Ulcerative colitis

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See Online for appendix

Ulcerative colitis is an idiopathic, chronic inflammatory disorder of the colonic mucosa, which starts in the rectum and generally extends proximally in a continuous manner through part of, or the entire, colon; however, some patients with proctitis or left-sided colitis might have a caecal patch of inflammation. Bloody diarrhoea is the characteristic symptom of the disease. The clinical course is unpredictable, marked by alternating periods of exacerbation and remission. In this Seminar we discuss the epidemiology, pathophysiology, diagnostic approach, natural history, medical and surgical management, and main disease-related complications of ulcerative colitis, and briefly outline novel treatment options. Enhanced understanding of how the interaction between environmental factors, genetics, and the immune system results in mucosal inflammation has increased knowledge of disease pathophysiology. We provide practical therapeutic algorithms that are easily applicable in daily clinical practice, emphasising present controversies in treatment management and novel therapies.

Introduction

Ulcerative colitis and Crohn's disease are the two main forms of inflammatory bowel disease. Despite some shared characteristics, these forms can be distinguished by differences in genetic predisposition, risk factors, and clinical, endoscopic, and histological features. The precise cause of inflammatory bowel disease is unknown; however, genetically susceptible individuals seem to have a dysregulated mucosal immune response to commensal gut flora, which results in bowel inflammation.[1]

Inflammation in ulcerative colitis is characteristically restricted to the mucosal surface. The disorder starts in the rectum and generally extends proximally in a continuous manner through the entire colon; however, some patients with proctitis or left-sided colitis might have a caecal patch of inflammation. Disease distribution is stratified by the extent of colonic involvement, from proctitis to left-sided colitis or extensive colitis (pancolitis).[2]

Epidemiology

Geography, age, and sex

Ulcerative colitis is more prevalent than Crohn's disease. North America and northern Europe have the highest incidence and prevalence rates of ulcerative colitis, with incidence varying from nine to 20 cases per 100 000 person-years, and prevalence rates from 156 to 291 cases per 100 000 people (table 1). Rates are lowest

in the southern hemisphere and eastern countries (appendix pp 1–2). Incidence has increased in countries that have adopted an industrialised lifestyle, which suggests that environmental factors might be crucial in the triggering of disease onset.

Ulcerative colitis has a bimodal pattern of incidence, with the main onset peak between ages 15 and 30 years,[12] and a second smaller peak between ages 50 and 70 years. Studies have noted either no preference regarding sex,[13] or a slight predilection for men.[12]

Genetic factors

A family history of inflammatory bowel disease is the most important independent risk factor.[14] The risk is particularly high in first-degree relatives: 5·7–15·5% of patients with ulcerative colitis have a first-degree relative with the same disease.[15,16] Furthermore, Ashkenazi Jews have a rate of ulcerative colitis that is three to five times higher than that of other ethnic groups, which suggests another genetic link. However, these differences are lessening, which supports the importance of environmental factors in the cause of the disease.[17] Finally, monozygotic twins have concordance rates for ulcerative colitis of 6–13%.[18,19]

Environmental factors

Incidence of ulcerative colitis is higher in developed countries than in developing countries, and in urban versus rural areas. These findings could be partly explained by increased access to health care and better medical records in more developed than less developed countries. Furthermore, improved sanitation in industrialised countries might reduce exposure to enteric infections during childhood, thus restricting maturation of the mucosal immune system, which could result in an inappropriate immune response when exposure to infectious microorganisms occurs later in life.[13,20]

Several environmental factors act as triggers or protective factors for ulcerative colitis, with cigarette smoking being the most consistent. A meta-analysis[21] showed that smoking is protective against ulcerative colitis compared with non-smoking (odds ratio [OR] 0·58, 95% CI 0·45–0·75). Patients with ulcerative colitis

who smoke tend to have a more mild disease course than do non-smokers, and disease activity is often increased in those who stop smoking.[22]

Episodes of previous gastrointestinal infection (eg, *Salmonella* spp, *Shigella* spp, and *Campylobacter* spp) double the risk of subsequent development of ulcerative colitis, which suggests that acute intestinal infection might lead to changes in gut flora, hence triggering the start of a chronic inflammatory process in genetically predisposed individuals.[23,24] Weak epidemiological evidence exists for an association between exposure to non-selective non-steroidal anti-inflammatory drugs and onset or relapse of ulcerative colitis.[25] Appendicectomy is protective against ulcerative colitis, with the effect mainly limited to patients with acute appendicitis before age 20 years.[26] A meta-analysis[27] showed that appendicectomy reduced the risk of development of ulcerative colitis by 69% (OR 0·31, 95% CI 0·25–0·38). Appendicectomy has been used to treat ulcerative colitis.[28]Although several retrospective studies[29,30] have postulated a seasonal variation in the occurrence of ulcerative colitis flares, this association is fairly weak.

No data support psychological stress as a trigger for onset or relapse of ulcerative colitis.[31] Use of oral contraceptives is moderately associated with disease onset.[32] Breastfeeding is protective against subsequent development of ulcerative colitis (0·56, 0·38–0·81), but only when the duration of breastfeeding is more than 3 months.[33]

Pathophysiology
Epithelial barrier
Figure 1 shows the pathophysiology of ulcerative colitis. The epithelial barrier, covered by a mucinous layer, is the first-line defence of the mucosal immune system, because it provides physical separation between host immune cells and luminal microbes, and synthesises antimicrobial peptides. In ulcerative colitis, synthesis and alteration of sulphation of some colonic mucin subtypes (mucin 2) is decreased.[34] Damage to the epithelial barrier leads to increased permeability, possibly due to defective regulation of tight junctions.[35] This barrier loss enables increased uptake of luminal antigens; however, whether such dysfunction precedes ulcerative colitis or results from chronic inflammation is unclear.

In addition to creation of a physical barrier, the intestinal epithelium contributes to host defence by producing antimicrobial peptides (eg, defensins), thus limiting bacterial invasion. Expression of selected human beta-defensins is upregulated in colonic samples of patients with ulcerative colitis. It is unclear whether this increase in defensin production is induced in response to microorganisms, inflammatory cytokines, or both.[36,37]

Commensal microflora
Normally, the intestinal immune system maintains equilibrium between tolerance to commensal flora and

	Country	Study period	Incidence*	Prevalence†
North America				
Herrinton LJ, et al[3]	USA (California)	1996–2002	12·0	155·8
Loftus CG, et al[4]	USA (Olmsted County, MN)	1990–2000	8·8	214
Kappelman MD, et al[5]	US (33 states)	2003–04	..	238
Bernstein CN, et al[6]	Canada	1998–2000	9·9–19·5	162–249
Europe				
Manninen P, et al[7]	Finland	1986–2000	19·6	291
Vind I, et al[8]	Denmark	2003–05	13·4	..
Bjornsson S, et al[9]	Iceland	1990–94	16·5	..
Stewenius J, et al[10]	Sweden	1958–82	9·4	..
Rubin GP, et al[11]	England	..	13·9	243·4

*Cases per 100 000 person-years. †Cases per 100 000 people.

Table 1: Incidence and prevalence rates of ulcerative colitis from selected countries

dietary antigens, and adequate responsiveness to enteric pathogens. Evidence from genetically engineered animal models, which develop chronic intestinal inflammation after colonisation with commensal gut bacteria, but remain disease free in bacteria-free conditions, suggests a primary role of non-pathogenic enteric bacteria in the pathogenesis of ulcerative colitis.[38,39] Studies in human beings likewise support the importance of enteric microflora, not only in the pathogenesis of the disease, but also potentially in the severity of intestinal inflammation[40] and disease phenotype (ulcerative colitis *vs* Crohn's disease).[41] Therefore, ulcerative colitis seems to result from a breakdown of the homoeostatic balance between the host's mucosal immunity and the enteric microflora, which results in an aberrant immune response against commensal non-pathogenic bacteria.

Antigen recognition
Antigens activate the innate immune response through interaction with macrophages and dendritic cells. Dendritic cells can send dendrites outside the epithelium, interdigitated in the intestinal epithelial cells, to sample bacteria and other antigens in the lumen.[42] The lamina propria is populated by macrophages and dendritic cells that present antigens to B cells and T cells, which leads to activation of adaptive immune responses. In patients with ulcerative colitis, numbers of activated and mature dendritic cells are increased with increased stimulatory capacity, and their circulating numbers correlate with disease activity, which suggests an important role of these cells in the start and perpetuation of inflammation.[43]

Dendritic cells express a broad range of microbial pattern-recognition receptors, including Toll-like receptors (TLR) and NOD-like receptors. The main role of TLR signaling is to provide defence against pathogens and protection from epithelial injury, thereby contributing to intestinal homoeostasis and maintenance of the epithelial barrier. Normal intestinal epithelial cells express mainly
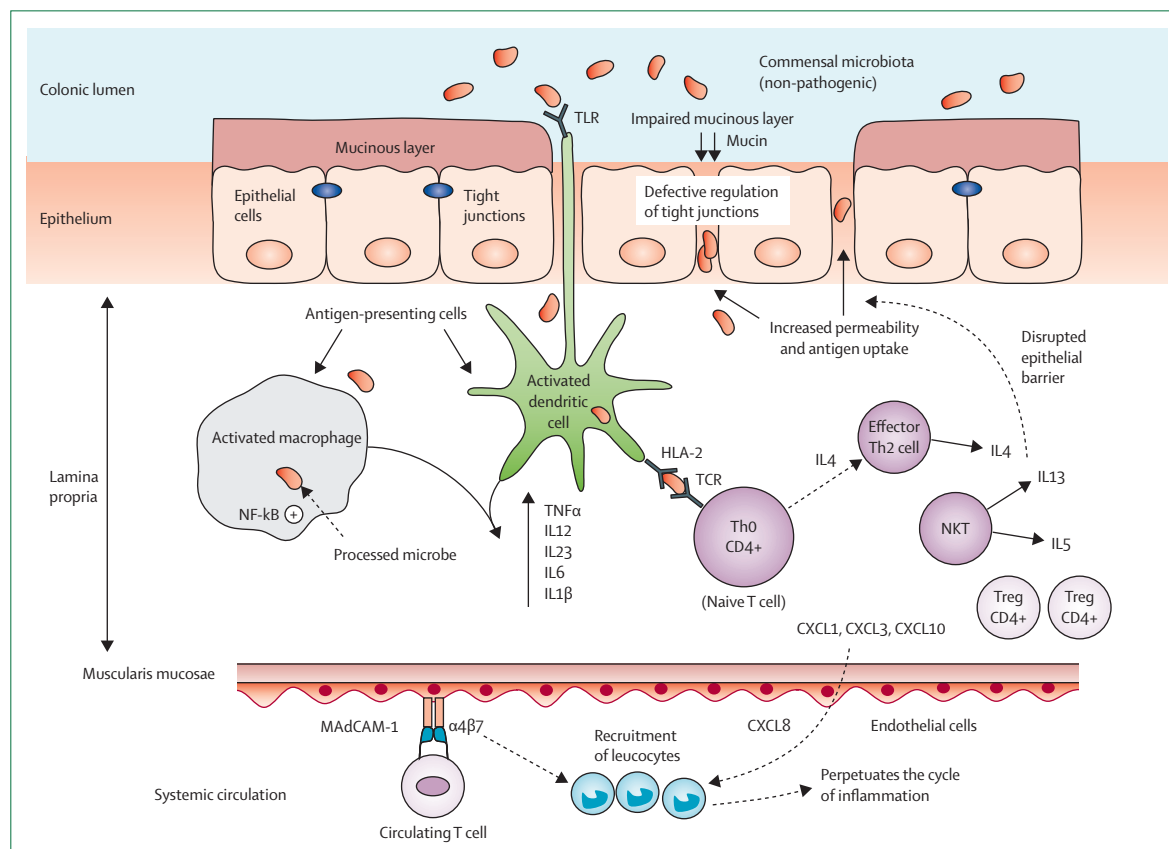
***Figure 1:* Pathophysiology of ulcerative colitis**
Disruption of tight junctions and the mucus film covering the epithelial layer causes increased permeability of the intestinal epithelium, resulting in increased uptake of luminal antigens. Macrophages and dendritic cells (innate immune cells), on recognition of non-pathogenic bacteria (commensal microbiota) through molecular pattern-recognition receptors (TLR), change their functional status from tolerogenic to an activated phenotype. Activation of NF-kB pathways stimulates the transcription of proinflammatory genes, resulting in increased production of proinflammatory cytokines (TNF-α, interleukins 12, 23, 6, and 1β). After processing of antigens, macrophages and dendritic cells present them to naive CD4 T-cells, promoting differentiation into Th2 effector cells, characterised by production of interleukin 4. Natural-killer T cells are the main source of interleukin 13, which has been associated with disruption of the epithelial cell barrier. Circulating T cells bearing integrin-α4β7 bind to colonic endothelial cells of the microvasculature through the mucosal vascular addressin-cell adhesion molecule 1, whose expression is enhanced in the inflamed intestine, leading to increased entry of gut-specific T cells into the lamina propria. Upregulation of inflammatory chemokines, such CXCL1, CXCL3, and CXCL8, leads to recruitment of circulating leucocytes which perpetuates the cycle of inflammation. TLR=Toll-like receptor. HLA=human leucocyte antigen. IL=interleukin. TNF=tumour necrosis factor. NF-κB=nuclear factor-κB. Th=T-helper. NKT=natural killer T-cell. CXCL=chemokine. Treg=regulatory T cell. MAdCAM-1=mucosal addressin-cell adhesion molecule 1.

TLR3 and TLR5, whereas TLR2 and TLR4 are scarce or absent.[44] By contrast, TLR4 expression is substantially increased in lamina propria cells of patients with ulcerative colitis.[45] Polymorphisms in TLRs can alter susceptibility to enteric infections or change the ability of the adaptive immune response to become tolerant to commensal bacteria. The TLR4 D299G polymorphism might be an important risk factor for ulcerative colitis in white patients.[46] Activation of TLRs triggers innate and adaptive immune responses that lead to activation of the transcription factor nuclear factor-κB (NF-κB) and other transcription factors that are important in activation of the inflammatory cascade.[47] In chronic intestinal inflammation, NF-kB regulates proinflammatory and cell survival functions in macrophages and T cells,[48,49] but is also protective in epithelial cells,[50] which makes its role in intestinal inflammation complicated and dependent on cell type.

Dysregulation of immunological responses
In the mucosa of patients with ulcerative colitis, the homoeostatic balance between regulatory and effector T-cells (eg, T-helper [Th] 1, Th2, and Th17) is disturbed. Evidence suggests that ulcerative colitis is associated with an atypical Th2 response mediated by non-classic natural killer T-cells producing interleukins 5 and 13. Interleukin 13 is of particular importance because it exerts cytotoxic functions against epithelial cells, including induction of apoptosis and alteration of the protein composition of tight-junctions.[35,51]

Natural killer T-cells are increased in the lamina propria of an inflamed colon and are capable of producing many Th2 cytokines; first interleukin 4, which is then rapidly superseded by interleukin 13.[52,53] Interleukin 13 can exert a positive feedback effect on natural killer T-cells, thus amplifying tissue injury. Interleukin 13 and natural killer T-cells seem to have a key role in the pathogenesis of

ulcerative colitis, because evidence[54] shows that blockade of this interleukin and depletion of these T cells can prevent colitis development. Loss-of-function mutations in either interleukin-10 receptor-1 or intereukin-10 receptor is associated with severe ulcerative colitis, probably because of an absence of interleukin-10 signalling.[55]

Tumor necrosis factor (TNF)-α is elevated in the blood,[56] stool samples[57] and mucosa[58] of patients with ulcerative colitis. These findings, together with the effectiveness of anti-TNF treatment for ulcerative colitis, corroborate the importance of TNF-α in the pathogenesis of the disease.

Leucocyte recruitment

Recruitment of circulating leucocytes from the systemic circulation to the inflamed mucosa by release of chemoattractants, such as CXCL8 (which is upregulated in patients with ulcerative colitis),[59] is important for amplification of the inflammatory response.

Proinflammatory cytokines upregulate the expression of adhesion molecules—eg, mucosal addressin cellular adhesion molecule-1 (MAdCAM-1)[60]—on the vascular endothelium of mucosal blood vessels, which promotes leucocyte adhesion and extravasation into the tissue, thus perpetuating the cycle of inflammation. MAdCAM-1, through interaction with α4β7 integrin, mediates lymphocyte homing to gut-associated lymphoid tissue during inflammation.[61] Antibodies to either MAdCAM-1 or its ligand α4β7 (eg, vedolizumab) and to the β7 subunit of this heterodimeric integrin (eg, etrolizumab) prevent lymphocyte recruitment and reduce the severity of colonic inflammation (appendix p 6).

Genetic factors

Genome-wide association studies have revolutionised the complex field of polygenic diseases and have led to the discovery of several susceptibility genes for ulcerative colitis, thus providing novel insights into disease pathogenesis. Associations within the major histocompatibility complex class-2 region near HLA-DRA are the most significant.[62] HLA haplotype DRB1*0103 is significantly associated with disease susceptibility, extensive disease, and an increased risk of colectomy (OR 84, 95% CI 9–785; $p<0.0001$).[63] Up to now, 47 susceptibility loci have been associated with ulcerative colitis, including 20 that overlap with Crohn's disease—eg, interleukins 23 and 10, and janus kinase-2 pathway genes (appendix pp 3–5).[64] Identification of risk loci specific for ulcerative colitis, such as hepatocyte nuclear factor-4α, CDH1, and laminin-β1, which code for proteins that play key parts in epithelial cell adhesion, emphasises the role of defective barrier function in disease pathogenesis.[65] Mutation in the protein E-cadherin is the first documented genetic correlation between colorectal cancer and ulcerative colitis.[66]

In summary, the main abnormality driving inflammation in ulcerative colitis involves an exaggerated T-cell

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Panel 1: Diagnosis of ulcerative colitis

Clinical features
- Rectal bleeding
- Diarrhoea
- Urgency
- Tenesmus
- Abdominal pain
- Fever (severe cases)
- Extraintestinal manifestations

Endoscopic features
- Loss of vascular pattern
- Erythema
- Granularity
- Friability
- Erosions
- Ulcerations
- Spontaneous bleeding

Pathological features
- Distortion of crypt architecture
- Crypt abscesses
- Lamina propria cellular infiltrate (plasma cells, eosinophils, lymphocytes)
- Shortening of the crypts
- Mucin depletion
- Lymphoid aggregates
- Erosion or ulceration

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(modified atypical Th2) response, which causes mucosal hyper-responsiveness to commensal bacteria in genetically predisposed hosts. Evolving knowledge of disease pathophysiology is crucial for development of novel treatment strategies (appendix p 6).

Diagnosis

Diagnosis of ulcerative colitis is based on clinical symptoms confirmed by objective findings from endoscopic[67] and histological examinations (panel 1, figure 2). Infectious (eg, bacterial, parasitic, viral, and fungal) and non-infectious (eg, microscopic colitis, malabsorption of bile acid, bacterial overgrowth, malignant causes, and diarrhoea induced by drugs) causes of diarrhoea should be ruled out before a diagnosis is made. Inflammation generally starts in the rectum and extends proximally, in an uninterrupted pattern, involving part of, or the entire, colon. However, some patients with proctitis or left-sided colitis have a cecal patch of inflammation,[68] and rectal sparing is sometimes observed. Dependent on the colonic segments involved, disease extent can be classified as proctitis, left-sided colitis, or pancolitis.[2] Extent should be assessed at diagnosis, because knowledge of the anatomic extent of mucosal inflammation is essential for selection of appropriate topically administered treatments, and has prognostic implications for short-term and long-term follow-up. Classification of
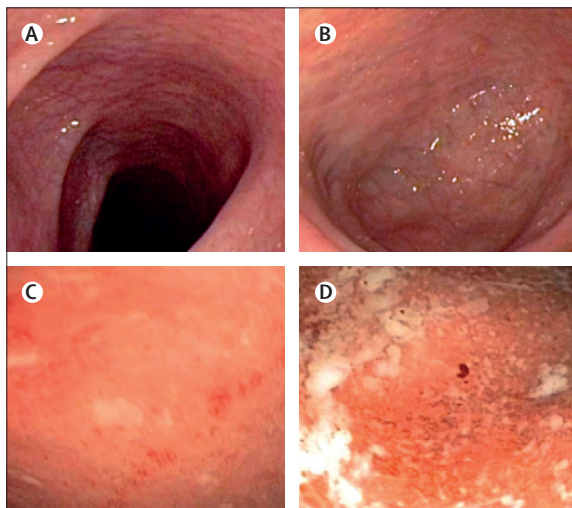
Figure 2: Mayo endoscopic score for ulcerative colitis
(A) Score 0=normal; endoscopic remission. (B) Score 1=mild; erythema, decreased vascular pattern, mild friability. (C) Score 2=moderate; marked erythema, absent vascular pattern, friability, erosions. (D) Score 3=severe; spontaneous bleeding, ulceration. Images courtesy of Elena Ricart.

Panel 2: Montreal classification of extent and severity of ulcerative colitis

- E1 (proctitis): inflammation limited to the rectum
- E2 (left-sided; distal): inflammation limited to the splenic flexure
- E3 (pancolitis): inflammation extends to the proximal splenic flexure
- S0 (remission): no symptoms
- S1 (mild): four or less stools per day (with or without blood), absence of systemic symptoms, normal inflammatory markers
- S2 (moderate): four stools per day, minimum signs of systemic symptoms
- S3 (severe): six or more bloods per day, pulse rate of ≥90 beats per min, temperature ≥37·5°C, haemoglobin concentration <105 g/L, erythrocyte sedimentation rate ≥30 mm/h

E=extent. S=severity.

disease severity is based on the number of daily stools and the presence (or absence) of systemic signs of inflammation, such as fever and tachycardia (panel 2).[2] Patients with pancolitis might sometimes show diffuse inflammation in the distal few cm of the terminal ileum. This symptom, known as backwash ileitis, and rectal sparing, are both highly associated with the presence of concomitant primary sclerosing cholangitis.[69] The appendix (p 7) shows other extraintestinal manifestations.

Natural history of the disease
The clinical course of ulcerative colitis is characterised by alternating periods of remission and relapse. At diagnosis, most patients have mild to moderate symptoms, and less than 10% have severe disease.[70] On the basis of the pattern of disease activity in time, patients can be classified into different subgroups. In a population-based study, 580 (50%) of 1161 the patients remained in clinical remission or with mild symptoms

after 10 years of follow-up; in almost 661 (57%) of patients, the disease followed a chronic intermittent course; and 209 (18%) had chronic continuous activity.[71] A short period (2 years) from diagnosis to the first flare, presence of fever or weight loss at diagnosis, and active disease in the preceding year might increase the risk of subsequent relapse.[72]

Extension of colonic disease can occur in time. At diagnosis, 30–50% of patients have disease confined to the rectum or the sigmoid colon (distal colitis), 20–30% have left-sided colitis, and about 20% have pancolitis.[73] Of those with distal colitis, 25–50% progress to more extensive forms of the disease in time.[74] Patients who are diagnosed at a young age (eg, 15–30 years), and those with concomitant primary sclerosing cholangitis, are more likely to have extensive disease at presentation than are those diagnosed later in life. Disease flares associated with progression of anatomic extent (eg, from proctitis to left-sided colitis or pancolitis) usually follow a severe course and require more intensive medical treatment than do non-progressive flares.[75] The anatomical extent of mucosal inflammation is clearly one of the most important factors determining disease course; patients with more severe disease tend to have more extensive forms (pancolitis) than do those with less severe disease. Furthermore, disease extent is an important predictor of colectomy (patients with extensive colitis have a risk of 3·5 to four times greater than those with proctitis)[71,76] and colorectal cancer.[77] Colectomy rates within 10 years of diagnosis are 20–30%, increasing to 40% in patients with long-lasting and extensive disease.[72,78] In time, rates of colectomy decrease, with most done in the first 2 years of disease onset and in patients with pancolitis.[79]

Despite the often severe disease manifestations, patients with ulcerative colitis do not have an increased mortality risk compared with the general population.[80]

Management
Medical treatment
Treatment goals in ulcerative colitis have evolved from treatment of symptoms and induction of clinical remission to more stringent outcomes, including maintenance of steroid-free remission, prevention of hospital admission and surgery, mucosal healing, improved quality of life, and avoidance of disability.[81] Treatment for ulcerative colitis consists mainly of mesalazine, corticosteroids, immunosuppressive drugs, and monoclonal antibodies to TNF-α. Treatment success is dependent on several factors, such as use of the right drug for the right indication (induction vs maintenance), optimisation of the dose, and maximisation of drug adherence (non-adherence to mesalazine is associated with increased rates of relapse).[82]

Treatment should be tailored to disease activity (mild, moderate, severe) and the extent of colonic involvement (proctitis, left-sided colitis, or pancolitis; figure 3).[83–85]
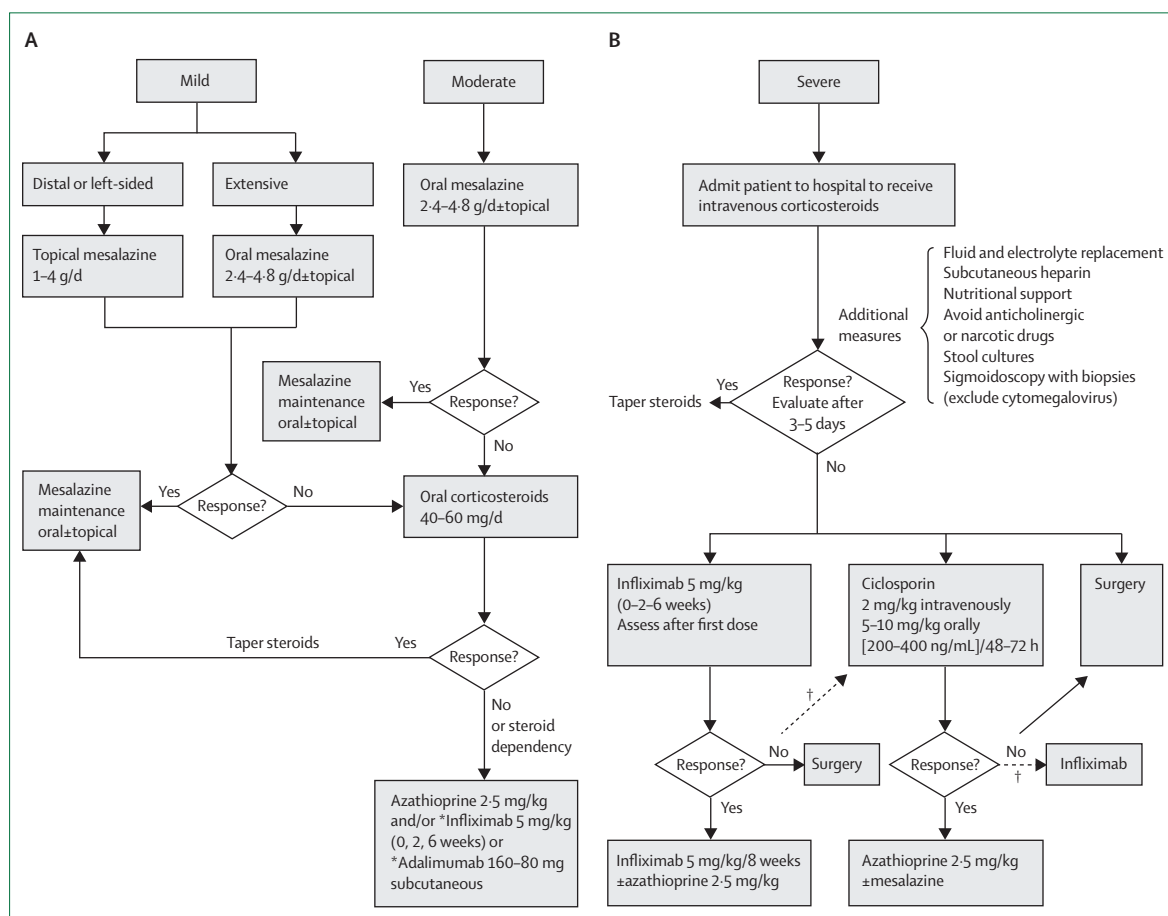
Figure 3: Treatment algorithm for ulcerative colitis of varying severities
(A) Mild to moderate ulcerative colitis. (B) Severe ulcerative colitis. †Carefully selected patients at specialist centres. *Dependent on the severity of symptoms and how quickly remission needs to be induced.

Induction of response and remission

Mild to moderately active disease

Mesalazine is the first-line treatment for mild to moderately active ulcerative colitis.[83–86] Oral mesalazine is available in different formulations (table 2) with different release characteristics (figure 4), all of which have similar effectiveness.[83,84,87] Mild to moderate proctitis is best treated with 1 g per day of topical mesalazine (suppositories), which is more effective than either topical steroids[88] or oral mesalazine. Mildly to moderately active proctosigmoiditis can be treated with topical or oral mesalazine, whereas extensive colitis should always receive oral mesalazine. Combined treatment (oral and topical) leads to higher remission rates than does either treatment alone.[89,90]

The optimum dose of oral mesalazine for induction of remission in mild disease is 2·4 g per day. Patients with moderate symptoms, those with previous steroid use, and those with a history of several drugs are more likely to benefit from higher doses (4·8 g per day) than are other patients.[91,92] Oral mesalazine generally acts in 2–4 weeks.[87] Probiotics are not effective.[93] If symptoms do not improve quickly, oral corticosteroids should be started.[84] Although almost 70% of patients respond to the first course of corticosteroids, 22% develop steroid dependency in the first year of treatment, and only half maintain corticosteroid-free remission.[94] For initial corticosteroid dosage, differences between prednisone 40 mg per day and 60 mg per day were not significant, and the 60 mg dose had increased toxic effects.[95] No randomised trials have assessed the optimum duration of corticosteroid treatment and a tapering protocol to maximise its effectiveness, but maximum dose should be maintained until a significant clinical improvement is achieved. Patients with corticosteroid-dependent disease, and those who relapse despite optimum doses of mesalazine, can be treated with azathioprine or mercaptopurine,[96] but the effectiveness of these drugs is fairly moderate.[97] The dose of azathioprine is 2·5 mg/kg daily and for mercaptopurine is 1–1·5 mg/kg. Outpatients with moderately active ulcerative colitis who do not respond to conventional treatment can be given infliximab or adalimumab,[98–100] either alone or in combination with azathioprine.

A comparative effectiveness trial showed that anti-TNF treatment with infliximab in combination with

	Manufacturer	Unit strength	Formulation	Sites of delivery	Daily dose	
					Induction of remission	Maintenance of remission
Olsalazine						
Dipentum	UCB Manufacturing, Rochester, NY, USA	250 mg tablets	5-ASA dimer linked by azo-bond	Colon	2–3 g*	1 g*
Sulfasalazine						
Azulfidine†	Pfizer, NY, USA	500 mg tablets (containing 200 mg 5-ASA)	5-ASA linked to sulfapyridine by azo-bond	Colon	4–6 g* (0·8–1·6 g 5-ASA)	4–6 g* (0·8–1·6 g 5-ASA)
Salazopyrin‡	Pfizer, Europe	500 mg tablets (containing 200 mg 5-ASA)	5-ASA linked to sulfapyridine by azo-bond	Colon	4–6 g* (0·8–1·6 g 5-ASA)	4–6 g* (0·8–1·6 g 5-ASA)
Balsalazide						
Colazal†	Saliz Pharmaceuticalos, Raleigh, NC, USA	750 mg tablets (containing 267 mg 5-ASA)	5-ASA linked to 4-aminobenzoyl-beta-alanine by azo bond	Colon	2–6·75 g* (0·7–2·4 g 5-ASA)	2–6·75 g* (0·7–2·4 g 5-ASA)
Colazide§	Almirall, London, UK	750 mg tablets (containing 267 mg 5-ASA)	5-ASA linked to 4-aminobenzoyl-beta-alanine by azo bond	Colon	2–6·75 g* (0·7–2·4 g 5-ASA)	2–6·75 g* (0·7–2·4 g 5-ASA)
Mesalazine						
Asacol†	Warner Chilcott Laboratories, Rockaway, NJ, USA	400 mg tablets	5-ASA coated with Eudragit-S	Distal ileum, colon	2·4–4·8 g¶	1·6 g–2·4 g¶
Asacol HD†	Warner Chilcott Laboratories, Rockaway, NJ, USA	800 mg tablets	5-ASA coated with Eudragit-S	Distal ileum, colon	2·4–4·8 g¶	1·6 g–2·4 g¶
Claversal‡	Merck Sharp, Madrid, Spain	250–500 tablets	5-ASA coated with Eudragit-L	Ileum, colon	1·5–4 g¶	0·75–4 g¶
Salofalk‡	Dr Falk Pharma, Freiburg, Germany	0·5§, 1¶, 1·5¶ g sachets	5-ASA coated with Eudragit-L	Ileum, colon	1·5–4 g¶	0·75–4 g¶
Salofalk Granu-Stix†	Dr Falk Pharma, Freiburg, Germany	0·5 , 1 g sachets	5-ASA coated with Eudragit-L100, polyacrylate-dispersion, povidone K (Eudragit-NE 40D, Nonoxinol 100), simeticone	Colon (80%), sigmoid and rectum	1·5–4·5 g¶	1·5–3 g¶
Apriso†	Salix pharmaceuticals, Raleigh, NC, USA	375 mg tablets	5-ASA coated with Eudragit-L100, polyacrylate-dispersion, povidone K (Eudragit-NE 40D, Nonoxinol 100), simeticone	Colon (80%), sigmoid and rectum	1·5–4·5 g¶	1·5–3 g¶
Pentasa‡	Ferring Pharmaceuticals, Kiel Germany	250–500 mg tablets, 1 g sachets	5-ASA microgranules coated in ethylcellulose	Small bowel, colon	2–4 g¶	1·5–4 g¶
Lialda†	Shire US, Wayne, PA, USA	1200 mg tablets	5-ASA coated with Multi Matrix system with lipophilic and hydrophilic matrices	Ileum, colon	2·4–4·8 g¶	2·4 g¶
Mezavant‡	Shire, Dublin, Ireland	1200 mg tablets	5-ASA coated with Multi Matrix system with lipophilic and hydrophilic matrices	Ileum, colon	2·4–4·8 g¶	2·4 g‡¶

5-ASA=5-aminosalicylic acid. *Divided doses. †USA. ‡Europe. §UK. ¶Single dose.

Table 2: Oral aminosalicylate formulations

azathioprine was more effective than either drug alone.[101] Combination treatment is the preferred strategy for most patients. In the UK, infliximab is not recommended in the outpatient setting because of a scarcity of data for cost-effectiveness.[83] Infliximab is given intravenously at 5 mg/kg at 0, 2, and 6 weeks, and every 8 weeks thereafter. Adalimumab is given subcutaneously at 160 mg at week 0, 80 mg at week 2, and then 40 mg every 2 weeks. The appendix (pp 8–9) shows contraindications and preventive measures before anti-TNF treatment.

Severe active disease

Patients with severe colitis should be admitted to hospital for treatment with intravenous corticosteroids (figure 3), because of their high risk for colectomy.[102] Concomitant infection with *Clostridium difficile* and cytomegalovirus should be ruled out.[103,104] The overall response rate to intravenous corticosteroids in severe acute colitis is almost 70%. After the first course of corticosteroids, rates of colectomy in the short term (from the same admission up to 2 months) are about 30%.[105] Early identification of patients for whom intravenous corticosteroids are likely to be ineffective, careful monitoring by gastroenterologists and surgeons, and early introduction of rescue treatments for patients with steroid-refractory disease are crucial to minimise morbidity and mortality. The likelihood of colectomy is related to disease severity[106] and presence of deep colonic ulcerations on admission.[107] Continued high numbers of daily stools, presence of fecal blood, and elevated concentrations of C-reactive protein after 3 days of intensive treatment with corticosteroids are the main factors associated with steroid refractoriness, with an
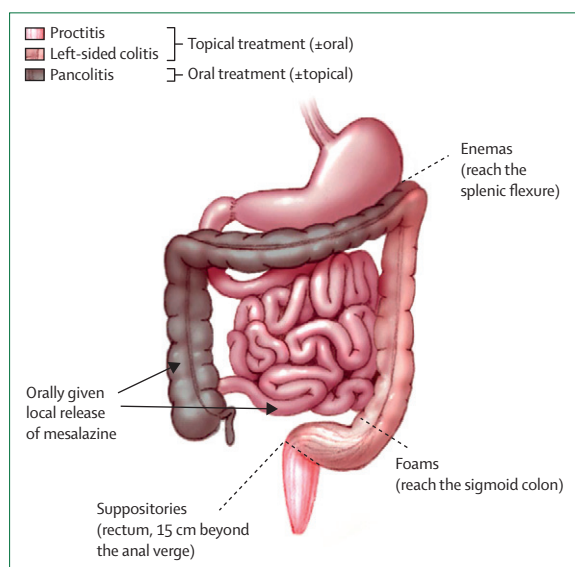
Proctitis — Topical treatment (±oral)
Left-sided colitis —
Pancolitis — Oral treatment (±topical)

Enemas (reach the splenic flexure)

Orally given local release of mesalazine

Foams (reach the sigmoid colon)

Suppositories (rectum, 15 cm beyond the anal verge)

Figure 4: **Release of mesalazine preparations**

immediate risk of colectomy up to 85%.[108] No improvement after 3–5 days of intravenous steroids is an indication to start immediate rescue treatment.[83,84] Infliximab, ciclosporine, tacrolimus, and surgery are all effective rescue treatments (figure 3).

Treatment strategies should be individualised for each patient, accounting for age, comorbidities, and maintenance treatment at the time of relapse (patients starting ciclosporine after azathioprine failure are more likely to need colectomy than are those who have not received azathioprine).[109] Ciclosporine and tacrolimus are highly effective for short-term clinical improvement with response rates of about 60–80%.[110,111] However, use of these drugs has been limited by serious adverse events[112] and low effectiveness for maintenance of colectomy-free remission in the long term.[109,111] Ciclosporine is first given intravenously at doses of 2–4 mg/kg per day,[110,113] and is then converted to an oral microemulsion at doses of 5–10 mg/kg. Doses are adjusted to maintain trough serum concentrations between 200 and 400 ng/mL. Tacrolimus is given orally at doses of 0·1–0·2 mg/kg. Doses are adjusted to maintain trough serum concentrations between 5 and 10 ng/mL. The appendix (p 10) lists adverse effects of ciclosporine and tacrolimus. Patients given steroids and ciclosporine or tacrolimus should receive prophylaxis with cotrimoxazole against *Pneumocystis jirovecii*.[114] Similar to ciclosporine, infliximab is likewise highly effective, achieving clinical response rates of 70% (95% CI 65–71) and remission rates of 40% (36–44).[115] Infliximab is first given intravenously at a dose of 5 mg/kg at weeks 0, 2, and 6.

Whether the optimum rescue treatment in patients with severe steroid-refractory colitis is ciclosporine (or alternatively tacrolimus) or infliximab is unclear. A randomised trial showed similar short-term response rates

with both drugs (ciclosporine 85·4% *vs* infliximab 85·7%; p=0·97) and no difference in colectomy rates after 3 months (18% *vs* 21%; p=0·66).[116] In view of these similar outcomes, infliximab might be preferred compared with ciclosporine because it can be continued as maintenance treatment in responding patients, particularly in those for whom azathioprine has been ineffective. Switching of cyclosporine to infliximab or vice versa could be effective rescue treatment for carefully selected patients at specialist centres.[117] Nevertheless, this strategy has a substantial risk of serious adverse events with restricted effectiveness in the long term.[118]

Maintenance of remission
Mesalazine is the basis of treatment for maintenance of remission in ulcerative colitis. However, the most appropriate maintenance treatment for an individual patient is established by several factors, including disease extent and severity, treatment for induction of remission, and failure of previous maintenance treatments. Most patients can stay in remission using oral once-daily mesalazine at doses of 1·6–3·0 g per day, maintaining remission rates of about 70–90%.[119,120] No significant dose–response relation has been noted between different doses.[121] Remission of proctitis and distal colitis can be maintained with rectal mesalazine; probiotics are not effective.[93] Corticosteroids, either topical or oral, are not effective for maintenance of remission. Patients who have frequent relapses despite optimum doses of mesalazine, those with steroid dependency, and those previously treated with cyclosporine or tacrolimus for a severe flare, should be given azathioprine[122] or antiTNF drugs for maintenance of remission.[96,98,99,123] Azathioprine discontinuation is associated with a high rate of relapse.[124]

Patients with steroid-refractory ulcerative colitis who have responded to induction with infliximab or adalimumab should be maintained on this treatment,[125] because scheduled retreatment (every 8 weeks for infliximab and every 2 weeks for adalimumab) is effective for maintenance of remission and mucosal healing,[98,99] and for reduction of hospital admission and colectomy rates.[126] In the UK, infliximab and adalimumab are not recommended for maintenance treatment because of low rates of steroid-free remission.[83] Mucosal healing at week 8 is associated with a reduced rate of colectomy in the next year, and some clinicians have already incorporated endoscopic assessment at week 8 into clinical practice.[127]

Surgery for ulcerative colitis
Treatment
Although the basis of ulcerative colitis treatment is medical, about 20–30% of patients eventually need surgery.[78,128] Indications for surgical treatment of ulcerative colitis are divided into emergency, urgent, and elective. Emergency procedures are done for life-threatening complications of fulminant colitis that is unresponsive to medical treatment. Urgent surgery is indicated in

patients with severe ulcerative colitis admitted to hospital who do not respond to intensive medical treatment. Refractoriness or intolerance to long-term maintenance treatments and dysplasia or colorectal cancer are the main indications for elective procedures.[129] Although mortality related to severe attacks of ulcerative colitis has substantially decreased to less than 1% in past decades,[105] a delay in indicated surgery can increase the risk of postoperative complications and mortality.[130]

Choice of surgical procedure is dependent on several factors, including indication (urgent or elective), patient comorbidities, and surgeon expertise. The aim of emergency and urgent surgery is to restore patient health by removal of the burden of the inflamed colon. Hence, the main procedure in these situations is a subtotal colectomy with a temporary ileostomy with no removal of the rectal stump.[129] Construction of the pouch should be avoided in the acute setting because of a high risk of pelvic bleeding, sepsis, and injury to pelvic nerves. After the patient has fully recovered, a restorative operation with construction of the ileal-pouch anal anastomosis (IPAA) and ileostomy closure can be done with a reduced risk of complications.

Proctocolectomy with IPAA is the standard of care for elective surgery (figure 5). Although colectomy with IPAA can be done at the time of pouch construction without a diverting ileostomy (one stage), the two-stage procedure is almost always preferred to minimise the risk of pelvic sepsis.[131] With the advent of new technologies, laparoscopic proctocolectomy is evolving and becoming the procedure of choice in centres with much experience of this technique. Laparoscopic colectomy facilitates subsequent proctectomy and reservoir construction,[132] and is associated with a reduction in time to diverting ileostomy closure after creation of the IPAA.[133] Although proctocolectomy with IPAA construction is the standard of care for surgical treatment, total colectomy with ileorectal anastomosis could be considered for carefully selected patients—eg, elderly people; however, in these cases, continued surveillance of the rectum is needed because of the persistent cancer risk.

Complications

Proctocolectomy is associated with substantial short-term and long-term morbidity. Early postoperative small-bowel obstruction occurs in up to 15% of patients after IPAA.[134] Pelvic sepsis is the most serious early complication of ileal pouch surgery, with rates up to 20%,[135] and is the main cause of pouch failure. Early treatment is essential to minimise the negative effect on the long-term pouch outcomes. Preoperative use of corticosteroids[136] and infliximab,[137] but not azathioprine,[138] increases the risk of postoperative septic complications in the short-term. Long-term complications include small bowel obstruction (30% at 10 years),[134] anastomotic strictures (8–14% at 10 years),[139] pouchitis (50% by 3–4 years),[140] sexual dysfunction, female infertility with a three times increased risk after IPAA,[141] and pouch failure.

Risk of colorectal cancer in ulcerative colitis is increased in patients with long-standing disease compared with the general population, with a cumulative risk of 2% after 10 years of diagnosis, 8% after 20 years, and 18% after
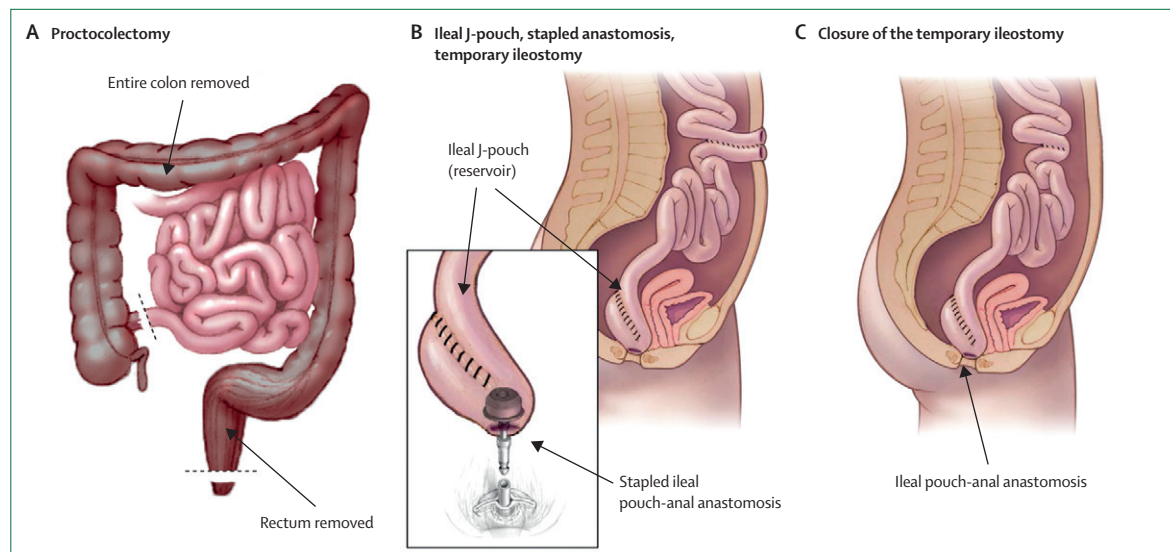

***Figure 5:* Proctocolectomy with ileal pouch-anal anastomosis**
(A) Proctocolectomy. (B) Ileal J-pouch, stapled anastomosis, and temporary ileostomy. (C) Closure of the temporary ileopstomy. The entire surgical procedure is based on four steps: removal of the colon; pelvic dissection and rectum removal sparing the pelvic nerves and the anal sphincter; construction of the ileal pouch, usually with the last 30–40 cm of the terminal ileum; and anastomosis of the pouch to the canal anal. Ileal pouch-anal anastomosis can be done either with the double-stapled technique (as shown), or with mucosectomy and hand-sewn anastomosis; the stapled anastomosis is associated with better functional outcomes than the hand-sewn technique. The main drawback of the stapled technique is the risk of future episodes of inflammation in the remaining 1·5–2 cm of the rectal mucosa (cuffitis), which usually responds well to topical treatment.
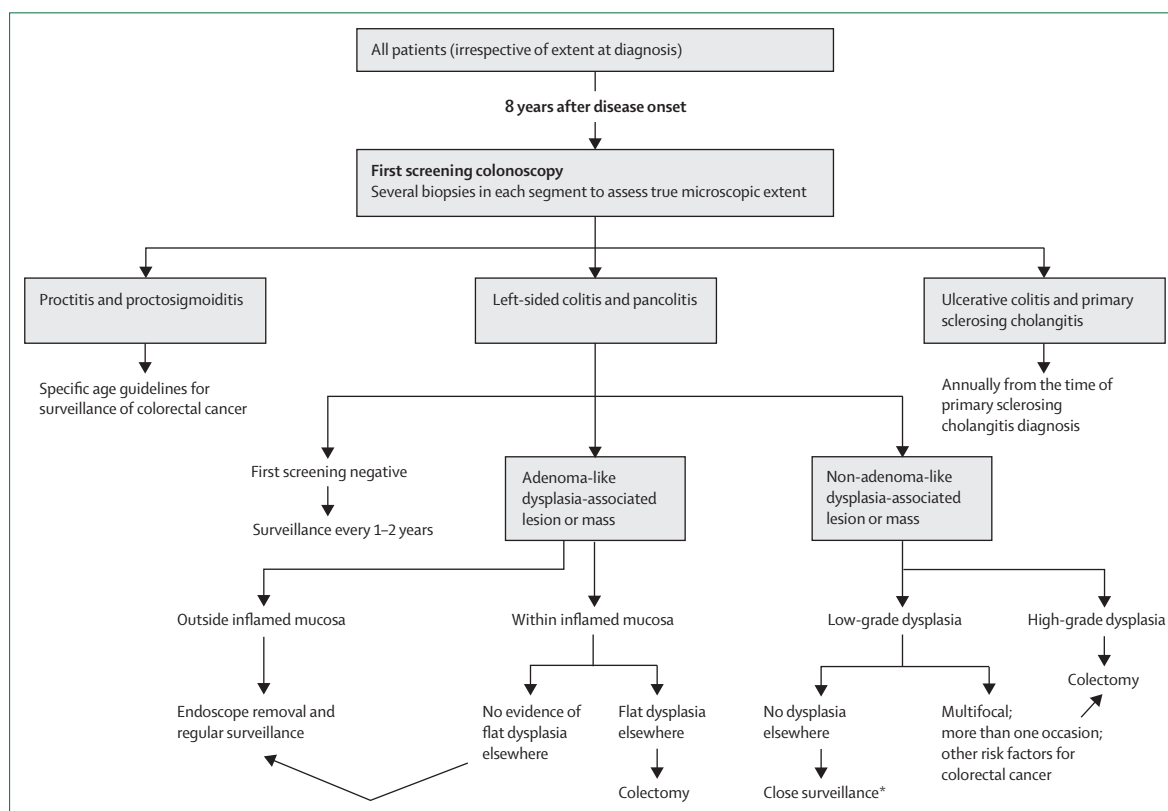
Figure 6: Surveillance of dysplasia in patients with ulcerative colitis[144–46]
*Controversial.

30 years.[142] Colorectal cancer in patients with ulcerative colitis arises from unifocal or multifocal dysplastic mucosa in areas of chronic inflammation. Thus, for surveillance purposes, disease extent should be defined as the most extensive disease at any time assessed histologically, rather than by endoscopic appearance.[143] Guidelines recommend that all patients must undergo a screening colonoscopy, with several biopsies throughout the entire colon, after 8 years of disease onset to assess the true microscopic extent of the disease.[144–146]

Several factors have been associated with an increased risk of colorectal cancer in patients with ulcerative colitis, with disease duration and extensive disease firmly established as the two most important. Pancolitis has a risk that, compared with the general population, is 14·8 times (95% CI 11·4–18·9) greater than that of colorectal cancer; left-sided colitis has an intermediate risk, and proctitis and proctosigmoiditis have little or no increased risk.[147] Other factors that raise the risk of colorectal cancer include endoscopic and histological severity of inflammation,[148] positive family history of sporadic colorectal cancer (two-times increased risk), strictures, shortened tubular colon, and several post-inflammatory pseudopolyps (two-times increased risk). In patients with a concomitant diagnosis of primary sclerosing cholangitis, risk of colorectal cancer is up to

four times greater than that in those with no primary sclerosing cholangitis. In patients with the disorder, endoscopic surveillance should start at the time of primary sclerosing cholangitis diagnosis and continue annually thereafter.[149] Surveillance programmes should ideally be done in quiescent phases of the disease, because reactive atypia can be confounded with dysplasia in the presence of active inflammation.

Diagnosis of high-grade dysplasia in patients with ulcerative colitis is a strong recommendation for colectomy. By contrast, recommendations for flat low-grade dysplasia are controversial (figure 6). For the methodology of colonoscopic surveillance, four-quadrant non-targeted biopsy specimens, obtained from every 10 cm of the colon and rectum, have been regarded as the standard of care.[150] However, evidence now shows that chromoendoscopy yields significantly (7%, 95% CI 3·2–11·3) more intraepithelial neoplastic lesions than do random biopsies, and this technique will probably become the standard of care.[151]

Despite many efforts to identify chemoprevention strategies that help reduce rates of colorectal cancer in patients with ulcerative colitis, little evidence is available. Results of one meta-analysis suggested that mesalazine , when taken on a long-term basis, can reduce the risk of colorectal cancer in patients with ulcerative colitis

(OR 0·51, 95% CI 0·37–0·69).[152] A large registry study showed that thiopurines were associated with a decrease of three times in the incidence of colorectal neoplasia in patients with extensive disease.[153] Finally, a placebo-controlled trial of ursodeoxycholic acid in patients with primary sclerosing cholangitis showed a protective effect against colorectal dysplasia and cancer in patients with concomitant ulcerative colitis.

Contributors
IO participated in the search of bibliography, writing of the report, creation of tables and figures, and approved the final draft. LE, MT, DCB, and WJS did the critical revision of the report and approved the final draft.

Conflicts of interest
DCB has received research support from Abbott, Astellas, Biocodex, Facet Biotech, and Shire; fees for consultancy from Abbott, AstraZeneca, Bayer Schering Pharma, Cellerix, TiGenix, Genentech, medac autoimmun, MSD, Otsuka, Facet Biotech, UCB; and lecture fees from Abbott, AstraZeneca, Dr Falk Pharma, Ferring, MSD, Otsuka, Shire, and UCB. All DCB's activities and contracts are in conformity with the FSA-Kodex Fachkreise (voluntary self-monitoring code for expert consultants to the pharmaceutical industry), have been checked by the legal Department of Charité Universitätsmedizin Berlin, and have been approved by the directorate of the Faculty of Medicine of Charité Universitätsmedizin Berlin. WJS has received research support from Abbott Laboratories, Bristol Meyers Squibb, Genentech, Glaxo Smith Kline, Janssen, Takeda, Novartis, Pfizer, Procter and Gamble Pharmaceuticals, Shire Pharmaceuticals, and UCB Pharma; fees for consultancy from Abbott Laboratories, ActoGeniX NV, AGI Therapeutics, Alba Therapeutics Corporation, Albireo, Alfa Wasserman, Amgen, AM-Pharma BV, Anaphore, Astellas Pharma, Athersys, Atlantic Healthcare Limited, Aptalis, BioBalance Corporation, Boehringer-Ingelheim Inc, Bristol Meyers Squibb, Celegene, Celek Pharmaceuticals, Cellerix SL, Cerimon Pharmaceuticals, ChemoCentryx, CoMentis, Cosmo Technologies, Coronado Biosciences, Cytokine Pharmasciences, Eagle Pharmaceuticals, Eisai Medical Research, Elan Pharmaceuticals, EnGene, Eli Lilly Enteromedics, Exagen Diagnostics, Ferring Pharmaceuticals, Flexion Therapeutics, Funxional Therapeutics Limited, Genzyme Corporation, Roche, Gilead Sciences, Given Imaging, Glaxo Smith Kline, Human Genome Sciences, Ironwood Pharmaceuticals, Janssen, KaloBios Pharmaceuticals, Lexicon Pharmaceuticals, Lycera Corporation, Meda Pharmaceuticals, Merck Research Laboratories, MerckSerono, Millennium Pharmaceuticals, Nisshin Kyorin Pharmaceuticals, Novo Nordisk, NPS Pharmaceuticals, Optimer Pharmaceuticals, Orexigen Therapeutics, PDL Biopharma, Pfizer, Procter and Gamble, Prometheus Laboratories, ProtAb Limited, Purgenesis Technologies, Relypsa, Salient Pharmaceuticals, Salix Pharmaceuticals, Santarus, Schering Plough Corporation, Shire Pharmaceuticals, Sigmoid Pharma Limited, Sirtris Pharmaceuticals, , SLA Pharma (UK) Limited, Targacept, Teva Pharmaceuticals, Therakos, Tillotts Pharma AG, TxCell SA, UCB Pharma, Viamet Pharmaceuticals, Vascular Biogenics Limited, Warner Chilcott UK Limited, and Pfizer; and lecture fees from Abbott Laboratories, Bristol Meyers Squibb, Janssen. All other authors declare that they have no conflicts of interest.

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