative colitis, in part because about 25% of cancers occur in patients without detected, preceding or associated dysplasia.

Molecular biological techniques (e.g. looking for DNA aneuploidy, p53 heterozygosity) are likely, in due course, to supersede dependence on the colonoscopic detection of dysplasia for the prevention of colorectal cancer in ulcerative colitis.

Colitis of uncertain type or etiology

Colitis of uncertain type or etiology (CUTE), in which the clinical, endoscopic and histological features of the disease do not allow its definite classification as either ulcerative colitis or Crohn's colitis (see Chapter 2),

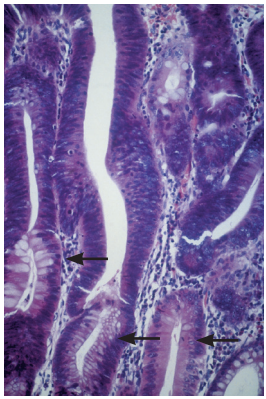

Figure 7.4 Severe epithelial dysplasia in ulcerative colitis, showing glandular distortion, stratification of the epithelium with heaping of nuclei, and nuclear polymorphism and hyperchromaticism. Note the normal crypts at the bottom of the picture (arrowed). Photomicrograph courtesy of Professor RM Feakins, Barts and The London School of Medicine and Dentistry, London, UK.

is managed like acute severe ulcerative colitis. However, in patients needing surgery, it is usually advisable to avoid the immediate formation of an ileoanal pouch, in view of the high risk of pouch failure if the diagnosis proves to be Crohn's disease (see Chapter 9).

Key points – medical management of ulcerative colitis

- The treatment of ulcerative colitis depends on disease extent and severity.
- Active ulcerative colitis is treated primarily with corticosteroids and aminosalicylates, with ciclosporin (cyclosporine) for acute severe disease only, and with infliximab, vedolizumab or surgery for refractory disease.
- Maintenance of remission in ulcerative colitis is usually achieved with aminosalicylates, although thiopurines and sometimes anti-TNFα agents or vedolizumab are required.
- Colonoscopic surveillance, usually involving chromo-endoscopy with targeted biopsy, is an essential part of remission management.
- Patients with ulcerative colitis should participate in decisions about their treatment, particularly in relation to possible surgery.

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8 Medical management of Crohn's disease

Treatment of Crohn's disease not only depends on disease activity and site, as in ulcerative colitis, but also needs to be tailored according to the individual's clinical presentation and its dominant underlying pathological explanation. Inflammation, obstruction, abscess and fistula require different therapeutic approaches, and they often need to be distinguished by appropriate investigation before specific treatment is begun. Drug therapy in Crohn's disease is generally less effective than in ulcerative colitis, and dietary and surgical treatment correspondingly more important.

General measures

Explanation, psychosocial support and hospital care. Newly diagnosed patients with Crohn's disease need a full explanation of their illness, preferably assisted by the written information provided by patient support groups (see Table 6.1 and Useful resources). A substantial minority of patients are sufficiently disturbed psychologically by the chronically disabling nature of their illness to need more formal psychosocial help. Out- and inpatient care is best undertaken by a specialist multidisciplinary hospital team.

Dietary advice and nutritional support. All patients should be carefully assessed in relation to their nutritional intake and status, the latter by measurement of weight and height and calculation of body mass index (BMI = weight [kg]/height [m]^2; normal BMI 19–25).

Patients with stricturing small-bowel Crohn's disease should avoid high-residue foods (e.g. citrus fruit, nuts, sweetcorn, uncooked vegetables) that might cause bolus obstruction. Special dietary and nutritional modifications are needed for those with extensive small-bowel Crohn's disease, or short-bowel syndrome (see Chapter 2). Sick inpatients may need enteral or parenteral nutrition to restore nutritional deficits, while liquid formula diets provide a primary therapy option for some with active small-bowel Crohn's disease.

Non-specific drugs. Diarrhea in Crohn's disease has a number of different causes, each requiring a different therapeutic approach (see Table 2.1).

Codeine phosphate and loperamide are often useful for the symptomatic control of diarrhea that is due to active disease or previous bowel resection. As in active ulcerative colitis, however, they should be avoided in active Crohn's colitis in case they provoke colonic dilation.

Colestyramine (cholestyramine) sachets, 4 g one to three times daily, or colesevalam tablets, which are more palatable, often help patients with Crohn's disease complicated by bile-salt-induced diarrhea as a result of extensive terminal ileal disease or resection (see 'Bile-salt malabsorption', pages 31 and 136). By binding bile salts, these agents may, however, exacerbate or induce steatorrhea and malabsorption of fat-soluble vitamins; they may also directly bind with and prevent the absorption of other drugs and should not, therefore, be given simultaneously with other therapies.

Hematinics (oral or intravenous iron, oral folate and intramuscular vitamin B_{12}), calcium, magnesium, zinc and fat-soluble vitamins (A, D, E and K) may be needed for the replacement of particular deficiencies, as may appropriate drugs for incipient or established osteoporosis (see Chapter 3).

Subcutaneous heparin to reduce the risk of arterial and venous thrombosis is recommended for those admitted with active Crohn's disease.

Drugs to avoid. Non-steroidal anti-inflammatory drugs (NSAIDs) may precipitate relapse of Crohn's disease and should, if possible, be avoided. Likewise, in patients with small-bowel stricturing due to Crohn's disease, delayed-release drugs should not be prescribed in case they cause bolus obstruction. Anecdotal evidence suggests that oral iron can exacerbate relapses, and its prescription is best postponed until remission has been achieved. In those who are frequently hospitalized because of pain, use of opioids should be minimized to avoid narcotic addiction.

Treatment of active Crohn's disease

Who needs hospital admission? The heterogeneous presentation of Crohn's disease makes assessment of disease activity more complicated than in ulcerative colitis. For clinical trials, a large number of multifactorial clinical and/or laboratory-based scoring systems, such as the Crohn's Disease Activity Index (CDAI) and Harvey-Bradshaw Index, have been devised, but none is suitable for ordinary clinical use. The working

definitions of the American College of Gastroenterology (Table 8.1) are more practical. Many patients with active Crohn's disease can be looked after as outpatients, but those with moderate-to-severe and severe-to-fulminant disease need prompt, and in the latter instance immediate, hospital admission. In patients with Crohn's colitis, indications for admission resemble those for acute severe ulcerative colitis (see Chapter 7).

General measures. As for those with ulcerative colitis, patients with active Crohn's disease should be looked after by a multidisciplinary team with special expertise in IBD in a specialist gastroenterology clinic or ward (see Table 6.1). Options for treatment (medical, nutritional, surgical) are wider than in ulcerative colitis, and it is essential that the patient with Crohn's disease is kept fully informed about his or her illness, and takes a place at the center of the therapeutic decision-making process.

TABLE 8.1

American College of Gastroenterology's working definition of disease activity in Crohn's disease

Activity	Features
Remission	Asymptomatic patients
Mild to moderate	Outpatients able to take oral nutrition, with symptoms but no fluid depletion, fever, abdominal tenderness, painful mass or obstruction
Moderate to severe	Patients who have not responded to treatment of mild to moderate disease, or those with more prominent symptoms including fever, weight loss > 10%, abdominal pain or tenderness (without rebound), intermittent nausea or vomiting (without obstructive findings) or anemia
Severe to fulminant	Patients with persisting symptoms despite outpatient oral steroids, or those with high fever, persistent vomiting, intestinal obstruction, rebound tenderness, cachexia or abscess

Adapted from Hanauer SB, Meyers S. *Am J Gastroenterol* 2001;96:635–43.

Establishing the diagnosis, clinicopathological problem and severity. For many patients, the diagnosis of Crohn's disease and identification of its principal site will have been made before he or she presents with a relapse. Investigations, therefore, are directed primarily at clarifying the dominant clinicopathological process so as to optimize subsequent treatment. In individuals presenting acutely for the first time, the diagnosis must be established (Table 8.2; see also Tables 4.1–4.4).

Clinical evaluation. Symptoms of active terminal ileal and ileocecal Crohn's disease are described in Chapter 2. Where the diagnosis of Crohn's disease has not yet been made, acute appendicitis with a mass may be particularly hard to differentiate from Crohn's disease, except with laparoscopy or laparotomy. In elderly patients presenting de novo, cecal carcinoma and lymphoma need careful consideration, while in some ethnic groups, for example South Asians, ileocecal tuberculosis must be excluded.

In Crohn's colitis, diarrhea is a more prominent symptom than pain; questions to be asked of previously undiagnosed patients are outlined in the section on acute severe ulcerative colitis in Chapter 7. External abdominal or perianal fistulas are usually clinically obvious, but direct questions may be necessary to identify enterovesical or enterovaginal fistulas (see page 28).

Blood tests. As in ulcerative colitis, the main value of blood tests is in assessing and monitoring disease activity, which is related directly to the platelet count and C-reactive protein, and inversely to serum albumin. However, in very sick patients, particularly those with extensive small-

TABLE 8.2

Management of active ileocecal Crohn's disease

General measures

Explanation, psychosocial support

- physicians, specialist nurses
- patient support groups

Specialist multidisciplinary care

- physicians, surgeons, nutritionists, nurses, counselor

(CONTINUED)

TABLE 8.2 (CONTINUED)

Establishing the diagnosis, site, extent and severity

Clinical evaluation

- complete blood cell count, C-reactive protein, ferritin, iron, transferrin, folate, B_{12}, albumin, liver function tests, calcium, magnesium, zinc
- stool microscopy, culture, *Clostridium difficile* toxin
- plain abdominal X-ray
- consider ileocolonoscopy and biopsy, MRI, small-bowel barium radiology, ultrasound, CT scan, leukocyte scan

Monitoring progress

Daily clinical assessment
Stool chart
4-hourly temperature, pulse
Alternate daily complete blood cell count, C-reactive protein, urea and electrolytes, albumin
Daily plain abdominal X-ray (in patients with obstruction)

Supportive treatment

Fluids, electrolytes (sodium, potassium), blood transfusion
Nutritional supplementation; low-residue diet if small-bowel strictures
Subcutaneous heparin
Hematinics (iron, B_{12}, folate)
Analgesia, antidiarrheals
Avoid NSAIDs, delayed-release drugs

Specific treatments (separately or in combination)

Stop smoking

Medical

- intravenous (hydrocortisone or methylprednisolone) then oral corticosteroids (prednisolone or budesonide) (not if fistula, abscess or perianal disease)
- consider metronidazole, ciprofloxacin, clarithromycin
- consider azathioprine/MP
- consider anti-TNFα therapy

Nutritional (in-patients only)

- liquid formula diet

Surgical

- resection or stricturoplasty

CT, computed tomography; MP, mercaptopurine; MRI, magnetic resonance imaging; NSAID, non-steroidal anti-inflammatory drug; TNF, tumor necrosis factor.

bowel disease and steatorrhea, there may be laboratory evidence of malnutrition and malabsorption (anemia and low levels of serum iron, folate, B_{12}, albumin, calcium, magnesium, vitamin D, zinc and essential fatty acids). A raised neutrophil count suggests intra-abdominal abscess, but corticosteroids also cause leukocytosis by demarginating intravascular neutrophils.

Stool microbiology. As in ulcerative colitis (see page 95), diarrhea in Crohn's disease may be due to intercurrent infection, particularly with *Clostridium difficile* toxin. Stool samples should therefore be sent for microbiological analysis in all patients presenting with a recent onset of diarrhea.

Endoscopy and biopsy. In those with right iliac fossa pain where the diagnosis of Crohn's disease is in doubt, colonoscopy to the terminal ileum, with appropriate biopsies, can be helpful. It can also be used to balloon-dilate short strictures. In established Crohn's colitis, colonoscopy during acute relapse is not routinely necessary and may be unsafe, as in active ulcerative colitis (see Chapter 7). In previously undiagnosed patients, digital rectal examination and cautious sigmoidoscopy may show rectal induration or ulceration, or the presence of perianal disease. Furthermore, biopsies of macroscopically normal rectal mucosa may reveal epithelioid granulomas in a minority of patients with more proximal Crohn's disease.

Plain abdominal X-ray. A plain film is essential if intestinal obstruction is suspected. It may also show a mass in the right iliac fossa and, in active Crohn's colitis, provide information about disease extent and severity.

Barium radiology. As indicated in Chapter 4, barium follow-through has been largely superseded by MRI scanning for small-bowel imaging, but contrast fistulography remains useful occasionally in patients with abdominal sinuses or fistulas.

Radiolabeled leukocyte scans. ^{99}Technetium-labeled hexamethylpropyleneamine oxime (^{99}Tc-HMPAO) scanning can help to identify, non-invasively, not only sites of intestinal inflammation, as in ulcerative colitis, but also intra-abdominal abscesses in those with fever and/or an abdominal mass (see Chapter 4); again, this test is being replaced now by MRI, ultrasound and CT scan.

Ultrasound, CT scan and MRI. Abdominal ultrasound and CT scanning can be very useful in active Crohn's disease for the evaluation

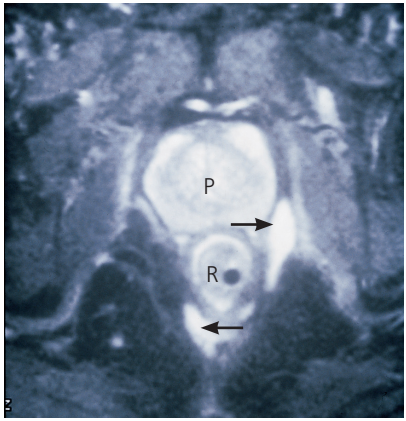

Figure 8.1 MRI showing a high-intensity signal track (arrowed) in a patient with Crohn's disease, indicating a posterior perianal collection with a fistulous track extending into the left ischiorectal fossa. P, prostate; R, rectum. Reproduced courtesy of Dr A McLean, Barts Health NHS Trust, London, UK.

and percutaneous drainage of localized collections (see Chapter 4); the last should be used selectively because of its high radiation dosage. Endoluminal ultrasound and MRI (Figure 8.1) are useful for the anatomic delineation of perianal abscesses and fistulas.

Supportive treatment. Patients with active Crohn's disease, like those with acute severe ulcerative colitis, need meticulous supportive treatment, including as necessary:

- intravenous fluids and electrolytes
- intravenous iron or, occasionally, blood transfusion for severe iron deficiency anemia
- prophylactic subcutaneous heparin.

General nutritional and dietary measures, drug therapy and drugs to avoid are outlined in Table 8.2.

Active ileocecal Crohn's disease

Therapeutic options include drugs, a liquid formula diet and surgery (see Chapter 9), as separate alternatives or in combination, depending on the patient's age, presentation and personal preference (see Table 8.2). The possible treatment pathway is shown in Figure 8.2.

Drug therapy

Corticosteroids. In active disease, 60–80% of patients show symptomatic improvement when given oral steroids. Conventionally,

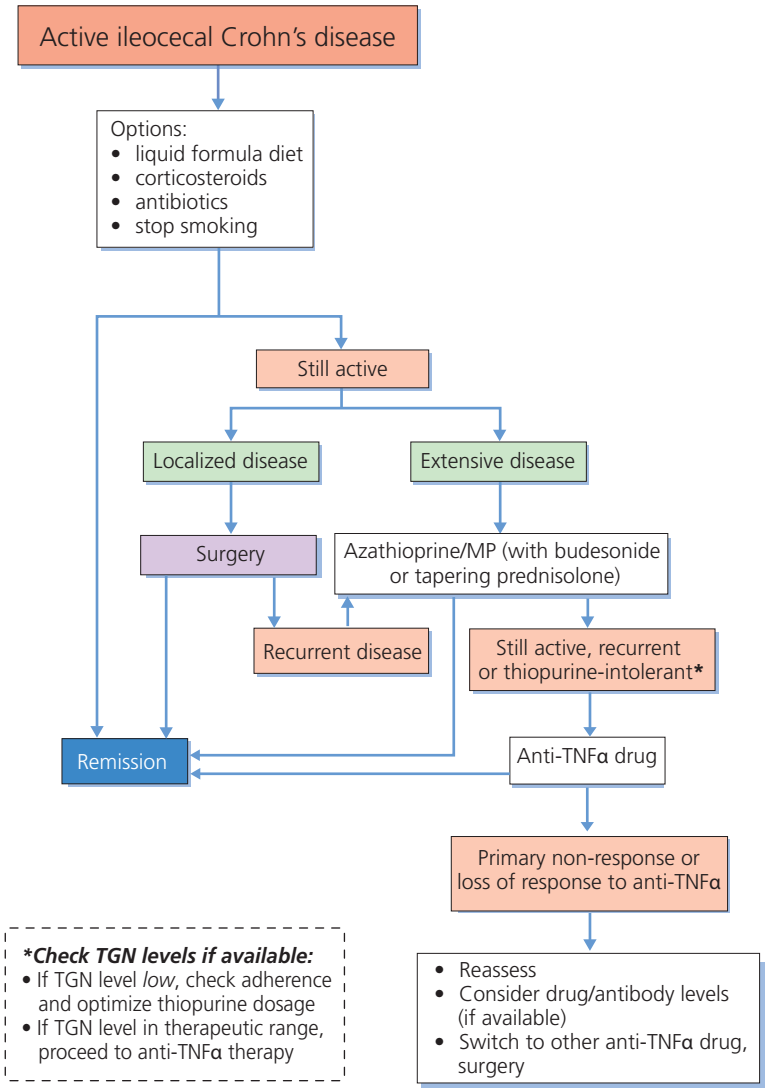

Figure 8.2 General principles of managing active Crohn's disease using a 'step-up' strategy (see text). Each step will depend on detailed evaluation of the individual, local practice and discussion of the options under consideration. For example, in some centers, methotrexate may be tried before anti-TNFα drugs in patients stopping thiopurines; in others, anti-TNFα agents may be introduced earlier than shown in this figure in patients with extensive disease. MP, mercaptopurine; TGN, thioguanine nucleotide; TNF, tumor necrosis factor.

prednisolone, 40–60 mg/day, is used, the dose being tapered by 5 mg every 7–10 days once improvement has begun, usually after 3–4 weeks. Very sick patients or those needing to fast because of intestinal obstruction need intravenous corticosteroids at least initially (e.g. hydrocortisone, 300–400 mg/day; methylprednisolone, 40–60 mg/day). In those able to take oral treatment in whom systemic steroid side effects are a major problem, budesonide (controlled ileal release, 9 mg/day) can be used. It is important, however, to avoid giving any form of corticosteroid to patients with fistulating disease or an existing abscess because of the risk of producing or exacerbating sepsis (see Chapter 5).

Up to 30% of patients with Crohn's disease may be difficult to wean off steroids after relapse. Of these, many will be able partially or totally to discontinue steroid therapy on the introduction of an immunomodulatory agent, or after surgical resection of short-segment disease. Those unable to discontinue steroids altogether and who are unsuitable for surgery should be offered anti-tumor necrosis factor (TNF)α therapy; only a tiny minority cannot be weaned off steroids altogether thereafter.

Aminosalicylates. Patients with only mildly active ileocecal disease, most of whom can be managed as outpatients, can be tried on high-dose oral mesalazine; about 40% will go into remission in 2–3 months. As indicated in Chapter 5, however, the role of 5-ASAs in Crohn's disease is minor.

Metronidazole and ciprofloxacin are modestly effective in mild to moderately active colonic Crohn's disease, but they are insufficiently potent for use as sole therapy in patients who are ill enough to need admission. Reports of the efficacy of clarithromycin and rifabutin, alone or in combination, need confirmation.

Immunosuppressive drugs. Patients who do not respond to corticosteroids, or relapse on their withdrawal, and who need to avoid operative treatment if possible because of extensive disease or previous surgery, can be treated with adjunctive oral azathioprine, 2.0–2.5 mg/kg/day, or mercaptopurine (MP), 1.0–1.5 mg/kg/day, the dose of steroids being reduced and/or phased out altogether as remission is achieved. Such patients must be well enough to wait for up to 4 months for this to occur. The side effects of azathioprine and MP make frequent blood counts and liver function tests mandatory; dosing and adherence can be assessed using thioguanine nucleotide (TGN) assays (see page 67 and Table 5.4).

Azathioprine and MP are long-term options for Crohn's disease. However, in patients maintained in full remission on azathioprine or MP, the risk of relapse after 4 years of treatment appears to be similar whether the drug is continued or stopped. In view of the potential toxicity associated with long-term use of these drugs, their withdrawal should be considered for those who are still in full remission after 4 years of treatment.

Methotrexate is effective in about 40% of patients with steroid-refractory Crohn's disease when given intramuscularly or orally once a week. Its use is usually reserved for those who are unresponsive to, or intolerant of, thiopurines, and it requires appropriate monitoring (see Chapter 5).

Anti-TNFα drugs (infliximab, adalimumab or certolizumab pegol) are used for patients with Crohn's disease refractory to steroids and/or conventional immunomodulatory drugs, and for whom surgery is inappropriate (see Table 5.6). This treatment produces clinical remission in about one-third of patients and a substantial improvement in another third. Most patients are maintained on regular injections or infusions thereafter, in conjunction with an immunomodulatory drug such as azathioprine (see pages 65–9), at least for the first 6 months. In patients who become asymptomatic on anti-TNFα therapy it is advisable to reassess their disease activity after about a year; for example, with ileocolonoscopy, small-bowel MRI and/or, less invasively and expensively, fecal calprotectin. Consideration can be given to stopping anti-TNFα therapy for those who are in complete remission at that time, given the risk of side effects and healthcare costs; in patients who do stop anti-TNFα treatment, ongoing remission maintenance with a thiopurine or methotrexate is advisable. How to manage loss of response to an anti-TNFα drug is described below (also see pages 73–4 and 76).

In most countries, anti-TNFα therapy is reserved for patients who fail to respond to, or are intolerant of, all other treatments for Crohn's disease (i.e. corticosteroids and an immunomodulator) and with disease too extensive for surgery. However, since anti-TNFα drugs induce mucosal healing in many patients, and thereby improve the natural history of the disease, there is an increasingly vocal argument for early introduction of these agents, using a 'top-down' rather than the more conventional 'step-up' approach.

Vedolizumab. This new biological agent (see page 78) has proven efficacy in Crohn's disease. It can produce a response and remission in patients with a waning response or primary non-response to anti-TNFα drugs.

Dietary therapy. A liquid formula diet is an alternative primary therapy in patients with a poor response to corticosteroids (especially those admitted to hospital), or a preference for avoiding them, those with extensive small-bowel disease and children (see Chapter 10). It is also much safer than steroid therapy, particularly in patients with penetrating disease. Liquid formula diets can be either elemental (amino acid based), oligomeric protein hydrolysate (containing peptides) or polymeric protein (containing whole protein and more palatable), and is usually given for about 6 weeks as the sole nutritional source (Table 8.3).

This approach is probably as effective as corticosteroid therapy in the short term, as about 60% of patients achieve remission. Unfortunately, however, after the resumption of a normal diet many patients relapse (50% at 6 months). Whether this can be prevented by the selective and gradual reintroduction of particular low-fat low-fiber foods to which individual patients are not intolerant, or by the intermittent use of further enteral feeding for short periods, remains to be proven. Nevertheless, in patients who do tolerate a liquid formula diet, it can be used for several weeks as a bridge to, for example, azathioprine.

The success of enteral nutrition as a primary therapy for Crohn's disease is also limited by:

- its cost
- the unpleasant taste of some of the available preparations
- the frequent need to give the feed by nasogastric tube
- poor concordance with the necessary feeding regimen.

Nevertheless, such therapy does offer a valuable alternative in the well-motivated minority of adults for whom it is appropriate.

Surgery (limited right hemicolectomy) is indicated in the 20–40% of patients whose ileocecal disease does not respond to drug or dietary therapy, particularly if they have short-segment (less than 20 cm) rather than extensive disease (see Chapter 9). Indeed, some patients prefer surgery to the prospect of pharmacological or nutritional treatment of uncertain duration. There are no controlled data to confirm which approach is best. After surgery there is a 50% chance of recurrent symptoms at 5 years and of further surgery at 10 years; taking a long-term thiopurine and stopping smoking may reduce these risks by up to 50%.

TABLE 8.3

Enteral nutrition in Crohn's disease

Indications	
Active small-bowel Crohn's disease	
Undernutrition in IBD	
Mainly for inpatients	
Preparations	
Elemental, oligomeric, polymeric	
Side effects	
Intolerance	Taste, boredom, nasogastric tube, nausea
Diarrhea	Concurrent antibiotics, hyperosmolality, too fast administration
Metabolic	Fluid overload or depletion, hypo- or hyperglycemia, low sodium/potassium/phosphate
Pulmonary aspiration	
Placement difficulties	
Monitoring	
Fluid balance chart	
Twice-weekly weight, urea and electrolytes, glucose, albumin	
Contraindications	
Severe diarrhea	
Patient refusal	
Mechanisms of action (all speculative)	
Hypoallergenic	
Bowel rest	
Altered bacterial flora	
Reduced gut permeability	
Altered gut immunity	
Nutritional repletion (including essential micronutrients)	

Specific treatment of other presentations of active Crohn's disease

The general principles of the management of other presentations of active Crohn's disease are the same as those described above. Specific aspects of management are outlined below.

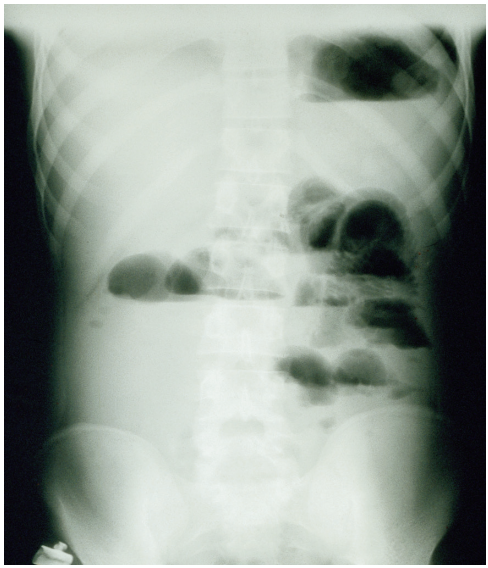

Figure 8.3 Plain abdominal X-ray showing fluid levels and distended bowel loops due to small-intestinal obstruction as a result of terminal ileal stricturing in Crohn's disease.

Obstructive small-bowel Crohn's disease. In patients presenting with obstructive symptoms and signs (Chapter 2), and with corresponding abnormalities on plain abdominal X-ray (Figure 8.3), the principal difficulty lies in deciding whether stricturing is due to active inflammation, fibrosis with scarring or even adhesions. Sometimes laboratory markers (e.g. raised platelet count, C-reactive protein) and/or MRI, CT or radiolabeled leukocyte scans can help to identify individuals with active inflammatory Crohn's disease, but in many instances a short trial of intravenous corticosteroids is given in addition to intravenous fluids and, if necessary, nasogastric suction (Table 8.4). Parenteral nutrition is required if resumption of an oral diet is not likely in 5–7 days.

If the stricture is in the upper jejunum, terminal ileum or colon, enteroscopic or colonoscopic balloon dilation can be undertaken (Figure 8.4). In patients who do not settle after 48–72 hours of conservative treatment, surgery is needed; the options are local resection or, for short and/or multiple strictures, stricturoplasty (see Chapter 9). Those responding to conservative therapy should be advised to take a low-residue diet to reduce the chance of recurrent symptoms.

TABLE 8.4

Specific treatments for other presentations of active Crohn's disease*

Subacute obstruction	Trial of intravenous corticosteroids Intravenous fluids and nasogastric suction (if necessary) Surgery for non-responders: local resection or stricturoplasty
Intra-abdominal abscess	Broad-spectrum antibiotics Percutaneous or surgical drainage
Intestinal fistula	Enteral or parenteral nutrition Oral metronidazole (for up to 3 months) Oral azathioprine or MP Anti-TNFα agent Surgery: local resection
Perianal disease	Oral metronidazole (for up to 3 months), ciprofloxacin Oral azathioprine or MP Anti-TNF agent Surgery: drain abscesses, seton sutures for chronic fistulas
Oral and upper GI disease	Treat as in other sites Topical or intralesional corticosteroids Omeprazole for duodenal disease

*Presentations other than ileocecal disease (Table 8.2) or Crohn's colitis (Table 8.5).
GI, gastrointestinal; MP, mercaptopurine; TNF, tumor necrosis factor.

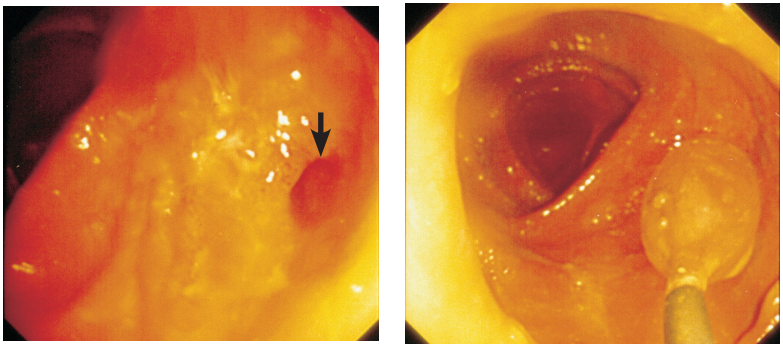

Figure 8.4 Colonoscopic balloon dilation of an anastomotic stricture in Crohn's disease: (a) narrowed ileocolonic anastomosis (arrowed); (b) through-the-scope balloon inserted into stricture and inflated.

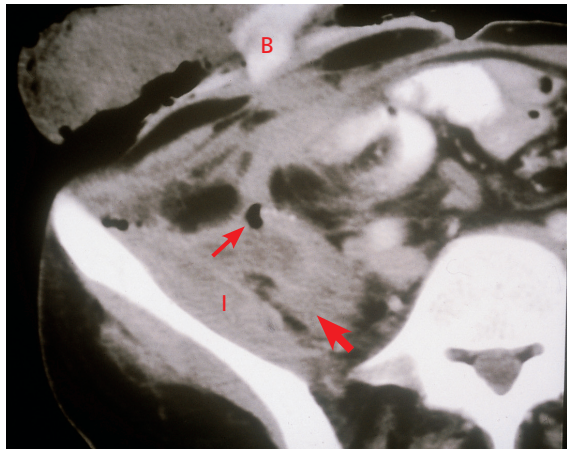

Figure 8.5 CT scan showing a psoas abscess in a patient with an ileostomy after total colectomy for Crohn's disease. Note the ileostomy bag (B) on the anterior abdominal wall with a short fistula (small arrow) leading from dilated prestomal small bowel into an abscess in psoas muscle (large arrow) adjacent to iliacus (I). Reproduced courtesy of Dr A McLean, Barts Health NHS Trust, London, UK.

Intra-abdominal abscess. Ultrasound, CT, MRI or radiolabeled leukocyte scans are usually used to confirm the diagnosis of intra-abdominal abscess in patients with Crohn's disease who present with pain, weight loss, diarrhea and fever with or without a tender mass (Figure 8.5). Broad-spectrum antibiotics are given and the abscess drained either percutaneously under radiological control and/or surgically (see Table 8.4). When oral food intake is likely to be restricted for more than 5 days, parenteral nutrition should be started. Subsequent treatment is of the underlying pathological process, for example ileocecal inflammation.

Intestinal fistula. The relevant anatomic connections are clarified using MRI, contrast radiology and/or CT scans (see Chapter 4). Nutritional well-being should be restored using enteral or parenteral nutrition (see Table 8.4). Where there is no obstruction distal to the site of intestinal fistulas, medical therapy with oral, rectal or intravenous metronidazole and/or oral azathioprine or MP will cause a few fistulas to heal. Anti-TNFα therapy is a newer option, but its efficacy in closing fistulas that are

not perianal is limited. Almost all patients with enterourinary or enterovaginal fistulas, and most with enterocutaneous fistulas, require surgical resection of the fistula and local resection of involved intestine and/or other viscera (see Chapter 9).

Perianal disease. Non-suppurative perianal Crohn's disease may respond to oral metronidazole and/or ciprofloxacin given for up to 3 months, and to azathioprine or MP in the long term (see Table 8.4). Healing of perianal fistulas occurs in a high proportion of patients treated with anti-TNFα drugs; however, fistulas often reopen if the treatment is discontinued. Those with suppurating perianal Crohn's disease need surgery, minimized as far as possible (see Chapter 9). In severe perianal disease, however, surgery with diversion ileostomy or, in refractory cases, proctocolectomy may eventually prove necessary.

TABLE 8.5

Specific treatment of active Crohn's colitis

Medical therapy

- Corticosteroids, intravenous (hydrocortisone or methylprednisolone) then oral (prednisolone)
- 5-ASA orally (for mild cases)
- Metronidazole orally (for mild cases)
- Azathioprine/MP orally if response can be postponed for up to 4 months
- Anti-TNFα drug for non-responders

Nutritional therapy

- Liquid formula diet

Surgery

- Total colectomy with permanent ileostomy (ileoanal pouch contraindicated)
- Segmental resection for stricture

5-ASA, 5-aminosalicylate; MP, mercaptopurine; TNF, tumor necrosis factor.

Crohn's colitis. The treatment of active Crohn's colitis resembles that of active ulcerative colitis (see Table 7.1 and Table 8.5). The main aim is to prevent the need for surgery necessitating permanent ileostomy. Anti-TNF drugs are increasingly used as primary therapy in this setting, since they produce better mucosal healing than corticosteroids (see Chapter 5) and because Crohn's colitis responds less well than ileocecal Crohn's to liquid formula diets.

Unlike ulcerative colitis, moderately active Crohn's colitis may be improved by oral metronidazole, 400 mg twice daily, for up to 3 months if tolerated. In patients who require total colectomy, permanent ileostomy is preferable to an ileoanal pouch because of the high incidence of pouch failure and sepsis in Crohn's disease (see Chapter 9). In rare individuals with refractory segmental colitis, local resection of short diseased segments can be performed.

Acute colonic dilatation is even more rare in acute severe Crohn's than it is in ulcerative colitis.

Oral and upper gastrointestinal Crohn's disease. Treatment of oral and upper gastrointestinal Crohn's disease follows the usual principles outlined above. Patients with oral Crohn's disease are best managed in close conjunction with specialists in oral medicine. Particular treatment options include topical and intralesional steroids and topical tacrolimus paste; some food constituents should be avoided (e.g. benzoate and cinnamon). Duodenal Crohn's disease may respond to omeprazole; endoscopic balloon dilation of strictures can also be helpful, but surgery may be technically demanding and complicated by fistulation.

Maintaining remission

A key prophylactic measure in patients who smoke is to stop: the risk of relapse in non-smokers at 5 years is reduced by about 30%. The efficacy of drug prophylaxis depends on whether remission has been achieved by medical or surgical treatment.

Strategies for maintaining remission are listed in Table 8.6, and its goals, namely to optimize both quality of life and mucosal healing, are outlined in Table 6.2.

TABLE 8.6

Maintenance of remission in Crohn's disease

All patients

- Stop smoking

Remission achieved by medical treatment

- Azathioprine/MP or methotrexate
- Anti-TNFα therapy or vedolizumab for refractory disease

Remission achieved by surgery

- Metronidazole (3 months only)
- Azathioprine/MP for aggressive disease
- Anti-TNFα therapy for disease refractory to thiopurines

MP, mercaptopurine; TNF, tumor necrosis factor.

Remission after medical treatment. Meta-analysis shows that, unlike in ulcerative colitis, long-term aminosalicylates have little or no prophylactic effect in this setting. Corticosteroids have no prophylactic role. In patients who depend on long-term corticosteroids and in whom symptoms recur whenever the dose is reduced, azathioprine, MP and methotrexate are of proven value in maintaining remission and reducing steroid requirements. As indicated above, long-term anti-TNFα drugs are effective at keeping many patients with otherwise refractory Crohn's disease in steroid-free remission.

Some patients lose their response to, or deteriorate on, anti-TNFα therapy after some months or years. Such patients need reassessment to ensure that this is not due to a complication (e.g. abscess), the development of a fibrous stricture or other non-inflammatory problem such as bile salt malabsorption: these conditions would need specific treatment other than or instead of the anti-TNFα agent.

If reassessment indicates ongoing inflammatory disease, the loss of response may be due to low circulating anti-TNFα levels, which in the case of infliximab can be measured, together with antibody levels (antibodies to infliximab; ATI, see pages 73–4), in many centers. In patients with low infliximab or adalimumab levels who do not have circulating

antibodies (ATIs) to the drug, increasing the dose of the anti-TNFα agent (e.g. infliximab from 5 to 10 mg/kg every 8 weeks) or reducing the dosing interval (e.g. from every 8 to every 6 weeks) is recommended. In patients with low drug levels with high antibody titers, the advice is to switch to an alternative anti-TNFα agent. In those with ongoing disease activity despite good drug levels, the rational course is to change to a different class of drug, for example vedolizumab, or to consider including the patient in a clinical trial of a novel agent (see Chapter 5).

Remission after surgical treatment. After resection for ileocecal disease, patients have a 50% chance of recurrence needing further surgery at 10 years. Oral metronidazole, 400 mg three times daily for 3 months postoperatively, reduces the symptomatic relapse rate at 1 year, but not beyond this period. Thiopurines appear to have a prophylactic role after surgery. However, because of their potential side effects and the need for careful blood monitoring (see page 68), many gastroenterologists confine the prophylactic use of these drugs to patients with aggressive disease (e.g. with abscesses or fistulation), after confirmation of recurrent mucosal disease by ileocolonoscopy performed 6 months after surgery, and/or after two or more operations. Similarly, there may be a place for early use of an anti-TNFα agent in the postoperative setting for patients with aggressive disease despite optimized thiopurine therapy.

Follow-up

The rarity with which primary care providers see Crohn's disease, and the wide variety of its manifestations and complications, mean that most patients should be followed up in specialist hospital clinics (see Table 6.1).

Patients with active disease or those receiving therapy need more frequent hospital review for:

- adjustment of their treatment according to the progress of their disease
- monitoring of side effects (see Tables 5.1, 5.3 and 5.4).

For the minority of patients in remission who are receiving no therapy, follow-up may take place at annual intervals, and may need to include tests to check for:

- occult disease activity (blood count, C-reactive protein, fecal calprotectin levels)

- undernutrition (weight and body mass index; serum albumin, calcium, vitamin D and sometimes magnesium and zinc levels; folate; and serum vitamin B_{12} levels in those with terminal ileal disease or resection)
- osteoporosis (bone densitometry)
- other complications of Crohn's disease, such as liver disease (liver function tests)
- colonoscopic surveillance and biopsy for dysplasia in patients with extensive Crohn's colitis, as for those with extensive ulcerative colitis (see pages 50 and 95).

Key points – medical management of Crohn's disease

- The treatment of active Crohn's disease depends on its site and the nature of the pathological process causing the symptoms.
- Therapeutic options for active Crohn's disease include corticosteroids, antibiotics, a liquid formula diet, immunomodulatory agents, anti-TNFα drugs, vedolizumab and surgery.
- All patients with Crohn's disease should be encouraged to stop smoking, given the adverse effect of smoking on the natural history of the disease.
- Patients with Crohn's disease should participate in decisions about their treatment, particularly in relation to the use of new biological therapies or surgery.

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9 Surgery

The management of IBD requires close liaison between physician and colorectal surgeon. Specialist nursing care, including that from a stoma therapist, is also necessary both pre- and postoperatively. Dietitians and counselors may also play a key role in preparing patients physically and psychologically for surgery. In most centers, surgery is undertaken laparoscopically although conversion to a conventional laparotomy incision may be required for safety reasons, particularly if adhesions or anatomic variants are encountered. Laparoscopy is less invasive than laparotomy and is preferable to patients; its clinical advantages include reduced perioperative morbidity with faster recovery time, reduced risk of adhesions and fewer incisional hernias.

Surgery rates have diminished in recent decades for both ulcerative colitis and Crohn's disease. While innovative drug therapy may have contributed, other factors are probably more important and include a progressive shift from surgical to medical care, the development of specialist teams and practice guidelines, patient advocacy groups and earlier diagnosis. However, in some instances, surgery remains an appropriate early option, notably for localized or short-segment ileal disease that is fibrotic and causing obstructive symptoms.

Ulcerative colitis

Indications for surgery (Table 9.1) are as follows.

Emergency colectomy, after appropriate immediate resuscitation (see Chapter 7), is necessary for colonic perforation or massive hemorrhage.

Urgent colectomy is needed for patients with acute severe ulcerative colitis who deteriorate, do not respond to intensive medical treatment in 5–8 days or develop acute colonic dilatation that does not respond within 24 hours to more intense medical treatment (see Chapter 7).

Elective colectomy is indicated in refractory, often steroid-dependent chronic active ulcerative colitis, and dysplasia or frank carcinoma. Occasionally, elective colectomy may be necessary in children with chronically active disease to prevent growth retardation (see Chapter 10).

TABLE 9.1

Surgery in ulcerative colitis

Indication	
Emergency	Colonic perforation
	Massive colonic hemorrhage
Urgent	Deterioration or non-response to medical treatment of acute severe ulcerative colitis in 5–8 days
	Acute colonic dilatation
Elective	Chronic active (steroid-dependent or refractory) ulcerative colitis
	Dysplasia or cancer
	Growth retardation in children (rarely)

Options

Restorative proctocolectomy with ileoanal pouch
Pan-proctocolectomy with ileostomy
Colectomy with ileorectal anastomosis (exceptionally – see text)

Options for surgery are outlined below and summarized in Table 9.1 and Figure 9.1.

Pan-proctocolectomy with permanent ileostomy has the lowest morbidity and mortality of the available surgical options, is technically the easiest and involves only one operation.

Note: only under exceptional circumstances should colectomy with ileorectal anastomosis be considered (e.g. older patients with relative rectal sparing who could not cope with a stoma or are unsuitable for an ileoanal pouch because of frailty or poor anal sphincter function). It is contraindicated as a permanent solution in other patients with pronounced rectal inflammation, as they will continue to have bleeding, diarrhea and urgency postoperatively. It is also inappropriate in young patients in view of the long-term risk of cancer developing in the retained rectum, for which regular sigmoidoscopy with biopsies for dysplasia would be necessary indefinitely (see Chapter 7).

Restorative proctocolectomy with ileoanal pouch is the most recently devised procedure for ulcerative colitis, and avoids the need for permanent

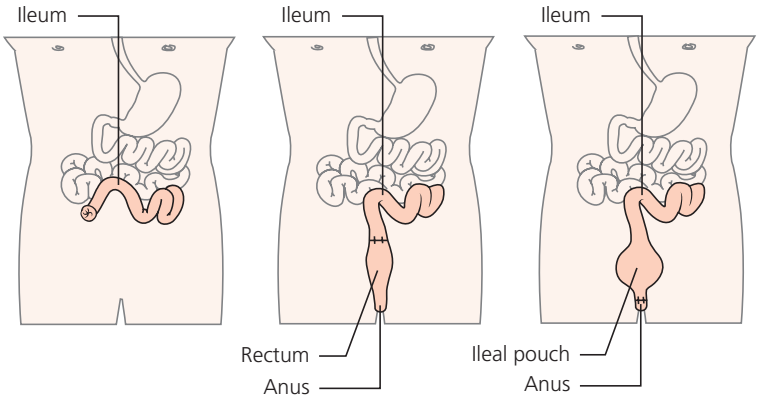

Figure 9.1 Surgical options in ulcerative colitis: (a) panproctocolectomy with ileostomy; (b) subtotal colectomy with ileorectal anastomosis (undertaken very rarely) ; (c) total colectomy with ileoanal pouch.

ileostomy. It is now the favored operation in younger patients (particularly those younger than 60 years) in whom preoperative confirmation of normal anal sphincter function minimizes the risk of postoperative incontinence of liquid pouch contents. The operation to fashion an ileoanal reservoir ('pouch') is technically difficult, usually requiring a temporary loop ileostomy that is closed at a second operation a few months later.

Complications of the different surgical options are as follows.

Ileostomy. Although proctocolectomy and ileostomy have the lowest morbidity and mortality of operations for ulcerative colitis, ileostomy incurs a readmission rate of about 50% in 10 years. Complications are listed in Table 9.2: specialist stoma therapists are crucial for their management. Because of its effects on body image, hygiene, and social and sexual function, a small minority of patients find an ileostomy impossible to adapt to psychologically.

Ileoanal pouch. Complications of ileoanal pouch surgery (Table 9.3) lead to excision of the pouch and conversion to permanent ileostomy ('pouch failure') in about 10% of patients. Early pouch failure is so common with Crohn's colitis that formation of an ileoanal pouch is generally contraindicated after colectomy for Crohn's disease or colitis of uncertain type or etiology (CUTE). Even in patients judged to have had

TABLE 9.2

Complications of ileostomy

Complication	Comment
Early	
Skin problems	Rare now with stoma therapists and improved appliances
Adhesive intestinal obstruction	May need surgery
Necrosis, fistulas, retraction, parasternal herniation	Requires refashioning of stoma
Excess stomal output (normal approximately 500 mL/day)	Improves with time postoperatively; avoid salt depletion in hot weather
Psychological disturbance	Some patients cannot come to terms with stoma (see text)
Late	
Sexual dysfunction	Due to psychogenic factors or surgical pelvic nerve damage
Uric acid renal stones	Due to excess alkaline stomal output

successful pouch surgery, daytime stool frequency is four to seven, urgency is common and nocturnal incontinence is present in about 20%.

Pouchitis. Villous atrophy and colonic metaplasia occur normally in ileoanal pouches. The diagnosis of pouchitis is made in patients with worsening diarrhea and/or bleeding, endoscopic signs of inflammation and histological evidence of acute inflammation with neutrophil infiltration and ulceration. In some cases it is caused by ischemia which should be suspected if pouchitis is asymmetrical. In most cases it represents a recurrent ulcerative colitis-like condition in the pouch with genetic, immunologic and microbial factors contributing to the pathogenesis. The importance of host susceptibility is shown by the fact that patients undergoing the same operation for familial *polyposis coli* seldom develop pouchitis. About 40% of patients will have at least one episode in the first 10 years after pouch construction. Therapeutic options include metronidazole (10 mg/kg in divided daily doses) for at least 10 days, ciprofloxacin alone or in combination with metronidazole, and topical or oral corticosteroids or aminosalicylates (as for ulcerative colitis; see Chapter 7).

TABLE 9.3
Complications of ileoanal pouch

Complication	Comment
Early	
Pelvic sepsis	Needs antibiotics, drainage and/or surgery
Anastomotic leaks	Needs pouch tube drainage and sometimes surgery
Adhesive intestinal obstruction	May need surgery
Late	
Poor function	Excessive diarrhea, urgency, incontinence
Sexual dysfunction	Due to psychogenic factors or surgical pelvic nerve damage
Female infertility	Up to 50%, probably due to tubal adhesions
Pouchitis	See page 132
Vitamin B_{12} deficiency	Treat with intramuscular hydroxocobalamin
Iron deficiency	Treat with oral iron supplements
Pouch failure	Needs conversion to ileostomy (in 10%)

Anti-tumor necrosis factor (TNF) agents are used very occasionally in patients with non-responsive pouchitis. Probiotic treatment, particularly after antibiotics, has been reported to be effective, but the results in different centers are variable. A minority of patients with refractory pouchitis require pouch resection and a permanent ileostomy.

Crohn's disease

Indications. Surgery is indicated primarily for disease refractory to medical and/or nutritional therapy, or for complications (Table 9.4). In Crohn's disease, unlike ulcerative colitis, surgery is not curative: recurrence at the surgical anastomosis or elsewhere in the gastrointestinal tract is common.

Options. The major principle of surgery for Crohn's disease is to conserve as much bowel as possible; excision of the minimum amount of bowel necessary to remove macroscopic disease is recommended.

TABLE 9.4

Surgery in Crohn's disease

Indications	
Emergency	Free perforation (rare)
	Massive hemorrhage (rare)
Urgent/soon	Small-bowel obstruction
	Small-bowel inflammation refractory to medical treatment
	Crohn's colitis
	Intra-abdominal abscess
	Enterocutaneous, -urinary or -vaginal fistulas
	Perianal abscess
	Acute colonic dilatation (rare)
	Carcinoma (rare)
Options	
Small-bowel disease	Local resection
	Stricturoplasty
Terminal ileal disease	Right hemicolectomy
Colitis	Pan-proctocolectomy with ileostomy
	Colectomy with ileorectal anastomosis (rarely)
	Segmental resection for localized disease (rarely)
Perianal disease	Lay open complex fistulas, drain with seton sutures
	Drain abscesses
	Temporary diversion of fecal stream by loop ileostomy to allow distal healing
	Proctectomy (for refractory disease)

Small-bowel or ileal resection. Discrete segments of small bowel are removed with an end-to-end anastomosis. Ileocecal disease is excised with a limited right hemicolectomy, in which the ileum is anastomosed to the ascending colon, with removal of involved ileum, cecum and appendix.

Stricturoplasty. In patients with obstructive symptoms due to very short and/or multiple strictured segments of small-bowel Crohn's disease, the risk of short-bowel syndrome (see Chapter 2) following excision can be averted by stricturoplasty, in which a longitudinal incision of the stricture is sewn up transversely, with consequent widening of the gut lumen (Figure 9.2).

Surgery for colonic Crohn's disease. For patients with extensive Crohn's colitis refractory to medical therapy, the safest operation is proctocolectomy with ileostomy (see Figure 9.1). Ileoanal pouch creation is contraindicated by a high frequency of anastomotic leaks and sepsis, which necessitate its removal. Even in patients with rectal sparing, the recurrence rate is much higher with colectomy and ileorectal anastomosis than with proctocolectomy and ileostomy, making the latter preferable. In rare patients with localized colonic disease, segmental resection (unlike in ulcerative colitis) is a reasonable option.

Surgery for perianal disease. As in other sites of Crohn's disease, surgery should be minimized, not least because of the risks of inducing incontinence as a result of iatrogenic sphincter damage. Abscesses require drainage, and complex chronic fistulas may need insertion of loose (seton) sutures to facilitate continued drainage. Defunctioning ileostomy or colostomy may allow healing of severe perianal disease by diverting the fecal stream, but recurrence after closure of the stoma is common. Strictures can be treated with cautious dilation (to avoid sphincter damage). The threshold for biopsy should be low in view of the occasional development of anal carcinoma in patients with chronic perianal Crohn's disease. Proctectomy is sometimes needed for severe and refractory anorectal Crohn's disease.

Complications of removing the terminal ileum for ileocecal or ileal Crohn's disease (right hemicolectomy) are summarized below and in Table 9.5.

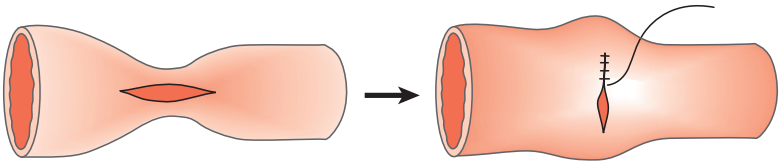

Figure 9.2 Stricturoplasty for Crohn's disease: (a) longitudinal incision through stricture; (b) incision sewn up transversely to widen lumen.

TABLE 9.5

Long-term complications of resection for ileocecal Crohn's disease

Recurrence of Crohn's disease

Bile-salt malabsorption

- Cholegenic diarrhea
- Enteric hyperoxaluria, urinary oxalate stones
- Gallstones

Vitamin B_{12} deficiency

Recurrence of Crohn's disease. In about 70% of patients, colonoscopy shows recurrent aphthoid ulceration, usually immediately proximal to the anastomosis, 1 year after right hemicolectomy. Postoperative treatment with oral metronidazole for 3 months reduces the endoscopic recurrence rate at 1 year, but the effect of such therapy on the symptomatic recurrence rate of 50% at 5 years and the rate of need for repeat surgery of 50% at 10 years is not clear (see Chapter 8). In patients with aggressive penetrating disease, thiopurines and sometimes even anti-TNFα drugs are prophylactic options. Stopping smoking reduces the recurrence rate and is essential advice to every smoking patient with Crohn's disease.

Bile salt malabsorption. By removing their site of absorption, terminal ileal resection leads to the passage of primary bile salts (cholate and chenodeoxycholate) into the colon, where they:

- induce mucosal secretion of water and electrolytes (with resultant diarrhea)
- increase mucosal permeability to dietary oxalate (predisposing to enteric hyperoxaluria and urinary oxalate stones)
- cause fecal loss of bile salts (increasing the risk of cholesterol gallstones).

As intestinal adaptation occurs postoperatively, cholegenic diarrhea often improves; in the interim, symptomatic treatment with antidiarrheal agents, such as codeine phosphate or loperamide, or with a bile-salt-binding ion-exchange resin such as colestyramine (cholestyramine) or colesevalam may help. Enteric hyperoxaluria is treated with a low-oxalate (see page 40) low-fat high-calcium high-fluid diet.

Vitamin B_{12} deficiency. After surgery involving terminal ileal resection, particularly if more than 100 cm has been removed, patients should have annual checks of their serum vitamin B_{12} level, with replacement by hydroxocobalamin, 1000 μg intramuscularly every 3 months, in the event of deficiency.

Key points – surgery

- Surgery offers a long-term solution for ulcerative colitis, but there is always a risk of recurrence of Crohn's disease after resection.
- Through discussions with their physician, surgeon, IBD nurse and stoma therapist, the patient should be closely involved in the decision to undertake surgery.
- Surgery rates have declined in recent decades but surgery remains a good early option for patients with localized ileal Crohn's disease causing obstructive symptoms.
- Patients need regular follow-up after surgery for prompt identification and management of complications of their disease and its surgery.

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10 IBD in pregnancy, childhood and old age

IBD can behave differently, and presents different management challenges, at different stages of life. In this chapter, we outline, in separate sections, features of IBD and its care relating to fertility, pregnancy and lactation, childhood and old age.

Fertility

Female fertility is not impaired except in active IBD. Because of the risk of inadequate absorption, women with diarrhea due to small-bowel Crohn's should not rely exclusively on the oral contraceptive pill to prevent pregnancy. Fertility is reduced as a result of azoospermia in male patients taking sulfasalazine, but this can be reversed within a few weeks by switching to an alternative aminosalicylate (see Tables 5.2 and 5.3).

There is an increased risk of infertility in women with an ileo-anal pouch after a colectomy (see Chapter 9), probably due to Fallopian tube adhesions. Women should consider deferring pouch construction until they have completed their family.

Pregnancy and lactation

Outcome of pregnancy is normal in women with quiescent IBD at the time of conception, but there is an increased rate of spontaneous abortion, premature delivery and stillbirth in those with persistently active disease. As in other contexts, a multidisciplinary approach to the care of IBD patients who are pregnant is advised, with close liaison between gastroenterologist and the obstetric team.

Pregnancy itself has no consistent effect on the activity of IBD, although the disease occasionally flares early in the puerperium.

Treatment. Corticosteroids and aminosalicylates can be used safely during pregnancy and lactation; withholding them exposes the mother and fetus unnecessarily to the adverse consequences of active disease. Azathioprine and mercaptopurine (MP) appear to be safe in pregnancy and do not seem to adversely affect immune function in offspring; mothers taking thiopurines

should not be discouraged from breastfeeding. Other immunomodulatory drugs and metronidazole are contraindicated in pregnancy.

Use of anti-TNFα drugs during pregnancy has not been associated with an adverse outcome; but where the clinical setting permits they should be withheld in the last trimester to avoid placental transfer to the newborn. Trace amounts of anti-TNFα agents may enter breast milk but a significant risk to the neonate is unlikely: mothers taking these drugs can therefore breastfeed.

Surgery is occasionally necessary in very sick women, for example those with non-responsive acute severe ulcerative colitis or sepsis complicating Crohn's disease; it is associated with a high rate of fetal loss.

Vaginal delivery appears safe for women without perianal disease or with quiescent perianal disease. The optimal mode of delivery for those with active perianal disease is uncertain but many clinicians favor Cesarean section. Each instance should be discussed between the patient and her obstetrician and gastroenterologist.

Key points – IBD in pregnancy and lactation

- Fertility is not significantly impaired by well-controlled IBD.
- Women should be encouraged to achieve disease remission before attempting conception.
- Pregnancy does not increase the risk of disease exacerbation.
- The well-being of the mother is the single most important factor influencing the outcome of pregnancy; theoretical risks of commonly used drugs for the unborn are outweighed by the benefit of health maintenance in the mother.
- Thiopurines do not appear to increase the risk of complications during pregnancy or lactation, but methotrexate, other immunomodulatory drugs and metronidazole are contraindicated.
- Anti-TNFα biologics can cross the placenta in the third trimester but any risk to the fetus appears to be low. Many clinicians recommend discontinuation of anti-TNFα therapy at the start of the third trimester.
- Vaginal delivery is safe for women without perianal disease or with quiescent perianal disease. For those with active perianal disease, Cesarean section is often advised.

Key references – IBD in pregnancy and lactation

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Childhood

Children differ from adults because they are developing physically, immunologically and emotionally. IBD in children requires special diagnostic and therapeutic considerations.

Incidence. Pediatric patients account for about 20–25% of newly diagnosed IBD. Genetic factors are likely to be more important when IBD

presents in childhood than in adulthood. Monogenic inheritance accounts for a subset of very early-onset IBD in pre-schoolers (see Chapter 1).

Diagnosis of IBD in children is often delayed. It should be considered early in children not only with classic symptoms, such as pain and diarrhea (see Chapter 2), but also in those with delayed growth and puberty. Differential diagnoses include cows' milk protein allergy, allergic enterocolitis and immune deficiencies.

Children with ulcerative colitis present more commonly with extensive disease than adults; in Crohn's disease, oral involvement and extensive small-bowel disease are much more frequent than in adults. Children are also more likely than adults to present with extraintestinal manifestations such as arthritis or erythema nodosum (Chapter 3).

Prompt referral to a specialist pediatric gastroenterology unit is advised for appropriate investigation (Chapter 4). Because of the lifetime exposure to diagnostic radiation and the increased sensitivity to radiation in young patients, it is particularly important to keep diagnostic radiation to the minimum necessary (Chapter 4).

Treatment. The principles of treatment for children are the same as for adults. However, the adverse effects of IBD on growth and pubertal

Key points – IBD in childhood

- IBD presents in childhood or adolescence in up to 25% of patients.
- Genetic influences are more likely, especially in pre-schoolers.
- Atypical presentations are more common than in adulthood, e.g. short stature, delayed puberty or extraintestinal manifestations.
- IBD is more likely to be extensive than in adults.
- Vigilance for pubertal and growth retardation is critical.
- A liquid formula diet has primacy over drug treatment in children with active Crohn's disease.
- Early use of immunomodulatory drugs and/or anti-TNFα agents can minimize use of corticosteroids, can offset risk of growth impairment and is not associated with greater risk than in adulthood.

development mean that active disease should be suppressed as soon as possible, undernutrition reversed and prolonged courses of corticosteroids avoided. In pediatric and adolescent Crohn's disease, more so than in the adult disease, enteral nutrition with a liquid formula diet, given if necessary by fine-bore nasogastric tube, plays a major primary therapeutic role.

Because of the need to maintain growth and development, prepubertal colectomy for ulcerative colitis and resection for Crohn's disease are also more frequently used than in adults. Azathioprine is a useful option in steroid-dependent children in whom surgery is inappropriate or declined. Infliximab and adalimumab are invaluable additions to therapy in those refractory to or intolerant of thiopurines and/or methotrexate. In all children with IBD, growth should be carefully monitored on weight-for-height charts.

Key references – IBD in childhood

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Old age

Incidence. Improvements in medical therapy of IBD, the low impact of IBD on mortality, and increased longevity within the general population mean that an increasing proportion of patients with IBD is elderly. In addition to those patients who grow old with their IBD (and with their doctors), an important subset of patients have their first onset of disease when they are elderly and this raises special management issues (Table 10.1). Some studies show a bimodal distribution of IBD incidence with up to one-third of all new cases of Crohn's disease occurring in the elderly population.

Treatment. Clinicians have been used to treating IBD in young adults but need to be familiar also with the special issues that arise in older patients. These include difficulties with diagnosis, management of comorbidities,

TABLE 10.1

IBD in the elderly

Diagnostic difficulty

- Increased risk of delayed or misdiagnosis
- Weight loss, bleeding, fever and paradoxical constipation may be more prominent
- Disease distribution seems to favor more colonic disease in patients with Crohn's disease and distal colitis in those with ulcerative colitis

Differential diagnosis

- Infectious, ischemic, diverticular and drug-induced colitides
- Colorectal neoplasia

Clinical course

- Often mild but confounded by comorbidities

Treatment

- Drug therapy should and usually can be conservative
- Steroid toxicity more likely: increased risk of osteoporosis and fractures
- Pharmacokinetics of most drugs are altered
- Greater vigilance for adverse effects with biologics, immunomodulatory and other drugs is essential
- Greater risk of polypharmacy and drug interactions
- Surgery carries higher risk

polypharmacy and drug interactions. This is compounded by a doubt regarding the extrapolation of data from clinical trials because the elderly have often been excluded from drug trials either because of age per se or comorbidity. Other problems that should be anticipated include the limited physiological reserve of elderly patients and difficulties with memory and cognition which may affect adherence to treatment.

Fortunately, IBD in older patients usually takes a milder course than in younger ones, so that corticosteroids, immunomodulatory and anti-TNFα drugs are required less often. Consideration of use of these drugs should take into account the much higher risk of severe side effects which they carry in the elderly. Similarly, surgery in the elderly, who often have concurrent disease, is more hazardous than in younger people.

Key points – IBD in the elderly

- IBD is increasingly common in the elderly as a result both of pre-existing disease and of new onset in older patients.
- Presenting symptoms may be atypical.
- Disease course is usually mild.
- Medical therapies (particularly corticosteroids, thiopurines, methotrexate and anti-TNFα agents) carry greater risks than in younger patients.
- Surgery is more dangerous than in younger people.

Key references – IBD in the elderly

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11 Prognosis

Patients with IBD must cope with considerable uncertainty and waiting in relation to the outcome of tests and treatments. However, in recent years their experience of illness has greatly improved because of advances in diagnostics, particularly imaging, and greater attention to the detail of medical and surgical therapy. No longer should one expect to encounter short-bowel syndrome, Cushingoid deformities, malnutrition or stunted growth, nor iatrogenic opiate addiction. The majority of patients can expect to lead a full and productive life, most of which should be free of disabling illness.

An important and emerging comorbidity is the risk of obesity and obesity-related metabolic disease. Whether this reflects the lifestyle of the general population or is, in part, influenced by anti-inflammatory and immunomodulatory treatment in people with IBD is unclear.

Ulcerative colitis

Mortality. The risk of death in ulcerative colitis is highest in the first year of diagnosis and relates mainly to first attacks of acute severe ulcerative colitis. In this setting, fewer than 1% of patients now die, the principal causes of death being pulmonary embolism, perforation and sepsis. The overall mortality associated with ulcerative colitis is no different from that of the normal population, the risks of ulcerative colitis and associated colorectal cancer and sclerosing cholangitis possibly being counterbalanced by the non-smoking status of most patients with the disease (see Chapter 1).

Morbidity. Most patients experience a relapsing and remitting course of disease; 70% of untreated patients have flare-ups annually. In patients with distal disease at presentation, extension to involve the proximal colon occurs in about 20% after 10 years. The cumulative colectomy rate in patients with total colitis is 10–25% at 15 years.

Cancer risk. The risk of colorectal cancer is increased in those who have had subtotal or total ulcerative colitis for more than 10 years, the cumulative risk having fallen in recent decades from around 20% to 5–10% at 30 years, perhaps due to better control of inflammatory disease activity. Comorbidity with sclerosing cholangitis is an added risk factor. The prognosis of colonic cancer complicating ulcerative colitis resembles that of patients without colitis. Colonoscopic surveillance programs are widely used, but have not been proven to reduce mortality from colonic cancer in ulcerative colitis.

Crohn's disease

Mortality. The cumulative mortality of Crohn's disease is approximately twice that in the general population. Death is predominantly from sepsis, pulmonary embolism, and complications of surgery and immunosuppressive therapy in those with severe chronic disease.

Morbidity. A higher proportion of patients with Crohn's disease than with ulcerative colitis show a chronic active rather than a relapsing remitting course of disease. Surgery is required in about 50% of patients in the first 10 years after diagnosis. Of those having an operation, 50% will need further surgery in the next 10 years, the risks being higher in those with ileal and ileocolonic disease than in those with purely colonic disease. Complications of obesity and obesity-related metabolic disorders are, like Crohn's itself, aggravated by smoking.

Key points – prognosis

- Mortality in ulcerative colitis resembles that in the general population, but in Crohn's disease it is increased twofold.
- Causes of death in patients with severe IBD include sepsis, pulmonary embolism, colorectal cancer, sclerosing cholangitis and complications of surgical and immunosuppressive therapy.
- An increasing proportion of patients are now either overweight or obese and require treatment or preventive measures against metabolic syndrome and insulin resistance.

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Useful resources

UK

Crohn's and Colitis UK
Tel (support): +44 (0)121 737 9931
Tel (info): 0300 222 5700
info@crohnsandcolitis.org.uk
www.crohnsandcolitis.org.uk

Ileostomy and Internal Pouch Support Group
Tel: +44 (0)1702 549859
Toll-free: 0800 018 4724
info@iasupport.org
www.iasupport.org

USA

Crohn's and Colitis Foundation of America
Toll-free: 800 932 2423
info@ccfa.org
www.ccfa.org

International

Crohn's and Colitis Australia
Helpline: 1800 138 029
Tel: +61 (0)3 9815 1266
info@crohnsandcolitis.com.au
www.crohnsandcolitis.com.au

Crohn's and Colitis Canada
Tel: +1 416 920 5035
Toll-free: 1 800 387 1479
support@crohnsandcolitis.ca
www.crohnsandcolitis.ca

European Crohn's and Colitis Organisation (ECCO)
Tel: +43 (0)1 710 22420
ecco@ecco-ibd.eu
www.ecco-ibd.eu

European Federation of Crohn's and Ulcerative Colitis Associations
Tel: +32 2 540 84 34
www.efcca.org

Other websites

www.guts4life.com
www.ibdetermined.org
www.ibdsupport.org

Additional reading

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