Gastroenterology 2

Inflammatory bowel disease: clinical aspects and established and evolving therapies

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Crohn's disease and ulcerative colitis are two idiopathic inflammatory bowel disorders. In this paper we discuss the current diagnostic approach, their pathology, natural course, and common complications, the assessment of disease activity, extraintestinal manifestations, and medical and surgical management, and provide diagnostic and therapeutic algorithms. We critically review the evidence for established (5-aminosalicylic acid compounds, corticosteroids, immunomodulators, calcineurin inhibitors) and emerging novel therapies—including biological therapies—directed at cytokines (eg, infliximab, adalimumab, certolizumab pegol) and receptors (eg, visilizumab, abatacept) involved in T-cell activation, selective adhesion molecule blockers (eg, natalizumab, MLN-02, alicaforsen), anti-inflammatory cytokines (eg, interleukin 10), modulation of the intestinal flora (eg, antibiotics, prebiotics, probiotics), leucocyte apheresis and many more monoclonal antibodies, small molecules, recombinant growth factors, and MAP kinase inhibitors targeting various inflammatory cells and pathways. Finally, we summarise the practical aspects of standard therapies including dosing, precautions, and side-effects.

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This is the second in a Series of two articles about inflammatory bowel disease

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Introduction

Following the discussion of the cause and immunobiology in part 1 of this Series,[1] we focus here on the clinical aspects of inflammatory bowel disease.

Ulcerative colitis

Definition

Ulcerative colitis is a relapsing non-transmural inflammatory disease that is restricted to the colon. Dependent on the anatomic extent of involvement, patients can be classified as having proctitis, left-sided colitis (involving the sigmoid colon with or without involvement of the descending colon), or pancolitis. A few patients also develop ileal inflammation (backwash ileitis), which occasionally complicates differentiation from Crohn's ileocolitis (table 1). Patients typically present with bloody diarrhoea (often nocturnal and postprandial), passage of pus, mucus, or both, and abdominal cramping during bowel movements. Severe symptoms are less common in left-sided colitis and proctitis.

Making the diagnosis and assessing disease activity

Ulcerative colitis is a clinical diagnosis, confirmed by objective findings from endoscopic and histological studies. Non-inflammatory bowel disease causes of colitis need to be ruled out (panel 1).[2] The appearance of ulcerative colitis in current and emerging diagnostic modalities is summarised in figure 1.

Search strategy and selection criteria

We searched Medline, Web of Science, and abstracts from major meetings in 2005 and 2006. We used the medical subject heading (MeSH) terms "inflammatory bowel disease", "ulcerative colitis", and "Crohn's disease".

In clinical practice, disease activity is typically described as mild (up to four bloody stools daily and no systemic toxicity), moderate (four to six bloody stools daily and minimal toxicity), or severe (more than six stools daily and signs of toxicity, such as fever, tachycardia, anaemia, raised erythrocyte sedimentation rate).[3,4] Patients with fulminant ulcerative colitis usually have more than ten bloody stools daily, continuous bleeding, anaemia requiring blood transfusion, abdominal tenderness, and colonic dilation on plain abdominal radiographs (figure 1). Although no formal definition of fulminant colitis exists,

	Ulcerative colitis	Crohn's disease
Clinical features		
Haematochezia	Common	Rare
Passage of mucus or pus	Common	Rare
Small-bowel disease	No (except backwash ileitis)	Yes
Can affect upper-gastrointestinal tract	No	Yes
Abdominal mass	Rare	Sometimes in right lower quadrant
Extraintestinal manifestations	Common	Common
Small-bowel obstruction	Rarely	Common
Colonic obstruction	Rarely	Common
Fistulas and perianal disease	No	Common
Biochemical features		
Anti-neutrophil cytoplasmic antibodies	Common	Rarely
Anti-saccharomyces cerevisiae antibodies	Rarely	Common
Pathological features		
Transmural mucosal inflammation	No	Yes
Distorted crypt architecture	Yes	Uncommon
Cryptitis and crypt abscesses	Yes	Yes
Granulomas	No	Yes, but rarely in mucosal biopsies
Fissures and skip lesions	Rarely	Common

Table 1: **Differential diagnosis of ulcerative colitis and Crohn's disease**

Panel 1: **Non-inflammatory bowel disease causes of enteritis and colitis**

Infectious

- Bacterial: *Campylobacter* spp, *Salmonella* spp, *Shigella* spp, *Clostridium difficile, Escherichia coli* (enterotoxigenic *E coli*), *Yersinia* spp (especially in Crohn's disease), gonococci, *Chlamydia trachomatis, Mycobacterium tuberculosis,* atypical mycobacteria
- Parasitic: *Entamoeba histolytica, Cryptospora* spp, *Isospora* spp, *Trichuris trichura,* strongyloidis
- Viral: cytomegalovirus, herpes simplex (in proctitis), HIV
- Mykotic: *Candida* spp, *Aspergillus* spp

Non-infectious

- Inflammatory: diverticulitis, microscopic colitis (collagenous and lymphocytic), eosinophilic gastroenteritis, graft *vs* host disease, radiation related, Behçet's syndrome, sarcoidosis
- Toxic: postoperative diversion colitis, bile acid loss, non-steroidal anti-inflammatory and other drugs , laxative use or abuse, antineoplastic chemotherapy
- Malignant: colorectal cancer, small-bowel cancer, neuroendocrine tumours, lymphoma, metastatic neoplasms
- Vascular: ischaemic colitis, vasculitis

the name usually describes patients who present with severe ulcerative colitis complicated by high fevers, extensive bleeding, grossly raised biochemical markers of inflammation, or weight loss. Some patients will also develop toxic megacolon. In clinical trials, clinical and endoscopic disease activity can be measured with a variety of disease-activity indices (webtable).[5]

See Online for webtable

Natural history

The distribution of disease activity in a cohort of patients is remarkably constant each year.[6] Half the patients are in clinical remission at any given time, although 90% have an intermittent course. In the first 3–7 years after diagnosis, 25% of patients were in remission, 18% had activity every year, and 57% had intermittent relapses. The only significant predictor of remission or relapse was disease activity in the preceding year. After 10 years, the colectomy rate was 24%.[6] More than half the patients with left-sided colitis will progress proximally during 25 years. During the same period, patients with more extensive disease regress in about 75% of cases.[7]

Overall, patients with ulcerative colitis have a normal life expectancy.[8]

Medical management

Induction of response and remission

An algorithm for inducing response and remission in patients with active ulcerative colitis is shown in figure 2 (see panel 2 for explanation of figure 2). First-line therapy for patients with mild to moderate ulcerative colitis is 5-aminosalicylic acid (mesalazine), which include oral and rectal mesalazine formulations and oral pro-drugs (sulfasalazine [5-aminosalicylic acid linked to sulfapyridine], olsalazine [5-aminosalicylic acid dimer] and balsalazide [5-aminosalicylic acid linked to 4-aminobenzoyl-β-alanine], table 2).[3,4] A systematic review showed no differences between mesalazine formulations and pro-drugs in absorption and systemic exposure to 5-aminosalicylic acid.[9] Controversy exists about the optimum induction dose of 5-aminosalicylic acid compounds in active ulcerative colitis. Some earlier trials showed a dose-response between 800 and 4800 mg per day,[10] but later trials could not consistently show a dose-response between 1500 and 4800 mg per day.[10–13] Doses of 1500–2400 mg per day of oral 5-aminosalicylic acid will be effective in most patients, dose escalation to between 3000 and 4800 mg per day or use of these higher doses initially can result in an increase in absolute response rates of about 10% (table 3).

Proctitis and left-sided ulcerative colitis might respond better to rectal mesalazine or corticosteroids rather than oral 5-aminosalicylic acid compounds or systemic corticosteroids. Corticosteroids that are effective when given rectally include hydrocortisone, budesonide, and beclomethasone.[43] When compared with rectal hydrocortisone, no differences with respect to clinical, endoscopic, and histological response occur with rectal budesonide.[44] When compared with rectal mesalazine, both budesonide and prednisolone rectal formulations were less effective (table 3).[44]

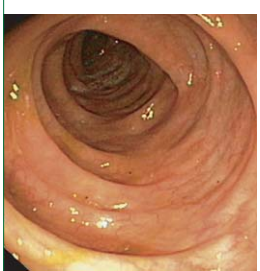
Patients who do not respond to oral 5-aminosalicylic acid compounds or rectal therapy or both should be treated with oral prednisone 40 mg per day up to 1 mg/kg per day or equivalent (table 3).[3,4,45] A population-based study showed that 34% of patients with ulcerative colitis needed corticosteroids to achieve remission. At 4 weeks, 54% of patients achieved complete remission and an additional 30% achieved a part response; however, at 1 year, 49% of patients had a prolonged response, 22% had become steroid dependent, and 29% needed surgery.[46] Outpatients with moderate to severe active ulcerative colitis despite treatment with 5-aminosalicylic acid, corticosteroids, azathioprine, and mercaptopurine can be treated with infliximab, a chimeric monoclonal antibody to tumour necrosis factor (TNF) α (table 3).[41] Infliximab is given at a dose of 5 mg/kg at week 0, week 2, and week 6.

Patients with severely active ulcerative colitis and those for whom oral corticosteroids have not worked, need to be admitted to hospital for intravenous corticosteroids (table 3 and figure 2).[3,4,45] Ciclosporin, tacrolimus, and infliximab are all effective in patients with severe ulcerative colitis who do not respond to intravenous corticosteroids.[38–40,42,47,48] Ciclosporin is given intravenously as a 24-h continuous infusion at doses of 2–4 mg/kg per day and tacrolimus is dosed orally to achieve serum trough concentrations of 5–15 ng/mL (table 3). At present, data are insufficient to determine which of these three treatments is most effective in this patient population.

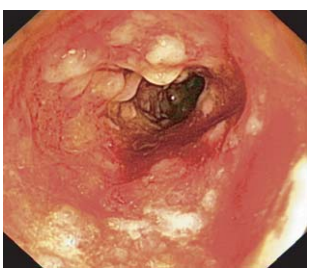
Maintenance of remission

Figure 2 shows an algorithm for maintaining remission in patients with ulcerative colitis. First-line therapy for the maintenance of remission is oral mesalazine

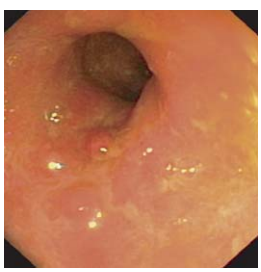
Ulcerative colitis | **Crohn's disease**



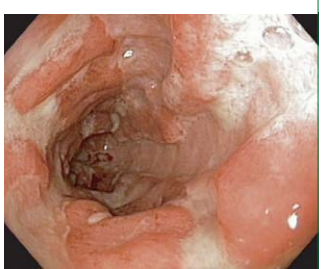
Transverse colon in patient in remission. Typical post-inflammatory changes—ie, loss of fine vascular pattern



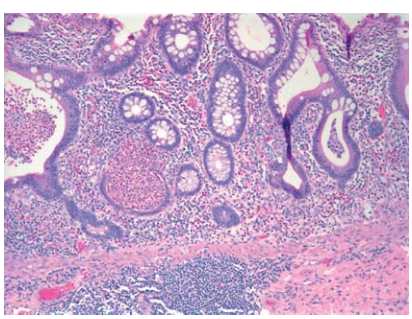
Descending colon: pancolitis with irregular surface due to extensive ulcerations, spontaneous haemorrhage, and pseudopolyps



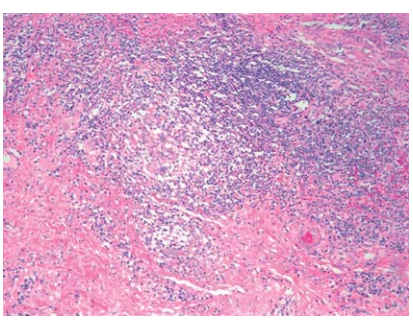
Terminal ileum: friability of mucosa with erythema, loss of ramifying vascular pattern, and lymphoid hyperplasia



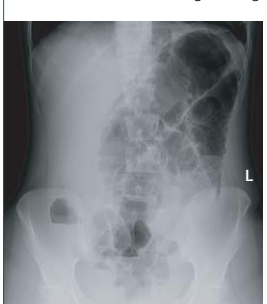
Sigmoid colon: linear and serpinguous ulcerations and patchy inflammation ultimately resulting in cobblestone pattern



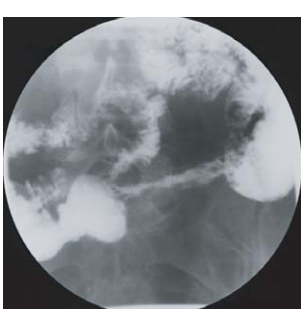
Mucosal biopsy: active ulcerative colitis with marked architectural distortion, cryptitis, and crypt abscesses.
Original magnification 100x, H&E



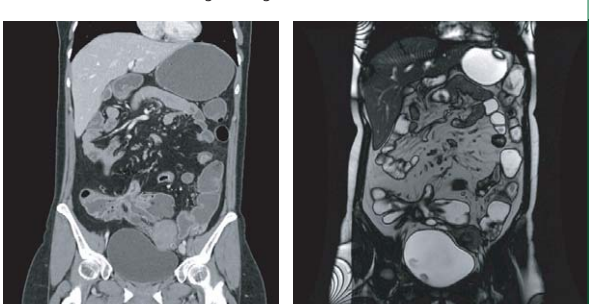
Mucosal biopsy: loosely formed granuloma with giant cells and surrounding lymphoid cuff in case of active Crohn's disease.
Original magnification 200x, H&E



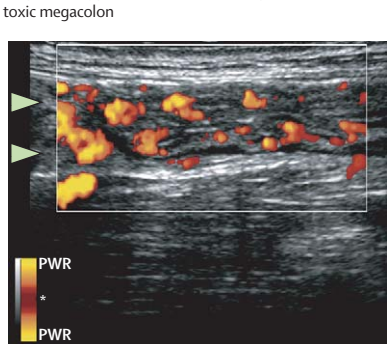
Abdominal plain radiograph: extreme colonic distension (7 cm) and absent haustral pattern, typical of toxic megacolon



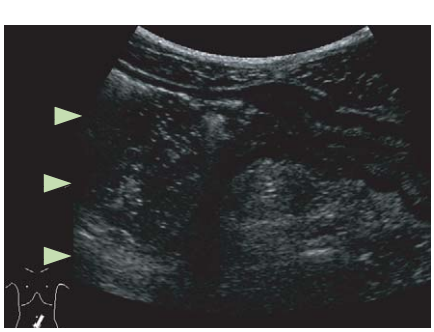
Classic small bowel follow through radiographic study, showing jejunal stenosis in patient with Crohn's disease



CT-based (left) and MRI-based (right) enterography showing an ileocaecal-sigmoid fistula in patient with Crohn's disease



Abdominal ultrasound: thickened, hyperaemic colonic wall in acute colitis



Abdominal ultrasound: prestenotic dilatation in patient with symptomatic stricture

Figure 1: **Common and distinct features of ulcerative colitis and Crohn's disease**
H&E=haematoxylin and eosin stain.

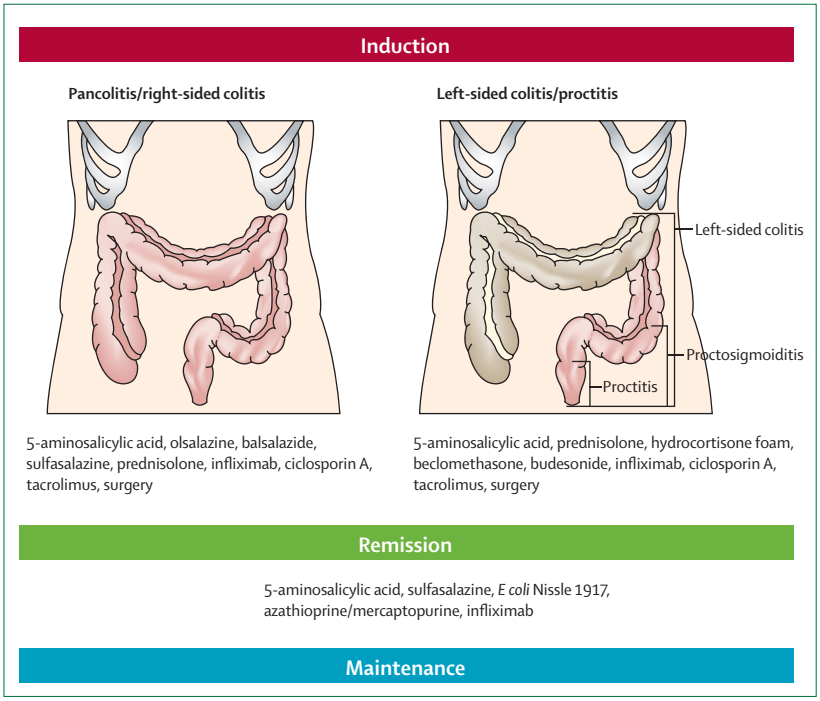


Figure 2: **Stepwise approach to the management of ulcerative colitis**
See panel 2 for explanation of this figure.

formulations and pro-drugs (table 3).[3,4,9] No obvious dose-response differences could be established between 800 and 3000 mg per day for maintenance therapy with oral 5-aminosalicylic acid.[10] Available data suggest a minimum oral daily dose of 1500 mg mesalazine, 2000 mg sulfasalazine, or 1000 mg olsalazine to maintain remission. Rectal mesalazine can be used as an alternative to oral dosing in patients with left-sided colitis or proctitis (table 3).

Patients who relapse while on oral 5-aminosalicylic acid compounds, those who are steroid-dependent, and those with severe ulcerative colitis who need induction therapy with ciclosporin or tacrolimus can be treated with azathioprine or mercaptopurine.[3,4,45] The efficacy data for azathioprine and mercaptopurine therapy for the treatment of ulcerative colitis are, however, sparse and inconsistent (table 3).[35–37,45] Azathioprine is dosed at 2–3 mg/kg per day and mercaptopurine at 1·0–1·5 mg/kg per day. Methotrexate has not proven effective for ulcerative colitis.[49] Infliximab is effective for maintenance of remission and is steroid-sparing in patients who are unable to maintain remission or who remain steroid-dependent despite treatment with 5-aminosalicylic acid, azathioprine, mercaptopurine, or all of these (table 3).[41]

Surgical management

Emergency surgery is indicated in patients with life-threatening complications, such as perforation, refractory rectal bleeding, and toxic megacolon not responsive to medical management.[50] Elective surgery

Panel 2: Management of ulcerative colitis

Mild to moderately active ulcerative colitis in outpatients with left-sided (distal colitis and proctitis) or extensive disease

Mild to moderately active ulcerative colitis is initially managed with oral 5-aminosalicylic acid compounds. For patients with left-sided disease, topical 5-aminosalicylic acid, either alone or in combination with oral 5-aminosalicylic acid, is an alternative therapeutic approach. If topical therapy is used, suppositories are most appropriate for proctitis, whereas more extended disease affecting the sigmoid or greater parts of the left colon need the addition of enemas or foams. Oral or topical 5-aminosalicylic acid doses of more than 1500 mg per day are sufficient to induce remission. Oral or topical 5-aminosalicylic acid should be continued as maintenance therapy in patients who respond to induction therapy with 5-aminosalicylic acid. Moderately active ulcerative colitis that does not respond to 5-aminosalicylic acid and severe (but not fulminant) disease requires treatment with oral corticosteroids given at a dose of 40–60 mg of prednisolone per day (or equivalent). Patients who often require steroid therapy should be started on azathioprine at 2·5 mg/kg bodyweight per day or mercaptopurine at 1·5 mg/kg bodyweight per day. Induction therapy with infliximab at a dose of 5 mg/kg at 0, 2, and 6 weeks followed by maintenance therapy every 8 weeks could be considered in outpatients with steroid dependent or refractory disease or and should be used in patients failing azathioprine or 6-mercaptopurine monotherapy. Alternatives to infliximab are adalimumab given subcutaneously as a loading dose of 160 mg at week 0 and 80 mg at week 2, followed by a maintenance dose of 40 mg every other week and, in the near future, certolizumab pegol given subcutaneously as a loading dose of 400 mg at weeks 0, 2, and 4, followed by a maintenance dose of 400 mg every 4 weeks.

Severe or fulminant colitis in inpatients

Fulminant colitis requires close interaction of gastroenterologists and surgeons to ensure a timely referral for emergency colectomy if indicated. Medical therapy is indicated in patients with severe ulcerative colitis who do not seem toxic (focal abdominal tenderness, suspected or known sepsis). Intravenous corticosteroids at a dose of 60 mg up to 1 mg/kg bodyweight are the first line of treatment accompanied by supportive therapy with intravenous fluids. Bowel rest or parenteral nutrition are not indicated in patients with severe ulcerative colitis, but should be prescribed in patients with toxic megacolon where surgery might be imminent. Routine broad-spectrum antibiotics are not indicated in the absence of abdominal infection.

For patients who do not respond to 5 days of intravenous corticosteroids, several medical alternatives exist in addition to colectomy. Ciclosporin, tacrolimus, and infliximab are all effective. Ciclosporin is given intravenously as a 24-h continuous infusion at doses of 2–4 mg/kg per day. Tacrolimus is dosed orally to achieve serum trough concentrations of 5–15 ng/mL.

Generic name	Proprietary name	Formulation	Sites of delivery	Unit strength
Mesalazine	North American Asacol*	Eudragit-S coated tablets (release at pH ≥7·0)	Terminal ileum, colon	400 mg
Mesalazine	Asacol 800	Eudragit-S coated tablets (release at pH ≥7·0)	Terminal ileum, colon	800 mg
Mesalazine	Mesavant (EU), Lialda (USA) (SDP 476)	Advanced, multimatrix system	Terminal ileum, colon	1200 mg
Mesalazine	UK, Italy, Netherlands Asacol†	Eudragit-S coated tablets (release at pH ≥7·0)	Terminal ileum, colon	400 mg
Mesalazine	Salofalk‡, Mesasal, Claversal‡	Eudragit-L coated tablets (release at pH ≥6·0)	Distal ileum, colon	250 mg, 500 mg
	Salofalk Granu-Stix‡	Eudragit-L100, polyacrylate-dispersion, povidone K (Eudragit-NE 40 D, Nonoxinol 100), simeticone	80% colon, sigmoid colon, rectum	500 mg, 1000 mg
	Claversal Micropellets§	Eudragit L-100-55, Eudragit S-100, dispersible cellulose	Ileocaecal valve, colon, left-sided colon	1500 mg
	Claversal Foam§	Eudragit L-100-55, Eudragit S-100, dispersible cellulose		5 g foam (1000 mg 5-ASA)
Mesalazine	Pentasa¶	Ethylcellulose-coated microgranules (time dependent release) available as a tablet, capsule or sachet	Duodenum, ileum, colon	250 mg and 500 mg tablets; 500 mg capsules; 1000 mg sachets
Olsalazine	Dipentum	5-aminosalicylic acid dimer linked by azo-bond, available as a gelatin capsule	Colon	250 mg
Sulfasalazine	Azulfidine, Salazopyrin	5-aminosalicylic acid linked to sulfapyridine by azo-bond available as a tablet	Colon	500 mg (200 mg 5-ASA)
Sulfasalazine	Azulfidine/Salazopyrin EN-tabs	5-aminosalicylic acid linked to sulfapyridine by azo-bond, available as a tablet coated with cellulose acetate phthalate	Colon	500 mg (200 mg 5-ASA)
Balsalazide	Colazide, Colazal	5-aminosalicylic acid linked to 4-aminobenzoyl-β-alanine by azo-bond, available as a capsule	Colon	750 mg (262 mg 5-ASA)

5-ASA=5-aminosalicylic acid. *North American Asacol: originally developed by Tillotts Laboratories, Colpermin, UK (later changed name to Tillotts Pharma AG, Ziefen, Switzerland), then Norwich Eaton, Norwich, NY, USA, currently Procter and Gamble, Cincinnati, Ohio, USA. Marketed by Procter and Gamble in North America. Manufactured with original Tillotts Laboratories manufacturing process. †UK, Italy, Netherlands Asacol: purchased from Tillotts Laboratories by Smith Kline French Laboratories (later changed name to Smith Kline Beecham and then GlaxoSmithKline), Giuliani, and Byk-Gulden. Differences might exist in Eudragit-S coating thickness, excipients, and manufacturing processes. No published data establishing the bioequivalence of North American Asacol and UK, Italy, Netherlands Asacol. ‡Manufactured by Dr Falk Pharma in Germany.§Manufactured by Merckle Recordati in Germany. ¶United States Pentasa: 250 mg capsule from Shire Pharmaceuticals (previously developed and marketed by Marion Laboratories, which later merged into Hoechst-Marion-Roussel, then Aventis and now Sanofi). Pentasa is manufactured and distributed by Ferring Pharmaceuticals.

Table 2: **5-aminosalicylic acid formulations**

is indicated in patients with dysplasia or cancer, ulcerative colitis refractory to medical management, or intolerance to long-term immunosuppression or other medical therapies.[51,52]

The most widely accepted surgical technique is total proctocolectomy with ileal J-pouch-anal anastomosis (figure 3). Debate exists about the technical aspects of this procedure, such as mucosectomy versus double-staple technique, the role of temporary diverting ileostomy, the optimum patient age, the role of ileal J-pouch-anal anastomosis in indeterminate colitis, and the advantages of laparoscopic versus open surgery.[51] An alternative to the ileal J-pouch-anal anastomosis is proctocolectomy with Brooke ileostomy.[51]

Proctocolectomy with ileal J-pouch-anal anastomosis might be complicated by the development of pouchitis, high stool frequency, faecal incontinence, reduced fertility, and need for reoperation. A meta-analysis of pooled incidences of complications of ileal J-pouch-anal anastomosis in 9317 patients after a median follow-up of 36·7 months showed pouch failure in 6·8% (increasing to 8·5% after follow-up >60 months), pelvic sepsis in 9·5%, and severe, mild, and urge faecal incontinence in 3·7%, 17%, and 7·3%, respectively.[53]

Crohn's disease

Definition

Crohn's disease is a relapsing, transmural inflammatory disease of the gastrointestinal mucosa that can affect the entire gastrointestinal tract from the mouth to the anus. Typical presentations include the discontinuous involvement of various portions of the gastrointestinal tract and the development of complications including strictures, abscesses, or fistulas (table 1 and figure 1). The Vienna classification was developed to describe the distinct clinical phenotypes of Crohn's disease with respect to disease location and occurrence of complications.[54,55] The anatomical location and behaviour of the disease according to the Vienna classification changes over time. At diagnosis, the disease is located in the terminal ileum in 47%, the colon in 28%, the ileocolon in 21%, and the upper gastrointestinal tract in 3%. Disease behaviour is classified as non-stricturing and non-penetrating in 70% of patients, stricturing in 17%, and penetrating (fistulas or abscesses or both) in 13% of all patients at diagnosis (figure 1).[56] The clinical presentation is largely dependent on disease location and can include diarrhoea, abdominal pain, fever, clinical signs of bowel obstruction, as well as passage of blood or mucus or both.

Drug	Dose	Mildly to moderately active		Refractory	Severely active	Remission maintenance	
		Distal	Extensive			Distal	Extensive
Sulfasalazine	Induction 2–6 g per day Maintenance 2–4 g per day	Yes[14]	Yes[14]	Yes*	No†	Yes[15]	Yes[15]
Mesalazine suppositories	Induction 0·5–1·5 g per day Maintenance 0·5–1 g per day	Yes[16]	No	Yes*	No†	Yes[17]	No
Mesalazine enemas	Induction 1–4 g per day Maintenance 1–4 g per day	Yes[18]	Yes (adjunctive therapy)[19]	Yes*	No†	Yes	No
Oral mesalazine	Induction 1·6–4·8 g per day Maintenance 0·75–4 g per day	Yes[11,20–22]	Yes[11,20–22]	Yes*	No†	Yes[23,24]	Yes[23,24]
Olsalazine	Maintenance 1–2 g per day	No[25]‡	No[25]‡	No‡	No‡	Yes[26]	Yes[26]
Balsalazide	Induction 6·75 g per day (equivalent to mesalamine 2·4 g per day) Maintenance 4 g per day (equivalent to mesalamine 1·4 g per day)	Yes[27]	Yes[27]	Yes*	No†	Yes[28]	Yes[28]
Hydrocortisone enemas	Induction 100 mg per day	Yes[29]	No	Yes*	Yes§	No[29]	No
Budesonide enemas	Induction 2–8 mg per day	Yes[30]	No	Yes*	Yes§	No	No
Oral corticosteroids cortisone	Induction 100 mg per day	Yes[31]	Yes[31]	Yes*	No	No	No
Oral corticosteroids prednisone	Induction 40–60 mg per day	Yes[32]	Yes[32]	Yes*	No	No[33]	No[33]
Intravenous corticosteroids prednisolone	Induction 60 mg per day	No	No	Yes[34]¶	Yes[34]	No	No
Oral azathioprine	Maintenance 2–2·5 mg/kg per day	No[35]	No[35]	Yes[36]	No	Yes[36,37]	Yes[36,37]
Intravenous ciclosporin	Induction 2–4 mg/kg per day	No	No	No	Yes[38,39]	No	No
Oral tacrolimus	Induction target blood level 5–15 ng/mL	No	No	No	Yes[40]	No	No
Intravenous infliximab	Induction 5 or 10 mg/kg at weeks 0, 2, and 6 Maintenance 5 or 10 mg/kg every 8 weeks	Yes[41]	Yes[41]	Yes[41]	Yes[42]	Yes[41]	Yes[41]

*Typically continued as a carryover of treatment for mildly to moderately active disease when additional agents are added. †Typically discontinued because of the possibility of intolerence to sulfasalazine, mesalazine, or balsalazide. ‡Diarrhoea often occurs at higher doses in patients with active ulcerative colitis. §Adjunctive therapy to intravenous corticosteroids. ¶Some patients who do not respond to oral corticosteroids will respond to intravenous corticosteroids.

Table 3: **Ulcerative colitis—evidence-based indications for treatment**

Making the diagnosis and assessing disease activity

No definitive diagnostic test exists for Crohn's disease. Instead, the diagnosis is made on the basis of history and physical examination, supplemented with objective findings from endoscopic, radiological, laboratory, and histological studies (figure 1). In clinical practice, disease activity is typically described as mild to moderate (ambulatory patients able to tolerate oral alimentation without manifestations of dehydration, toxicity, abdominal tenderness, painful mass, obstruction or >10% weight loss), moderate to severe disease (failure to respond to treatment for mild disease, more prominent symptoms of fever, weight loss, abdominal pain or tenderness, intermittent nausea and vomiting without obstruction, or significant anaemia) and severe to fulminant disease (persisting symptoms on corticosteroids, high fevers, persistent vomiting, evidence of intestinal obstruction, rebound tenderness, cachexia, or evidence of an abscess).

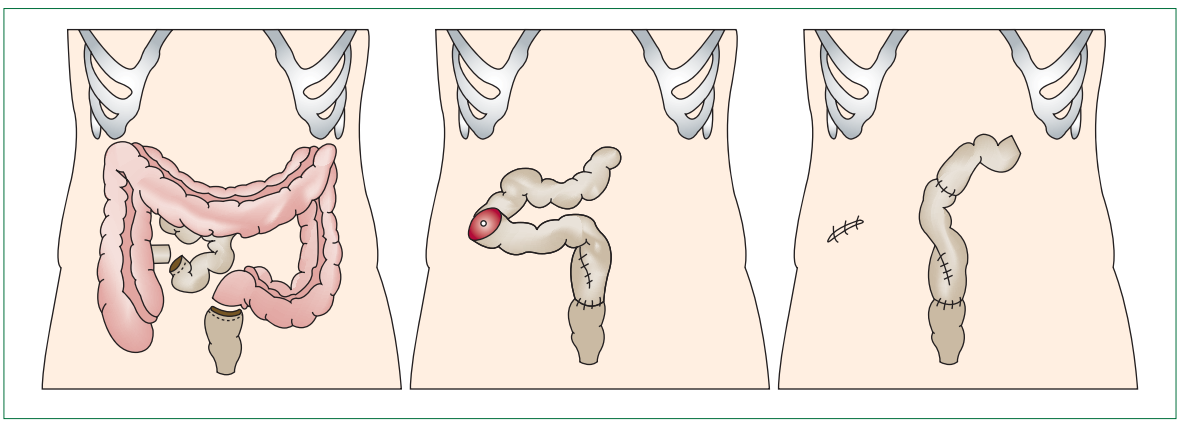


Figure 3: **Schema of the proctocolectomy with ileo-pouch anal anastomosis surgical procedure**

Remission refers to asymptomatic patients or those without inflammatory sequelae, including patients who responded to medical or surgical intervention without evidence of residual disease. Steroid-dependent patients are not regarded as being in remission.[3,57,58] In clinical trials, clinical and endoscopic disease activity can be measured with a variety of disease activity indices (webtable).[59]

Natural course

Although the anatomical location of Crohn's disease is fairly stable, behaviour of the disease varies substantially during its course. The most prominent change is from non-stricturing to either stricturing (in 27%) or penetrating (in 29%) disease.[56] After the first year after diagnosis, 10–30% of patients with Crohn's disease have an exacerbation, 15–25% have low activity, and 55–65% are in remission. 13–20% of patients with Crohn's disease have a chronic active course of disease activity, 67–73% have a chronic intermittent course and only 10–13% remain in remission for several years.[60,61] After 20 years, most patients with Crohn's disease will require surgery.[62] The life expectancy of patients with Crohn's disease is slightly reduced.[63]

Medical management

Induction of remission

An algorithm for inducing response and remission in patients with active inflammatory Crohn's disease is shown in figure 4 (see panel 3 for explanation of figure 4). First-line therapy for patients with mild to moderate disease is controversial. Sulfasalazine at doses of 3000–4500 mg per day is effective for induction of remission in active disease (with most benefit in patients with colonic involvement),[64,65] but is limited by sulfa-related intolerance in some patients. Somewhat surprisingly, mesalazine has not consistently proved efficacious. Two trials of mesalazine at doses of 3200–4000 mg per day showed efficacy[66,67] whereas two other trials with 4000 mg per day of mesalazine that were never fully reported failed to show efficacy.[66–68] A meta-analysis, which included the three largest trials, did not show a clinically important treatment effect (table 4).[68] Budesonide, a corticosteroid with extensive first-pass hepatic metabolism and targeted delivery to the ileum and right colon via a formulation that is pH and time dependent, markedly reduces side-effects of systemic corticosteroids. Controlled trials have shown that budesonide 9 mg per day is more effective than placebo and oral 5-aminosalicylic acid 4000 mg per day, and has similar efficacy to prednisolone for the induction of remission in active Crohn's disease.[94] Unlike conventional corticosteroids, oral budesonide does not impair bone metabolism and does not result in osteoporosis (table 4).[95] The most rigorous studies of antibiotics for active Crohn's disease failed to show efficacy for induction of remission.[78,79] On the basis of these data, sulfasalazine can be recommended for

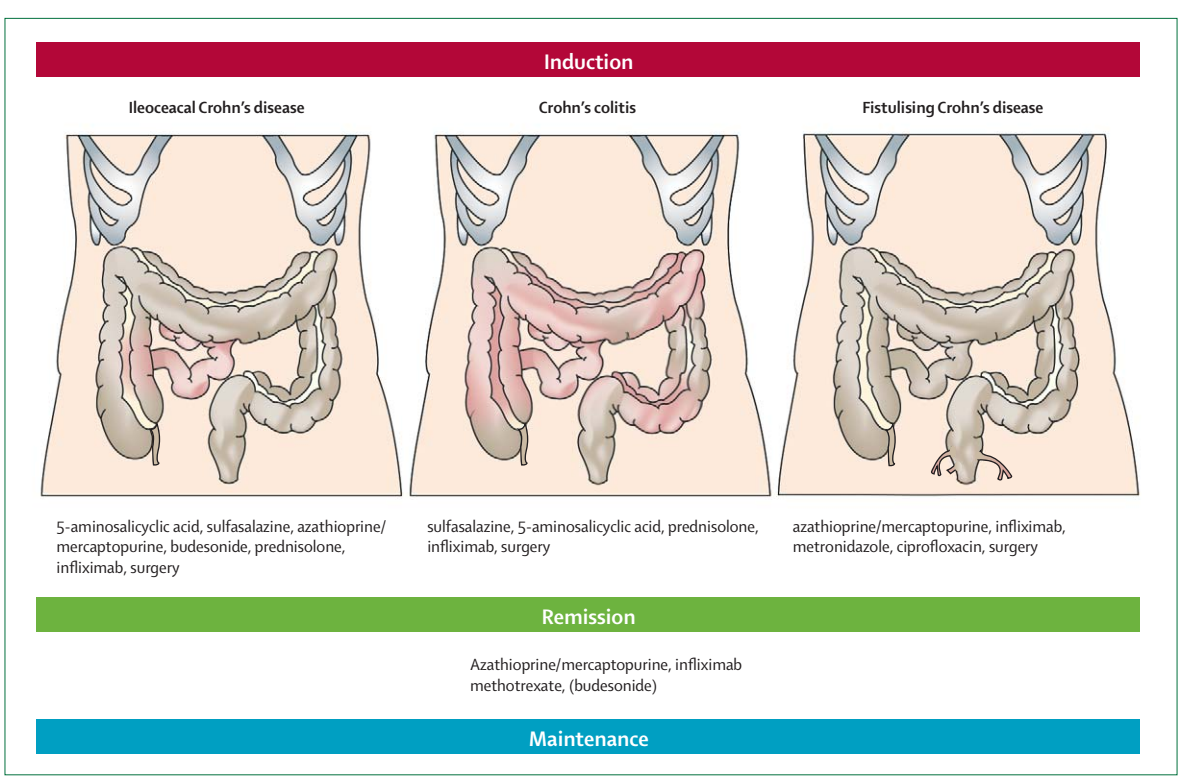


Figure 4: **Stepwise approach to the management of Crohn's disease**
See panel 3 for explanation of this figure.

Panel 3: **Management of Crohn's disease**

Inflammatory Crohn's disease in outpatients

The optimum first-line therapy for mild Crohn's disease is dependent on the disease location. Patients with ileal or ileocaecal disease might be induced into remission with budesonide at 9 mg daily. In patients with mild ileocaecal or colonic disease, remission might be induced with sulfasalazine at 4000 mg per day. The use of sulfasalazine is limited by its toxicity. The efficacy of mesalazine at doses of 3200 mg or more per day for first-line induction therapy is not evidence-based and is controversial among experts, but is widely used in clinical practice. Patients who do not respond to first-line therapy should receive induction therapy with 40–60 mg oral prednisolone per day. In general, infliximab at 5 mg/kg bodyweight at weeks 0, 2, and 6 is reserved for patients who do not enter remission with prednisolone. An alternative to infliximab is adalimumab given subcutaneously as a loading dose of 160 mg at week 0 and 80 mg at week 2 and, in the near future, certolizumab pegol (UCB Pharma, Smyrna, GA, USA) given subcutaneously as a loading dose of 400 mg at weeks 0, 2, and 4. Azathioprine and mercaptopurine are not ideal induction agents because of their slow onset of action. 5-aminosalicylic acid is not effective for maintenance of remission in patients with Crohn's disease. Budesonide maintenance therapy modestly prolongs the time to relapse. The main maintenance agents for Crohn's disease are azathioprine 2·5 mg/kg or mercaptopurine 1·5 mg/kg. An alternative to azathioprine or 6-mercaptopurine is maintenance therapy with methotrexate at 15 to 25 mg per week given intramuscularly or subcutaneously. Maintenance therapy of 5 mg/kg infliximab every 8 weeks, alternatively adalimumab given subcutaneously at 40 mg every other week, or in near future also certolizumab pegol given subcutaneously at 400 mg every 4 weeks, therapies can be added to immunosuppressive therapy with azathioprine, 6-mercaptopurine, or methotrexate if needed to maintain a steroid-free remission. Surgery should be considered in patients with obstructive complications and those who have not responded to medical therapy.

Fulminant and refractory inflammatory Crohn's disease in inpatients

In patients with fulminant inflammatory Crohn's disease, remission might be induced with intravenous corticosteroids, such as methylprednisolone at a dose of 1·0–1·5 mg/kg bodyweight per day. Intravenous infliximab at a dose of 5 mg/kg bodyweight at weeks 0, 2, and 6 is an alternative as main therapy in these patients and can be used in patients who do not respond to intravenous corticosteroids. An alternative to infliximab is adalimumab given subcutaneously as a loading dose of 160 mg at week 0 and 80 mg at week 2 and, in the near future, certolizumab pegol given subcutaneously as a loading dose of 400 mg at weeks 0, 2, and 4. Surgery might be an appropriate initial therapy for patients with fulminant ileocaecal disease with obstructive complication or those unable to tolerate medical therapy.

Fistulising Crohn's disease

Fistulising Crohn's disease requires close interaction between surgeons and gastroenterologists. Remission might be induced with antibiotics (ciprofloxacin at 1000 mg per day or metronidazole at 1000–1500 mg per day), infliximab at a dose of 5 mg/kg at weeks 0, 2, and 6, or fistulotomy or drainage with setons or both. An alternative to infliximab is adalimumab, which is given subcutaneously as 160 mg at week 0 and 80 mg at week 2, and then 40 mg subcutaneously every other week beginning at week 4. Patients with fistulising Crohn's disease can be maintained on azathioprine 2·5 mg/kg or 6-mercaptopurine at 1·5 mg/kg monotherapy or combined with infliximab 5 mg/kg every 8 weeks maintenance therapy.

induction therapy in patients with mildly to moderately active disease with colonic involvement, and budesonide can be recommended in patients with ileal or right colonic involvement or both. The use of mesalazine, although widely practised, is not evidence based and could cause patient harm (increased rates of hospital admission and surgery during a relapse) as a result of the withholding of other effective therapies.

Patients who do not respond to sulfasalazine, mesalazine, or budesonide, and outpatients with moderate to severe disease are treated with oral prednisone 40 mg per day up to 1 mg/kg per day, or equivalent (table 4).[3,45,57,58,64,65] A recent population-based study reported that 44% of patients with Crohn's disease needed corticosteroids to achieve remission.[46] At 4 weeks, 58% of patients achieved complete remission and an additional 26% achieved a part response; however, at 1 year, 32% of patients had a prolonged response, 28% became steroid dependent, and 40% required surgery (table 4).[46] Patients with moderate to severe disease despite treatment with sulfasalazine, mesalamine, budesonide, conventional corticosteroids, and azathioprine, mercaptopurine, or methotrexate can be treated with infliximab (table 4).[86] Infliximab is given at a dose of 5 mg/kg at 0, 2, and 6 weeks. An alternative to infliximab is a fully human anti-tumour necrosis factor (anti-TNF) antibody, adalimumab, given subcutaneously with a loading dose of 160 mg at week zero and 80 mg at week two. In the near future, a pegylated anti-TNF antibody FAb′ fragment certolizumab pegol (UCB Pharma, Smyrna, GA, USA) will become available that is given subcutaneously at a dose of 400 mg at weeks 0, 2, and 4.[90,92]

Maintenance of remission

An algorithm for maintaining remission in patients with inflammatory Crohn's disease is shown in figure 4. All maintenance trials with sulfasalazine and most maintenance trials with mesalazine in patients with medically induced remission have not shown efficacy.[70,71] Although oral 5-aminosalicylic acid is widely used for maintenance of medically induced remission in patients with Crohn's disease, this practice is not evidence based (table 5). Budesonide 6 mg prolongs the time to relapse and maintains remission for 6 months but less than a year.[77]

Patients who are steroid dependent, and those with moderate to severe disease needing induction therapy with conventional corticosteroids can be treated with azathioprine, mercaptopurine, or methotrexate.[3,45,57,58,81,84,85]

In patients with active Crohn's disease, the likelihood of

response to azathioprine or mercaptopurine is increased after 17 weeks and the clinical response to methotrexate does not occur for 6–8 weeks, indicating that because of the slow onset of action, these drugs should mainly be considered as maintenance rather than induction drugs. Therefore, in patients with active Crohn's disease, these drugs should generally be combined with more rapid-acting drugs, such as budesonide, conventional corticosteroids, and infliximab. One study showed that once azathioprine or mercaptopurine maintenance therapy is initiated, it should be continued indefinitely (table 5).[114] Azathioprine is dosed at 2–3 mg/kg per day and mercaptopurine at 1·0–1·5 mg/kg per day. Methotrexate is given parenterally at doses of 25 mg per week for maintenance therapy.[84,85]

Infliximab is effective for maintenance of remission, steroid-sparing, and mucosal healing in patients who are unable to maintain remission or who remain steroid dependent despite treatment with azathioprine, mercaptopurine, or methotrexate (table 5).[87,115] For maintenance therapy, infliximab is given at a dose of 5 mg/kg every 8 weeks. Episodic dosing is associated with immunogenicity (loss of efficacy and infusion reactions).[116,117] Alternatives to infliximab are adalimumab given subcutaneously for maintenance therapy as 40 mg subcutaneously every other week. Certolizumab pegol will be available in the near future which is given subcutaneously for maintenance therapy as 400 mg every 4 weeks.[91,92]

Management of fistulising Crohn's disease

An algorithm for management of fistulas in patients with Crohn's disease is shown in figure 4. Antibiotic therapy with ciprofloxacin 1000 mg per day or metronidazole is widely used for the first-line treatment of fistulas in Crohn's disease, and is recommended in practice guidelines,[3,45,57,58,118] but placebo-controlled trials are nearly non-existent. Azathioprine or mercaptopurine are used as a second-line treatment of Crohn's disease fistulas. A meta-analysis of five controlled trials in which fistula closure was a secondary endpoint reported a pooled odds ratio was 4·44 favouring fistula healing.[81] Patients with active fistulising disease despite treatment with antibiotics and azathioprine or mercaptopurine can be treated with infliximab.[88,89] Infliximab is given as 5 mg/kg at 0, 2, and 6 weeks for induction and then every 8 weeks for maintenance (table 4). An alternative to infliximab is adalimumab which is given subcutaneously as 160 mg at week 0 and 80 mg at week 2, and then 40 mg every other week beginning at week 4.[91]

Drug	Dose	Mildly to moderately active		Refractory and severely active		Perianal fistulas		Postoperative maintenance
		Induction	Maintenance	Induction	Maintenance	Induction	Maintenance	
Oral sulfasalazine	Induction 3–6 g per day	Yes[64,65]	No[64,65]					No[69]
Oral mesalazine		No[66-68]	No[70,71]*					No[70,72]*
Oral corticosteroids prednisone	Induction 0·25 mg per kg to 0·75 mg per kg	Yes[64]	No [64]	Yes[64]	No[64]			No[73]
Oral corticosteroids methyl-prednisolone	Induction 48 mg per day	Yes[65]	No[65]	Yes[65]	No[65]			
Intravenous corticosteroids prednisone	Prednisone 60 mg per day			Yes[74]				
Budesonide	Induction 9 mg per day Maintenance 6 mg per day	Yes[75,76]	No[77]†		Yes†			No
Metronidazole†	Induction 10–20 mg per kg per day	No[78,79]*				Yes‡		No[80]§
Azathioprine	Azathioprine 2–3 mg per kg per day	No¶	No||	No¶	Yes[81]	No¶	Yes[81]	Yes[82]
Mercaptopurine	Maintenance 1–1·5 mg/kg per day	No¶	No||	No¶	Yes[81]	No¶	Yes[81]	Yes[83]
Methotrexate	Induction 25 mg per week Maintenance 15–25 mg per week			Yes[84]§	Yes[85]			
Infliximab	Induction 5 or 10 mg/kg at weeks 0, 2, and 6 Maintenance 5 or 10 mg/kg every 8 weeks			Yes[86]	Yes[87]	Yes[88]	Yes[89]	
Adalimumab	Induction 160 mg at week 0 and 80 mg at week 2 Maintenance 40 mg every other week or weekly			Yes[90]	Yes[91]	Yes in a subgroup analysis[91]	Yes in a subgroup analysis[91]	
Certolizumab pegol	Induction 400 mg at weeks 0, 2, and 4 Maintenance 400 mg every 4 weeks			Yes[92]	Yes[93]	No data	No data	

*Recommended in current practice guidelines and widely used in clinical practice. Evidence for controlled clinical trials does not consistently support efficacy. †Budesonide 6 mg per day significantly increases time to relapse, but does not meet conventional criteria for maintenance of remission at 1 year in patients with medically induced remission. Budesonide 6 mg is effective as a steroid-sparing agent in patients who are dependent on prednisone or prednisolone. ‡Recommended in current practice guidelines and widely used in clinical practice. Evidence based on uncontrolled studies only, no controlled trials ever done. §Studies show short-term reduction in recurrence of severe endoscopic lesions, no difference in clinical remission rates at 1 year. ¶Slow onset of action precludes or limits use as induction agent. ||Toxicity profile of agent precludes use for this indication.

Table 4: **Crohn's disease—evidence-based indications for treatment**

Compound (generic name)	Manufacturer	Therapeutic target	Compound class	References
Adalimumab (D2E7)	Abbott, Parsippany, PA, USA	TNF	Fully humanised mAb	
Certolizumab pegol (CDP870)	UCB Pharma, Smyrna, GA, USA	TNFα, T cells	Humanised FAb′	
Golimumab (CNTO148)	Centocor, Malvern, PA, USA	TNFα, T cells	Fully humanised mAb	
Abatacept	Bristol Myers Squibb, New York, NY, USA	T cells, dendritic cells, macrophages	Fusion protein	96
Daclizumab	PDL Biopharma, Fremont, CA, USA	Interleukin 2	Humanised mAb	97
Basiliximab	Cerimon Pharmaceuticals, South San Francisco, CA, USA	Interleukin 2	Chimaeric mAb	98
RDP58	Genzyme, Cambridge, MA, USA	TNFα, interferon γ, interleukin 2, interleukin 12, haem-oxygenase 1	Decapeptide	99
Visilizumab	PDL Biopharma, Fremont, CA, USA	T cells	Humanised mAb	100
MLN02 (LDP02)	Millenium Pharmaceuticals, Cambridge, MA, USA	α4β7-Integrin	Humanised mAb	101
Alicaforsen enemas	Isis Pharmaceuticals, Carlsbad, CA, USA	Intracellular adhesion molecule 1	Antisense oligonucleotide	102–104
Interferon α2a polyethylene glycol	Schering-Plough, Kenilworth, NJ, USA	T cells	Interferon	105
Interferon β 1a	Serono International, Geneva, Switzerland	T cells	Interferon	106
Trichuris suis eggs	Falk Pharma, Frieburg, Germany	T cells	Parasite eggs	107
Cellulose acetate bead column	Otsuka, Tokyo, Japan	Leucocytes	Apheresis	108
Polyethylenephtarate fiber column	Asahi, Tokyo, Japan	Leucocytes	Apheresis	109
E coli Nissle 1917		Enteric microflora	Probiotic	110
Tetilomast (OPC-6535)	Otsuka, Tokyo, Japan	Granulocytes	Thiazole (PDE4 inhibitor)	111
Repifermin (KGF2)	Human Genome Sciences., Rockville, MD, USA	Epithelial cells	Growth factors	112
Epidermal growth factor	Heber Biotec, Havana, Cuba	Epithelial cells	Growth factors	113

mAb=monoclonal antibody. TNFα=tumour necrosis factor α.

Table 5: **Investigational therapies for ulcerative colitis**

Compound (generic name)	Manufacturer	Therapeutic	Compound class	References
Adalimumab (D2E7)	Abbott, Parsippany, PA, USA	TNFα, T cells	Humanised mAb	90,91,120
Certolizumab pegol (CDP870)	UCB Pharma, Smyrna, GA, USA	TNFα	Humanised FAb′	92,93,121
CDP571	UCB Pharma, Smyrna, GA, USA	TNFα	Humanised mAb	122,123
Etanercept	Amgen, Thousand Oaks, CA, USA	TNFα	Soluble p75 receptor fusion protein	124
Onercept	Serono International, Geneva, Switzerland	TNFα	Soluble p55 receptor	125
Visilizumab	PDL Biopharma, Fremont, CA, USA	T cells	Humanised mAb	126
Fontolizumab	PDL Biopharma, Fremont, CA, USA	Interferon γ	Humanised mAb	127,128
Abatacept	Bristol Myers Squibb, New York, NY, USA	T cells, dendritic cells, macrophages	Fusion protein	96
Kremezin (AST-120)	Ocera Therapeutics, San Diego, CA, USA	Unknown	Adsorbtive carbon	129
Semapimod (CNI-1493)	Cytokine Pharma Sciences, King of Prussia, PA, USA	TNFα	MAP kinase inhibitor	130
Doramapimod (BIRB796)	Boehringer Ingelheim, Ingelheim, Germany	Multiple	MAP kinase inhibitor	131
Thalidomide	Celgene, Summit, NJ, USA	TNFα	ImID	132,133
CNT01275	Centocor, Malvern, PA, USA	Interleukin 12/23p40	Humanised mAb	..
ABT-874 (J695)	Abbott, Parsippany, PA, USA	Interleukin 12	Humanised mAb	134
STA-5326 mesylate	Synta Pharmaceuticals, Lexington, MA, USA	Interleukin 12/23	Small molecule	135
Atlizumab (MRA)	Chugai Pharmaceuticals, Fremont, CA, USA	Interleukin 6	Humanised mAb	136
Interleukin 10	Schering-Plough, Kenilworth, NJ, USA	Interleukin 10	Recombinant human cytokine	137–139
Oprelvekin (Interleukin 11)	Wyeth, Madison, NJ, USA	Interleukin 11	Recombinant human cytokine	140
Natalizumab	Elan, Dublin, Ireland	α4-integrin	Humanised mAb	141–144
Alicaforsen (ISIS-2302)	Isis Pharmaceuticals, Carlsbad, CA, USA	Intracellular adhesion molecule 1	Antisense oligonucleotide	145,146
Sagramostim	Berlex (Schering AG), Berlin, Germany	PMN+macrophages	Growth factors	147
Epanova	Tillotts Pharma AG, Ziefen, Switzerland	Reactive radicals	Omega 3 fatty acids	148
Somatotropin (HGH)	Genentech, South San Francisco, CA, USA	Intestinal epithelium	Growth factors	149

mAb=monoclonal antibody. TNFα=tumour necrosis factor α.

Table 6: **Investigational therapies for Crohn's disease**

Surgical management

Although surgery might be necessary to induce remission or to treat complications in some patients, it will not cure Crohn's disease. In general, in patients with colonic disease, indications for emergency and elective surgery are similar to those for ulcerative colitis.[50,52] Specific indications for surgery include formation of fibrotic strictures leading to symptoms of part or complete bowel obstruction, internal fistulas complicated by abdominal abscess, enterovesical fistulas, and enterocutaneous fistulas.[51]

The optimum therapy for post-operative maintenance of remission in patients with Crohn's disease remains to be determined. Budesonide and conventional corticosteroids are not effective. Mesalazine at doses of 3000–4000 mg per day has a modest effect according to a meta-analysis, but the largest and most rigorous of the individual trials was negative.[70,72] Azathioprine and mercaptopurine might be effective, but the controlled trials showed inconsistent results and only modest efficacy.[82,83] Metronidazole showed short-term efficacy, and ordnidazole given for a year was effective (table 4).[80,119]

Extraintestinal manifestations of inflammatory bowel disease

Up to 25% patients with Crohn's disease and ulcerative colitis will develop extraintestinal disease manifestations or complications (figure 5). Extraintestinal manifestations usually respond to treatment of the underlying disease.

Emerging therapies for inflammatory bowel disease

Advances in knowledge of the immunology of inflammatory bowel disease and in bioengineering have led to new therapeutic concepts that target almost every aspect of the inflammatory process.[1] Tables 5 and 6 show agents grouped by underlying therapeutic strategy or concept.

Blockade of TNF

The chimeric monoclonal antibody to TNFα, infliximab, was introduced into clinical practice for the treatment of Crohn's disease in 1997, and is now used for induction and maintenance therapy in both Crohn's disease and ulcerative colitis. In addition to infliximab, two other anti-TNF agents, adalimumab and certolizumab pegol, have also proved efficacious in Crohn's disease (figure 6). Several other anti-TNF strategies were assessed in controlled clinical trials. Etanercept, a fully human dimeric fusion protein consisting of the extracellular ligand-binding portion of the human p75 TNF receptor linked to the Fc portion of IgG_1, onercept (Serono International, Geneva, Switzerland), a recombinant form of the human soluble p55 TNF receptor binding protein, and CDP571 (UCB Pharma, Smyrna, GA, USA), a humanised IgG_1 monoclonal antibody to TNFα, were not efficacious for induction or maintenance of response or remission in patients with Crohn's disease.[122–125] This lack of efficacy was in the past attributed to their failure to lyse cell-bound TNF or induce

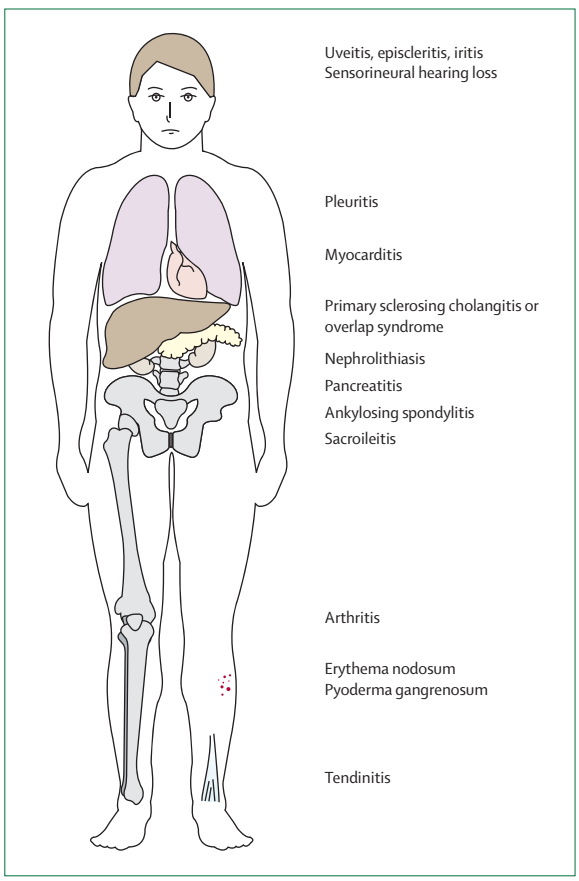


Figure 5: **Common extraintestinal manifestations of inflammatory bowel disease**

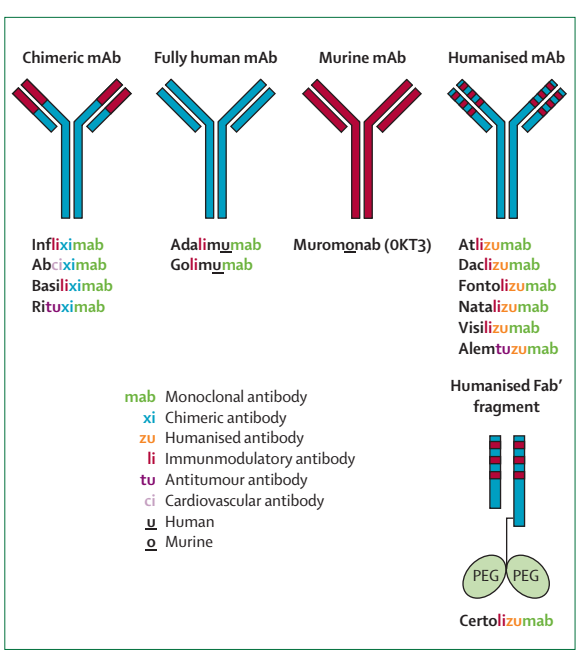


Figure 6: **US Food and Drug Administration nomenclature of therapeutic antibodies used in inflammatory bowel disease and other diseases**

apoptosis in T cells and monocytes, or both, but this theory is questioned by new data showing induction of apoptosis by etanercept and clinical efficacy of certolizumab pegol, a non-apoptotic anti-TNF agent.[92,93,127,150]

Modulation of other key cytokines

Three phase II trials in Crohn's disease with fontolizumab (PDL Biopharma, Fremont, CA, USA), a humanised interferon-γ antibody, did not meet the primary endpoint, but a subgroup of patients given multiple higher doses did benefit.[128,151] Interleukin 12 and 23 are targeted by two humanised interleukin 12/23 antibodies, *ABT-874* and *CNTO 1275*, as well as a small molecule apilimod mesylate (STA-5326). A phase II study of *ABT-874* in patients with active Crohn's disease suggested clinical benefit. Phase II and III studies of recombinant human tenovil (rHIL-10) in patients with active and steroid-dependent Crohn's disease did not demonstrate efficacy, possibly owing to inability to achieve sufficient mucosal concentrations when given subcutaneously.[137,138] Intestinal delivery of interleukin 10 with bacterial vectors (*LL-Thy12* - interleukin 10 secreting *Lactococcus* spp) or when given rectally with gelatin microspheres (*GM-IL-10*) might revive this concept.[139]

Compound (generic name)	Precautions adverse events	Monitoring	Maternal safety
Mesalamine	Rarely pancreatitis	Creatinine	B
Sulfasalazine	Rarely pancreatitis	Creatinine	B
Olsalazine	Rarely pancreatitis	Creatinine	C
Cortisone	Increased risk of (opportunistic) infection, endocrine impairment	Glucose, blood pressure	C
Prednisolone	Increased risk of (opportunistic) infection, endocrine impairment	Glucose, blood pressure	C
Hydrocortisone	Increased risk of (opportunistic) infection, endocrine impairment	Glucose, blood pressure	C
Budesonide	Increased risk of (opportunistic) infection	None	Not studied
Azathioprine, 6-mercaptopurine	Increased risk of lymphoma, increased risk of (opportunistic) infection	FBC, LFT	D
Methotrexate	Increased risk of lymphoma, increased risk of (opportunistic) infection; increased risk of pulmonary and liver fibrosis	FBC, LFT	X
Tacrolimus	Increased risk of lymphoma, increased risk of (opportunistic) infection	FBC, LFT, glucose, renal function	C
Ciclosporin	Increased risk of lymphoma, increased risk of (opportunistic) infection	FBC, LFT, renal function	C
Infliximab, adalimumab	Increased risk of lymphoma, increased risk of (opportunistic) infection	Rule out tuberculosis, congestive heart failure, and infection(s)	B

FBC=full blood count. LFT=liver function tests. FDA Pregnancy categories: A=controlled studies in animals and women have shown no risk in first trimester; possible fetal harm remote. B=either animal studies have not shown a fetal risk but no controlled studies in pregnant women, or animal studies have shown adverse effect not confirmed in controlled studies in women in first trimester. C=no controlled studies in human beings have been done, animal studies have shown adverse events, or studies in humans and animals not available; give if potential benefit outweighs risk. D=positive evidence of fetal risk available, but benefit might outweigh risk if life-threatening or serious disease. X=studies in animals or humans show fetal abnormalities, drug contraindicated. Data from references 45,156.

Table 7: **Safety and monitoring of commonly used inflammatory bowel disease drugs**

Blockade of T cells

Phase I and II studies with visilizumab, a humanised anti-CD3 antibody, in patients with severe ulcerative colitis refractory to intravenous corticosteroids have shown clinical benefit.[100] Placebo-controlled phase III trials are continuing. Two studies with basiliximab and daclizumab, monoclonal antibodies blocking the interleukin-2 receptor α-chain (CD25) on the surface of activated T cells, and approved for prevention of graft rejection in transplantaion, generated contradictory results.[97,98] A phase II placebo-controlled study of basiliximab is planned. Another interesting concept is the blockade of the co-stimulatory signal required for T-cell activation with CTLA-4-Ig (abatacept), which is approved for rheumatoid arthritis and phase II and III studies in patients with inflammatory bowel disease are planned.[96]

Blockade of inflammatory cell migration and adhesion

Selective adhesion molecule inhibitors interfere with the migration of leucocytes to the sites of inflammation by targeting adhesion molecules, such as α4-integrin or α4β7-integrin. Two phase-II studies with natalizumab, a monoclonal α4-integrin antibody, suggested efficacy for induction of remission in patients with active Crohn's disease.[141,142] In a phase III study,[143] natalizumab was not efficacious in patients with active Crohn's disease, but a subgroup analysis showed efficacy in patients with C-reactive protein concentrations above the normal range. Another phase III trial[144] in patients with active Crohn's disease and C-reactive protein above the upper limit of normal showed efficacy for induction of both response and remission. Finally, a phase III study[143] showed efficacy for natalizumab in maintaining response and remission and steroid-sparing in patients with Crohn's disease who responded to natalizumab induction therapy. The success of α4-integrin blockade with natalizumab is tempered by the report of three cases of progressive multifocal leucoencephalopathy caused by the human polyoma JC virus in patients with multiple sclerosis and Crohn's disease treated with natalizumab, leading to an estimated risk of 1 in 1000.[152] The US Food and Drug Administration has approved natalizumab for multiple sclerosis with the requirement of mandatory participation in a risk-management and registry programme. A phase II study[101] with MLN02 (LDP02; Millennium Pharmaceuticals, Cambridge, MA, USA), a monoclonal antibody that targets α4β7-integrin showed efficacy in patients with active ulcerative colitis.

Safety and monitoring of medical treatments for inflammatory bowel disease

Many medical therapies inflammatory bowel disease, particularly immunosuppressants and modulators, are associated with important side-effects. Systemic corticosteroid toxicities include moon face, acne, infection (including increase risk of abdominal and pelvic abscess in patients with Crohn's disease), ecchymoses, hyper-

tension, hirsutism, petechial bleeding, striae, diabetes mellitus, osteonecrosis, osteoporosis, myopathy, psychosis, cataracts, and glaucoma.[43,45] Azathioprine and mercaptopurine toxicities include pancreatitis, fever, rash, arthralgias, malaise, nausea, diarrhoea, thrombocytopenia, hepatitis, nodular regenerative hyperplasia, veno-occlusive disease, leucopenia, infection (including neutropenic sepsis and opportunistic infections), and lymphoma.[45,153–155] Methotrexate toxicities include rash, nausea, diarrhoea, mucositis, hypersensitivity pneumonitis, bone-marrow suppression, infection, raised transaminases, and hepatic fibrosis or cirrhosis.[45] Ciclosporin and tacrolimus toxicities include hypertension, headaches, paraesthesias, seizures (ciclosporin only), gingival hyperplasia (ciclosporin only), hypertrichosis (ciclosporin only), diabetes mellitus (tacrolimus only), anaphylaxis (ciclosporin only), infection (sepsis and opportunistic infection), renal insufficiency.[45] Anti-TNFα antibody (infliximab, adalimumab, certolizumab pegol) toxicities include infusion reactions (infliximab only), delayed-type hypersensitivity reactions (infliximab only), injection site reactions (adalimumab and certolizumab pegol only), formation of autoantibodies (mainly infliximab), demyelination (optic neuritis, multiple sclerosis), drug-induced lupus, worsening of congestive heart failure, reactivation of latent tuberculosis, serious infections (both sepsis and opportunistic infections), non-Hodgkin's lymphoma, and possibly solid tumour malignancies (table 7).[45,157,158]

Neoplastic complications of inflammatory bowel disease

Patients with ulcerative colitis and Crohn's disease have an increased risk of developing malignancies including colon cancer in patients with ulcerative colitis and Crohn's colitis and small-bowel carcinoma in patients with Crohn's enteritis.[159] A screening colonoscopy with a minimum of 30 mucosal biopsies should be done in patients with ulcerative colitis to rule out colonic neoplasia, dysplasia, or cancer, 8–10 years after onset of ulcerative colitis symptoms. Patients with extensive colitis or left-sided colitis who have a negative screening colonoscopy should then begin surveillance colonoscopy, again with a minimum of 30 mucosal biopsies, undertaken every 1–2 years. At 20 years, consideration should be given to yearly surveillance, because colorectal cancer risk increases with duration of colitis.[52] Patients with primary sclerosing cholangitis have an increased risk of developing colorectal cancer and should undergo surveillance yearly as soon as the clinician becomes aware that the patient has both ulcerative colitis and sclerosing cholangitis.[52,160] Several studies suggest that the long term use of 5-aminosalicylic acid and sulfasalazine are associated with a lower risk of colorectal cancer in patients with ulcerative colitis.[161] No agreement exists, however, about whether this effect is specific for these compounds or related to the generally better control of inflammation in patients adhering to 5-aminosalicylic acid or sulfasalazine regimens. Colectomy is indicated in patients with ulcerative colitis with high-grade dysplasia or multifocal flat low-grade dysplasia (two or more biopsies with low-grade dysplasia from a single screening or surveillance examination), repetitive flat low-grade dysplasia (two or more examinations with at least a single focus of low-grade dysplasia), or evidence of, or highly suspected, colorectal cancer.[50] To date no evidence exists that screening for colonic dysplasia and cancer with surveillance colonoscopy prolongs survival in patients with extensive colitis. However, cancers are diagnosed at an earlier stage and have correspondingly a better prognosis. Indirect evidence also suggests that this is a cost-effective approach.[162]

Small-bowel cancer in patients with Crohn's disease is distinct from de novo small-bowel cancer in those without inflammatory bowel disease. It occurs earlier and is mostly restricted to the inflamed areas of the ileum.[163] Patients who have had only small intestinal Crohn's disease without colonic involvement are not thought to be at higher risk for colorectal cancer than the general population. For patients with Crohn's colitis, the risk of colorectal cancer is similar to that for ulcerative colitis if there is similar surface-area involvement and disease duration. Screening and surveillance recommendations are thus similar to those for ulcerative colitis.

Conflict of interest statement

DCB has received research support from Astellas (formerly Fujisawa), Laboratoire Biocodex, PDL Biopharma (formerly Protein Design Labs); has served as a consultant for Abbott Laboratories, AstraZeneca, Elan, Essex Pharma, medac autoimmun, Otsuka Pharma, PDL Biopharma (formerly Protein Design Labs), Schering, Centocor, UCB Pharma; and has participated in continuing medical education events indirectly sponsored by Abbott Laboratories, AstraZeneca, Dr. Falk Pharma, Ferring, Essex Pharma, UCB Pharma. WJS has received research support from Abbott Laboratories, Amgen (formerly Immunex), AstraZeneca, Centocor, ChemoCentryx Inc, Elan, Glaxo Smith Kline, Human Genome Sciences, Otsuka America Pharmaceuticals, PDL Biopharma (formerly Protein Design Labs), Pfizer (formerly Pharmacia Upjohn), Procter and Gamble Pharmaceuticals, Salix, Schering Plough, Serono, Shire Pharmaceuticals, TechLab Inc, Targacept Inc, UCB Pharma (formerly Celltech); has served as a consultant for Abbott Laboratories, Alizyme, Alza Corporation, Amgen (formerly Immunex), AstraZeneca, Berlex, BioBalance Corporation, Boehringer-Ingelheim Inc, Bristol Meyers Squibb, Celgene, Cerimon Pharmaceuticals Inc, Centocor, ChemoCentryx Inc, CombinatoRx, Inc, Elan, FlexPharm Ltd, Glaxo Smith Kline, Genentech, Hoffman LaRoche, Inc, Human Genome Sciences, Hutchison Medipharma, Ltd, Inflabloc Pharmaceuticas (formerly Pharmadigm, Inc), Inotek Pharmaceutical Corporation, ISIS Pharmaceuticals, Jacobus Pharmaceutical Company, Johnson & Johnson Pharmaceutical Research & Development, Millennium Pharmaceuticals Inc., Nisshin Kyorin Pharmaceutical Co, Ltd, Novartis, NPS Pharmaceuticals, Otsuka America Pharmaceuticals, PDL Biopharma (formerly Protein Design Labs), Procter and Gamble Pharmaceuticals, Prometheus Laboratories, Renovia, Renovis Inc, Salix, Schering Plough, Serono, Shire Pharmaceuticals, Synta Pharmaceuticals Inc, Targacept Inc, Teva Pharmaceuticals. Therakos, UCB Pharma (formerly Celltech), Vela Pharmaceuticals, ViaCell Inc; and has participated in continuing medical educationevents indirectly sponsored by Abbott Laboratories, AstraZeneca, Centocor, Elan, Otsuka America Pharmaceuticals, PDL Biopharma (formerly Protein Design Labs), Procter and Gamble Pharmaceuticals, Prometheus Laboratories, Salix, Schering Plough, Shire Pharmaceuticals, UCB Pharma (formerly Celltech).

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