Ulcerative colitis

Helen Steed

Abstract

Ulcerative colitis is a chronic idiopathic inflammatory disease affecting the large intestine. In this chapter, we review current concepts in its assessment and management.

Keywords Biologics; biosimilars; diarrhoea; inflammatory bowel disease; management; MRCP; ulcerative colitis

Key points

- Ulcerative colitis can be classified according to severity using the Montreal classification
- Faecal calprotectin can be used to screen young patients and reduce unnecessary invasive investigations
- Adherence to 5-aminosalicylic acid maintenance treatment is important for reducing the risk of relapse
- Oral immunomodulators, usually in the form of thiopurines, are second-line corticosteroid-sparing agents
- Biologicals and biosimilar treatments can be used for management but pose an increased risk of opportunistic infections that should be proactively managed

Introduction

Ulcerative colitis (UC) is a chronic life-long illness and one of two main forms of inflammatory bowel disease (IBD) that characteristically affect the colon. The annual incidence is approximately 10–12 per 100,000 people, and it is three times as common as Crohn's disease. The age of onset peaks at 15–25 and 55–65 years old, with men and women equally affected. The aetiology remains incompletely understood and probably represents complex interactions between genetic factors, environmental factors, smoking history and immune system actions among others (Figure 1). This is discussed in depth in a previous publication in this journal Gwo-Tzer et al. *Medicine* 2015; **43(5):** 276–281.

Clinical approach

Diarrhoea is a common presenting symptom, and the history is key to eliciting the pattern that might make a diagnosis of IBD more likely.

History

Patients commonly report an insidious onset of diarrhoea in the form of increased frequency and softer consistency of stools, and >90% of patients report rectal bleeding, mucus in the stool, a sense of urgency, tenesmus and abdominal pains. Symptoms tend to be consistent, and flare-ups last for many weeks at a time. Symptoms lasting >6 weeks help to differentiate UC from infectious colitis. A family history of IBD or a history of stopping smoking should lower the threshold for further assessment.

Fifteen per cent of patients report marked bloody diarrhoea, significant abdominal pain, fever, nausea, vomiting and weight loss; this represents severe disease, and admission may be required.

Extraintestinal manifestations include arthralgia, episcleritis and erythema nodosum. These precede gastrointestinal symptoms in 10% of patients, and are seen in 10–20% of presentations.

Helen Steed *MB ChB MD FRCP is a Consultant Gastroenterologist at the Royal Wolverhampton NHS Trust, UK. Her research interests are inflammatory bowel disease (pregnancy, parenthood planning, faecal and stool biomarkers) and bile acid malabsorption. Competing Interests: none declared.*

Examination

Findings on physical examination tend to be unremarkable or non-specific. There is usually mild tenderness in the lower abdomen, indicating moderate to severe inflammation, and examination findings are often normal in mild UC. In severe cases of systemic toxicity, evidence of dehydration, hypotension, fever, tachycardia, significant tenderness, abdominal distension and pallor can be signs of acute severe disease requiring inpatient treatment. Table 1 summarizes the characteristics of severity.

Investigations

Diagnosis is made at endoscopy with histological confirmation, but there is a role for laboratory testing and radiology.

Laboratory testing: infectious colitis is a differential diagnosis, and UC is an independent risk factor for *Clostridium difficile* infection. *C. difficile* is seen in up to 5% of acute admissions with a flare-up of UC, and can increase the risk of colectomy, so it is important to identify or exclude it early.

In subacute disease, significant disease can exist with normal inflammatory markers. In acute flare-ups, raised white cell, platelet or C-reactive protein (CRP) values can be seen. Anaemia is found in 20% of patients.

In management of chronic disease, frequency of blood testing is often dictated by clinical well-being and drug therapy.

Faecal calprotectin measurement has been validated as a non-invasive way of differentiating irritable bowel syndrome and IBD in the population aged <45 years with diarrhoea. Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided in the 6 weeks preceding sampling, to minimize risk of a false-positive result. Once a person has been diagnosed with IBD, NSAIDs should be avoided as they can cause flare-ups, although short-term cyclooxygenase-2 inhibitors are thought to be safe. Regular faecal calprotectin measurements are made in patients with IBD to monitor disease activity and reduce the need for invasive endoscopic testing.

Endoscopy and histology: endoscopy is used to obtain histological results and confirm the extent of disease (Table 2).

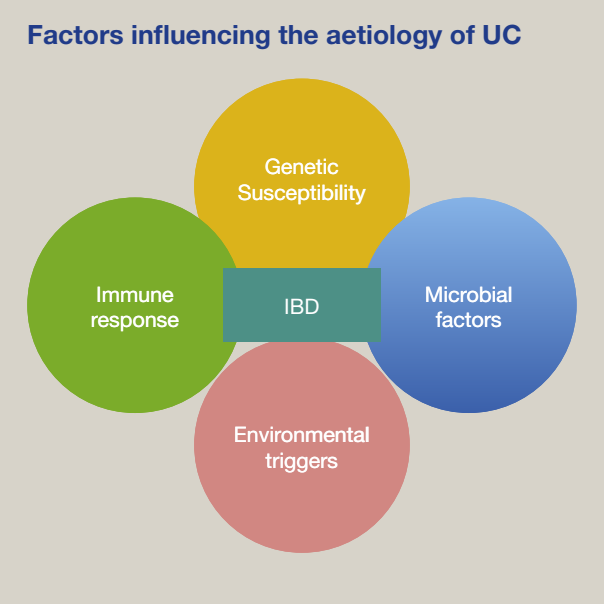

Figure 1

Montreal classification[1]

Severity of UC

Mild

- <4 stools a day with or without blood, normal CRP/ESR, no systemic signs of toxicity

Moderate

- 4–6 stools a day with minimal signs of toxicity

Severe

- >6 bloody stools a day and systemic toxicity in the form of severe, tachycardia, anaemia or elevated ESR/CRP

Fulminant

- >10 stools a day, continuous bleeding, toxicity as described above, abdominal tenderness and distension. The patient may require blood transfusions, and abdominal X-ray may demonstrate colonic dilatation

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; UC, ulcerative colitis.

Table 1

Classification of extent and distribution

Classification	Description	Distribution of disease	Additional information
E1	Proctitis	Rectum only	
E2	Left-sided disease	Rectum, sigmoid and descending colon	
E3	Extensive	Includes colon proximal to splenic flexure, including the whole colon	Can include terminal ileum – backwash ileitis

Table 2

Microscopically, UC is characterized by inflammatory infiltration of the lamina propria causing acute and chronic inflammation, crypt branching and villous atrophy.

Radiology: an abdominal radiograph can be used in the management of fulminant or acute severe colitis. Abnormalities seen are a drainpipe or lead pipe appearance, thumb-printing and mucosal oedema, and dilatation of the colon (Table 3 shows examples of the radiographic changes in UC). Daily abdominal X-rays in fulminant colitis are used to monitor for deterioration.

Management

Mild to moderate disease

Table 4 describes induction of remission in mild to moderate UC. Once remission has been achieved, long-term maintenance therapy using reduced doses of mesalazine (dosage between 1.2 and 2.4 g a day is recommended to reduce the risk of flare-up). Once-daily dosing is as effective as twice or three times a day dosing and can improve adherence. Adherence to 5-aminosalicylic acid (5-ASA) medication is a governing factor in risk of relapse, with a 5-fold higher risk in patients who collect <80% of their maintenance 5-ASA prescriptions.[2]

If oral mesalazine is ineffective, treatment with corticosteroids is indicated. Budesonide MMX is licensed for inducing remission in mild to moderate UC. The main benefit of budesonide is the high first-pass metabolism, which results in minimal systemic absorption and therefore reduced adverse effects. Alternatively, a reducing course of oral prednisolone is used along with a concomitant combination calcium and vitamin D supplement. Co-prescription is recommended because of the increased association of osteoporosis with repeated use of glucocorticoids. Glucocorticoids reduce the effect of vitamin D, and low vitamin D levels are associated with more aggressive disease. Corticosteroids should be used to induce remission but have no role in maintenance therapy; they should therefore not be used for this purpose, given their short- and long-term adverse effects (Table 5).

Patients who are unable to maintain remission on 5-ASA alone, or have become corticosteroid-dependent, are escalated to corticosteroid-sparing immunosuppressive therapy. This is typically an oral thiopurine agent, such as azathioprine or 6-mercaptopurine. Measurement of drug levels in the form of metabolites 6-thioguanine nucleotide (6-TGN) and 6-methylmercaptopurine (6-MMPN) can be used to titrate the effect. Adverse effects can include abnormal liver function tests, leucopenia, pancreatitis, flu-like illness, nausea and vomiting, fatigue, hair loss, and skin sensitivity that can increase the risk of skin cancer and lymphoma.

In the event of thiopurines being ineffective or inadequately tolerated, biological agents become the treatment of choice.

Severe disease

The Truelove and Witts severity index was published in 1955 and is still used for assessing severity; severe disease is defined as >6 bloody stools a day, tachycardia, fever and anaemia.

Intravenous corticosteroids remain the mainstay of conventional treatment for patients admitted with severe UC (Table 3).

Endoscopy, histology and radiological features of ulcerative colitis

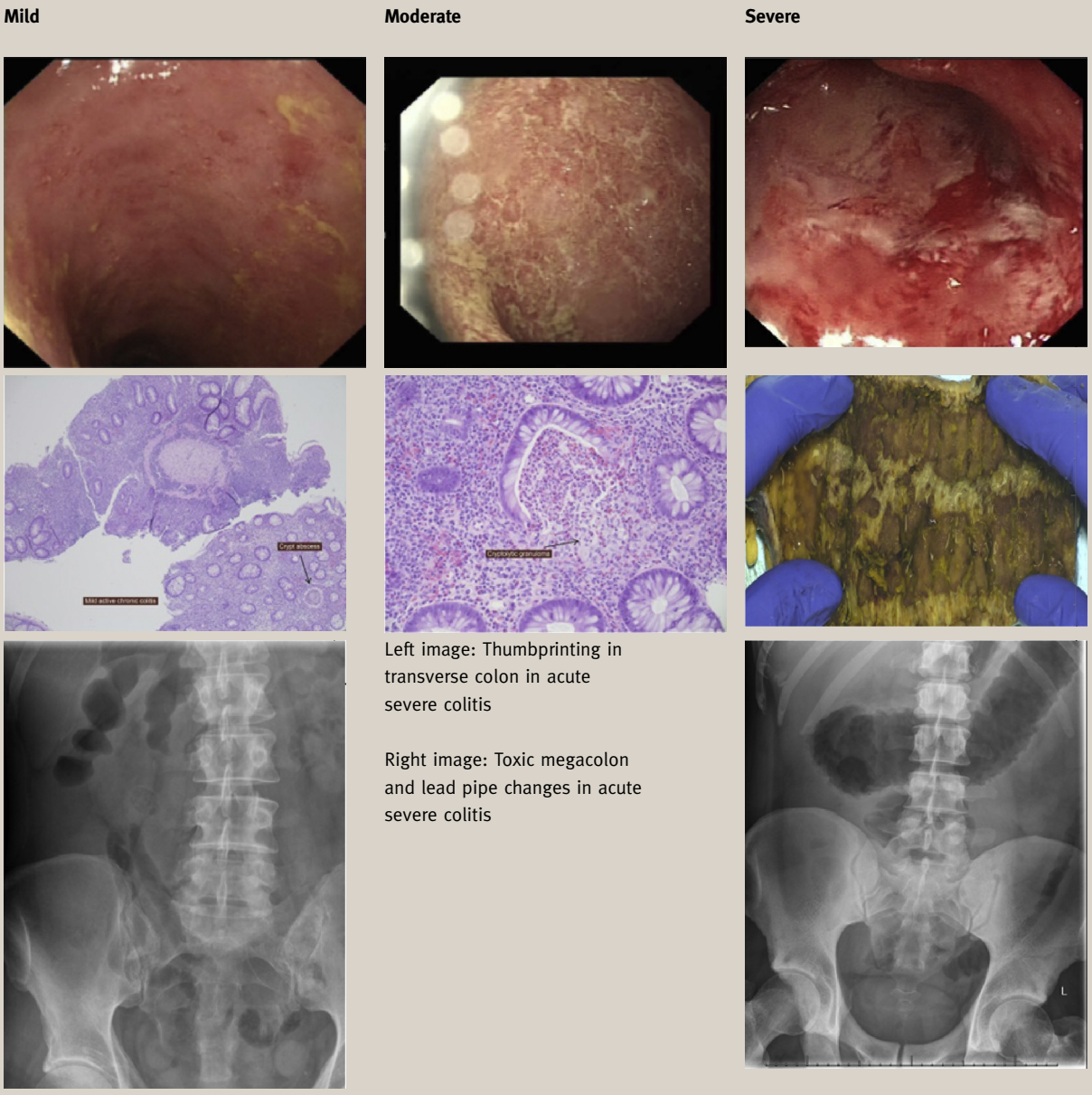

Table 3

These measures should be taken alongside supportive management including intravenous fluids, dietetic input, correction of electrolyte abnormalities, low-molecular-weight heparin and management of anaemia. Management should be shared between the gastroenterology team and the colorectal surgeon. Stool cultures must be sent to exclude *C. difficile*, and an unprepared flexible sigmoidoscopy is recommended to exclude cytomegalovirus, especially in corticosteroid refractory disease.

By day 3, a decision should be made on the effectiveness of the response to intravenous corticosteroids. Rescue therapy can be started, in the form of the biological agent infliximab or ciclopsorin, which are comparable. Further evaluation should be made between days 4 and 7, and colectomy, with appropriate preoperative counselling, can be considered for failure to respond. Approximately two-thirds of patients will respond to corticosteroid treatment, and one-third need a colectomy. Deep ulceration is associated with a corticosteroid failure rate of 85% and with colectomy, as are high CRP and low serum albumin concentrations. Case-series report colectomy rates of 20–75% after infliximab for steroid-refractory UC.

The choice between infliximab and ciclosporin should be individualized as these drugs are comparable in effectiveness. However, ciclosporin should be avoided in individuals with low

Inducing remission in mild to moderate UC

Extent	First line	Second line	Third line	Fourth line
E1	Mesalazine suppositories (topical)	Corticosteroid enemas	Mesalazine orally	Corticosteroids[a]
E2	Combination mesalazine topical and oral	Corticosteroids[a]	Biologicals	
E3	Combination mesalazine topical and oral	Corticosteroids[a]	Biologicals	

[a] In moderate disease, it may be appropriate to initiate corticosteroids alongside mesalazine treatment.

Table 4

magnesium and cholesterol concentrations because of a heightened risk of neurological adverse effects.

Biological agents and biosimilars

The expanded availability of biological agents over the last few years has increased the treatment options for UC and allowed biologics to be used for subacute and moderate disease. Corticosteroid-refractory disease should be treated with a thiopurine or an anti-tumour necrosis factor (TNF) agent (preferably in combination with a thiopurine), vedolizumab or methotrexate.[3]

Anti-TNF agents include infliximab, adalimumab and golimumab and their biosimilars. These bind free membrane-bound TNF and prevent cytokines from binding to the surface receptor and exerting their biological activity. In one study, corticosteroid-free remission at week 30 after infliximab treatment occurred in 21.5% of participants, compared with 7.2% of those given placebo. Rates were higher in randomized controlled trials of adalimumab, 31% of patients being corticosteroid-free at week 16, but this fell to 13.3% at 1 year. Golimumab offers rates of 20.7% corticosteroid-free remission at week 54.

Biosimilars are drugs that are molecularly very close to the original biological agent that has come off patent. Use to date suggests that biosimilars are equivocal to the original agents in efficacy, with no new safety signals.

Adverse effects of glucocorticoids

Short term	Weight gain, adrenal suppression, Cushingoid appearance, mood changes including depression and psychosis, increased susceptibility to infection, including reactivation of tuberculosis, hypertension, gastritis, insomnia, polyuria, nocturia, acne, oedema, delayed wound healing, weakness, amenorrhoea
Long term	Adrenal suppression, thin skin, easy bruising, osteoporosis, cataracts, glaucoma, increased susceptibility to infection, including reactivation of tuberculosis, pancreatitis, peptic ulcer disease, intestinal perforation, hypertension, aseptic necrosis, proximal myopathy, amenorrhoea, diabetes mellitus-hyperglycaemia, glycosuria, hypokalaemia, hypocalcaemia, hyperlipidaemia, growth retardation, acne, oedema, hirsuitism, hyperpigmentation, neuropathy

Table 5

Vedolizumab is a recombinant monoclonal antibody that binds to $\alpha_4e\beta_7$-integrin, blocking the interaction between the integrin and mucosal addressing cell adhesion molecule-1 (MAdCAM-1); this inhibits the migration of memory T lymphocytes into inflamed gastrointestinal tissue. Vedolizumab remission rates were reported to be 38.5% at week 52 compared with 13.9% in the placebo group.

Janus kinase pathway inhibitors prevent phosphorylation and activation of signal transducers and activators of transcription that affect intracellular activity, including gene expression. Tofacitinib is licensed for use in moderate to severe UC and administered orally.[4]

Opportunistic infections

Patients should be screened for tuberculosis (TB), hepatitis B and C, HIV, Epstein–Barr virus and varicella-zoster, and appropriate vaccinations offered as necessary before commencing high-dose corticosteroids or other immunomodulators. In patients with active or latent tuberculosis, antituberculosis chemotherapy should be commenced 3 weeks before initiating biologics and expert advice should be sought. However, even if latent TB is treated, reactivation can occur when biologic drugs are used.

In immunocompromised patients, routine vaccinations such as pneumococcal vaccination and annual influenza vaccines should be encouraged. Patients on immunomodulating drugs who develop bacterial infections experience more severe infections. Withholding the immunomodulating agents while active infections are managed is advised, and experts should be consulted before reintroducing these drugs.

Diet

No specific dietary restrictions are currently recommended in UC. Elemental and parental nutrition have no therapeutic role in the treatment of UC outside of use in severely ill patients as nutritional support.

Surgery

Surgery is indicated in a number of settings, the most common being failure of or loss of response to medical therapy. Other indications for surgery include development of adenocarcinoma and in some cases dysplasia, although the availability of effective endoscopic resection techniques is increasing. Data suggest that 25–35% of patients still require surgery for UC. Surgery can be required urgently or can be elective. In most cases, it takes the form of a subtotal colectomy with formation of an ileostomy or panproctocolectomy.

Urgent surgery is required in patients who develop toxic megacolon or fulminant colitis that is refractory to medical

management, and in rare cases of uncontrolled bleeding. For individuals undergoing subtotal colectomy, a subsequent procedure to form an ileal pouch–anal anastomosis (J pouch') can be offered.

Prognosis

In a study considering the first 5 years of diagnosis, 13% of participants had an indolent course with no relapse, 74% had two or more relapses, and 13% had an aggressive course with disease activity every year.[5] Remission tends to be defined as three or fewer stools a day with no bleeding and no mucosal lesions on endoscopy.

Malignancy

UC is associated with an increased risk of colonic adenocarcinoma, and 3–5% of patients develop this. Duration, extent of disease, failure to achieve mucosal healing and family history of colorectal cancer contribute to the risk of developing colorectal cancer. These factors dictate the frequency of surveillance, starting 8–10 years after diagnosis and taking the form of regular chromoendoscopy. In patients with concurrent primary sclerosing cholangitis, annual surveillance with colonoscopy is recommended irrespective of the extent and duration of disease. 5-ASA (>1.2 g/day) agents have a chemopreventive effect, and life-long treatment is recommended. ◆

KEY REFERENCES

1 Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006; **55:** 749–53.

2 Ford AC, Achkar JP, Khan KJ, et al. Efficacy of 5-aminosalicylates in ulcerative colitis: systematic review and meta-analysis. *Am J Gastroenterol* 2011; **106:** 601–16.

3 Ford AC, Sandborn WJ, Khan KJ, et al. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol* 2011; **106:** 644–59. quiz 660.

4 Sandborn WJ, Su C, Sands BE, et al. For the OCTAVE Induction 1, OCTAVE Induction 2, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2017; **376:** 1723–36.

5 Hendriksen C, Kreiner S, Binder V. Long term prognosis in ulcerative colitis – based on results from a regional patient group from the county of Copenhagen. *Gut* 1985; **26:** 158–63.

TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 23-year-old man presented with a 2-week history of bloody diarrhoea and abdominal pain.
On clinical examination, his temperature was 38.0°C, and heart rate 120 beats/minute. There was left-sided abdominal tenderness.

Investigations

- Abdominal X-ray showed thumb-printing
- Serum C-reactive protein 220 mg/litre (<10)

What is the most appropriate investigation to carry out next?

A. Colonoscopy
B. Flexible sigmoidoscopy
C. Stool microscopy, culture and sensitivity
D. Calprotectin
E. CT abdomen/pelvis

Question 2

A 35-year-old woman had been treated for acute severe ulcerative colitis with intravenous hydrocortisone 100 mg days for 3 days. She had been passing 14 bloody motions over a 24-hour period but this had reduced to seven soft, blood-streaked bowel motions a day. She still had some abdominal pain, but this had improved, she was eating better, and her abdomen was soft, with mild tenderness on examination.

Investigations

- Haemoglobin 80 g/litre (115–165)
- White cell count 14 × 10^9/litre (4.0–11.0)
- Platelets 520 × 10^9/litre (150–400)
- Potassium 3.0 mmol/litre (3.5–4.9)
- Serum magnesium 0.35 mmol/litre (0.75–1.05)
- Serum C-reactive protein 110 mg/litre (<10) (down from 220)
- Stool cultures negative for *C. difficile*
- Flexible sigmoidoscopy showed deep ulceration of the splenic flexure

What treatment should now be commenced?

A. Convert hydrocortisone to oral corticosteroids
B. Continue hydrocortisone
C. Ciclosporin
D. Vedolizumab
E. Infliximab

Question 3

A 27-year-old woman presented 10 weeks' pregnant with softer stools with blood two or three times a day. She had been found to have ulcerative colitis and was taking a maintenance dose of mesalazine and azathioprine. She was eating well and had some mild abdominal pain, but was also experiencing fatigue and pain in the lumbar spine.

Investigations

- Serum C-reactive protein <5 mg/litre (<10)
- Stool cultures negative

What is the most appropriate action to take next?

A. Refer for flexible sigmoidoscopy
B. Increase mesalazine to a treatment dose
C. Start an oral prednisolone-reducing course
D. Stop the azathioprine and start corticosteroids
E. Refer to the obstetric team