View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Elsevier - Publisher Connector

Ulcerative colitis

Ingrid Ordás, Lars Eckmann, Mark Talamini, Daniel C Baumgart, William J Sandborn

Lancet 2012; 380: 1606–19

Published Online
August 20, 2012
http://dx.doi.org/10.1016/S0140-6736(12)60150-0

Division of Gastroenterology (I Ordás MD, Prof L Eckmann MD, Prof W J Sandborn MD), **Department of Surgery** (Prof M Talamini MD), **University of California, San Diego, CA, USA; Division of Gastroenterology, Hospital Clinic, Centro de Investigación Biomédica en Red en el Área temática de Enfermedades Hepáticas y Digestivas, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain** (I Ordás); **and Department of Medicine, Division of Gastroenterology and Hepatology, Charité Medical Centre, Virchow Hospital, Medical School of the Humboldt-University of Berlin, Berlin, Germany** (Prof D C Baugmart MD)

Correspondence to:
Dr William J Sandborn, Division of Gastroenterology, University of California San Diego, La Jolla, CA 92093-0956, USA
wsandborn@ucsd.edu

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]

Search strategy and selection criteria

We searched PubMed, Cochrane, and Ovid between 2000 and 2012 with medical subject heading terms "ulcerative colitis" and "inflammatory bowel diseases", combined with the subheadings "diagnosis", "epidemiology", "etiology", "pathophysiology", "genetics", "therapy", "surgery", and "complications". We critically reviewed all relevant articles published in English. For treatment and prevention strategies, we regarded randomised placebo-controlled trials and meta-analyses as the most important study types. We reviewed relevant abstracts presented at major gastrointestinal meetings.

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]

	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**

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 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

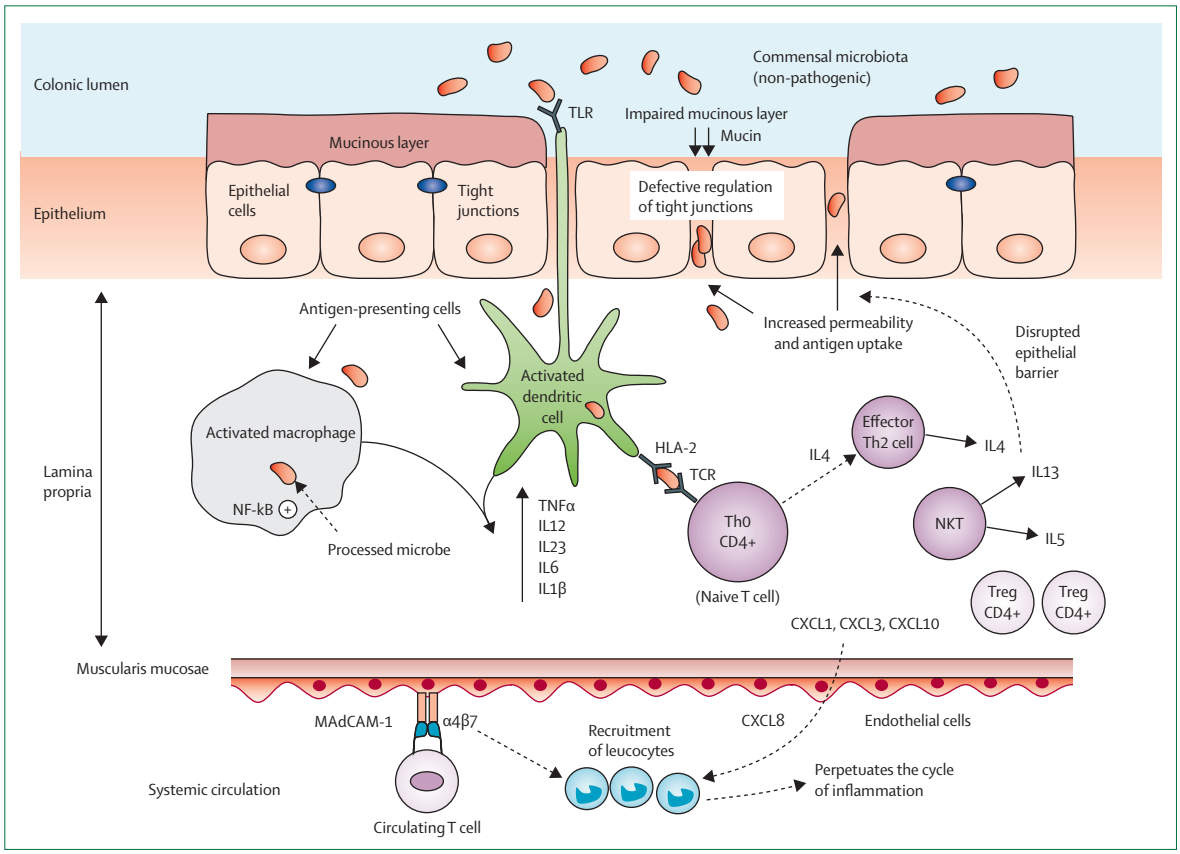

Figure 1: **Pathophysiology of ulcerative colitis**
Disruption of tight junctions and the mucus film covering the epithelial layer causes increased permeability of the intestinal epithelium, resulting in increased uptake of luminal antigens. Macrophages and dendritic cells (innate immune cells), on recognition 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 (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).

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

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

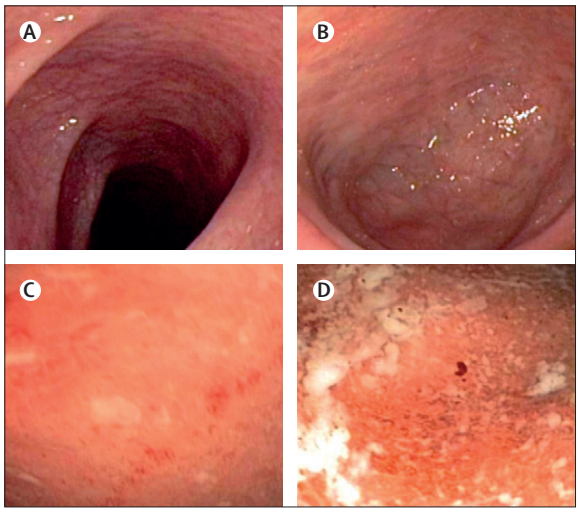

Figure 2: **Mayo endoscopic score for ulcerative colitis**
(A) Score 0=normal; endoscopic remission. (B) Score 1=mild; erythema, decreased vascular pattern, mild friability. (C) Score 2=moderate; marked erythema, absent vascular pattern, friability, erosions. (D) Score 3=severe; spontaneous bleeding, 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]

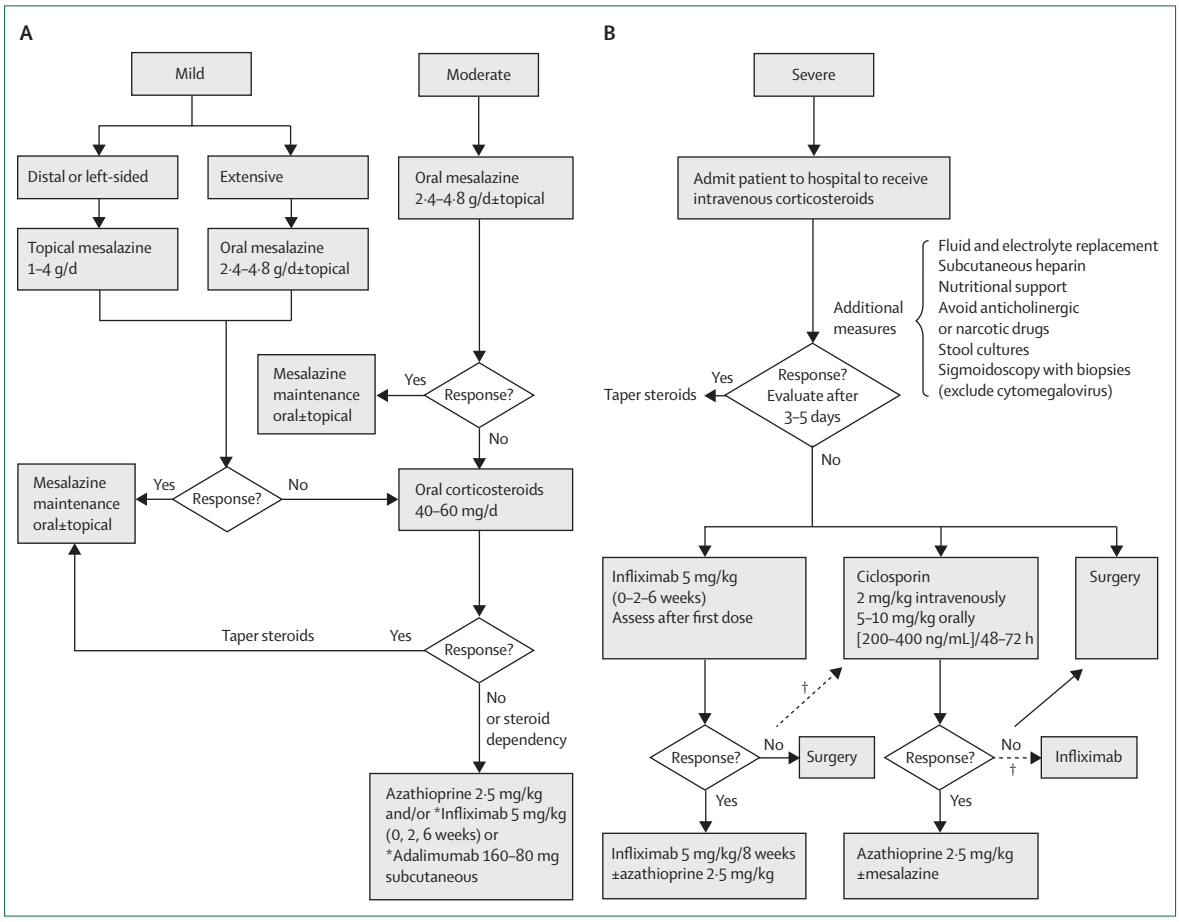

Figure 3: **Treatment algorithm for ulcerative colitis of varying severities**
(A) Mild to moderate ulcerative colitis. (B) Severe ulcerative colitis. †Carefully selected patients at specialist centres.*Dependent on the severity of symptoms and how quickly remission needs to be induced.

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

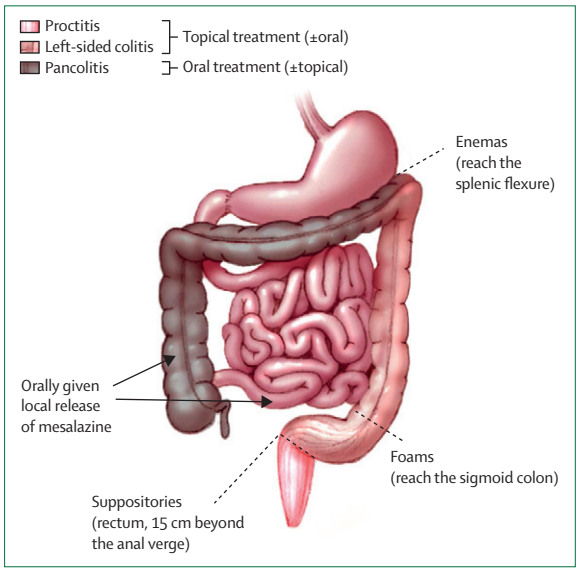

Figure 4: **Release of mesalazine preparations**

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

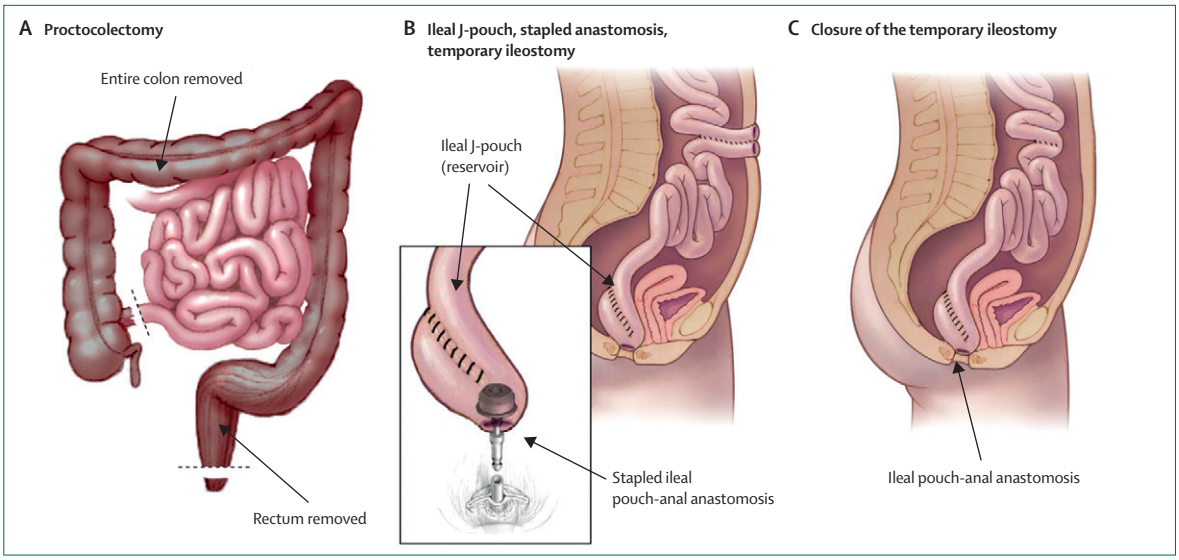

Figure 5: **Proctocolectomy with ileal pouch-anal anastomosis**
(A) Proctocolectomy. (B) Ileal J-pouch, stapled anastomosis, and temporary ileostomy. (C) Closure of the temporary ileopstomy. The entire surgical procedure is based on four steps: removal of the colon; pelvic dissection and rectum removal 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.

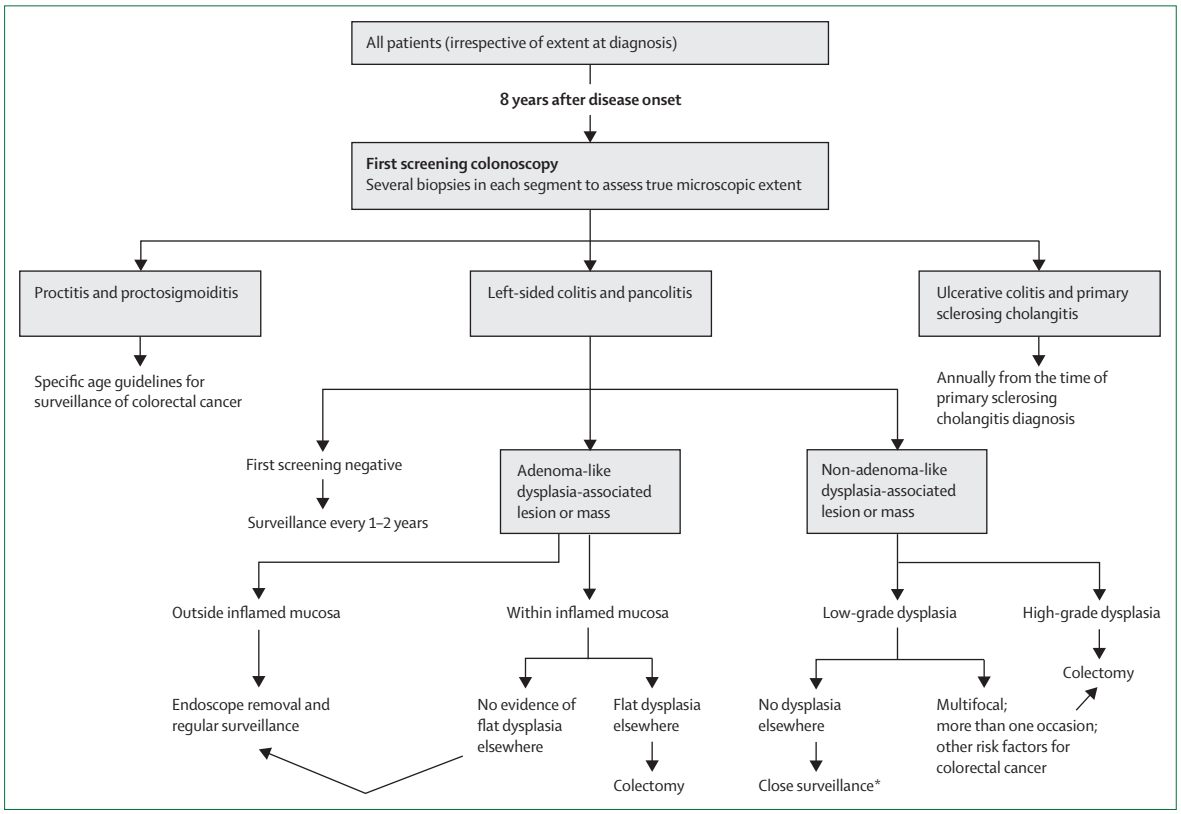

Figure 6: **Surveillance of dysplasia in patients with ulcerative colitis**[144-46]
*Controversial.

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.

References

1 Abraham C, Cho JH. Inflammatory bowel disease. *N Engl J Med* 2009; **361:** 2066–78.

2 Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: Report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005; **19** (suppl A)**:** 5–36.

3 Herrinton LJ, Liu L, Lewis JD, Griffin PM, Allison J. Incidence and prevalence of inflammatory bowel disease in a Northern California managed care organization, 1996-2002. *Am J Gastroenterol* 2008; **103:** 1998–2006.

4 Loftus CG, Loftus EV Jr, Harmsen WS, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940-2000. *Inflamm Bowel Dis* 2007; **13:** 254–61.

5 Kappelman MD, Rifas-Shiman SL, Kleinman K, et al. The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. *Clin Gastroenterol Hepatol* 2007; **5:** 1424–29.

6 Bernstein CN, Wajda A, Svenson LW, et al. The epidemiology of inflammatory bowel disease in Canada: a population-based study. *Am J Gastroenterol* 2006; **101:** 1559–68.

7 Manninen P, Karvonen AL, Huhtala H, Rasmussen M, Collin P. The epidemiology of inflammatory bowel diseases in Finland. *Scand J Gastroenterol* 2010; **45:** 1063–67.

8 Vind I, Riis L, Jess T, et al, and the DCCD study group. Increasing incidences of inflammatory bowel disease and decreasing surgery rates in Copenhagen City and County, 2003–2005: a population-based study from the Danish Crohn colitis database. *Am J Gastroenterol* 2006; **101:** 1274–82.

9 Björnsson S, Jóhannsson JH. Inflammatory bowel disease in Iceland, 1990–1994: a prospective, nationwide, epidemiological study. *Eur J Gastroenterol Hepatol* 2000; **12:** 31–38.

10 Stewénius J, Adnerhill I, Ekelund G, et al. Ulcerative colitis and indeterminate colitis in the city of Malmö, Sweden. A 25-year incidence study. *Scand J Gastroenterol* 1995; **30:** 38–43.

11 Rubin GP, Hungin AP, Kelly PJ, Ling J. Inflammatory bowel disease: epidemiology and management in an English general practice population. *Aliment Pharmacol Ther* 2000; **14:** 1553–59.

12 Loftus EV Jr, Sandborn WJ. Epidemiology of inflammatory bowel disease. *Gastroenterol Clin North Am* 2002; **31:** 1–20.

13 Bernstein CN, Rawsthorne P, Cheang M, Blanchard JF. A population-based case control study of potential risk factors for IBD. *Am J Gastroenterol* 2006; **101:** 993–1002.

14 Orholm M, Munkholm P, Langholz E, Nielsen OH, Sørensen TI, Binder V. Familial occurrence of inflammatory bowel disease. *N Engl J Med* 1991; **324:** 84–88.

15 Monsén U, Broström O, Nordenvall B, Sörstad J, Hellers G. Prevalence of inflammatory bowel disease among relatives of patients with ulcerative colitis. *Scand J Gastroenterol* 1987; **22:** 214–18.

16 Farmer RG, Michener WM, Mortimer EA. Studies of family history among patients with inflammatory bowel disease. *Clin Gastroenterol* 1980; **9:** 271–77.

17 Birkenfeld S, Zvidi I, Hazazi R, Niv Y. The prevalence of ulcerative colitis in Israel: a twenty-year survey. *J Clin Gastroenterol* 2009; **43:** 743–46.

18 Tysk C, Lindberg E, Järnerot G, Flodérus-Myrhed B. Ulcerative colitis and Crohn's disease in an unselected population of monozygotic and dizygotic twins. A study of heritability and the influence of smoking. *Gut* 1988; **29:** 990–96.

19 Orholm M, Binder V, Sørensen TI, Rasmussen LP, Kyvik KO. Concordance of inflammatory bowel disease among Danish twins. Results of a nationwide study. *Scand J Gastroenterol* 2000; **35:** 1075–81.

20 López-Serrano P, Pérez-Calle JL, Pérez-Fernández MT, Fernández-Font JM, Boixeda de Miguel D, Fernández-Rodríguez CM. Environmental risk factors in inflammatory bowel diseases. Investigating the hygiene hypothesis: a Spanish case-control study. *Scand J Gastroenterol* 2010; **45:** 1464–71.

21 Mahid SS, Minor KS, Soto RE, Hornung CA, Galandiuk S. Smoking and inflammatory bowel disease: a meta-analysis. *Mayo Clin Proc* 2006; **81:** 1462–71.

22 Beaugerie L, Massot N, Carbonnel F, Cattan S, Gendre JP, Cosnes J. Impact of cessation of smoking on the course of ulcerative colitis. *Am J Gastroenterol* 2001; **96:** 2113–16.

23 García Rodríguez LA, Ruigómez A, Panés J. Acute gastroenteritis is followed by an increased risk of inflammatory bowel disease. *Gastroenterology* 2006; **130:** 1588–94.

24 Porter CK, Tribble DR, Aliaga PA, Halvorson HA, Riddle MS. Infectious gastroenteritis and risk of developing inflammatory bowel disease. *Gastroenterology* 2008; **135:** 781–86.

25 Takeuchi K, Smale S, Premchand P, et al. Prevalence and mechanism of nonsteroidal anti-inflammatory drug-induced clinical relapse in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2006; **4:** 196–202.

26 Andersson RE, Olaison G, Tysk C, Ekbom A. Appendectomy and protection against ulcerative colitis. *N Engl J Med* 2001; **344:** 808–14.

27 Koutroubakis IE, Vlachonikolis IG. Appendectomy and the development of ulcerative colitis: results of a metaanalysis of published case-control studies. *Am J Gastroenterol* 2000; **95:** 171–76.

28 Bolin TD, Wong S, Crouch R, Engelman JL, Riordan SM. Appendicectomy as a therapy for ulcerative proctitis. *Am J Gastroenterol* 2009; **104:** 2476–82.

29 Lewis JD, Aberra FN, Lichtenstein GR, Bilker WB, Brensinger C, Strom BL. Seasonal variation in flares of inflammatory bowel disease. *Gastroenterology* 2004; **126:** 665–73.

30 Tysk C, Järnerot G. Seasonal variation in exacerbations of ulcerative colitis. *Scand J Gastroenterol* 1993; **28:** 95–96.

31 Vidal A, Gómez-Gil E, Sans M, et al. Life events and inflammatory bowel disease relapse: a prospective study of patients enrolled in remission. *Am J Gastroenterol* 2006; **101:** 775–81.

32 Cornish JA, Tan E, Simillis C, Clark SK, Teare J, Tekkis PP. The risk of oral contraceptives in the etiology of inflammatory bowel disease: a meta-analysis. *Am J Gastroenterol* 2008; **103:** 2394–400.

33 Klement E, Cohen RV, Boxman J, Joseph A, Reif S. Breastfeeding and risk of inflammatory bowel disease: a systematic review with meta-analysis. *Am J Clin Nutr* 2004; **80:** 1342–52.

34 Van Klinken BJ, Van der Wal JW, Einerhand AW, Büller HA, Dekker J. Sulphation and secretion of the predominant secretory human colonic mucin MUC2 in ulcerative colitis. *Gut* 1999; **44:** 387–93.

35 Heller F, Florian P, Bojarski C, et al. Interleukin-13 is the key effector Th2 cytokine in ulcerative colitis that affects epithelial tight junctions, apoptosis, and cell restitution. *Gastroenterology* 2005; **129:** 550–64.

36 Rahman A, Fahlgren A, Sitohy B, et al. Beta-defensin production by human colonic plasma cells: a new look at plasma cells in ulcerative colitis. *Inflamm Bowel Dis* 2007; **13:** 847–55.

37 Rahman A, Fahlgren A, Sundstedt C, Hammarström S, Danielsson A, Hammarström ML. Chronic colitis induces expression of β-defensins in murine intestinal epithelial cells. *Clin Exp Immunol* 2011; **163:** 123–30.

38 Sartor RB, Sandborn WJ. Kirsner's inflammatory bowel diseases. 6th ed. Edinburgh: Elsevier; 2003.

39 Taurog JD, Richardson JA, Croft JT, et al. The germfree state prevents development of gut and joint inflammatory disease in HLA-B27 transgenic rats. *J Exp Med* 1994; **180:** 2359–64.

40 Swidsinski A, Ladhoff A, Pernthaler A, et al. Mucosal flora in inflammatory bowel disease. *Gastroenterology* 2002; **122:** 44–54.

41 Frank DN, Robertson CE, Hamm CM, et al. Disease phenotype and genotype are associated with shifts in intestinal-associated microbiota in inflammatory bowel diseases. *Inflamm Bowel Dis* 2011; **17:** 179–84.

42 Niess JH, Brand S, Gu X, et al. CX3CR1-mediated dendritic cell access to the intestinal lumen and bacterial clearance. *Science* 2005; **307:** 254–58.

43 Hart AL, Al-Hassi HO, Rigby RJ, et al. Characteristics of intestinal dendritic cells in inflammatory bowel diseases. *Gastroenterology* 2005; **129:** 50–65.

44 Cario E, Podolsky DK. Differential alteration in intestinal epithelial cell expression of toll-like receptor 3 (TLR3) and TLR4 in inflammatory bowel disease. *Infect Immun* 2000; **68:** 7010–17.

45 Vamadevan AS, Fukata M, Arnold ET, Thomas LS, Hsu D, Abreu MT. Regulation of Toll-like receptor 4-associated MD-2 in intestinal epithelial cells: a comprehensive analysis. *Innate Immun* 2010; **16:** 93–103.

46 Shen X, Shi R, Zhang H, Li K, Zhao Y, Zhang R. The Toll-like receptor 4 D299G and T399I polymorphisms are associated with Crohn's disease and ulcerative colitis: a meta-analysis. *Digestion* 2010; **81:** 69–77.

47 Zhang FX, Kirschning CJ, Mancinelli R, et al. Bacterial lipopolysaccharide activates nuclear factor-kappaB through interleukin-1 signaling mediators in cultured human dermal endothelial cells and mononuclear phagocytes. *J Biol Chem* 1999; **274:** 7611–14.

48 Rogler G, Brand K, Vogl D, et al. Nuclear factor kappaB is activated in macrophages and epithelial cells of inflamed intestinal mucosa. *Gastroenterology* 1998; **115:** 357–69.

49 Spehlmann ME, Eckmann L. Nuclear factor-kappa B in intestinal protection and destruction. *Curr Opin Gastroenterol* 2009; **25:** 92–99.

50 Eckmann L, Nebelsiek T, Fingerle AA, et al. Opposing functions of IKKbeta during acute and chronic intestinal inflammation. *Proc Natl Acad Sci USA* 2008; **105:** 15058–63.

51 Heller F, Fromm A, Gitter AH, Mankertz J, Schulzke JD. Epithelial apoptosis is a prominent feature of the epithelial barrier disturbance in intestinal inflammation: effect of pro-inflammatory interleukin-13 on epithelial cell function. *Mucosal Immunol* 2008; **1** (suppl 1)**:** S58–61.

52 Fuss IJ, Heller F, Boirivant M, et al. Nonclassical CD1d-restricted NK T cells that produce IL-13 characterize an atypical Th2 response in ulcerative colitis. *J Clin Invest* 2004; **113:** 1490–97.

53 Steel AW, Mela CM, Lindsay JO, Gazzard BG, Goodier MR. Increased proportion of CD16(+) NK cells in the colonic lamina propria of inflammatory bowel disease patients, but not after azathioprine treatment. *Aliment Pharmacol Ther* 2011; **33:** 115–26.

54 Heller F, Fuss IJ, Nieuwenhuis EE, Blumberg RS, Strober W. Oxazolone colitis, a Th2 colitis model resembling ulcerative colitis, is mediated by IL-13-producing NK-T cells. *Immunity* 2002; **17:** 629–38.

55 Glocker EO, Kotlarz D, Boztug K, et al. Inflammatory bowel disease and mutations affecting the interleukin-10 receptor. *N Engl J Med* 2009; **361:** 2033–45.

56 Murch SH, Lamkin VA, Savage MO, Walker-Smith JA, MacDonald TT. Serum concentrations of tumour necrosis factor alpha in childhood chronic inflammatory bowel disease. *Gut* 1991; **32:** 913–17.

57 Braegger CP, Nicholls S, Murch SH, Stephens S, MacDonald TT. Tumour necrosis factor alpha in stool as a marker of intestinal inflammation. *Lancet* 1992; **339:** 89–91.

58 Masuda H, Iwai S, Tanaka T, Hayakawa S. Expression of IL-8, TNF-alpha and IFN-gamma m-RNA in ulcerative colitis, particularly in patients with inactive phase. *J Clin Lab Immunol* 1995; **46:** 111–23.

59 Matsuda R, Koide T, Tokoro C, et al. Quantitive cytokine mRNA expression profiles in the colonic mucosa of patients with steroid naïve ulcerative colitis during active and quiescent disease. *Inflamm Bowel Dis* 2009; **15:** 328–34.

60 Briskin M, Winsor-Hines D, Shyjan A, et al. Human mucosal addressin cell adhesion molecule-1 is preferentially expressed in intestinal tract and associated lymphoid tissue. *Am J Pathol* 1997; **151:** 97–110.

61 Panés J, Granger DN. Leukocyte-endothelial cell interactions: molecular mechanisms and implications in gastrointestinal disease. *Gastroenterology* 1998; **114:** 1066–90.

62 Silverberg MS, Cho JH, Rioux JD, et al. Ulcerative colitis-risk loci on chromosomes 1p36 and 12q15 found by genome-wide association study. *Nat Genet* 2009; **41:** 216–20.

63 Bouma G, Crusius JB, García-González MA, et al. Genetic markers in clinically well defined patients with ulcerative colitis (UC). *Clin Exp Immunol* 1999; **115:** 294–300.

64 Anderson CA, Boucher G, Lees CW, et al. Meta-analysis identifies 29 additional ulcerative colitis risk loci, increasing the number of confirmed associations to 47. *Nat Genet* 2011; **43:** 246–52.

65 Barrett JC, Lee JC, Lees CW, et al, and the UK IBD Genetics Consortium, and the Wellcome Trust Case Control Consortium 2. Genome-wide association study of ulcerative colitis identifies three new susceptibility loci, including the HNF4A region. *Nat Genet* 2009; **41:** 1330–34.

66 Wheeler JM, Kim HC, Efstathiou JA, Ilyas M, Mortensen NJ, Bodmer WF. Hypermethylation of the promoter region of the E-cadherin gene (CDH1) in sporadic and ulcerative colitis associated colorectal cancer. *Gut* 2001; **48:** 367–71.

67 Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med* 1987; **317:** 1625–29.

68 D'Haens G, Geboes K, Peeters M, Baert F, Ectors N, Rutgeerts P. Patchy cecal inflammation associated with distal ulcerative colitis: a prospective endoscopic study. *Am J Gastroenterol* 1997; **92:** 1275–79.

69 Loftus EV Jr, Harewood GC, Loftus CG, et al. PSC-IBD: a unique form of inflammatory bowel disease associated with primary sclerosing cholangitis. *Gut* 2005; **54:** 91–96.

70 Langholz E, Munkholm P, Nielsen OH, Kreiner S, Binder V. Incidence and prevalence of ulcerative colitis in Copenhagen county from 1962 to 1987. *Scand J Gastroenterol* 1991; **26:** 1247–56.

71 Solberg IC, Lygren I, Jahnsen J, et al, and the IBSEN Study Group. Clinical course during the first 10 years of ulcerative colitis: results from a population-based inception cohort (IBSEN Study). *Scand J Gastroenterol* 2009; **44:** 431–40.

72 Langholz E, Munkholm P, Davidsen M, Binder V. Course of ulcerative colitis: analysis of changes in disease activity over years. *Gastroenterology* 1994; **107:** 3–11.

73 Langholz E, Munkholm P, Nielsen OH, Kreiner S, Binder V. Incidence and prevalence of ulcerative colitis in Copenhagen county from 1962 to 1987. *Scand J Gastroenterol* 1991; **26:** 1247–56.

74 Langholz E, Munkholm P, Davidsen M, Nielsen OH, Binder V. Changes in extent of ulcerative colitis: a study on the course and prognostic factors. *Scand J Gastroenterol* 1996; **31:** 260–66.

75 Etchevers MJ, Aceituno M, García-Bosch O, et al. Risk factors and characteristics of extent progression in ulcerative colitis. *Inflamm Bowel Dis* 2009; **15:** 1320–25.

76 Hoie O, Wolters FL, Riis L, et al, and the European Collaborative Study Group of Inflammatory Bowel Disease. Low colectomy rates in ulcerative colitis in an unselected European cohort followed for 10 years. *Gastroenterology* 2007; **132:** 507–15.

77 Jess T, Loftus EV Jr, Velayos FS, et al. Risk of intestinal cancer in inflammatory bowel disease: a population-based study from olmsted county, Minnesota. *Gastroenterology* 2006; **130:** 1039–46.

78 Langholz E, Munkholm P, Davidsen M, Binder V. Colorectal cancer risk and mortality in patients with ulcerative colitis. *Gastroenterology* 1992; **103:** 1444–51.

79 Magro F, Rodrigues A, Vieira AI, et al. Review of the disease course among adult ulcerative colitis population-based longitudinal cohorts. *Inflamm Bowel Dis* **18:** 573–83.

80 Jess T, Gamborg M, Munkholm P, Sørensen TI. Overall and cause-specific mortality in ulcerative colitis: meta-analysis of population-based inception cohort studies. *Am J Gastroenterol* 2007; **102:** 609–17.

81 Peyrin-Biroulet L, Cieza A, Sandborn WJ, et al, for the International Programme to Develop New Indexes for Crohn's Disease (IPNIC) group. Development of the first disability index for inflammatory bowel disease based on the international classification of functioning, disability and health. *Gut* 2012; **61:** 241–47.

82 Kane SV. Systematic review: adherence issues in the treatment of ulcerative colitis. *Aliment Pharmacol Ther* 2006; **23:** 577–85.

83 Kornbluth A, Sachar DB, and the Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2010; **105:** 501–23, quiz 524.

84 Travis SP, Stange EF, Lémann M, et al, and the for the European Crohn's and Colitis Organisation (ECCO). European evidence-based Consensus on the management of ulcerative colitis: Current management. *J Crohn's Colitis* 2008; **2:** 24–62.

85 Mowat C, Cole A, Windsor A, et al, and the IBD Section of the British Society of Gastroenterology. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2011; **60:** 571–607.

86 Marshall JK, Thabane M, Steinhart AH, Newman JR, Anand A, Irvine EJ. Rectal 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2010; **1:** CD004115.

87 Sutherland L, Macdonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2006; **2:** CD000543.

88 Marshall JK, Irvine EJ. Rectal corticosteroids versus alternative treatments in ulcerative colitis: a meta-analysis. *Gut* 1997; **40:** 775–81.

89 Safdi M, DeMicco M, Sninsky C, et al. A double-blind comparison of oral versus rectal mesalamine versus combination therapy in the treatment of distal ulcerative colitis. *Am J Gastroenterol* 1997; **92:** 1867–71.

90 Marteau P, Probert CS, Lindgren S, et al. Combined oral and enema treatment with Pentasa (mesalazine) is superior to oral therapy alone in patients with extensive mild/moderate active ulcerative colitis: a randomised, double blind, placebo controlled study. *Gut* 2005; **54:** 960–65.

91 Hanauer SB, Sandborn WJ, Dallaire C, et al. Delayed-release oral mesalamine 4.8 g/day (800 mg tablets) compared to 2.4 g/day (400 mg tablets) for the treatment of mildly to moderately active ulcerative colitis: The ASCEND I trial. *Can J Gastroenterol* 2007; **21:** 827–34.

92 Sandborn WJ, Regula J, Feagan BG, et al. Delayed-release oral mesalamine 4.8 g/day (800-mg tablet) is effective for patients with moderately active ulcerative colitis. *Gastroenterology* 2009; **137:** 1934–43, e1–3.

93 Sang LX, Chang B, Zhang WL, Wu XM, Li XH, Jiang M. Remission induction and maintenance effect of probiotics on ulcerative colitis: a meta-analysis. *World J Gastroenterol* 2010; **16:** 1908–15.

94 Faubion WA Jr, Loftus EV Jr, Harmsen WS, Zinsmeister AR, Sandborn WJ. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. *Gastroenterology* 2001; **121:** 255–60.

95 Baron JH, Connell AM, Kanaghinis TG, Lennard-Jones JE, Jones AF. Out-patient treatment of ulcerative colitis. Comparison between three doses of oral prednisone. *BMJ* 1962; **2:** 441–43.

96 Ardizzone S, Maconi G, Russo A, Imbesi V, Colombo E, Bianchi Porro G. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. *Gut* 2006; **55:** 47–53.

97 Leung Y, Panaccione R, Hemmelgarn B, Jones J. Exposing the weaknesses: a systematic review of azathioprine efficacy in ulcerative colitis. *Dig Dis Sci* 2008; **53:** 1455–61.

98 Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005; **353:** 2462–76.

99 Sandborn WJ, Van Assche G, Reinisch R, et al. Adalimumab induces and maintains remission in patients with miderate-to-severe ulcerative colitis. *Gastroenterology* **142:** 257–65.

100 Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. *Gut* 2011; **60:** 780–87.

101 Panaccione R, Gosh S, Middleton S, et al. Infliximab, azathioprine, or infliximab + azathioprine for treatment of moderate to severe ulcerative colitis: The UC SUCCESS trial. *J Crohn's Colitis* 2011; **5:** S3–12.

102 Ananthakrishnan AN, Issa M, Beaulieu DB, et al. History of medical hospitalization predicts future need for colectomy in patients with ulcerative colitis. *Inflamm Bowel Dis* 2009; **15:** 176–81.

103 Ananthakrishnan AN, McGinley EL, Saeian K, Binion DG. Temporal trends in disease outcomes related to Clostridium difficile infection in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2011; **17:** 976–83.

104 Kandiel A, Lashner B. Cytomegalovirus colitis complicating inflammatory bowel disease. *Am J Gastroenterol* 2006; **101:** 2857–65.

105 Turner D, Walsh CM, Steinhart AH, Griffiths AM. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. *Clin Gastroenterol Hepatol* 2007; **5:** 103–10.

106 Dinesen LC, Walsh AJ, Protic MN, et al. The pattern and outcome of acute severe colitis. *J Crohn's Colitis* 2010; **4:** 431–37.

107 Carbonnel F, Lavergne A, Lémann M, et al. Colonoscopy of acute colitis. A safe and reliable tool for assessment of severity. *Dig Dis Sci* 1994; **39:** 1550–57.

108 Travis SP, Farrant JM, Ricketts C, et al. Predicting outcome in severe ulcerative colitis. *Gut* 1996; **38:** 905–10.

109 Moskovitz DN, Van Assche G, Maenhout B, et al. Incidence of colectomy during long-term follow-up after cyclosporine-induced remission of severe ulcerative colitis. *Clin Gastroenterol Hepatol* 2006; **4:** 760–65.

110 Lichtiger S, Present DH, Kornbluth A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* 1994; **330:** 1841–45.

111 Baumgart DC, Macdonald JK, Feagan B. Tacrolimus (FK506) for induction of remission in refractory ulcerative colitis. *Cochrane Database Syst Rev* 2008; **3:** CD007216.

112 Arts J, D'Haens G, Zeegers M, et al. Long-term outcome of treatment with intravenous cyclosporin in patients with severe ulcerative colitis. *Inflamm Bowel Dis* 2004; **10:** 73–78.

113 Van Assche G, D'Haens G, Noman M, et al. Randomized, double-blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. *Gastroenterology* 2003; **125:** 1025–31.

114 Rahier JF, Ben-Horin S, Chowers Y, et al, and the on behalf of the European Crohn's and Colitis Organisation (ECCO). European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohn's Colitis* 2009; **3:** 47–91.

115 Gisbert JP, González-Lama Y, Maté J. Systematic review: Infliximab therapy in ulcerative colitis. *Aliment Pharmacol Ther* 2007; **25:** 19–37.

116 Laharie D, Bourreille A, Branche J, et al. Ciclosporin versus infliximab in acute severe ulcerative colitis refractory to intravenous steroids: A randomized study. *J Crohn's Colitis* 2011; **5:** S3–12.

117 Leblanc S, Allez M, Seksik P, et al, and the GETAID. Successive treatment with cyclosporine and infliximab in steroid-refractory ulcerative colitis. *Am J Gastroenterol* 2011; **106:** 771–77.

118 Maser EA, Deconda D, Lichtiger S, Ullman T, Present DH, Kornbluth A. Cyclosporine and infliximab as rescue therapy for each other in patients with steroid-refractory ulcerative colitis. *Clin Gastroenterol Hepatol* 2008; **6:** 1112–16.

119 Kruis W, Jonaitis L, Pokrotnieks J, et al, and the International Salofalk OD Study Group. Randomised clinical trial: a comparative dose-finding study of three arms of dual release mesalazine for maintaining remission in ulcerative colitis. *Aliment Pharmacol Ther* 2011; **33:** 313–22.

120 Kamm MA, Lichtenstein GR, Sandborn WJ, et al. Randomised trial of once- or twice-daily MMX mesalazine for maintenance of remission in ulcerative colitis. *Gut* 2008; **57:** 893–902.

121 Sutherland L, Macdonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2006; **2:** CD000544.

122 Gisbert JP, Linares PM, McNicholl AG, Maté J, Gomollón F. Meta-analysis: the efficacy of azathioprine and mercaptopurine in ulcerative colitis. *Aliment Pharmacol Ther* 2009; **30:** 126–37.

123 Timmer A, McDonald JW, Macdonald JK. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2007; **1:** CD000478.

124 Hawthorne AB, Logan RF, Hawkey CJ, et al. Randomised controlled trial of azathioprine withdrawal in ulcerative colitis. *BMJ* 1992; **305:** 20–22.

125 D'Haens GR, Panaccione R, Higgins PD, et al. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organization: when to start, when to stop, which drug to choose, and how to predict response? *Am J Gastroenterol* 2011; **106:** 199–212, quiz 213.

126 Sandborn WJ, Rutgeerts P, Feagan BG, et al. Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab. *Gastroenterology* 2009; **137:** 1250–60, quiz 1520.

127 Colombel JF, Rutgeerts P, Reinisch W, et al. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterology* 2011; **141:** 1194–201.

128 Leijonmarck CE, Persson PG, Hellers G. Factors affecting colectomy rate in ulcerative colitis: an epidemiologic study. *Gut* 1990; **31:** 329–33.

129 Cohen JL, Strong SA, Hyman NH, et al, and the Standards Practice Task Force American Society of Colon and Rectal Surgeons. Practice parameters for the surgical treatment of ulcerative colitis. *Dis Colon Rectum* 2005; **48:** 1997–2009.

130 Randall J, Singh B, Warren BF, Travis SP, Mortensen NJ, George BD. Delayed surgery for acute severe colitis is associated with increased risk of postoperative complications. *Br J Surg* 2010; **97:** 404–09.

131 Williamson ME, Lewis WG, Sagar PM, Holdsworth PJ, Johnston D. One-stage restorative proctocolectomy without temporary ileostomy for ulcerative colitis: a note of caution. *Dis Colon Rectum* 1997; **40:** 1019–22.

132 Indar AA, Efron JE, Young-Fadok TM. Laparoscopic ileal pouch-anal anastomosis reduces abdominal and pelvic adhesions. *Surg Endosc* 2009; **23:** 174–77.

133 Fajardo AD, Dharmarajan S, George V, et al. Laparoscopic versus open 2-stage ileal pouch: laparoscopic approach allows for faster restoration of intestinal continuity. *J Am Coll Surg* 2010; **211:** 377–83.

134 MacLean AR, Cohen Z, MacRae HM, et al. Risk of small bowel obstruction after the ileal pouch-anal anastomosis. *Ann Surg* 2002; **235:** 200–06.

135 Heuschen UA, Hinz U, Allemeyer EH, et al. Risk factors for ileoanal J pouch-related septic complications in ulcerative colitis and familial adenomatous polyposis. *Ann Surg* 2002; **235:** 207–16.

136 Aberra FN, Lewis JD, Hass D, Rombeau JL, Osborne B, Lichtenstein GR. Corticosteroids and immunomodulators: postoperative infectious complication risk in inflammatory bowel disease patients. *Gastroenterology* 2003; **125:** 320–27.

137 Selvasekar CR, Cima RR, Larson DW, et al. Effect of infliximab on short-term complications in patients undergoing operation for chronic ulcerative colitis. *J Am Coll Surg* 2007; **204:** 956–62, discussion 962–63.

138 Mahadevan U, Loftus EV Jr, Tremaine WJ, et al. Azathioprine or 6-mercaptopurine before colectomy for ulcerative colitis is not associated with increased postoperative complications. *Inflamm Bowel Dis* 2002; **8:** 311–16.

139 Galandiuk S, Scott NA, Dozois RR, et al. Ileal pouch-anal anastomosis. Reoperation for pouch-related complications. *Ann Surg* 1990; **212:** 446–52, discussion 452–54.

140 Penna C, Dozois R, Tremaine W, et al. Pouchitis after ileal pouch-anal anastomosis for ulcerative colitis occurs with increased frequency in patients with associated primary sclerosing cholangitis. *Gut* 1996; **38:** 234–39.

141 Waljee A, Waljee J, Morris AM, Higgins PD. Threefold increased risk of infertility: a meta-analysis of infertility after ileal pouch anal anastomosis in ulcerative colitis. *Gut* 2006; **55:** 1575–80.

142 Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut* 2001; **48:** 526–35.

143 Mathy C, Schneider K, Chen YY, Varma M, Terdiman JP, Mahadevan U. Gross versus microscopic pancolitis and the occurrence of neoplasia in ulcerative colitis. *Inflamm Bowel Dis* 2003; **9:** 351–55.

144 Farraye FA, Odze RD, Eaden J, Itzkowitz SH. AGA technical review on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. *Gastroenterology* 2010; **138:** 746–74.

145 Biancone L, Michetti P, Travis S, et al, and the for the European Crohn's and Colitis Organisation (ECCO). European evidence-based Consensus on the management of ulcerative colitis: Special situations. *J Crohn's Colitis* 2008; **2:** 63–92.

146 Cairns SR, Scholefield JH, Steele RJ, et al, and the British Society of Gastroenterology, and the Association of Coloproctology for Great Britain and Ireland. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). *Gut* 2010; **59:** 666–89.

147 Ekbom A, Helmick C, Zack M, Adami HO. Ulcerative colitis and colorectal cancer. A population-based study. *N Engl J Med* 1990; **323:** 1228–33.

148 Rutter M, Saunders B, Wilkinson K, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. *Gastroenterology* 2004; **126:** 451–59.

149 Kornfeld D, Ekbom A, Ihre T. Is there an excess risk for colorectal cancer in patients with ulcerative colitis and concomitant primary sclerosing cholangitis? A population based study. *Gut* 1997; **41:** 522–25.

150 Levine DS, Rabinovitch PS, Haggitt RC, et al. Distribution of aneuploid cell populations in ulcerative colitis with dysplasia or cancer. *Gastroenterology* 1991; **101:** 1198–210.

151 Subramanian V, Mannath J, Ragunath K, Hawkey CJ. Meta-analysis: the diagnostic yield of chromoendoscopy for detecting dysplasia in patients with colonic inflammatory bowel disease. *Aliment Pharmacol Ther* 2011; **33:** 304–12.

152 Velayos FS, Terdiman JP, Walsh JM. Effect of 5-aminosalicylate use on colorectal cancer and dysplasia risk: a systematic review and metaanalysis of observational studies. *Am J Gastroenterol* 2005; **100:** 1345–53.

153 Beaugerie L, Seksik P, Bouvier AM, et al. Thiopurine therapy is associated with a three-fold decrease in the incidence of advanced colorectal neoplasia in IBD patients with longstanding extensive colitis: results from the CESAME Cohort. *Gastroenterology* 2009; **136** (5 suppl 1)**:** A-54. Abstr 281.