

Optimising the treatment of inflammatory bowel disease

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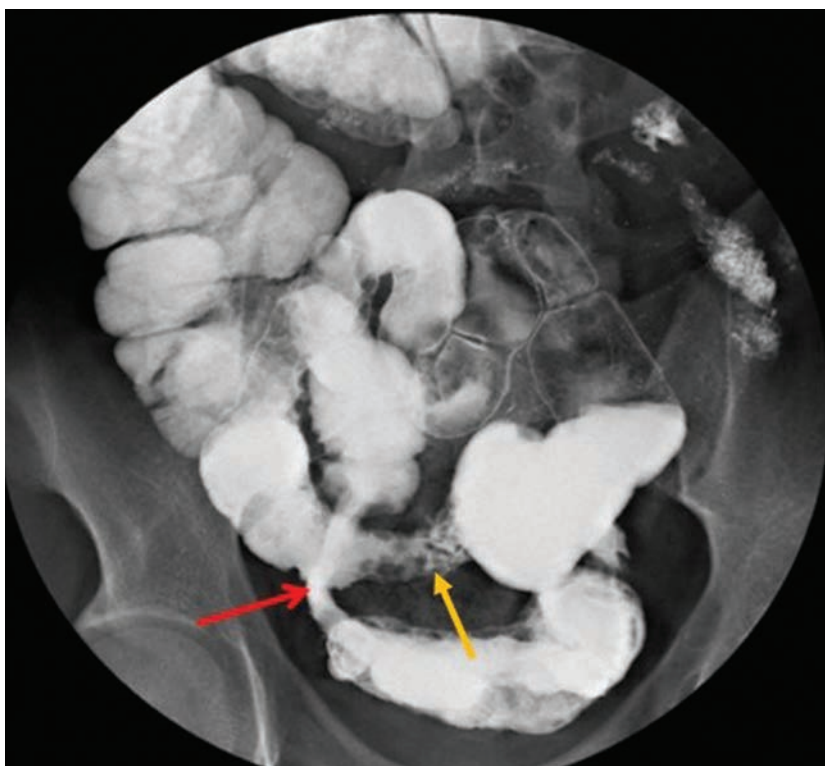
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Barium small bowel meal: Crohn's stricture affecting 40 cm of the terminal ileum (red arrow) with a proximal inflamed small bowel segment with cobble stoning and rose thorn ulcers (orange arrow)



INFLAMMATORY BOWEL DISEASE (IBD) MAINLY COMPRISES ULCERATIVE COLITIS (UC) AND CROHN'S

disease (CD) with approximately 5% of patients having an unspecified subtype known as IBD-unclassified (IBD-U).¹

IBD is a chronic inflammatory condition that runs a relapsing and remitting course, of varying severity.^{1,2,3} The aetiology remains unknown but includes genetic susceptibility, altered gut microbiota, changes in immunological response and environmental triggers.^{4,5} UC is more common with a prevalence of 240 per 100,000 compared with CD which has a prevalence of 157 per 100,000.^{6,7}

UC almost always affects the rectum, and extends proximally and continuously to the colon to a variable extent.³ Approximately 50% of people with UC have disease limited to the rectum (proctitis) or rectum and sigmoid colon (proctosigmoiditis), with only 3.3% having rectal sparing.^{1,3} CD most commonly affects the terminal ileum or colon but can affect any part of the gastrointestinal (GI)

tract from the mouth to the anus.⁸

Treatment options have expanded rapidly with the introduction of novel agents producing benefits in terms of symptom improvement but also reduced tissue damage. The biologics have resulted in a transformation in the treatment of IBD but also new challenges in terms of understanding drug toxicity and the causes of loss of response to these agents, for example, due to the development of antidrug antibodies.

ORGANISATION OF CARE

Prompt diagnosis and management requires early recognition, assessment and referral in primary care and is likely to affect clinical outcomes. In addition, GPs play an important role in monitoring treatment and assessment of disease flares.

A multidisciplinary approach in secondary care with gastroenterologists, specialist IBD nurses, colorectal surgeons with an interest in IBD and additional specialties including dietetic, psychology and pharmacy input is

How should diagnosis be confirmed?

What are the treatment approaches?

How should patients be monitored?

accepted as the standard of care,¹ but not all components are available to every patient. Additional specialty input may also be needed from obstetrics and stoma care at different points in an individual's management.¹

PRESENTATION

IBD may affect people at any age.⁹ The most common age of onset for CD is the early to mid-20s.¹⁰ UC has an initial peak at 15-25 years and a second smaller peak between 55 and 65.³

Current UK guidance suggests that people presenting to primary care with a six-week history of diarrhoea, with or without blood or mucus, and/or abdominal pain, discomfort or bloating should be suspected of having IBD. However, symptoms such as abdominal pain, bloating or altered bowel habit also occur in people with a wide range of other conditions, including irritable bowel syndrome.¹¹ Individual symptoms may not be strongly predictive of the presence of IBD but it has been suggested that combinations of clinical features

(rectal bleeding with diarrhoea, thrombocytosis, low MCV, low Hb or raised inflammatory markers; change in bowel habit with low MCV, thrombocytosis or low Hb; and diarrhoea with thrombocytosis) may raise the positive predictive value (PPV) for either IBD or colorectal cancer above 3%.¹² In practice, a threshold of 3-4 weeks will help differentiate self-limiting causes such as infection and in the presence of a negative stool culture or severe symptoms, earlier referral should be considered.¹³

Smoking is an important risk factor in CD, whereas in UC the disease predominantly affects former smokers and nonsmokers.¹

Chronic diarrhoea is a common symptom in UC and CD.^{2,3} Weight loss, rectal bleeding and nocturnal diarrhoea are clinical features that indicate a need for further investigation.¹

The vast majority (90%) of people with UC report bloody stools¹⁴ compared with < 50% of those with CD.¹⁵ Diarrhoea in UC is commonly associated with urgency both during the day and night. Urgency reflects rectal involvement and the stool frequency and presence of blood are markers of disease severity. This may be associated with lower cramping abdominal pain.⁹

The severity of an acute episode or flare of UC is usually described using the criteria of Truelove and Witts,³ shown in table 1, below.

CD is characterised by a triad of abdominal pain, diarrhoea and weight loss. Perianal disease is more common in CD and can consist of skin tags, fissures, abscesses and fistulae.¹⁵

Associated symptoms of pain and discharge are intrusive and debilitating but may be under-reported by people with CD and under-appreciated by clinicians. Upper GI CD is rare in adults: symptoms may include upper abdominal pain, nausea and vomiting.¹

Fatigue is a common and debilitating symptom in IBD.¹ It may be related to a range of causes including anaemia or iron deficiency, sleep disturbance from pain or diarrhoea and depression but there may be no underlying explanation.¹

IBD can also affect other parts of the body in approximately 25% of cases.^{16,17} Patients may suffer from arthropathies, skin manifestations such as erythema nodosum and pyoderma gangrenosum, ocular conditions such as episcleritis, scleritis and uveitis, aphthous oral ulcers, osteopenia, primary sclerosing cholangitis and autoimmune hepatitis.^{16,17}

ASSESSMENT

The differential diagnoses for chronic abdominal pain and diarrhoea are shown in table 2, below, right.

A history of foreign travel, diarrhoeal illnesses and other contacts should be sought. Antibiotics may be associated with self-limiting diarrhoea or more severe *Clostridium difficile* colitis. A range of drugs including proton pump inhibitors, NSAIDs, acarbose and sertraline can be associated with microscopic colitis.^{18,19}

If IBD is suspected, the severity of symptoms should be assessed and risk factors such as smoking history and family history reviewed. In primary care the following investigations should be considered:

- Stool microscopy and culture, and *Clostridium difficile* toxin assay to exclude infective causes^{1,3}
- Microscopy and culture for amoebic or Shigella dysentery should be carried out if travel history is suggestive¹
- Blood tests: full blood count (FBC), urea and electrolytes (U&E), inflammatory markers: CRP and ESR and haematinics
- Anaemia may be due to iron deficiency (frequently unrecognised in established IBD), B₁₂ or folate deficiency or anaemia of chronic disease
- CRP, ESR and platelet count may be raised due to the acute inflammatory phase response
- Faecal calprotectin: Faecal calprotectin is a protein released by intestinal neutrophils. It is a non-invasive test, both sensitive and specific for intestinal inflammation that can be used to investigate people who

have had chronic symptoms for more than six weeks,¹¹ who are low risk for malignancy and where others causes have been excluded.¹ The British Society of Gastroenterology (BSG) suggests a minimum of 100-250 µg/g to trigger colonoscopy investigation¹ though the yield in primary care can be low.²⁰ Faecal calprotectin is not sufficiently sensitive as an assessment for colorectal adenoma or carcinoma.¹

A normal faecal calprotectin is defined by the assay as < 50 µg/g stool. However, at this threshold, although the negative predictive value (NPV) is 98% the PPV is low at 20%.²⁰ The BSG suggests using a higher threshold to trigger colonoscopy investigation.¹ The York Faecal Calprotectin Pathway for primary care using a higher threshold of 100 µg/g for 'normal' had an NPV of 97% and a PPV of 40%. The pathway advises repeat faecal calprotectin within 2 weeks if >100 µg/g, routine referral to gastroenterology for a faecal calprotectin of 100-250 µg/g and urgent referral to gastroenterology if >250 µg/g.

REFERRAL AND DIAGNOSIS

All people with suspected IBD should be seen within four weeks from referral for a specialist assessment,¹¹ or more urgently if symptoms are indicative of a more severe disease course.¹¹ Patients should be referred directly to a consultant gastroenterologist specialising in IBD to ensure that there is no delay in diagnosis and treatment can be commenced quickly.¹¹ Treatment is usually initiated in secondary care. Patients fulfilling the Truelove and Witts' criteria for a severe flare require hospital admission.

The diagnosis of IBD is based on clinical features, imaging findings, macroscopic features on endoscopy and microscopic features on histology. The gold standard for diagnosis is histology following endoscopy or surgical resection.¹

Table 1

Truelove and Witts' classification of severity in ulcerative colitis²⁵

Disease activity	Mild	Moderate	Severe
Number of bloody stools/day	< 4	4-6	> 6
Temperature (°C)	Afebrile	Intermediate	> 37.8
Heart rate (beats/min)	Normal	Intermediate	> 90
Haemoglobin (g/L)	> 11	10.5-11	< 10.5
ESR (mm/hr)	< 20	20-30	> 30

A severe flare is currently defined on the basis of stool frequency, plus one or more of the additional features¹

Table 2

Differential diagnoses for chronic diarrhoea and abdominal pain

- Inflammatory bowel disease
- Irritable bowel syndrome²¹
- Bowel cancer⁹
- Coeliac disease¹
- Endometriosis and ovarian cancer⁹
- Infection



FIGURE 1
Mild ulcerative proctitis: erythema and decreased vascular pattern

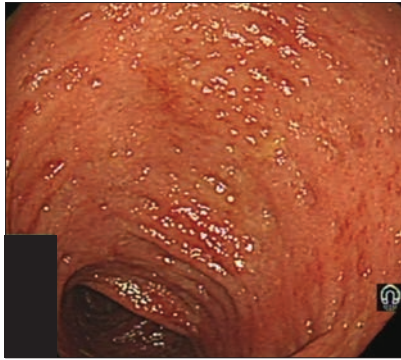


FIGURE 2
Left-sided ulcerative colitis: mucosa is friable with erythema and loss of the vascular pattern

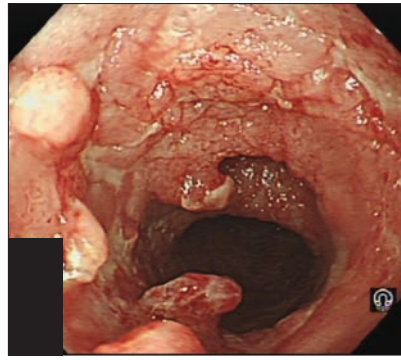


FIGURE 3
Severe left-sided ulcerative colitis: spontaneous bleeding with inflamed pseudopolyps



FIGURE 4
Barium small bowel meal: Crohn's stricture affecting 40 cm of the terminal ileum (red arrow) with a proximal inflamed small bowel segment with cobblestoning and rose thorn ulcers (orange arrow)

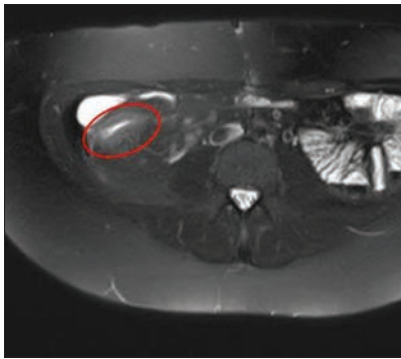


FIGURE 5
Small bowel MRI: 10 cm of thickened terminal ileum consistent with active terminal ileal Crohn's disease

UC is most commonly initially diagnosed with flexible sigmoidoscopy (see figures 1-3, above) and histological assessment of mucosal biopsies. This may be confirmed with ileocolonoscopy often carried out within the first year of diagnosis to define the full extent of disease.¹

In CD the first-line investigation is an ileocolonoscopy with mucosal biopsies from the colon and ileum.¹ Small bowel investigations such as barium meal (see figure 4, above), MR enterography (see figure 5, above) and capsule endoscopy (see figure 6, p14), based on local availability and expertise, further aid clinical diagnosis.^{15,22}

PHARMACOLOGICAL THERAPY

Treatment approaches for IBD cover two overlapping phases: induction and maintenance of remission.² The choice of treatment is guided by the extent and site of involvement, severity of disease and associated complications such as the presence of perianal disease.

Currently, a step up approach is often used. The debate remains as to

whether a more aggressive top down approach with earlier use of anti-TNF agents and immunosuppression may result in fewer long-term complications.

ULCERATIVE COLITIS

A summary of induction therapy for UC is shown in table 3, below.

Maintenance of remission^{1,3}

- 5-ASA: Proctitis or proctosigmoiditis — topical or oral 5-ASA alone or both topical 5-ASA and oral 5-ASA. Left-sided and extensive UC — oral 5-ASA

- Thiopurines: azathioprine or mercaptopurine: Used as first line in steroid-dependent disease — two or more inflammatory exacerbations that have required systemic corticosteroids in the past 12 months or patients who have had a single severe flare episode¹

- Biologic therapies (infliximab, adalimumab, golimumab, vedolizumab) and tofacitinib. These can be given with an immunosuppressant or as monotherapy.

CROHN'S DISEASE

Induction of remission^{1,2}

- Time limited course of corticosteroids. Systemic (oral) glucocorticosteroid. Oral budesonide can be considered if there is distal ileal, ileocaecal or right-sided colonic disease and if this is a first presentation or a single inflammatory>>

Table 3

Treatment to induce remission for mild-moderate ulcerative colitis^{3,6}

	Step 1 treatment	Step 2 treatment	Step 3 treatment
Mild-moderate proctitis or proctosigmoiditis	Topical 5-ASA* (enema or suppository)	Oral 5-ASA	Oral: or topical corticosteroid*
Mild-moderate extensive disease	High-dose oral 5-ASA and topical 5-ASA	High-dose oral 5-ASA and oral corticosteroid**	● Anti-TNF therapy (infliximab, adalimumab, golimumab) ● Vedolizumab ● Tofacitinib

*5-aminosalicylate

+topical steroids are less effective than topical aminosalicylates but may be considered if patients have had a previous adverse reaction to aminosalicylates or do not respond

†the starting dose for oral systemic corticosteroids is usually 40 mg daily, reduced at weekly intervals by 5 mg/day

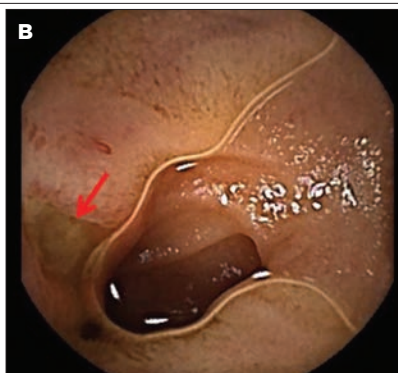
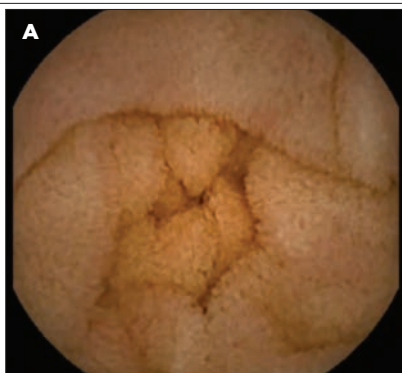
++the course of oral steroids should be time limited. Prolonged oral corticosteroid therapy is harmful and should be minimised and corticosteroids should never be used for maintenance. Bone protection (calcium carbonate and vitamin D) should be prescribed with oral corticosteroids¹

SYMPOSIUM GASTROENTEROLOGY

INFLAMMATORY BOWEL DISEASE

FIGURE 6

Small bowel capsule endoscopy:
A Normal small bowel
B Isolated terminal ileum ulcer in Crohn's disease
C Inflamed terminal ileum with erosions in Crohn's disease



exacerbation in a 12-month period, and conventional glucocorticosteroids are declined, contraindicated or not tolerated. Budesonide is associated with fewer side effects than systemic corticosteroids but may be less effective.

- Enteral nutrition. Exclusive enteral nutrition for 8 weeks may be used for mild to moderate disease but adherence is difficult and this approach is predominantly used in children with IBD.
- Addition of a thiopurine (azathioprine or mercaptopurine) or methotrexate
- Biologic therapies: Infliximab, adalimumab, vedolizumab, ustekinumab. These can be administered in combination with an immunosuppressant or as monotherapy.

Maintenance of remission^{1,2}

- Thiopurines
- Methotrexate if thiopurines are not tolerated, contraindicated or ineffective. Consider continued use if methotrexate was needed to induce remission.
- Biologic therapies: infliximab, adalimumab, golimumab, vedolizumab, ustekinumab.

SURGERY

Surgery may be required in UC as an emergency following admission for acute severe UC or electively for refractory or relapsing disease that is impairing quality of life or following the development of dysplasia or colorectal cancer.

Surgical options comprise panproctocolectomy either with a permanent ileostomy or an ileoanal pouch to preserve intestinal continuation and avoid a stoma. In 10% of those who undergo pouch surgery however, the surgery will be unsuccessful and a permanent stoma will be needed. Quality of life is good following pouch surgery. Median stool frequency is 5 times in 24 hours but without the urgency associated with active proctitis.^{1,3}

In CD, surgery may be required

for medically refractory active disease or complications such as chronic stricturing disease or an intra-abdominal abscess. Surgical control of sepsis including the insertion of setons into fistula tracks is central to the management of perianal CD before treatment with biologic agents.^{1,2}

MONITORING AND FOLLOW-UP

Treatment targets have moved from solely patient reported outcomes, clinical improvement and remission towards endoscopic and mucosal healing.¹ There is increasing evidence to suggest that the ongoing presence of endoscopic and histological inflammation or ulceration leads to further flares, a lack of sustained remission and a need for repeat corticosteroids and colectomy. In addition, endoscopic and histological remission reduces the risk of colorectal carcinoma in those with extensive colitis from UC or CD.¹

Live vaccines are contraindicated if the patient is on an immunosuppressant and should be avoided for at least three months after stopping the therapy. Immunomodulators should be withheld for four weeks after live vaccine administration.¹

The following vaccinations are recommended for patients taking glucocorticoids, thiopurines, methotrexate, anti-TNF agents or tofacitinib:¹

- Annual influenza vaccination
- Pneumococcal vaccination. It is affected by immunosuppression and should be given at least two weeks before starting treatment. A single booster should be given at five years
- IBD patients seronegative for hepatitis B should be offered the vaccine and anti-HBs response should be measured.¹

Drug monitoring

Clear shared care policies between primary care and the IBD centre on

drug monitoring should be established and communicated to the patient.

Requirements for specific medications are shown in table 4, p15. (A full list of drug side effects can be found in the BNF.)

Adherence to medications is vital and if non adherence is suspected, this should be explored and GPs may need to liaise with secondary care.¹

Smoking cessation

Smoking cessation should be encouraged, and patients should be referred to smoking cessation services. In CD, smoking increases the risk of further flares and surgery. In UC, patients should be warned that there is a risk of flare after cessation. However, the overall benefits of smoking cessation should be discussed.¹

Mental health

Anxiety and depression are common in IBD and often not identified or addressed. Access to psychological support is recommended in national guidance.¹ It should be treated in the same way as depression in other situations, but addressing disease activity is likely to help, as well as specific issues such as body image especially in relation to a stoma or planned surgery.

Colorectal cancer screening

Colonic involvement in IBD is a risk factor for colorectal cancer.¹ The risk of developing colorectal cancer is cumulative and starts to increase from ten years after symptom onset.²³ Those with colonic disease from IBD should be offered ileocolonoscopy eight years after symptom onset to assess cancer risk to determine the frequency of further colorectal screening and to evaluate extent of disease.¹

Flare management

Approximately 50% of IBD patients have at least one flare annually and

their GP is often the first to assess them.²⁴ Adherence to medication and potential triggers should be considered, and NSAIDs stopped.²⁴

A stool culture should be collected with a *Clostridium difficile* assay, FBC, U&E and CRP/ESR blood tests^{1,24} and a faecal calprotectin test performed.^{1,24}

Prompt recognition of a severe IBD flare (see table 1, p12) is fundamental, as this will require emergency admission⁶ and the on-call gastroenterologist and medical team should be contacted.^{22,24}

The definition of acute severe UC has been outlined above. Severe CD is defined as poor general health and one or more of: weight loss, fever, severe abdominal pain or frequent diarrhoea stools (> 3-4 per day).²

If hospital admission is not necessary, patients can be treated with appropriate medications to induce remission. The IBD team should be alerted whenever oral steroids have been administered²⁴ and informed if a patient has had two or more courses

within 12 months or a relapse occurred within six weeks of previous treatment.⁹

If a patient is under 16, has a stoma or fistula, has had surgery, is on biologic therapy or immunomodulators, medication changes should be made in collaboration with the specialist team.²⁴

CONCLUSION

Management of patients with IBD can be complex because of the variation in the course and severity of the disease, between individuals and over time. »

Table 4

Medications used in inflammatory bowel disease, side effects and monitoring requirements

Medication	Side effects	Monitoring
5-ASA	● Diarrhoea ● Headache ● Rarely, renal impairment¹	Baseline U&E and eGFR then 2-3 months after commencing 5-ASA and then annually long term ¹
Thiopurines	● Leukopenia, thrombocytopenia¹ ● Hepatotoxicity ● Pancreatitis ● Hypersensitivity (nausea and flu-like symptoms) ● Long-term azathioprine use is associated with: 1) Epstein Barr related and non-related lymphomas. Absolute risk remains low at 1/1,000 patient-years²⁷ 2) A 6-fold increased risk for non melanoma skin cancer. The risk is lower but persists with cessation of thiopurines²⁸ 3) Kidney and bladder cancer especially in men aged > 65. The increased risk is reversed on cessation of the drug²⁹	Baseline FBC, U&E and LFT, then at weeks 2, 4 and 8 and then at least three monthly¹ Thiopurine methyltransferase (TPMT) activity should be measured in secondary care prior to commencing thiopurines,² as absence can cause lethal bone marrow suppression. Patients should be advised to report abnormal bleeding, bruising or symptoms of infection^{2,26}
Methotrexate	● Leukopenia, thrombocytopenia ● Hepatotoxicity ● Pneumonitis ● Mucositis ● Renal failure³⁰	Baseline FBC, U&E and LFT, then at weeks 2, 4 and 8 and then at least three monthly¹ It is also important to consider the potential for any drug interactions,³⁰ particularly NSAIDs, aspirin and some antibiotics. Refer to the BNF²⁶ for a full list of potential drug interactions
Biologics and small molecules*	General side effects ● Infections including exacerbation of existing or latent infections i.e. TB. Risk of infections may not be present with vedolizumab as it is gut selective ● Injection site reactions ● Delayed infusion reactions: flu-like symptoms and arthralgia³¹ Class specific side effects ● Anti-TNF agents: worsening of heart failure and demyelination³¹ ● Tofacitinib: increased risk of pulmonary embolism with high doses (10 mg bd)²⁴ and elevated risk of herpes zoster infection³⁵	Monitoring is usually carried out in secondary care. If an infection is present, biologic therapy should be delayed until the infection has resolved or definitive treatment has been commenced, i.e. antibiotics
Corticosteroids	● Avascular necrosis of the hip is a serious complication of prolonged steroid use, so should be considered in high-risk patients presenting with hip pain¹ ● Long-term corticosteroids can be associated with osteoporosis, Cushing's syndrome, hyperglycaemia, cataracts or glaucoma⁹	Patients receiving corticosteroids should be taking calcium and vitamin D supplements and advised to make lifestyle changes to protect bone health. Patients who are high risk for osteoporosis should be commenced on bisphosphonate therapy¹

*Monoclonal antibodies to tumour necrosis factor- α (anti-TNF agents): infliximab, golimumab, adalimumab³¹

Monoclonal antibody to $\alpha 4\beta 7$ integrin: vedolizumab³²

Monoclonal antibody to IL-12 and IL-23: ustekinumab³³

Janus-associated tyrosine kinase (JAK) 1 and 3 inhibitor: tofacitinib³⁴

key points

SELECTED BY

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Inflammatory bowel disease (IBD) is a chronic inflammatory condition which runs a relapsing and remitting course. The aetiology remains unclear but is thought to involve genetic susceptibility, altered gut microbiota, changes in immunological response and environmental triggers. Ulcerative colitis (UC) is more common than Crohn's disease (CD). UC almost always affects the rectum and extends proximally and continuously to the colon to a variable extent. CD most commonly affects the terminal ileum or colon but can affect any part of the gastrointestinal tract from the mouth to the anus.

IBD may affect people at any age. The most common age of onset for CD is the early to mid-20s. UC has an initial peak at 15-25 years and a second smaller peak at 55-65. Chronic diarrhoea (≥ 4 weeks) is a common symptom of UC and CD. The vast majority (90%) of people with UC report bloody stools compared with less than 50% of those with CD. Diarrhoea in UC is commonly associated with urgency and there may be cramping lower abdominal pain. CD is characterised by a triad of abdominal pain, diarrhoea and weight loss. Perianal disease is more common in CD and can consist of skin tags, fissures, abscesses and fistulae.

Fatigue is common and may be idiopathic or due to anaemia, sleep disturbance or depression. IBD can also affect other parts of the body in around 25% of cases. Patients may suffer from arthropathies, erythema nodosum, pyoderma gangrenosum, ocular conditions such as episcleritis, scleritis and uveitis, aphthous oral ulcers, osteopenia, primary sclerosing cholangitis and autoimmune hepatitis.

If IBD is suspected, the severity of symptoms should be assessed and risk factors such as smoking history and family history reviewed. A full blood count, U&E, inflammatory markers (CRP and ESR) and haematinics should be requested. Patients should be asked about foreign travel and a stool sample sent for microscopy, culture and a *Clostridium difficile* toxin assay. Testing for amoebic or Shigella dysentery should be performed if the travel history is suggestive. In patients at low risk for malignancy, where other causes have been excluded and where there is diagnostic uncertainty, faecal calprotectin can be used as a rule-out test.

Patients fulfilling the Truelove and Witts' criteria for a severe flare require hospital admission. Otherwise patients with suspected IBD, should be referred directly to a consultant gastroenterologist specialising in IBD. UC is most commonly diagnosed with flexible sigmoidoscopy and histological assessment of mucosal biopsies. In CD the first-line investigation is an ileocolonoscopy with mucosal biopsies from the colon and ileum. IBD patients with colonic disease should be offered ileocolonoscopy eight years after symptom onset to assess cancer risk and determine the frequency of further colorectal screening.

Optimal patient care requires coordination between primary and secondary care regarding the medications used, drug monitoring, possible side effects and management of relapses. Clear referral pathways and good communication between healthcare professionals and the patient are vital to ensure timely treatment.

Competing interests

Professor Alan J Lobo has received speaker fees from, or been an advisory board member or carried out consultancy work for, Takeda, Janssen, MSD, Vifor, Shield Therapeutics, Abbvie, Pfizer, Janssen, and Medtronic.

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Useful information

Royal College of General Practitioners
Inflammatory Bowel Disease Toolkit
www.rcgp.org.uk/ibd

Crohn's & Colitis UK
www.crohnsandcolitis.org.uk

NICE clinical guidelines
NG129. Crohn's disease: management.
www.nice.org.uk/guidance/ng129

NG130. Ulcerative colitis: management
www.nice.org.uk/guidance/ng130

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