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Dr Sarah Taylor
MB ChB MRCP
Specialist Registrar

Professor Alan J Lobo
MD FRCP
Professor of Gastroenterology

Gastroenterology Unit, Royal Hallamshire Hospital,
Sheffield Teaching Hospitals, and University of Sheffield,
Sheffield, UK

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**AUTHORS**
**Dr Sarah Taylor**
MB ChB MRCP
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**Professor Alan J Lobo**
MD FRCP
Professor of Gastroenterology

Gastroenterology Unit, Royal Hallamshire Hospital, Sheffield Teaching Hospitals, and University of Sheffield, Sheffield, UK

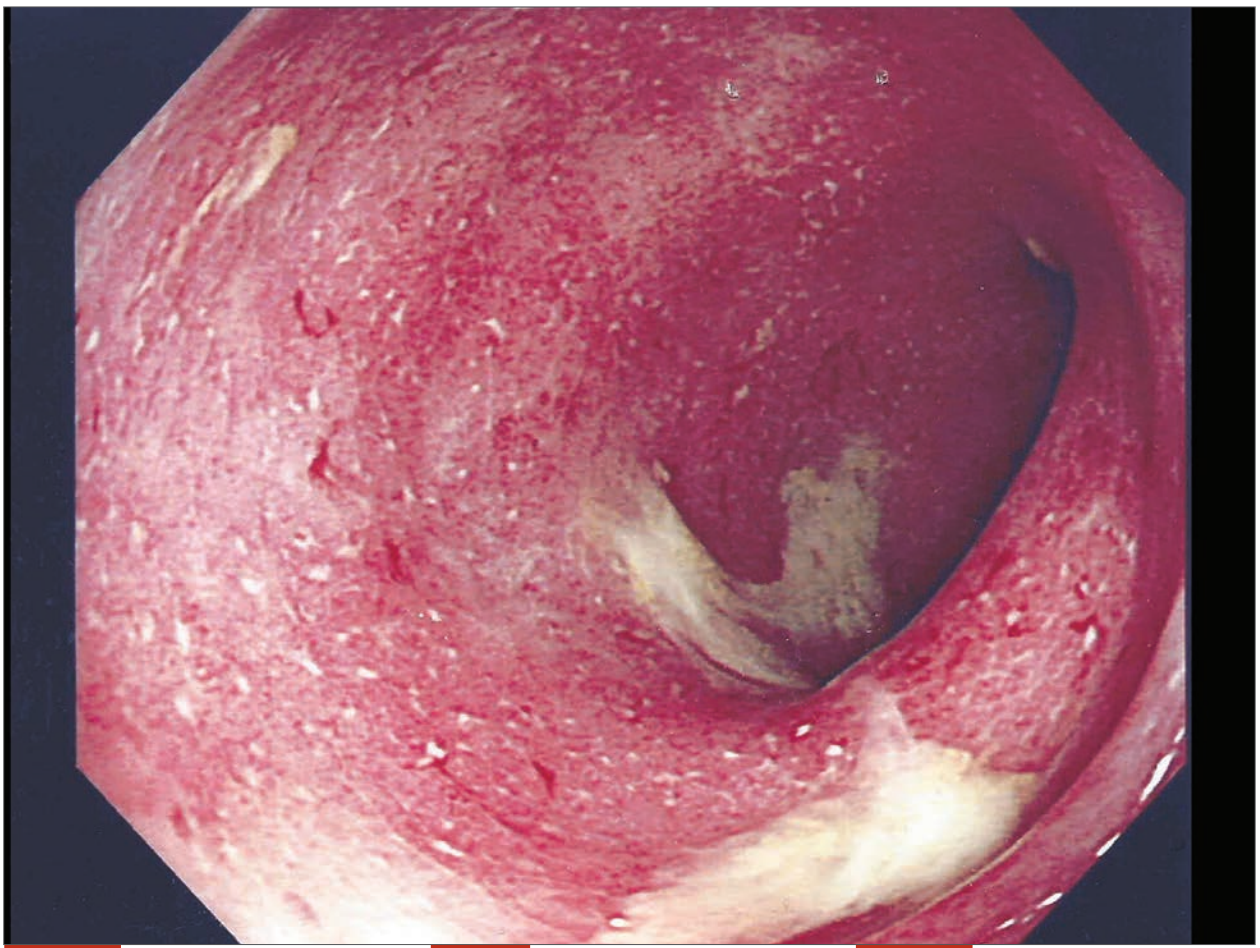


**FIGURE 1**
Colonoscopic appearance of the colonic mucosa in ulcerative colitis demonstrating erythema, loss of the mucosal vascular pattern and mild bleeding

## What are the clinical features in IBD?

**INFLAMMATORY BOWEL DISEASE (IBD) INCLUDES CROHN'S DISEASE AND ULCERATIVE COLITIS. BOTH** are chronic disorders of unknown aetiology, which characteristically run a relapsing and remitting course.

Data suggests that there are at least 115,000 people in the UK with a diagnosis of Crohn's disease[1] and around 146,000 with a diagnosis of ulcerative colitis.[2] Most studies show a peak incidence of ulcerative colitis and Crohn's disease in the second to fourth decades, with a possible, second, later peak reported in fewer studies.[3]

## How should patients be investigated?

Crohn's disease can affect any part of the gastrointestinal tract – most commonly the terminal ileum or colon. Perianal involvement is also common. Intestinal inflammation in Crohn's disease can extend transmurally. Ulcerative colitis almost always affects the rectum with a variable proximal extent and continuous distribution. Inflammation affects the mucosa only.

Genome wide association studies have shown that more than 200 genes are linked to Crohn's disease, ulcerative colitis, or both.[4] Abnormalities in intestinal immune responses and intestinal microbiota have also been demonstrated. Smoking is an important risk factor, doubling the risk of Crohn's disease.[5] Smoking is also associated with poorer outcomes following medical treatment and surgery.

## What are the management approaches?

### CLINICAL FEATURES

Lower gastrointestinal symptoms are common in the general population. Hence, patients with IBD may previously have received a diagnosis of irritable bowel syndrome[6] and there may be a delay in making the correct diagnosis.[6] This is particularly the case in patients with ileal Crohn's disease and those under 40.[6] »

The presence of weight loss, nocturnal diarrhoea and abnormal initial laboratory investigations (see below) make irritable bowel syndrome less likely. Typical symptoms of ulcerative colitis and Crohn's disease are listed in table 1, below.

The severity of an attack of ulcerative colitis is usually described using the criteria of Truelove and Witts,[2] (see table 2, below).

## INITIAL INVESTIGATIONS

IBD may be associated with a number of laboratory abnormalities:

- **Anaemia:** Anaemia may be caused by iron deficiency or chronic disease. It may also be a reflection of severe disease. Iron deficiency is frequently under-recognised as a cause of symptoms such as malaise and fatigue in IBD.
- **Thrombocytosis:** A raised platelet count is part of an acute phase reaction caused by active inflammatory disease but may also reflect functional hyposplenism in IBD.
- **Acute phase response:** Active inflammation is represented by raised CRP or ESR. A low albumin is also a reflection of inflammatory activity. The extent of the rise in CRP or ESR is greater in Crohn's disease than ulcerative colitis, where these markers may be normal in those with mild or moderately severe inflammation. Raised inflammatory markers also help identify those that are more likely to respond to therapies such as anti-TNF-α agents.
- **Stool culture:** Evidence of infection should always be sought when patients present initially and, in those with established IBD, during a severe flare, if symptoms flare following foreign travel or if clinical features suggest infection.
- **Faecal calprotectin:** Faecal calprotectin is a protein produced by intestinal neutrophils as part of an inflammatory response. Faecal calprotectin testing helps to distinguish between IBD and irritable bowel syndrome[7] with the aim of reducing the need for invasive investigations. It has a low specificity for IBD.

Testing for faecal calprotectin should not be carried out if bowel cancer is suspected or the diagnosis of IBS is unlikely, for example in those with weight loss, rectal bleeding, nutrient deficiency, nocturnal diarrhoea, perianal inflammation or sepsis. These patients should be referred for investigation or specialist opinion. NSAIDs should be stopped for four weeks before testing.

## DIAGNOSIS

NICE quality standards for IBD suggest that a delay in assessment and diagnosis in those suspected of having IBD may be associated with complications and a negative effect on quality of life and therefore that the interval from referral to specialist assessment should be no more than four weeks.[8]

More urgent assessment or even emergency admission may be needed in those with severe symptoms or complications.

Diagnosis of IBD involves endoscopy and biopsy. Histology may not be available – for example in small bowel Crohn's disease – and in this situation, typical radiological appearances help make the diagnosis.

Colonoscopy allows a diagnosis of ulcerative colitis and Crohn's disease of the colon to be made and the extent of inflammation to be assessed, which in turn helps guide treatment, see figure 1, p19.

Small bowel involvement in Crohn's disease can be assessed by MR enterography, small bowel barium meal/follow-through or capsule endoscopy according to local availability and practice.

Complications of Crohn's disease, for example intra-abdominal abscess formation or intestinal obstruction caused by stricturing, may be best assessed by initial CT scan.

## TREATMENT: ULCERATIVE COLITIS

Because of the relapsing and remitting nature of IBD, treatment requires phases to induce and then maintain remission. Some agents can be used in both phases of treatment.

Treatment to induce remission in ulcerative colitis depends on the extent of disease and its severity,[2] see table 3, opposite.

Acute severe ulcerative colitis should be regarded as a medical emergency and requires admission to hospital for assessment and intensive intravenous corticosteroid therapy.

Fluids and blood transfusion may be necessary. Prophylaxis against venous thromboembolism is essential. If patients do not settle rapidly on this regimen, escalation to treatment with ciclosporin or infliximab may be necessary. Approximately 20% of patients with acute severe ulcerative colitis do not settle with medical therapy and require colectomy.[9]

### Maintenance of remission

Aminosalicylates are the mainstay of maintenance treatment. Once daily dosing helps improve adherence and is as effective as split dose regimens. There is a small risk of nephrotoxicity and so patients should have renal function checked while on these medications.

Thiopurines are used for patients with steroid-dependent disease – defined as a requirement for two or more courses of systemic steroids in 12 months. Following a severe flare of symptoms, the risk of a further severe flare is high and azathioprine would normally be used to try to prevent this.[7]

In the UK, azathioprine (which is subsequently metabolised to mercaptopurine) is usually used initially and mercaptopurine may be used in those who are intolerant of azathioprine. Prior testing of thiopurine methyl transferase status is essential to avoid life-threatening severe leukopenia that may occur in 1:300 patients. Ongoing blood monitoring, particularly for milder, and usually reversible, leucopenia is also essential.[7]

**Table 1**

**Symptoms of inflammatory bowel disease**

| Ulcerative colitis | Crohn's disease |
|---|---|
| Bloody diarrhoea | Abdominal pain |
| Urgency of defecation | Diarrhoea |
| Rectal bleeding | Weight loss |
| Cramping lower abdominal pain | |

**Table 2**

**Truelove and Witts' criteria for assessing disease severity in ulcerative colitis**[2]

| Mild | Moderate | Severe |
|---|---|---|
| ● Stool frequency ≤ 4 in 24 hours<br>● No systemic features | ● Stool frequency 4–6 in 24 hours<br>● No pyrexia<br>● No tachycardia<br>● ESR ≤ 30mm/hr<br>● No anaemia | ● Stool frequency ≥ 6 in 24 hours plus one or more of:<br>— Pyrexia (>37.8°C)<br>— Tachycardia > 90 bpm<br>— ESR ≥ 30mm/hr<br>— Anaemia |

## TREATMENT: CROHN'S DISEASE

Again, disease site and the severity of symptoms should be taken into account when deciding on treatment.[1] At present, gastroenterologists still adopt a step-up approach to therapy. There is debate as to whether a more aggressive top-down approach with earlier use of anti-TNF-α agents and immunosuppressants may result in fewer long-term sequelae from tissue damage.

Controlled ileal release budesonide refers to locally released preparations of budesonide, which undergo extensive first pass metabolism in the liver. This results in fewer side effects than systemically available corticosteroids such as prednisolone – although with some reduction in comparative efficacy. They are effective in terminal ileal and ascending colonic Crohn's disease.

Systemic steroids such as prednisolone are effective for active small and large bowel Crohn's disease but associated with more side-effects than budesonide.

Methotrexate is effective for induction of remission and subsequent maintenance. It is usually administered intramuscularly or subcutaneously initially before switching to oral administration.

When prescribing, and consulting patients on, methotrexate it is essential to be clear about the dosing regimen (once per week). It is good practice to record the day of the week on which the dose is administered, to help prevent prescription errors.

Drug interactions should also be carefully checked. Serious interactions occur with trimethoprim.[10] Local arrangements for monitoring blood count and liver function should be followed. The drug is teratogenic and is absolutely contraindicated in pregnancy.

### Perianal Crohn's disease

Perianal manifestations of Crohn's disease include abscesses and fistulae, which can cause significant morbidity, impaired quality of life and result in frequent admissions. A multimodal approach is essential with close liaison between GPs, gastroenterology teams and specialist surgeons to allow rapid assessment (MRI scan and examination under anaesthetic), intervention and treatment.

Localised sepsis must be cleared and drained. Setons, usually silastic loops placed through a fistula track, help to ensure drainage continues and prevent abscesses recurring. They are usually placed as part of an examination under anaesthetic. Uncontrolled abscess formation leads to the development of complex, ramifying perianal fistulae. A seton allows infection to drain before an abscess develops by deliberately keeping the fistula open and allows control of sepsis to be achieved. Multiple setons can be placed.

Once it is clear that sepsis is fully drained, anti-TNF-α treatment may be started with the aim of healing the fistula - and at that point, the seton(s) may be removed. Some patients achieve such good control of their symptoms with setons, that they elect to leave them in place as long-term treatment.

### Maintenance of remission

The evidence for benefit from aminosalicylates in Crohn's disease is limited and so they are less widely used. Thiopurines and methotrexate may be used for steroid-dependent disease.

Anti-TNF-α agents also maintain remission. A number of monoclonal antibody therapies are currently available or will become available in the near future. Infliximab is administered by intravenous infusion, at 8 weekly intervals in the maintenance phase following induction therapy. Adalimumab and golimumab are given by subcutaneous injection (golimumab is currently approved for ulcerative colitis only).

The agents are effective for IBD refractory to systemic steroids and/or immunosuppressants such as azathioprine. They are also widely used for perianal Crohn's disease. Their use is associated with a number of positive and important outcomes including healing of inflamed and ulcerated intestinal mucosa, improved quality of life and reduced hospitalisation and need for surgery in patients with severe or refractory disease.

The optimal duration of therapy is uncertain. NICE guidance[11] is that withdrawal is considered in those in established remission at 12-month intervals. However, withdrawal of »

**Table 3**

**Treatment to induce remission for mild/moderate ulcerative colitis**[2]

| | Step 1 treatment | Step 2 treatment | Step 3 treatment |
|---|---|---|---|
| **Mild/moderate – distal disease (proctitis or proctosigmoiditis)** | ● Topical aminosalicylates as suppositories or enemas are more effective than topical steroids<br>● These may be used in combination with oral aminosalicylates<br>● Topical steroids are used in patients intolerant of aminosalicylates | ● Oral corticosteroids | See below for left-sided disease |
| **Mild/moderate – left-sided or extensive disease** | ● Oral aminosalicylate (high dose) either alone or in combination with topical aminosalicylate<br>● (Consider oral prednisolone if symptoms seem more severe but not enough to warrant admission) | ● Oral beclomethasone (added to aminosalicylates)<br>● Oral prednisolone | ● Anti-TNF-α therapy (infliximab, adalimumab, golimumab)<br>● Vedolizumab<br>● Tacrolimus |

anti-TNF-α therapy is also associated with a relapse rate of approximately 30-40% within 12 months.[12]

Side effects include infusion reactions which can sometimes be delayed, increased risk of infection (especially reactivation of latent TB), demyelinating disease and worsening of heart failure. There is also a rare association with aggressive hepatosplenic T-cell lymphoma, particularly in young males.

Combined therapy with anti-TNF-α and immunosuppressive therapies can be considered. While this offers reduced immunogenicity, there is some concern about increased risk of infection and possible increased risk of non-Hodgkin's lymphoma. However, the absolute rate of these events remains low and should be weighed against the benefits associated with treatment.[1]

Vedolizumab is an intravenously administered anti-integrin agent which is now approved for use in both ulcerative colitis and Crohn's disease. At present, it is most frequently used after patients have failed treatment with anti-TNF-α agents. It is slower to take effect than anti-TNF-α agents and so other concomitant treatment may be needed initially.[13]

## EXTRA-INTESTINAL MANIFESTATIONS

Approximately 25% of people with IBD will have extra-intestinal manifestations of the disease, involving skin, eyes, joints or the liver. Furthermore, it is felt that having one extra-intestinal manifestation may increase the risk of having a second.[14] Common extra-intestinal manifestations are listed in table 4, below.[14]

**Table 4**

**Extra-intestinal manifestations of IBD**[13]

| Extra-intestinal manifestation | Presentation/diagnosis | Additional comments |
|---|---|---|
| **Musculoskeletal disease (seronegative spondyloarthropathy)** | Inflammatory type arthritis typically affecting the spine, sacroiliac joint and peripheral joints | More common in patients with colonic disease |
| **Osteoporosis** | Consider bone density scan for any patient with IBD receiving prolonged courses of corticosteroids, presenting with a low trauma fracture, post-menopausal or hypogonadism | May be related to corticosteroid use, malabsorption, reduced physical activity, inflammatory bone resorption, low albumin |
| **Erythema nodosum** | Painful, palpable lumps found over the shins. Classically fade to a 'bruise' | Most common cutaneous lesion in IBD - prevalence 7.4%[15]<br>More common in Crohn's disease (CD) than ulcerative colitis (UC)<br>May precede diagnosis, therefore consider investigation for IBD if identified |
| **Pyoderma gangrenosum** | Rapidly enlarging, painful ulcer may develop in response to minor trauma | Prevalence 1-10% in UC; 0.5-20% in CD[16]<br>May respond well to anti-TNF-α therapy |
| **Aphthous stomatitis** | Oral ulceration – often related to disease activity | Seen in both CD and UC.<br>May respond to treatment of underlying disease activity or local steroids (lozenges or spray) |
| **Primary sclerosing cholangitis (PSC)** | Clinical picture and subsequent course is variable: from mild and stable to more severe progressive liver disease | 75% of patients with PSC may have IBD, but only 5% of UC patients and 2% of CD patients will develop PSC<br>Increased risk of cholangiocarcinoma and colorectal cancer |
| **Ocular inflammation** | **Episcleritis:** Acute redness in one or both eyes, irritation, and burning<br>Tenderness to palpation is common<br>Vision should not be affected<br>Will likely relate to bowel disease activity<br><br>**Scleritis:** More severe than episcleritis. May impair vision<br><br>**Uveitis:** Eye pain, visual blurring, photophobia, and headaches.<br>Signs include corneal clouding and conjunctival injection. Does not usually relate to bowel disease activity | **All eye disease:** More common in IBD with colonic or ileal involvement<br><br>**Episcleritis:** Should respond to treatment of underlying bowel disease activity<br><br>**Scleritis:** Requires high-dose oral steroids. Should be urgently referred for ophthalmological assessment if suspected<br><br>**Uveitis:** More common where other extra-intestinal manifestations are present. Consider urgent ophthalmology referral for assessment. Topical and systemic steroids need to be given promptly to avoid visual loss |

## key points

SELECTED BY

**Dr Peter Savill**
GP, Hampshire

**Data suggests that there are at least 115,000 people** in the UK with a diagnosis of Crohn's disease and around 146,000 with a diagnosis of ulcerative colitis. Crohn's disease can affect any part of the gastrointestinal tract – most commonly the terminal ileum or colon. Perianal involvement is also common. Intestinal inflammation in Crohn's disease can extend transmurally. Ulcerative colitis almost always affects the rectum with a variable proximal extent and continuous distribution. Inflammation affects the mucosa only.

**Lower gastrointestinal symptoms are common in the** general population. Hence, patients with IBD may previously have received a diagnosis of irritable bowel syndrome and there may be a delay in making the correct diagnosis. This is particularly the case in patients with ileal Crohn's disease and those under 40.

**Diagnosis of IBD involves endoscopy and biopsy.** Histology may not be available – for example in small bowel Crohn's disease – and in this situation, typical radiological appearances help make the diagnosis. Small bowel involvement in Crohn's disease can be assessed by MR enterography, small bowel barium meal/follow-through or capsule endoscopy according to local availability and practice. Complications of Crohn's disease, for example intra-abdominal abscess formation or intestinal obstruction caused by stricturing, may be best assessed by initial CT scan.

**Acute severe ulcerative colitis should be regarded as** a medical emergency and requires admission to hospital for assessment and intensive intravenous corticosteroid therapy. Fluids and blood transfusion may be necessary. Aminosalicylates are the mainstay of maintenance treatment. Thiopurines are used for patients with steroid-dependent disease – defined as a requirement for two or more courses of systemic steroids in 12 months. Controlled ileal release budesonide is effective in terminal ileal and ascending colonic Crohn's disease. Systemic steroids such as prednisolone are effective for active small and large bowel Crohn's disease but associated with more side-effects than budesonide. Methotrexate is effective for induction of remission and subsequent maintenance. A number of monoclonal antibody therapies are available or will become available in the near future.

**Approximately 25% of people with IBD will have** extra-intestinal manifestations of the disease, involving skin, eyes, joints or the liver. There is an increased risk of colorectal cancer in patients with ulcerative colitis estimated at 2% at 10 years, 8% at 20 years and 18% at 30 years. This risk starts to rise from about 10 years after disease onset.

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## CANCER RISK

There is an increased risk of colorectal cancer in patients with ulcerative colitis estimated at 2% at 10 years, 8% at 20 years and 18% at 30 years.[17] This risk starts to rise from about 10 years after disease onset and is more likely in those patients with ulcerative colitis and the following characteristics:

- Extensive disease (left-sided or greater). There is no increased risk compared with the general population in isolated proctitis
- Persistent inflammation
- Disease onset during childhood/adolescence
- Primary sclerosing cholangitis
- Positive family history – a first-degree relative developing colorectal cancer under the age of 50

In Crohn's disease affecting the whole colon, the risk is similar to those with ulcerative colitis and pancolitis.

Regular therapy with aminosalicylates, mercaptopurine or azathioprine may reduce cancer risk. Patients with extensive disease should be offered colonoscopic surveillance.[18]

## INFECTION

It is important to be aware of infection risk in IBD both due to the disease itself and the impact of treatment.

Factors include:

- Malnutrition due to malabsorption
- Potential related hyposplenism
- Treatment with prolonged courses of corticosteroids
- Treatment with immunosuppressive and anti-TNF-α agents

Live vaccines are contraindicated in patients on immunosuppressive therapy, however, flu vaccination should be offered to patients.

Patients should undergo screening for evidence of latent TB (chest X-ray, interferon gamma release assay and history of TB exposure), HIV and hepatitis B prior to anti-TNF-α therapy.

## ORGANISATION OF CARE

The care of patients with IBD should be undertaken by a multidisciplinary team that includes gastroenterologists with particular expertise in the management of IBD, nurse specialists in IBD, colorectal surgeons and specialist radiologists and histopathologists.[8]

The organisation of care should also include defined pathways for patients with suspected IBD to allow rapid access for those who experience a flare of their symptoms. IBD services and general practice should increasingly be looking at ways to support self-management programmes.

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## Useful information

**For healthcare professionals**
NICE guidance on IBD
**www.nice.org.uk**

British Society of Gastroenterology
**www.bsg.org.uk**

IBD standards
**www.ibdstandards.org.uk**

**For patients**
Crohn's and Colitis UK
**www.crohnsandcolitis.org.uk**

CICRA
Children with Crohn's and colitis
**www.cicra.org**

Ileostomy Association
**www.iasupport.org**