Ulcerative colitis: diagnosis and management

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This article summarises the essential facts on the diagnosis and treatment of ulcerative colitis and is aimed at general practitioners who manage this condition

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What is it, and who gets it?

Ulcerative colitis is a form of inflammatory bowel disease characterised by diffuse inflammation of the colonic mucosa. It affects the rectum and extends proximally along a variable length of the colon. The disease can be categorised as left sided colitis (inflammation up to the splenic flexure) or extensive colitis (inflammation beyond the splenic flexure). These categories are useful when formulating treatment options and planning the timing of surveillance colonoscopy, which is used to detect and prevent colorectal carcinoma. Colitis affects about one in 1000 people in the Western world.

What causes it?

The cause of inflammatory bowel disease is unclear, but it seems to occur in genetically susceptible people in response to environmental triggers. Ulcerative colitis is probably an autoimmune disease initiated by an inflammatory response to colonic bacteria.[1] From 10% to 20% of patients with the disease have at least one family member with inflammatory bowel disease (ulcerative colitis or Crohn's disease).[1]

Non-steroidal anti-inflammatory drugs can cause a flare-up of disease in some patients with inflammatory bowel disease.[2] Paracetamol is probably a safer option for analgesia, although mild non-steroidal anti-inflammatory drugs, such as ibuprofen, may be used occasionally if patients are told about the possibility of an increased risk of relapse. In contrast to Crohn's disease, smoking decreases the risk of ulcerative colitis.[3] Up to 50% of relapses of colitis are associated with gastroenteritis due to recognised pathogens.[4]

Clinical tips

Up to half of relapses of ulcerative colitis are associated with pathogens—stool should be obtained for culture in all cases of disease flare-up

The optimal starting dose of oral corticosteroids for an adult is prednisolone 40 mg once daily

Topical corticosteroids are less effective than topical mesalazine in achieving remission for patients with distal disease

How can I identify patients with ulcerative colitis?

A combination of history, assessment of endoscopic and radiological appearances, histology, and microbiology is needed to diagnose colitis (box 1). The cardinal symptoms of ulcerative colitis are:

- Bloody diarrhoea
- Urgency
- Tenesmus (straining at stool).

Mild distal colitis, in which rectal bleeding may be absent, can mimic irritable bowel syndrome. Colicky lower abdominal pain may occur, but severe pain is usually limited to severe colitis.

Stool cultures should be performed (particularly for *Clostridium difficile* toxin) even in patients with a relapse of known ulcerative colitis.[4] The presence of bloody diarrhoea for more than three weeks should alert the doctor to the possibility of inflammatory bowel disease, and endoscopy should be performed.

What are the extraintestinal manifestations?

Extraintestinal manifestations are common. They may or may not be related to the activity of the colitis.

Box 1: Diagnosing ulcerative colitis

Relevant history

Stool frequency, consistency, blood and mucous
Nocturnal diarrhoea
Weight loss
Family history
Extraintestinal manifestations (joints, rashes, eyes)
Travel abroad

Examinations

Pulse
Temperature
Abdominal tenderness
Abdominal distension

Investigations

Full blood count; liver function tests; erythrocyte sedimentation rate; measurement of C reactive protein, urea, and electrolytes
Stool culture and *Clostridium difficile* toxin assessment
Sigmoidoscopy and biopsy

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Related to the activity of the colitis:
- Erythema nodosum (found in 2-4% of cases)
- Aphthous ulcers (10%)
- Episcleritis
- Acute arthropathy (5-10%).

Usually related to the activity of the colitis:
- Pyoderma gangrenosum (1-2%)
- Anterior uveitis.

Not related to the activity of the colitis:
- Sacroileitis (12-15%)
- Ankylosing spondylitis (1-2%)
- Primary sclerosing cholangitis (3%).

What investigations should I do?

Endoscopy and a mucosal biopsy are essential for the diagnosis of ulcerative colitis. Although the endoscopic features of Crohn's disease and ulcerative colitis are different, considerable overlap occurs. In ulcerative colitis, the rectum is affected and the colon is ulcerated in a continuous and uniform way, except for a common patch of inflammation around the root of the appendix.[4] In Crohn's disease the rectum is often spared, areas of the colon are often unaffected, and the terminal ileum is often ulcerated.[4] It can be difficult to distinguish between ulcerative colitis and isolated colonic Crohn's disease in about one third of cases of colitis, and such patients can be described as having indeterminate colitis.

A plain abdominal x ray examination helps assess the extent of disease (ulcerated colon contains no solid faeces) and excludes toxic megacolon (transverse colon diameter >5 cm).

What are the aims of treatment?

Treatment aims to induce and then maintain remission. The choice and formulation of drug used depends on the severity and extent of disease.

What drugs should I use?

Aminosalicylates

Sulfasalazine was the main treatment for this disease for many years. When the active moiety was identified as 5-aminosalicylic acid, newer drugs were developed that did not contain sulfapyridine, which has potential side effects.

Mesalazine (5-aminosalicylic acid) is rapidly absorbed from the jejunum so the drug can be delivered to the colonic mucosa in several ways. Topical preparations can be applied per rectum. In oral preparations the active ingredient can be coated with a pH sensitive resin or semipermeable membrane for slow release (Pentasa, Ferring; Salofalk, Dr Falk; and Asacol, Procter and Gamble), or 5-aminosalicylic acid can be linked to another molecule by an azo bond that is enzymatically cleaved in the colon (balsalazide, olsalazine, and sulfasalazine).

Efficacy

Mesalazine (5-aminosalicylic acid) seems to be as effective as sulfasalazine at inducing remission.[5] Oral mesalazine is less effective than oral corticosteroids, however, so should be used as sole treatment only in mild attacks. Topical mesalazine is probably slightly more effective than topical corticosteroids. Oral mesalazine is mostly used to maintain remission—it reduces the relapse rate by about two thirds compared with placebo.[4] Mesalazine also seems to help reduce the risk of colorectal cancer—in one study, patients with ulcerative colitis who regularly took mesalazine had a 75% reduced risk of cancer.[6]

Adverse effects

Adverse effects occur in 10-45% patients treated with sulfasalazine and tend to be dose related. These side effects include headache, nausea, epigastric pain, and diarrhoea. Rare idiosyncratic reactions—which are not dose related—include Stevens-Johnson syndrome, pancreatitis, agranulocytosis, and alveolitis.[3]

Mesalazine is better tolerated—80% of people who cannot take sulfasalazine can take mesalazine and only 15% of people report adverse reactions to mesalazine.[3] These reactions include diarrhoea (3%), headache (2%), nausea (2%), and rash (1%). Interstitial nephritis and nephritic syndrome have been linked to the use of mesalazine, but these side effects are rare and are not clearly related to dose.[3]

Corticosteroids

Corticosteroids are used to induce remission in relapses of ulcerative colitis. They have no role in maintenance therapy. Corticosteroids may be applied topically (suppositories, liquid or foam enemas), orally (as prednisolone or prednisone), or intravenously (as hydrocortisone).

Efficacy and dosing

Oral prednisolone is usually started at 40 mg a day, with the aim of reducing the dose to zero during the next eight weeks.[7] This dose was established as optimal in a dose ranging trial in adults with colitis but withdrawal (steroid tailing) regimens have never been subjected to formal trial. The dose is reduced at one to two week intervals once symptoms have remitted (for example, from 40→30→20→15→10→5→0 mg a day).

Thiopurines

The thiopurines (azathioprine and its active metabolite 6-mercaptopurine) have been used for more than 30 years to modulate the immune response in patients with steroid refractory colitis.

Indications

Thiopurines may be used when patients are intolerant to corticosteroids; patients need two or more corticosteroid courses in a calendar year; disease relapses when the dose of prednisolone is less than 15 mg a day; or if disease relapses within six weeks of stopping steroids.[3] Azathioprine seems to be effective for at least five years, and increasing the duration of treatment will keep patients in remission for longer.[8]

Adverse effects

Adverse reactions include:
- Flu-like symptoms (myalgia, headache, and diarrhoea), which occur after two to three weeks and stop when the drug is withdrawn
- Gastrointestinal side effects (nausea and vomiting), which are seen in 28% of patients treated
- Leucopenia (5%), which can develop suddenly and behave unpredictably
- Hepatitis (0.3%)
- Pancreatitis (3.3%)
- Rash (2%)
- Infections (7.4%).[9 10]

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Box 2: Disease severity in ulcerative colitis

Mild
Fewer than four stools daily, with or without blood
No systemic disturbance
Normal erythrocyte sedimentation rate and C reactive protein values

Moderate
Four to six stools a day with minimal systemic disturbance

Severe
More than six stools a day containing blood and evidence of systemic disturbance (fever, tachycardia, anaemia, or hypoalbuminaemia)

Despite these side effects azathioprine seems to be safe for long term use as long as bone marrow toxicity and liver toxicity are monitored.[9] 6-Mercaptopurine can be used in patients who cannot tolerate azathioprine, as long as they have not had hypersensitivity reactions to azathioprine.[3]

Patients who take azathioprine should avoid allopurinol (a xanthine oxidase inhibitor) as it inhibits the breakdown of azathioprine and results in an increased risk of myelosuppression. Another enzyme, thiopurine methyl transferase, is also important in metabolism of azathioprine. Genetic polymorphisms of this enzyme occur. One in 300 people is severely deficient in this transferase and more likely to have adverse reactions, so this enzyme is now often measured before patients start treatment with azathioprine.

Thiopurines and risk of cancer
A recent meta-analysis suggested that patients with inflammatory bowel disease who take azathioprine have a slightly increased risk of lymphoma, particularly B cell lymphoma associated with Epstein Barr virus infection.[11] No increased risk has been shown for other cancers.

Methotrexate
Fewer trials have looked at the role of methotrexate in maintaining remission in colitis than in Crohn's disease. It is probably equally effective in both diseases.[12]

Ciclosporin
The calcineurin inhibitor ciclosporin is an effective salvage therapy for patients with severe refractory colitis and has a rapid onset of action.[13] It reduces the colectomy rate by 50% in the short term, but its use is controversial because of toxicity (drug associated mortality is about 3%) and the long term failure rate.

Infliximab
Tumour necrosis factor α has an important role in the inflammatory process in inflammatory bowel disease. Infliximab, a chimaeric monoclonal antibody to human tumour necrosis factor α, is an established treatment for Crohn's disease. The data for the role of infliximab in colitis are conflicting. A large trial showed it was effective in moderate to severe colitis,[14] but it is not generally used as maintenance therapy in this situation. Another study showed that infliximab can be used effectively and safely as rescue therapy in patients with acute severe or moderately severe attacks of colitis who do not respond to conventional treatment.[15]

Probiotics
Probiotics are live bacteria that are non-pathogenic and confer health benefits beyond their nutritional value. Clear evidence for the efficacy of probiotics in ulcerative colitis is lacking. However, a probiotic strain (*Escherichia coli* Nissle 1917) and the probiotic preparation VSL3 have shown promise.[16 17]

Antidiarrhoeal agents
Antidiarrhoeal agents do not reduce stool frequency in colitis and increase the risk of toxic megacolon.[4]

Antibiotics
Antibiotics are indicated if doubt exists about the diagnosis (for example, in the case of a first attack) or if the patient has recently travelled to an area where amoebic dysentery is endemic. Patients can be started on metronidazole and a quinolone empirically in this situation. Stool should be taken for culture (including assessment of *C difficile* toxin) in all patients.

Stool bulking agents or laxatives
Colonic motility is affected by inflammation and rapid transit occurs through the inflamed colon. In left sided disease, distal transit is rapid but proximal transit is slowed, which can result in proximal constipation.[18] Relief of proximal constipation by stool bulking agents or laxatives may help induce remission in proctitis.[4]

How can I induce remission?

The choice of treatment in an acute flare-up of colitis will be influenced by the extent and severity of disease (box 2).

Distal ulcerative colitis
Topical treatments (suppositories) can be used for disease that extends to the rectosigmoid junction. Foam or liquid enemas are useful for more proximal disease. A 100 ml enema may reach the splenic flexure.

Topical corticosteroids are probably less effective than topical mesalazine at achieving remission.[7] Up to half the dose of rectal prednisolone or hydrocortisone is absorbed, so long term use can have considerable side effects. Corticosteroids that are rapidly metabolised in the liver, such as prednisolone metasulfobenzoate, are less likely to cause systemic side effects.

Oral mesalazine alone or topical mesalazine alone are equally effective treatments, but combined treatment is more beneficial.[3] Oral corticosteroids may be needed if topical and oral therapy are ineffective.

Box 3: Indications for urgent hospital referral and colectomy

Hospital referral
Patients with severe colitis should be admitted to hospital for assessment and treatment
Patients with moderate disease who fail to respond to steroids within two weeks should be admitted to hospital
Patients who respond partially to treatment should be seen urgently in the outpatient department and treated for refractory colitis

Colectomy
Toxic megacolon; surgery should be performed within 24 hours unless the condition resolves
Severe ulcerative colitis that fails to respond to corticosteroid therapy within seven to 10 days
Chronic persisting colitis in a non-acute setting on the grounds of poor therapeutic response and poor quality of life
High grade dysplasia or cancer

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Sample questions

Here is a small sample of questions that you can find at the end of the module. To see all the questions and to get the answers, go to www.bmjlearning.com/ and search for "ulcerative colitis"

1. A woman who was recently diagnosed with ulcerative colitis attends the surgery and complains that she has started passing loose frequent stools. She opens her bowels five times a day and passes a little blood and mucous. She feels somewhat tired. She does not have a fever and her pulse is normal. How would you grade the severity of her flare-up of disease?
   a. Mild
   b. Moderate
   c. Severe
2. What treatments would be appropriate for this patient?
   a. Increase mesalazine from 1 g to 4 g a day and start prednisolone 40 mg a day
   b. Empirical antibiotic treatment
   c. Loperamide
3. The patient was given 40 mg prednisolone a day, mesalazine was increased to 4 g a day, and the results of stool culture were negative. She returned to the surgery two weeks later. Her symptoms were unchanged. Which one of the three options is the most appropriate?
   a. Start azathioprine
   b. Add topical mesalazine at a dose of 1 g a day
   c. Refer to hospital for assessment

Active left sided disease and extensive disease

Doses of oral mesalazine >3 g a day are associated with greater clinical improvement than lower doses.[3] Combined topical and oral treatment can help induce remission in left sided colitis and extensive colitis.[19 20] Oral corticosteroids are indicated in mild disease that fails to respond to topical treatment and in moderate disease (for example, patients with bloody diarrhoea).

Delays in treatment may increase the risk of colectomy. Patients should be treated promptly with an optimal dose of corticosteroids (40 mg prednisolone a day).[4]

Severe colitis

Severe colitis should be urgently referred to hospital (box 3). Surgery (colectomy) may be needed if medical treatment does not produce a substantial response within seven to 10 days (box 3).

How can I maintain remission?

Lifelong maintenance treatment with mesalazine is recommended for all patients. Topical mesalazine may be used in distal disease, with or without oral mesalazine.

Screening for colorectal cancer in ulcerative colitis

Patients with longstanding colitis have a fivefold to tenfold higher risk of colorectal cancer than age matched controls, and screening for colorectal cancer is offered to all patients with longstanding, extensive ulcerative colitis or Crohn's colitis.[21] Risk increases with younger age at onset, longer duration of disease, and increased extent of colonic involvement. Recent studies report that the incidence of colorectal cancer in colitis is falling, perhaps as a result of more rigorous adherence to maintenance mesalazine.[22]

Conclusion

Ulcerative colitis is a chronic condition with a relapsing remitting course. About two thirds of patients have clear cut and often long lasting remissions, but the overall colectomy rate is still about 25%. The extent and severity of disease should be assessed to identify the best approach for the induction and maintenance of remission.

Competing interests: JMR is a past or present member of advisory boards for Procter and Gamble, Schering-Plough, Chiesi, Falk, and Celltech and with the University of Liverpool and Provexis (UK) holds a patent for use of a soluble fibre preparation as maintenance treatment for Crohn's disease.

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