The term inflammatory bowel disease (IBD) describes two distinct conditions that cause inflammation of the gastrointestinal mucosa — Crohn’s disease (CD) affects the whole gastrointestinal tract and ulcerative colitis (UC) involves the colonic mucosa only. Since there is no medical therapy available to cure the disease, current treatment options aim to reduce intestinal inflammation, promote mucosal healing, reduce the risk of colorectal cancer (CRC), control symptoms and maintain remission.

Treatment strategies are continuously evolving, particularly for CD, for example, investigation of early combination therapies to modify the natural course of the disease. Increased consideration is being given to identifying patients at high risk of relapse who may profit from early initiation of aggressive “top-down” therapy in contrast to the traditional step-up strategies.1

Management guidelines
In the UK, management guidelines are issued by the British Society of Gastroenterology (BSG)2 and the European Crohn’s and Colitis Organisation (ECCO).3,4 Based on these guidelines, standards have been developed to ensure that patients with IBD throughout the UK receive consistent, high-quality care.5 These standards include, for example, ensuring that services meet specific minimum standards, are knowledge-based and are engaged with local and national networks. Following creation of the IBD standards, development began on an “Inflammatory bowel disease quality improvement project” (IBDQIP) — a web-based resource providing a self-assessment tool for services to benchmark their care, as well as a repository of useful documents and data for services to adapt for use in their own service; this is being piloted in the UK currently.

The National Institute for Health and Clinical Excellence is in the process of developing guidance for both CD and UC, which, in combination with the previously mentioned standards and IBDQIP, will shape the future of disease management and services for IBD in the UK.

Choice of preparation
Factors influencing the choice of treatment include the location of disease activity, product formulation, licensed indications, adverse effects, dosing frequency and cost. Non-adherence is a major factor contributing to treatment failure and is a particular issue during remission. Good adherence plays a major part in avoiding flare-ups and hospital admissions. One study showed a 61% increased risk of relapse for non-adherent patients compared with 11% for adherent patients. It is also important to note that adherence reduces the risk of CRC by 75%.8 Therefore, the choice of preparation must take into account patient compliance and reduce the pill burden wherever possible.

Rectal preparations tend to be less acceptable to patients but are effective, especially in distal disease. In general, foams do not spread as far as enemas (because of their low volume) but have better retention and patient acceptability. Enemas often bypass the rectum and are not as effective as suppositories for proctitis (see Box 1).

Box 1: Rectal preparations10

<table>
<thead>
<tr>
<th>FORMULATION</th>
<th>SITE OF ACTION</th>
<th>DISEASE EXTENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suppository</td>
<td>Rectum</td>
<td>Proctitis</td>
</tr>
<tr>
<td>Foam</td>
<td>Sigmoid colon</td>
<td>Proctosigmoiditis</td>
</tr>
<tr>
<td>Enema</td>
<td>Descending colon to splenic flexure and, in some cases, to the distal part of transverse colon</td>
<td>Left-sided (distal) colitis</td>
</tr>
</tbody>
</table>

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Aminosalicylates

Sulfasalazine is the prodrug of 5-aminosalicylic acid (5-ASA) and sulfapyridine (they are joined by an azo-bond). It relies on the anaerobic bacteria in the colon to cleave enzymatically the azo-bond that joins the two moieties together. The newer prodrugs olsalazine and balsalazide are cleaved in the same way.

5-ASA, or mesalazine, is the therapeutically active moiety of sulfasalazine, olsalazine and balsalazide. It is also available in mesalazine-only products. Mesalazine is thought to modulate inflammatory cytokine secretion and inhibit leukotrienes, prostaglandins and the nuclear factor NF-κB, which are responsible for the expression of pro-inflammatory molecules. Recent evidence suggests that mesalazine may have antineoplastic and potentially chemoprophylactic properties.

Orally ingested mesalazine is readily absorbed in the proximal small intestine and extensively metabolised. To protect mesalazine from this rapid and nearly complete absorption in the stomach and proximal small bowel, delayed-release and controlled-release preparations and prodrugs have been designed. These formulations release most of the mesalazine in the distal lumen or colon, making the drug available at the site of inflammation in UC. A table outlining the differences between various mesalazine preparations is available on PJ Online.11

In general, products containing mesalazine are not effective for the treatment of CD (see below); however, Pentasa might be of some use because it is the only preparation that releases mesalazine in the small bowel and the colon. Pentasa can therefore be considered for people with CD (although it is not licensed for this indication). In the presence of diarrhoea the efficacy of prodrugs could be reduced.

The sulphur content of the inactive moiety of sulfasalazine, sulfapyridine, causes dose-dependent adverse drug reactions, such as nausea, dyspepsia, headache, allergy, oligospermia and blood dyscrasias; therefore, the use of sulfasalazine is declining.

Adverse effects of mesalazine include headache, nausea, rash, abdominal pain, diarrhoea and bloating. Patients should be made aware that mesalazine can increase the sensitivity of skin to sunlight. Serious adverse reactions, such as blood dyscrasias, nephrotoxicity and interstitial nephritis, require treatment to be stopped, and patients should be encouraged to report signs of unexplained fever, sore throat, bruising or bleeding.

Aminosalicylates are the treatment of choice for mild-to-moderate UC and act topically on epithelial cells to induce and maintain remission. Adherence issues can often be more important to consider than efficacy data when choosing a suitable formulation.

Recent trials using high-dose treatment for active UC (>4g/day) and for maintenance of remission in UC (>2g/day) have shown increased efficacy compared with the traditional lower doses. In addition, recent maintenance trials demonstrated that once-daily dosing is as effective as multiple-daily dosing. This evidence supports the use of high-dose once-daily preparations such as mesalazine 2g granules, which may improve patient adherence. Nonetheless, the efficacy of high-dose once-daily preparations needs to be balanced against the cost of these products.11 Rectal mesalazine 1g daily is the preferred initial treatment for mild-to-moderate proctitis. The combined use of rectal and oral preparations to treat acute extensive flares is now advocated by most guidelines. The choice of rectal preparation must be tailored to the site of inflammation (see Box 1, p78).

ECCO and BSG guidelines suggest that sulfasalazine, high-dose mesalazine (3–6g) or rectal mesalazine may be of benefit in mild colonic CD. Recent Cochrane reviews reported modest efficacy for sulfasalazine and no effect of mesalazine in the induction of remission in active CD and concluded (in an earlier review) that currently there is insufficient evidence to support the use of mesalazine for maintenance treatment of CD. However, there is evidence that mesalazine could be better than placebo for the prevention of post-operative recurrence of CD.12–14

Continued on p81
**Antibiotics**

Based on the theory that infection triggers flare-ups of IBD, antibiotics have been investigated as a potential treatment option; metronidazole and ciprofloxacin are the most widely used. However, because of potential resistance and adverse effects, long-term therapy is not recommended. The use of antibiotics should be limited to patients with IBD and perianal fistulas, septic disease or symptoms of bacterial overgrowth. For other adjunct therapies see Box 2; surgical treatments are covered in Box 3 (p83).

**Corticosteroids**

Generally, short courses of corticosteroid are used to induce remission of severe, active IBD or if maintenance treatments have failed. Long-term therapy is not recommended routinely because of the adverse effects associated with corticosteroid use. Nonetheless, about 10–20% of patients with IBD will become corticosteroid-dependent.

Oral corticosteroids are more effective than sulfasalazine for inducing remission in moderate-to-severe IBD. Oral budesonide has high topical activity and low systemic bioavailability; however, a recent review suggested that budesonide (9mg daily) is inferior to prednisolone for the treatment of active CD and causes fewer side effects. The review also suggested that budesonide is no more effective for the maintenance of CD than placebo and that it is inferior to mesalazine for the treatment of active UC.11–13

Intravenous corticosteroids may be indicated when patients are admitted to hospital with refractory, severe IBD. Rectal corticosteroid formulations are less effective than rectal mesalazine but better than placebo for distal colitis. They are only suitable for patients who do not tolerate rectal mesalazine.

Oral prednisolone 40mg daily appears to be the optimal dose for the management of acute UC; doses below 20mg daily are not effective for inducing remission. For CD the usual dose is 0.5–0.75mg/kg/day. A slow tapering regimen is essential since rapid reduction is associated with early relapse. Because corticosteroids are ineffective in maintaining remission, plans for early introduction of immunosuppressants or biologic therapies are essential.

**Thiopurines**

Thiopurine medicines, such as azathioprine and mercaptopurine, inhibit RNA synthesis and modulate T-cells. Azathioprine is a prodrug of mercaptopurine; about 28% of patients who are unable to tolerate azathioprine (because of gastrointestinal side effects) are able to take mercaptopurine. Neither drug is licensed for the treatment of IBD.

Patients who are taking an aminosalicylate and require more than two courses of corticosteroid a year (or patients who are refractory to management with corticosteroids) are generally stepped up to receive either azathioprine or mercaptopurine after induction of remission (see Figure 1, p82). It is common practice to continue treatment with the aminosalicylate, but there is limited evidence to suggest that this is necessary. ‘The corticosteroid-sparing effect of thiopurines takes two to three months to be achieved.’

Influenza-like hypersensitivity reactions are a possible side effect of thiopurine therapy. They usually occur two to three weeks after starting treatment and resolve once treatment is stopped. Other adverse effects include nausea, vomiting, hepatotoxicity and pancreatitis. Immunosuppression and depression of bone marrow function can occur and patients should be monitored closely for these (usually via a local shared-care protocol). Before starting treatment with a thiopurine, a patient’s thiopurine methyltransferase enzyme activity should be measured because deficiency in this enzyme increases the risk of myelosuppression. Allopurinol affects the pathway for metabolism of thiopurines and therefore the dose of thiopurine should be adjusted (reduced to about a quarter of the normal dose). Currently, studies are being conducted to see if this interaction can be exploited for patients who respond to neither azathioprine nor mercaptopurine.

The recommended maintenance dose of azathioprine is 2–2.5mg/kg/day and for mercaptopurine is 1–1.5mg/kg/day; however, the actual treatment dose may be limited by leucopenia. Stopping thiopurine treatment should be considered after four years of remission.

**Box 2: Adjunct therapies**

When managing a patient with inflammatory bowel disease (IBD), the following adjunct therapies should be considered:

- **Vaccinations** Patients with IBD are generally immunosuppressed and are therefore at risk of opportunistic infections. Guidelines recommend that patients’ immunisation histories are documented at the time of diagnosis and that vaccinations (such as Varicella zoster, human papilloma virus and yearly influenza vaccines) are discussed. Baseline infectious diseases screening that includes HIV, hepatitis B and tuberculosis should be conducted.15

- **Thromboembolism prophylaxis** People with IBD have a higher risk of venous thromboembolism than people not suffering from the condition. Therefore, appropriate VTE prophylaxis is necessary for people with IBD who are in hospital.

- **Pain control** Appropriate advice on pain control is important. Non-steroidal anti-inflammatory drugs are contraindicated in IBD; there is a suggested link between NSAID use and precipitation of flare-ups because of an effect on the intestinal mucosal lining. Paracetamol is the analgesic of choice. Opioids should be used sparingly, especially so in an acute flare-up, since they may precipitate toxic megacolon and increase the risk of gut perforation by reducing intestinal motility. For similar reasons any medicine that affects gut motility (eg, antidiarrhoeals or anticholinergics) should be avoided during acute flare-ups.

- **Diet** A balanced, healthy diet is usually advised. Liquid feeds (polymeric or elemental diets) can reduce the need for corticosteroids in children with Crohn’s disease.

- **Probiotics** Research around the use of probiotics is hampered by gaps in understanding about probiotics and the pathogenesis of IBD. Current research is promising, but further studies are needed to determine suitable strains, factors influencing gut transit, appropriate formulation and dose, and monitoring parameters.

**Smoking** Smoking cessation should be offered to all patients suffering from IBD in view of the detrimental effects for patients with Crohn’s disease and after surgery.
Methotrexate and mycophenolate

The mode of action of methotrexate and mycophenolate in the treatment of IBD is not clear and neither medicine is licensed for the condition. There is no evidence that methotrexate is effective for the treatment of UC; however, for people with CD that is refractory to thiopurines, methotrexate is effective in inducing and maintaining remission — it reduces relapses by about half but there is a loss of efficacy over time. Because of the potential for serious adverse effects (namely hepatotoxicity and pneumonitis), patients need to be monitored carefully. If patients are managed in primary care, this should be done through a shared-care protocol as recommended in the recent National Patient Safety Agency alert on oral methotrexate. Addition of folic acid may alleviate gastrointestinal adverse effects.

The role of mycophenolate in the management of IBD is unclear and more research is needed into appropriate dosing and potential toxicity.

Ciclosporin and tacrolimus

The calcineurin inhibitors ciclosporin and tacrolimus affect the inflammatory cascade by blocking T-lymphocytes and inhibiting interleukins and cytokines. Neither ciclosporin nor tacrolimus has been proven useful for CD.

Because of its narrow therapeutic index and side effect profile, the use of ciclosporin is limited to refractory UC, as a rescue and bridge to starting treatment with immunomodulators or biologic medicines. Long-term outcomes indicate that only a minority of patients who require ciclosporin do not progress to colectomy. A study on the use of tacrolimus for UC did not provide statistically significant findings and further research is required. Ciclosporin is not licensed for use in UC, but doses of 2mg/kg/day intravenously (either as a continuous infusion or in divided doses) or 5.5mg/kg/day orally are used. A new study (CONSTRUCT) comparing the clinical and cost effectiveness of ciclosporin with infliximab in steroid-refractory UC, is currently recruiting patients in the UK. The study protocol recommends ciclosporin trough levels of 150–250ng/ml.

Due to the nephrotoxicity of the calcineurin inhibitors, close monitoring is required, including blood pressure, renal function, liver function and drug levels (weekly for the first three weeks and then monthly thereafter). Cholesterol and magnesium monitoring is required when starting therapy since low levels of cholesterol or magnesium increase the risk of seizures. Common adverse effects include malaise, tremor, headaches, hirsutism, abnormal liver function tests and gingival hyperplasia.

Biologics

Adalimumab and infliximab are monoclonal antibodies directed against tumour necrosis factor-alpha, which thereby interrupt the inflammatory cascade. Infliximab, a chimeric (murine/human) monoclonal antibody is given as a 5mg/kg infusion over two hours every eight weeks. Infusion reactions (minimised by slowing the infusion rate) and anaphylaxis are rare. Hypersensitivity reactions due to antibody formation may occur, especially if there is more than a one-year interval between infusions — these reactions can be delayed, occurring up to 12 days after the infusion. Recently, accelerated infusion protocols have been shown to be safe and well tolerated, for example, after four initial standard doses reducing the infusion time to one hour and then reducing the infusion time again after six doses to 30 minutes.

Adalimumab is a fully human monoclonal antibody, provoking less antibody formation and hypersensitivity reactions than infliximab. The 40mg dose is administered subcutaneously every two weeks by the patient. The dose can be increased to weekly if remission is not maintained.

NICE has produced guidance on the use of adalimumab and infliximab in CD, supporting maintenance treatment. NICE guidance supports the use of infliximab for severe UC and fistulating CD, but does not advise its use for maintenance treatment in sub-acute UC. A 2009 study showed that infliximab alone and infliximab combined with azathioprine are more effective in maintaining steroid-free remission than monotherapy with azathioprine at one year, supporting the "top down" approach to IBD management.

Certolizumab pegol has a longer half-life but the European Medicines Agency refused to give the drug marketing authorisation for the treatment of severe CD on risk/benefit grounds.

Natalizumab belongs to a new class of monoclonal antibodies called selective adhesion molecule inhibitors. It is approved by the US Food and Drug Administration for induction and maintenance of remission in CD, but requires a strict risk management scheme due to an underlying risk of progressive multifocal leukoencephalopathy. (In the UK, natalizumab is only licensed for the treatment of multiple sclerosis.)

Biologics increase the risk of infections and all patients must have a tuberculosis screen before starting treatment. ECCO guidelines on opportunistic infections in IBD advise on the appropriate screening for patients about to

### Figure 1: Step-up strategy for medical treatment of inflammatory bowel disease

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Box 3: Surgical treatment of inflammatory bowel disease

Modern surgery for inflammatory bowel disease (IBD) has developed with a better understanding of the anatomical distribution and natural history of ulcerative colitis (UC) and Crohn’s disease (CD). The management of patients who are likely to require surgery should be undertaken jointly by a colorectal surgeon and gastroenterologist in the setting of a specialist multidisciplinary team. The major difference in approach to surgery is based on the fact that UC can be cured with surgery whereas CD cannot; therefore, a more conservative approach with an emphasis on bowel conservation is taken in CD.

**Ulcerative colitis** Around 40% of people with UC will require surgery during their lifetime. Surgery can be elective or may be required in emergencies. Indications for surgery in acute colitis are:

- Failure to respond to medical therapy
- Toxic megacolon
- Colonic perforation
- Major lower-gastrointestinal haemorrhage

The operation of choice in the acute setting is a colectomy and end ileostomy with preservation of the rectal stump — that is, the resection of the colon and the proximal rectum. The small bowel is diverted to form a stoma (end ileostomy) on the abdominal wall. Surgery may be performed laparoscopically. For patients with chronic UC, surgery is indicated for:

- Recurrent and chronic symptoms despite adequate medical therapy
- Removing (or preventing) colorectal cancer

The cumulative risk of developing colorectal cancer in chronic UC is negligible within the first decade of onset, rising to 10–15% in the second decade and over 20% in the third decade. Therefore, patients with UC require careful colonoscopic surveillance. Where previous surgery for acute colitis has preserved the rectal stump the same risks for colorectal cancer apply.

In elective surgery, total resection of the colon is mandatory but intestinal continuity may be retained and a stoma avoided by joining the ileum and rectum (ileo-rectal anastomosis) or the ileum and the anus (ileo-anal anastomosis), or by using the end of the ileum to create a neo-rectum (ie, an ileal pouch reservoir) with an ileo-anal anastomosis.

The factors that influence the choice of procedure are beyond the scope of this article. However, construction of an ileal pouch is associated with the long-term complication of pouchitis — acute inflammation in the pouch, which can be caused by infection. Most cases will respond well to a course of metronidazole or co-amoxiclav. Probiotic therapy can prevent further episodes. A small proportion of patients will develop chronic pouchitis requiring salvage surgery to excise the pouch, followed by formation of a permanent end ileostomy.

**Crohn’s disease** An estimated 70% of patients with CD will require surgery at some time. A substantial number will require further surgery with an estimated annual reoperation rate of 2–10%. The emphasis is on bowel conservation with the resection of the minimum length of bowel to resolve the current episode and restore gut function. The common distribution patterns of CD are ileocolic (40%), small bowel alone (30%) and colon alone (30%), with an estimated 50% having perianal disease, which may co-exist with these.

The type of operation will depend on the anatomical distribution of the inflammation and the pathological process. Surgery is indicated where medical therapy fails to alleviate symptoms adequately or one of the following complications develops:

**Gastroduodenal disease (symptomatic)**

- Bleeding
- Duodenal stenosis

**Small bowel and ileocolic disease**

- Obstruction — resulting from narrowed segments of bowel (stenoses)
- Fistulas — abnormal tracts between bowel loops, bowel and other abdomino-pelvic organs, or bowel and skin.
- Intra-abdominal abscesses — which may be associated with fistulas
- Bleeding
- Perforation of small bowel or colon resulting in peritonitis

**Colorectal disease**

- Colitis

**Perianal disease**

- Anal fissure
- Abscess
- Anal fistula
- Stricture
start biologic therapy and all patients must be screened carefully for acute infections since the risk of septicaemia is high.1 Patients must be monitored for the development of lymphoma and other malignancies associated with the use of biologics.

Patients on a combination of corticosteroids, immunosuppressants and biologics are at increased risk of infections and should receive chemoprophylaxis against infections such as *Pneumocystis jiroveci* pneumonia.

### New therapies

The treatment of IBD is evolving — new biologic therapies are in development and other innovative treatments that have the potential to change the way IBD is managed in the future are also under investigation (see Box 4). Stem cell therapy seems to be a promising novel approach and the advances in mucosal immunology have revealed a broad set of new targets that may help to resolve the inflammation and symptoms of IBD. Research into T-cells might reveal new ways of controlling intestinal inflammation but, so far, has provided disappointing results in IBD.

### References


### Box 4: Experimental therapies for inflammatory bowel disease

<table>
<thead>
<tr>
<th>THERAPY</th>
<th>DESCRIPTION</th>
<th>STUDY DETAILS</th>
<th>POTENTIAL USE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stem cells</strong></td>
<td>Autologous stem cell transplantation</td>
<td>ASTIC study (ECCO research)</td>
<td>CD</td>
</tr>
<tr>
<td><strong>Alequol</strong></td>
<td>Autologous colon-extracted proteins</td>
<td>Phase II</td>
<td>CD</td>
</tr>
<tr>
<td><strong>Vedolizumab</strong></td>
<td>Human anti-integrin α4β7 monoclonal antibody</td>
<td>Phase III (GEMINI trials)</td>
<td>IBD</td>
</tr>
<tr>
<td><strong>Hook worms</strong></td>
<td>Proposed action via modulation of T-cells</td>
<td>Awaiting results from the Nottingham Study</td>
<td>IBD</td>
</tr>
<tr>
<td><strong>Delmitide</strong></td>
<td>Anti-inflammatory decapetide</td>
<td>Phase III</td>
<td>IBD</td>
</tr>
<tr>
<td><strong>Alicaforsen</strong></td>
<td>Antisense oligonucleotide, which inhibits intercellular adhesion molecule (ICAM-1)</td>
<td>Enema as effective as mesalazine but longer remission (UK named patient supply); intravenous in phase III</td>
<td>IBD</td>
</tr>
<tr>
<td><strong>Cannabidiol</strong></td>
<td>Fat-soluble extract from cannabis plant</td>
<td>Phase I and II</td>
<td>IBD</td>
</tr>
<tr>
<td><strong>Rosiglitazone</strong></td>
<td>Proposed protection of gut via agonism at peroxisome proliferator-activated receptor gamma (PPAR-γ)</td>
<td>Small studies showed efficacy alone or with mesalazine treatment</td>
<td>UC</td>
</tr>
<tr>
<td><strong>Rivenprost</strong></td>
<td>Proposed reduction of inflammation via prostaglandin E2 and EP4 agonism</td>
<td>Phase II</td>
<td>UC</td>
</tr>
<tr>
<td><strong>CCX282</strong></td>
<td>Reduces immune activation in the gut through CCR9 chemokine receptor antagonism</td>
<td>Phase III (PROTECT-1 study)</td>
<td>CD</td>
</tr>
<tr>
<td><strong>Laxinimum</strong></td>
<td>Oral immunomodulator</td>
<td>Phase II</td>
<td>CD</td>
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<tr>
<td><strong>VXG-1027</strong></td>
<td>Oral immunomodulator affecting NF-κβ</td>
<td>Phase I</td>
<td>IBD</td>
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<tr>
<td><strong>Teduglutide</strong></td>
<td>Glucagon-like peptide 2 analog that may promote mucosal healing</td>
<td>Phase II</td>
<td>CD</td>
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<tr>
<td><strong>Golimumab</strong></td>
<td>Human anti-TNF monoclonal antibody</td>
<td>Phase III</td>
<td>IBD</td>
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<tr>
<td><strong>Ustekinumab</strong></td>
<td>Human monoclonal antibody against interleukin-12 and interleukin-23</td>
<td>Phase II and III</td>
<td>CD</td>
</tr>
</tbody>
</table>

Key: CD = Crohn’s disease; IBD = inflammatory bowel disease; UC = ulcerative colitis