Current management options and recent advances in IBD

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The advent of biological therapies has revolutionised the management of inflammatory bowel disease, and the imminent introduction of anti-adhesion molecule therapy seems likely to have a big impact. Our Drug review outlines the current treatment options and examines some recent advances in diagnosis and management, followed sources of further information and an analysis of the prescription data.

Inflammatory bowel disease (IBD) affects approximately 400 per 100 000 people, the majority having either Crohn’s disease (CD) or ulcerative colitis (UC), with the remaining five per cent having IBD-unclassified (IBD-U). The lifetime risk of surgery for patients with CD is 70–80 per cent while 20–30 per cent of patients with UC will eventually require colectomy.\(^1\) Treatment goals in IBD have changed in recent years. Whereas previously symptomatic response was the aim of therapy, harder end-points such as mucosal healing and the prevention of admission to hospital, surgery and, ultimately, disability are now the goals of therapy. In order to achieve this, earlier use of disease-modifying therapy has become popular, particularly in patients with CD.

The advent of biological therapies has revolutionised the management of IBD; anti-TNF therapy has proved to be highly effective in appropriate patients with IBD and the imminent introduction of anti-adhesion molecule therapy also seems likely to have a big impact on the way we manage IBD. While these new drugs undoubtedly dramatically increase the healthcare costs of people with IBD, this must be balanced against the improvements in quality of life, reduction in healthcare usage and increase in work productivity that their recipients often experience.

**Diagnosis**
The diagnosis of IBD remains reliant on a combination of clinical, endoscopic, radiological and histological findings. Thus, while making a diagnosis in the setting of secondary care is relatively easy, it can be more challenging in primary care, not least because the symptoms of IBD in some patients are similar to those of people with functional gut disorders. It is perhaps for this reason that the diagnosis of IBD is often delayed,
a fact that is identified in patient surveys as one of the biggest issues in IBD care. For this reason, faecal calprotectin (FC) testing as a screening tool in primary care is likely to have a major impact on IBD management. FC is a neutrophil-derived protein that can be detected in the stool and is both sensitive and specific for discriminating between patients with IBD and functional gut disorders. Where adopted, it has allowed rapid detection of people who should be referred quickly to secondary care as well as those who may benefit more from treatments directed at functional disorders. It is likely to be adopted more widely in primary care over the coming years and is supported by NICE (see Figure 1).

Radiological assessment of IBD is shifting towards examinations that do not involve the use of ionising radiation. Thus magnetic resonance imaging and, to a lesser extent, ultrasound are being increasingly used for the assessment of small bowel CD. Computed tomography continues to have a role in patients with IBD but is more commonly used in patients with acute problems rather than as a diagnostic tool. Similarly, the role of capsule endoscopy, arguably the most major advance in endoscopy in the last 20 years, remains limited in the diagnosis of IBD although it certainly has a place in specific cases.

**Treatment of UC**

UC can be classified by severity as mild, moderate or severe based on symptoms along with endoscopic features or biomarkers. In general, a step-up approach to treatment is used progressing from mesalazine through to steroids and immunomodulating treatments, although for more severe disease, a more aggressive approach is often required.

**Induction of remission in mild to moderate UC**

Mesalazine is the first-line treatment for inducing remission in mild to moderate UC. This can be given either orally or rectally in the form of suppositories (for proctitis) or enemas (for left-sided disease), although the combination of oral and rectal preparations has been shown to be better than oral mesalazine alone. There are several preparations of oral mesalazine available with a variety of different release characteristics and choice of preparation is probably driven more by tolerance, dosing schedule and cost rather than by marked differences in efficacy. However, there are no head-to-head trials comparing different preparations and there is some evidence to suggest that patients failing on one preparation may do better on another preparation. Similarly, unnecessary switching of brands in patients responding well is probably not appropriate.

For mild to moderate disease that has failed to respond to mesalazine, a reducing course of oral prednisolone (starting at 40mg once daily and reducing by 5mg weekly) can be used to induce remission.

**Maintenance of remission in mild to moderate UC**

Mesalazine is an effective maintenance therapy in UC and while there is limited evidence to support a minimum dose, 2g daily is a reasonable lowest dose to use. Periodic monitor-

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**Table 1.** Truelove and Witts criteria for the diagnosis of acute severe colitis

<table>
<thead>
<tr>
<th>Activity</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
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<tbody>
<tr>
<td>number of bloody stools/day</td>
<td>&lt;4</td>
<td>4–6</td>
<td>&gt;6</td>
</tr>
<tr>
<td>temperature (°C)</td>
<td>afebrile</td>
<td>intermediate</td>
<td>&gt;37.8°C</td>
</tr>
<tr>
<td>pulse</td>
<td>normal</td>
<td>10.5–11</td>
<td>&gt;90</td>
</tr>
<tr>
<td>haemoglobin g/dl</td>
<td>&gt;11</td>
<td>20–30</td>
<td>&lt;10.5</td>
</tr>
<tr>
<td>erythrocyte sedimentation rate (mm/hr)</td>
<td>&lt;20</td>
<td></td>
<td>&gt;30</td>
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</table>
blood tests. Fortunately, the risk of serious side-effects, such as lymphoma, are extremely small, being somewhere in the region of 1:2–3000 per year in people under 50 years of age.\(^5\) More recently, it has also been recognised that there is a small increased risk of non-melanoma skin cancer in people taking thiopurines who should, therefore, be advised to take sensible precautions in the sun.

**Management of acute severe UC**

Patients who fit the Truelove and Witts criteria for having acute severe colitis (see Table 1) need admission to hospital under the joint care of a gastroenterologist and a colorectal surgeon, preferably with an interest in IBD. With appropriate medical and surgical management mortality should be <1 per cent.\(^7\) As with all flares of IBD, exclusion of intercurrent infection with common enteric pathogens, including *Clostridium difficile*, is mandatory. Patients who fail to improve after 72 hours of intravenous steroids have a risk of colectomy of around 85 per cent.\(^8\) In these patients, the use of intravenous cyclosporin or infliximab (Remicade), a monoclonal antibody against tumour necrosis factor, prevents colectomy, at least temporarily, in approximately 70 per cent of patients.

**Treatment of CD**

As with UC, CD can be classified by both its activity and its location. The most common form of CD affects the distal small bowel and the colon, although it can affect any part of the gastrointestinal tract. In addition, the disease is often classified by behaviour, such as inflammatory, strictureting or penetrating as well as by the presence of perianal disease. Certain disease phenotypes and characteristics (examples include presentation at a young age or the presence of deep colonic ulcers) are associated with a more aggressive disease course; such patients are more likely to be treated early in the disease course with disease-modifying therapies.

**Induction of remission in mild to moderate CD**

The role of 5-aminosalicylic acid (5-ASA) in the induction of remission of CD is limited to patients with mild disease in whom it may also be appropriate to consider no treatment.\(^10\) However, 5-ASA has no role for maintenance of remission. There is limited evidence for the use of antibiotics, although metronidazole has some efficacy in colonic CD while ciprofloxacin and metronidazole are widely used to treat Crohn’s-related perianal sepsis. Steroids are highly effective at inducing remission in luminal CD but have no place for the maintenance of remission. Furthermore, they tend not to induce mucosal healing and do not alter disease outcome. Instead, if used recurrently or for too long, their side-effect profile becomes unacceptable.\(^11,12\) While thiopurines can induce remission in CD, they do so too slowly to be used as such.\(^13\) Exclusive enteral feeding is widely used to induce remission in children with CD. It is also effective in adults but is less commonly used, perhaps because of the need for recipients to forego their usual diet.

**Maintenance of remission for mild to moderate CD**

Patients with mild disease may not require maintenance therapy, although this is a relatively unusual situation. In patients who have required steroids to induce remission, thiopurines tend to be used as the first-line maintenance therapy. Weekly methotrexate has also been shown both to induce and to maintain remission and should be given with folic acid supplementation. It is usually reserved for patients who are either intolerant of or resistant to thiopurines but in whom biologics are not indicated. All patients on immunosuppressants require blood monitoring and, while it is safe for women to continue thiopurines through pregnancy and during breastfeeding, methotrexate is teratogenic and must be discontinued before pregnancy is planned.

**Treatment of moderate to severe CD**

Moderate and severe CD, which is refractory to standard medical therapy, is best treated with anti-TNF therapy. Surgery should also be considered but is often neither necessary nor appropriate for inflammatory disease. There are currently two anti-TNF drugs in the UK for the treatment of CD, infliximab and adalimumab (Humira), as well as an anti-leucocyte trafficking molecule, vedolizumab. Adalimumab and infliximab have revolutionised the management of treatment-resistant CD over the last 15 years and their use is supported by NICE in specific circumstances. NICE also mandates disease reassessment after 12 months to confirm whether ongoing therapy is both appropriate and necessary. The drugs are both highly effective induction and maintenance agents not only for luminal CD but also for perianal disease.

Anti-TNF therapy is generally well tolerated and serious complications are rare. Loss of response occurs in anything up to 10 per cent of patients per year and normally relates to the production of antibodies. Measurement of anti-TNF drug

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**Table 2.** Colorectal cancer surveillance in IBD patients after 10 years; see BSG guidelines; FDR = first-degree relative

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Disease Description</th>
</tr>
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<tbody>
<tr>
<td>5 yearly</td>
<td>Left sided UC, Crohn’s disease affecting &lt;50% of the colon, pancolitis in remission</td>
</tr>
<tr>
<td>3 yearly</td>
<td>Mild pancolitis, family history of CRC in 1 FDR&gt;50 years old, post-inflammatory polyps</td>
</tr>
<tr>
<td>Yearly</td>
<td>Primary sclerosing cholangitis, family history of CRC in 1 FDR&lt;50 years old, strictureing disease, history of dysplasia, moderate to severe pancolitis</td>
</tr>
</tbody>
</table>
levels and anti-drug antibodies can be useful in preventing and managing loss of response as well as guiding the need for combination therapy with immunosuppressive agents, which improves efficacy but exposes patients to slightly greater risk. The most important side-effect of anti-TNF therapy is an increased risk of infection; common infections being the more frequent to occur rather than the better known but much lesser risk of reactivation of tuberculosis. To keep this in context, however, the infectious risk associated with long-term steroid use appears to be greater. Yearly flu vaccines as well as pneumococcal vaccination is recommended.

Vedolizumab (Entyvio) binds to gut-specific alpha 4 beta 7 integrins on T-cell lymphocytes preventing cells expressing these adhesion molecules from migrating out of the bloodstream and into the gut. Vedolizumab has recently been licensed for use in IBD but has yet to be assessed by NICE and therefore is unlikely to be widely available in the short term. Indeed, while anti-TNF therapy is also effective in UC, other than the use of infliximab as a rescue therapy for acute severe colitis, no biologic drugs currently have NICE approval for UC.

Pregnancy
Doctors and patients often have understandable concerns about the use of IBD medication in pregnancy. However, with the exception of methotrexate, the risk of active disease in pregnancy far outweighs the largely theoretical risk associated with the drugs mentioned in this article. Individualised care needs to be provided to all pregnant mothers with IBD and this should include a careful discussion about drug therapy with a specialist. Ideally, these conversations are best had prior to planning pregnancy although this is not always possible. Flares of disease should be managed with drug therapy where possible; the benefits of steroids and anti-TNF therapy to control active disease in pregnancy far outweigh the risks of their use. Mesalazine and thiopurines are also safe during both pregnancy and breastfeeding.

Extra-intestinal manifestations
Extra-intestinal manifestations (EIMs) affect 30 per cent of patients with IBD. The activity of some of these mirror inflammatory activity in the gut (episcleritis, erythema nodosum and type 1 arthropathies) while others are independent of intestinal inflammation (scleritis, pyoderma gangrenosum, axial and type 2 arthropathies). Primary sclerosing cholangitis (PSC) affects up to 8 per cent of patients with IBD. These patients are at increased risk of both cholangiocarcinoma and colorectal cancer (CRC).

CRC surveillance
The risk of CRC in IBD is increased in patients with extensive colonic disease. The main risk factors are disease activity and extent as well as the length of time since diagnosis. All patients with UC and extensive colonic CD should have a repeat colonoscopy 8–10 years after diagnosis with the exception of patients with PSC who should have yearly colonoscopy from the time of diagnosis. British Society of Gastroenterology (BSG) guidelines on CRC surveillance in IBD guide the interval between colonoscopies thereafter (see Table 2).

Conclusion
The effects of active disease on patients with IBD, most of whom are young, can be marked. As an economically productive group of people with a lifetime of care ahead of them, the financial implications for society are important to remember. However, on an individual level, the effects of uncontrolled symptoms on social activities and quality of life are equally important. Nevertheless, good management, which includes early diagnosis as well as appropriate therapy driven by a multidisciplinary team, normally allows good disease control. Recent advances in IBD are summarised in Table 3.

References

Declaration of interests
Dr Warner has no declarations. Dr Irving has received hono- raria for speaking on behalf of or acting in an advisory capacity for AbbVie, MSD, Takeda, Warner Chilcott, Shire, Ferring and Tillotts Pharma.

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Table 3. Summary of the recent advances in IBD

| Use of FC as a non-invasive marker of inflammation |
| Measurement of thiopurine metabolite monitoring to optimise drug dosing |
| Measurement of infliximab and adalimumab levels to dose escalate or drug switching |
| Launch of new drug targeting adhesion molecules (vedolizumab) to treat IBD |

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**Guidelines**

*Crohn’s disease: Management in adults, children and young people.* CG152. NICE. October 2012.


*Ulcerative colitis: Management in adults, children and young people.* CG166. NICE. June 2013.


**NICE’s appraisal of infliximab, adalimumab and golimumab for the second line treatment of moderately to severely active ulcerative colitis (including review of TA140 and TA262) is expected January 2015.**

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**Prescription review**

In 2013, GPs in England wrote 2.1 million prescriptions for aminosalicylates at a cost of £88 million, and 110 000 prescriptions for steroids at a cost of £7 million, for the treatment of IBD.

5-ASA prescribing was dominated by mesalazine (59 per cent of volume, 87 per cent of spending). Of this, Asacol MR e/c 400mg tablets (25 per cent of prescriptions) and Pentasa m/r 5000mg tablets (21 per cent) were the most popular, together accounting for 41 per cent of spending. The most expensive mesalazine formulations were Salofalk 2g enema (£101.93 per script) and Mezavant XL e/c 1.2g tablets (£101.90). The otherwise inexpensive sulfasalazine included the most costly single item, with the oral suspension 250mg per 5ml costing £125.97 per script.

Steroids were much less frequently prescribed. Budesonide was the most popular (37 per cent of volume, 44 per cent of cost), almost all of which was for oral formulations. It was relatively expensive but less so than the prednisolone foam enema.

<table>
<thead>
<tr>
<th></th>
<th>No. scrip (000s)</th>
<th>NIC (£000)</th>
<th>Cost per script</th>
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<td><strong>Steroids</strong></td>
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<td>budesonide</td>
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<td>prednisolone retention enema</td>
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</table>

*Table 4. Number and cost of prescriptions for the treatment of IBD, England, 2013*