Ulcerative colitis

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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,10 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.15

Genetic factors

A family history of inflammatory bowel disease is the most important independent risk factor.9 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.7 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.11,20

Several environmental factors act as triggers or protective factors for ulcerative colitis, with cigarette smoking being the most consistent. A meta-analysis21 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.

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. Weak epidemiological evidence exists for an association between exposure to non-selective non-steroidal anti-inflammatory drugs and onset or relapse of ulcerative colitis. Appendicectomy is protective against ulcerative colitis, with the effect mainly limited to patients with acute appendicitis before age 20 years. A meta-analysis 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. Although several retrospective studies 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. Use of oral contraceptives is moderately associated with disease onset. 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.

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. Damage to the epithelial barrier leads to increased permeability, possibly due to defective regulation of tight junctions. 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.

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. 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 and disease phenotype (ulcerative colitis vs Crohn’s disease).

Therefore, ulcerative colitis seems to result from a breakdown of the homeostatic 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. 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.

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
TLR3 and TLR5, whereas TLR2 and TLR4 are scarce or absent. By contrast, TLR4 expression is substantially increased in lamina propria cells of patients with ulcerative colitis. 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. 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. In chronic intestinal inflammation, NF-κB regulates proinflammatory and cell survival functions in macrophages and T cells, but is also protective in epithelial cells, 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 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 as 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. MAAdCAM-1=mucosal addressin-cell adhesion molecule 1.
ulcerative colitis, because evidence 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 interleukin-10 receptor is associated with severe ulcerative colitis, probably because of an absence of interleukin-10 signalling. Tumor necrosis factor (TNF)-α is elevated in the blood, stool samples 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), 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)—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. 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. 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). 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). 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. Mutation in the protein E-cadherin is the first documented genetic correlation between colorectal cancer and ulcerative colitis.

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).

Diagnosis

Diagnosis of ulcerative colitis is based on clinical symptoms confirmed by objective findings from endoscopic 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, and rectal sparing is sometimes observed. Dependent on the colonic segments involved, disease extent can be classified as proctitis, left-sided colitis, or pancolitis. 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
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 stools 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.

Panel 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.

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). 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. 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) and colorectal cancer. Colectomy rates within 10 years of diagnosis are 20–30%, increasing to 40% in patients with long-lasting and extensive disease. In time, rates of colectomy decrease, with most done in the first 2 years of disease onset and in patients with pancolitis. Despite the often severe disease manifestations, patients with ulcerative colitis do not have an increased mortality risk compared with the general population.

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. 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).

Treatment should be tailored to disease activity (mild, moderate, severe) and the extent of colonic involvement (proctitis, left-sided colitis, or pancolitis; figure 3).
**Induction of response and remission**

**Mild to moderately active disease**

Mild to moderately active ulcerative colitis is best treated with 1 g per day of topical mesalazone (suppositories), which is more effective than either oral mesalazone or topical mesalazone. Mild to moderately active proctitis is best treated with 1 g per day of topical mesalazone, whereas extensive colitis should always receive oral mesalazine. Combined treatment (oral and topical) leads to higher remission rates than does either treatment alone.

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. Oral mesalazine generally acts in 2–4 weeks. Probiotics are not effective. If symptoms do not improve quickly, oral corticosteroids should be started. 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. 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. 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, but the effectiveness of these drugs is fairly moderate. 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, either alone or in combination with azathioprine.

A comparative effectiveness trial showed that anti-TNF treatment with infliximab in combination with...
azathioprine was more effective than either drug alone.\textsuperscript{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.\textsuperscript{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.\textsuperscript{102} Concomitant infection with \textit{Closstridium difficile} and cytomegalovirus should be ruled out.\textsuperscript{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%.\textsuperscript{105} Early identification of patients for whom intravenous corticosteroids are likely to be ineffecive, 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\textsuperscript{106} and presence of deep colonic ulcerations on admission.\textsuperscript{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

### Table 2: Oral aminosalicylate formulations

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Unit strength</th>
<th>Formulation</th>
<th>Sites of delivery</th>
<th>Daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Olsalazine</strong></td>
<td></td>
<td></td>
<td></td>
<td>Induction of remission</td>
</tr>
<tr>
<td>Dipentum</td>
<td>250 mg tablets</td>
<td>5-ASA dimer linked by azo-bond</td>
<td>Colon</td>
<td>2–3 g*</td>
</tr>
<tr>
<td><strong>Sulfasalazine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azulfidine†</td>
<td>500 mg tablets (containing 200 mg 5-ASA)</td>
<td>5-ASA linked to sulfapyridine by azo-bond</td>
<td>Colon</td>
<td>4–6 g*</td>
</tr>
<tr>
<td>Salazopyrin†</td>
<td>500 mg tablets (containing 200 mg 5-ASA)</td>
<td>5-ASA linked to sulfapyridine by azo-bond</td>
<td>Colon</td>
<td>4–6 g*</td>
</tr>
<tr>
<td><strong>Balsalazine</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Colazal†</td>
<td>750 mg tablets (containing 200 mg 5-ASA)</td>
<td>5-ASA linked to 4-aminobenzyl-beta-alanine by azo bond</td>
<td>Colon</td>
<td>2–6·75 g*</td>
</tr>
<tr>
<td>Colazide§</td>
<td>750 mg tablets (containing 200 mg 5-ASA)</td>
<td>5-ASA linked to 4-aminobenzyl-beta-alanine by azo bond</td>
<td>Colon</td>
<td>2–6·75 g*</td>
</tr>
<tr>
<td><strong>Mesalazine</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Asaco†</td>
<td>400 mg tablets</td>
<td>5-ASA coated with Eudragit-S</td>
<td>Distal ileum, colon</td>
<td>2·4–4·8 g†</td>
</tr>
<tr>
<td>Asacol® HD†</td>
<td>800 mg tablets</td>
<td>5-ASA coated with Eudragit-S</td>
<td>Distal ileum, colon</td>
<td>2·4–4·8 g†</td>
</tr>
<tr>
<td>Claversal†</td>
<td>250–500 tablets</td>
<td>5-ASA coated with Eudragit-L</td>
<td>Ileum, colon</td>
<td>1·5–4·5 g†</td>
</tr>
<tr>
<td>Salofalk†</td>
<td>0·5, 1, 1·5 g sachets</td>
<td>5-ASA coated with Eudragit-L</td>
<td>Ileum, colon</td>
<td>1·5–4·5 g†</td>
</tr>
<tr>
<td>Salofalk Granu-Stix†</td>
<td>0·5, 1 g sachets</td>
<td>5-ASA coated with Eudragit-L100, polyacrylate-dispersion, povidone K (Eudragit-NE 400, Nonoxinol 100), simeticone</td>
<td>Colon (80%), sigmoid and rectum</td>
<td>1·5–4·5 g†</td>
</tr>
<tr>
<td>Apriso†</td>
<td>375 mg tablets</td>
<td>5-ASA coated with Eudragit-L100, polyacrylate-dispersion, povidone K (Eudragit-NE 400, Nonoxinol 100), simeticone</td>
<td>Colon (80%), sigmoid and rectum</td>
<td>1·5–4·5 g†</td>
</tr>
<tr>
<td>Pentasa†</td>
<td>250–500 mg tablets, 1 g sachets</td>
<td>5-ASA microgranules coated in ethylcellulose</td>
<td>Small bowel, colon</td>
<td>2–4 g†</td>
</tr>
<tr>
<td>Lialda†</td>
<td>1200 mg tablets</td>
<td>5-ASA coated with Multi Matrix system with lipophilic and hydrophilic matrices</td>
<td>Ileum, colon</td>
<td>2·4–4·8 g†</td>
</tr>
<tr>
<td>Mezavant†</td>
<td>1200 mg tablets</td>
<td>5-ASA coated with Multi Matrix system with lipophilic and hydrophilic matrices</td>
<td>Ileum, colon</td>
<td>2·4–4·8 g†</td>
</tr>
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</table>

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

The appendix (pp 8–9) shows contraindications and preventive measures before anti-TNF treatment.
immediate risk of colectomy up to 85%. No improvement after 3–5 days of intravenous steroids is an indication to start immediate rescue treatment. 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 those who have not received azathioprine). Ciclosporine and tacrolimus are highly effective for short-term clinical improvement with response rates of about 60–80%. However, use of these drugs has been limited by serious adverse events and low effectiveness for maintenance of colectomy-free remission in the long term. Ciclosporine is first given intravenously at doses of 2–4 mg/kg per day, 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*. 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). 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). 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 ciclosporine to infliximab or vice versa could be effective rescue treatment for carefully selected patients at specialist centres. Nevertheless, this strategy has a substantial risk of serious adverse events with restricted effectiveness in the long term.

**Maintenance of remission**

Mesoralazine 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 mesoralazine at doses of 1.6–3.0 g per day, maintaining remission rates of about 70–90%. No significant dose–response relation has been noted between different doses. Remission of proctitis and distal colitis can be maintained with rectal mesoralazine; probiotics are not effective. Corticosteroids, either topical or oral, are not effective for maintenance of remission. Patients who have frequent relapses despite optimum doses of mesoralazine, those with steroid dependency, and those previously treated with ciclosporine or tacrolimus for a severe flare, should be given azathioprine or antiTNF drugs for maintenance of remission. Azathioprine discontinuation is associated with a high rate of relapse.

Patients with steroid-refractory ulcerative colitis who have responded to induction with infliximab or adalimumab should be maintained on this treatment, because scheduled retreatment (every 8 weeks for infliximab and every 2 weeks for adalimumab) is effective for maintenance of remission and mucosal healing and for reduction of hospital admission and colectomy rates. In the UK, infliximab and adalimumab are not recommended for maintenance treatment because of low rates of steroid-free remission. 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.

**Surgery for ulcerative colitis**

**Treatment**

Although the basis of ulcerative colitis treatment is medical, about 20–30% of patients eventually need surgery. 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. Although mortality related to severe attacks of ulcerative colitis has substantially decreased to less than 1% in past decades, a delay in indicated surgery can increase the risk of postoperative complications and mortality.

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. 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. 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, and is associated with a reduction in time to diverting ileostomy closure after creation of the IPAA. 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. Pelvic sepsis is the most serious early complication of ileal pouch surgery, with rates up to 20%, 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 and infliximab, but not azathioprine, increases the risk of postoperative septic complications in the short-term. Long-term complications include small bowel obstruction (30% at 10 years), anastomotic strictures (8–14% at 10 years), pouchitis (50% by 3–4 years), sexual dysfunction, female infertility with a three times increased risk after IPAA, 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
30 years. 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. 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.

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. Other factors that raise the risk of colorectal cancer include endoscopic and histological severity of inflammation, 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. 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. 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.

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.
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. 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, Allo Wasserman, Amgen, AM-Pharma BV, Anaphore, Astellas Pharma, Athensys, Atlantic Healthcare Limited, Aptalis, BioBalance Corporation, Boehringer-Ingelheim Inc, Bristol Meyers Squibb, Celgene, Cellek Pharmaceuticals, Cellerix SL, Cerimon Pharmaceuticals, ChemoCentryx, CoMentis, Cosmo Technologies, Coronado Biosciences, Cytokine Pharmasciences, Eagle Pharmaceuticals, Eisai Medical Research, 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, Lexison Pharmaceuticals, Lycera Corporation, Meda Pharmaceuticals, Merck Research Laboratories, MerckSerono, Millennium Pharmaceuticals, Nissin Kynor 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, Signoid Pharma Limited,Sirius Pharmaceuticals, SLA Pharma (UK) Limited, Targacept, Teva Pharmaceuticals, Therakos, Tillotts Pharma AG, TeCell 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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