Inflammatory bowel disease (IBD) is the collective name for ulcerative colitis (UC) and Crohn's disease (CD), which characteristically run a chronic, and largely unpredictable, relapsing and remitting course in terms of both frequency and severity. Around one in 700 people are affected with IBD in the UK, which commonly occurs between the ages of 15 and 40, although any age group can be affected (Loftus, 2004). Treatment of active disease episodes with a combination of drugs, diet and appropriately timed surgery, and maintenance of remission thereafter form the basis of management. This article aims to give a brief overview of the currently available and emerging medical options and medical management strategies.

Aetiology
The cause is uncertain but it is clear that genes, interacting with an environmental trigger(s), probably the normal bacterial flora, lead to an abnormal immunological reaction and play a huge part in the development of the disease (Hart et al, 2002). The results of an extensive study of DNA from over 2000 patients in the UK has led to the discovery of three new genes associated with susceptibility to CD, in particular lack of ability to clear bacteria from cells (The Wellcome Trust, 2007). Although a direct genetic cause is not certain, current knowledge and understanding of disease behaviour should substantially advance the development of more specific and targeted treatments, as well as enable older treatments to be used in more effective ways.

Smoking is probably the strongest environmental risk factor for the development of CD and often produces a worse course of disease (Johnson et al, 2005). Sufferers are more likely to be smokers than non-smokers, in particular women who smoke, therefore smoking cessation strategies should form an integral part of the management plan. The deleterious effects of smoking are unclear but may have some effect on the blood supply to the intestine. Conversely, smoking appears to be protective of UC, which tends to be associated with non-smokers or ex-smokers.

Diagnosis
Diagnosis includes a combination of symptom history and presenting clinical features supported by...
Clinical focus

Box 1. Differential diagnosis of IBD

- Ulcerative colitis
- Crohn’s disease
- Microscopic colitis, e.g. collagenous colitis, lymphocytic colitis
- Infection, e.g. yersinia, ileocaecal tuberculosis
- Malignancy, e.g. colorectal cancer, lymphoma,
- Irritable bowel syndrome (IBS)
- Drugs, e.g. non-steroidal anti-inflammatory treatment (NSAIDs)
- Malabsorption, e.g. coeliac
- Ischaemic colitis
- Appendix mass
- Behcet’s vasculitis

Laboratory findings from blood tests including raised inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate. Stool culture, including Clostridium difficile toxin, is essential to exclude infection. Radiological imaging of the bowel and direct visualization of the mucosa by ileo-colonoscopy, with biopsy of the mucosa for histological analysis, usually provides confirmation. The advent of wireless capsule endoscopy has improved the diagnosis of small bowel CD (Lasbner, 2006).

Many conditions can mimic IBD (Box 1); it is therefore essential to exclude these, in particular infective causes, to ensure that the most appropriate and effective treatment is instituted (Guan, 2000).

Clinical features and symptoms

Symptoms tend to be variable according to disease site and severity, and although CD and UC are symptomatically similar there are some distinctive differences in terms of features and disease behaviour (Box 2), which may affect the overall management. Features common to both include:

- Frequent and urgent bloody diarrhoea (bloody in colonic Crohn’s) often associated with mucus
- Tenesmus
- Crampy abdominal pain
- Anorexia, weight loss and fever can be a feature of the more severe disease
- Fatigue—possibly due to anaemia and low iron levels (may persist even in remission)
- Strictureing or narrowing of the intestine in CD can lead to obstructive symptoms such as constipation and vomiting in association with abdominal pain
- Toxic megacolon (dilation of the colon) can be a feature of severe colitis.

Extra-intestinal manifestations principally involving the joints, skin and eyes are seen in both conditions (Kethu, 2006). Some, but not all, are related to active intestinal inflammation and often resolve on treatment. One or more of these manifestations can occur simultaneously and tend to be more common in colonic disease. Gallstones and renal stones may be a feature of small bowel CD as a result of malabsorption of a variety of minerals.

Treatment

Previous treatment strategies have simply focused on resolving symptoms and making patients feel better. However, mucosal healing and maximizing quality of life tend to be the ultimate goal of modern approaches to treatment. Options largely depend on diagnosis, disease site and severity, and should include discussion with the patient as part of the decision-making process.

Aminosalicylates

Aminosalicylates (5-ASAs) are anti-inflammatory drugs that act at various levels of the immune response and are indicated for the treatment of mild to moderately active UC and the maintenance of remission. Aminosalicylates tend to be of limited benefit for remission in CD, although there is some evidence to suggest a reduction in post-surgical recurrence of the disease, limited to the small bowel if used in high doses (Lochs et al, 2000).

The active 5-ASA molecules are designed to reach the colon through a number of different mechanisms such as:

- Slow, continuous release throughout the intestine (Pentasa)
- Modified release or pH-dependent (Asacol MR, Salofalk and generic Ipocol and Mesren MR)
- Azo-bond (sulphasalazine, balsalazide, olsalazine).

Liquid-retention enemas, foam enemas and suppositories are available for rectal or left-sided disease, but combined use of oral and topical therapy
## Box 2. Differences between Crohn's disease and ulcerative colitis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Crohn's disease</th>
<th>Ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution</td>
<td>Can affect any part of the gastrointestinal tract</td>
<td>Affects large bowel only</td>
</tr>
<tr>
<td>Endoscopy findings</td>
<td>Rectum frequently spared</td>
<td>Rectum always affected</td>
</tr>
<tr>
<td></td>
<td>Inflammation discontinuous with presence of 'skip lesions'</td>
<td>Inflammation is continuous and uniform</td>
</tr>
<tr>
<td></td>
<td>Bowel wall is thickened and has a 'cobble stone' appearance owing to deep ulcers and edema</td>
<td>Bowel wall is thin with loss of vascular pattern</td>
</tr>
<tr>
<td>Radiology</td>
<td>Strictures are common</td>
<td>Occur less commonly</td>
</tr>
<tr>
<td></td>
<td>Deep fistures and fistulae are common</td>
<td>Occur less commonly</td>
</tr>
<tr>
<td></td>
<td>Asymmetrical inflammation</td>
<td>Symmetrical inflammation</td>
</tr>
<tr>
<td>Histology</td>
<td>Presence of discrete granulomas are almost diagnostic</td>
<td>Granulomas are rare but may be in association with damaged cells</td>
</tr>
<tr>
<td></td>
<td>Inflammation is transmural</td>
<td>Inflammation is usually confined to mucosa</td>
</tr>
<tr>
<td></td>
<td>The increase in white cells tend to be lymphocytes</td>
<td>The increase in white cells tend to be polymorphs</td>
</tr>
<tr>
<td>Diet</td>
<td>Remission can be achieved with elemental and maintained with exclusion diets</td>
<td>No benefit on inflammatory process with these diets</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Patients often thin and can be malnourished owing to intestinal malabsorption of nutrients</td>
<td>Weight loss usually related to the severity of active disease</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea – only sometimes with blood</td>
<td>Diarrhoea with blood is common</td>
</tr>
<tr>
<td></td>
<td>Abdominal mass common</td>
<td>Rarely occurs</td>
</tr>
</tbody>
</table>

appears to be more effective than either used alone even in extensive disease (Marteau et al, 2005). The choice and potential efficacy of the drug may be largely dependent on disease site and behaviour; for example, an azo-bonded preparation may be more effective in left-sided disease, and modified release or pH-dependent preparations in more extensive disease. Factors such as severe diarrhoea or concomitant medications may alter the colonic environment, thereby affecting optimal release. Therefore, it is often worthwhile considering a slow-release formula in these circumstances. The generic formulations have not been subject to the same controlled clinical trials as proprietary formulations and, at least anecdotally, have been associated with relapse in previously stable patients. Therefore prescribing by brand may be important.

Treatment is generally well tolerated but headaches, abdominal pain and paradoxically, a worsening of colitis symptoms can occur and dose reduction or treatment cessation may be necessary. Renal and myeloproliferative disorders are a reported risk and therefore renal function and full blood count should be monitored regularly (Van Staa et al, 2004).

There is a reported reduction in the risk of developing colorectal cancer associated with longstanding and extensive UC by as much as 75% with all forms of 5-ASA (Eaden et al, 2000). This information should serve to improve concordance with taking maintenance medication. Novel treatment strategies,
"Mucosal healing and maximizing quality of life tend to be the ultimate goal of modern approaches to treatment."

including high dosing, rectal gels and simplified dosing regimens, should also improve tolerability and acceptability (Kane, 2005).

Corticosteroids
Corticosteroids remain the standard treatment for more severe and usually extensive active disease. They generally bring a rapid relief of symptoms but are not recommended for maintenance in view of the side-effect profile, including moon-face, weight gain, acne, dyspepsia, mood swings, diabetes and septic complications, which often outweigh the benefits (Faubion et al, 2001). Prednisolone is the most common oral preparation and enemas, in the form of foam (Predfoam, Colifoam) or liquid preparations (Predsol, Prednema, Entocort) and suppositories (Predsol) are available for diseases confined to the left colon; however, combined use of oral and topical therapy appears to be more effective in clinical practice. Osteoporosis is a risk of long-term therapy, although reduced bone density can also occur after a short course of treatment. Therefore concomitant prescribing of calcium and vitamin D3 supplements is recommended with additional bone densitometry for patients likely to be taking steroids for 3 months or more (Compston, 2003).

Budesonide is a topically acting steroid tablet effective in the terminal ileum and right colon, and is therefore more suitable for CD. It is associated with fewer side-effects than conventional steroids because of less systemic bioavailability, owing to first-pass metabolism in the liver and should be considered as an alternative where possible (Kane et al, 2002). A targeted oral preparation of prednisolone mesasulphobenzoate, used topically in distal UC, seems to be similarly effective throughout the colon (Cameron et al, 2003) and should be available for commercial use in the future.

In severe cases, hospitalization for intravenous therapy with hydrocortisone or methyl prednisolone may be required with immunomodulators for maintenance of remission.

Immunomodulatory therapy
Thiopurines
Although unlicensed, azathioprine and its metabolite, 6-mercaptopurine, are effective immunosuppressive agents in both CD and UC, but the exact mechanism of action is not clear (Ansari et al, 2002). In addition to a disease-modifying effect on the immune response, thiopurines also have steroid-sparing properties, although delayed efficacy of up to 12 weeks usually means that concomitant steroid treatment is necessary to control more immediate symptoms. Reversible bone marrow toxicity and hepatitis are a risk, so close monitoring of the blood count and liver function on initiation of treatment and subsequently every 2–3 months is essential. Approximately 30% of patients will have to stop treatment as a result of side effects such as nausea, vomiting, flu-like illness, bone marrow suppression or lack of clinical response. The agent 6-mercaptopurine can be substituted safely in many cases where patients are intolerant of azathioprine (Lees et al, 2007). Although lymphoma has been reported, the benefits outweigh the risks and a recent review by Fraser et al (2002) confirms the long-term safety of these treatments.

Methotrexate
Methotrexate is generally indicated in patients intolerant or resistant to azathioprine, but seems to be more effective in CD than UC (Feagan et al, 2000). In clinical trials, weekly injections of 25 mg have proved effective in achieving remission, which can be maintained with a dose of 15 mg weekly. The drug can also be administered orally. Side-effects such as rash, nausea, diarrhoea and stomatitis are fairly common, and although co-prescription of folic acid can help, treatment withdrawal is necessary in around 5% of patients. Methotrexate should be avoided in pregnancy, breastfeeding and conception, for males included, until at least 3 months after the last treatment as methotrexate is teratogenic.

Ciclosporin
Ciclosporin is a fungal metabolite that has a specific action on lymphocytes and is rapidly effective in the treatment of severe refractory UC, avoiding the need for colectomy in some cases (Campbell et al, 2005). It is usually given intravenously followed by oral administration as a 'bridge' to maintenance therapy with the slower acting thiopurines, although oral therapy is also effective. Prophylaxis against opportunistic infections with co-administration of cotrimoxazole may be indicated, especially if concomitant immunosuppression therapy is used or during prolonged treatment, although 3–6 months is the usual recommendation.

Nephrotoxicity limits the use of ciclosporin, although other side-effects such as hirsuitism, tremor and gingival hyperplasia can be problematic. Lower doses may minimize these effects (Van Assche et al, 2003). Blood tests including full blood count, renal function, magnesium, cholesterol and blood pressure should be checked before treatment. Ciclosporin levels, renal function and full blood count are recommended at defined intervals thereafter. A number of drugs will affect ciclosporin levels and for the same reason,
Clinical focus

Common food intolerances include wheat, yeast, dairy products and caffeine.

patients should be advised to avoid grapefruit and its juices.

Biological therapies
Infliximab is a monoclonal chimeric (mouse/human) antibody licensed to treat severe active CD and has been associated with mucosal healing and closure of fistulae (Present et al, 1999). It binds to and neutralizes the effect of tumour necrosis factor (TNF)-α, a potent proinflammatory mediator, which is overexpressed in active disease. It is administered by intravenous infusion and therefore requires hospitalization, although day treatment is usual. The response is rapid with the benefits usually seen in 1–2 weeks and sustained for 8–12 weeks, but patients often require repeat treatments as maintenance (Rutgeerts et al, 2004). It is also effective in UC (Rutgeerts et al, 2005) and has recently been given a licence for use in moderate to severe cases. Adalimumab, a fully humanized anti-TNF treatment recently licensed for active CD, is given by subcutaneous injection, thereby avoiding the need for hospital treatment, and has also proved effective in some patients who no longer respond to infliximab (Sandborn et al, 2007). A number of other anti-TNF treatments, including certolizumab pegol, are undergoing clinical trials (Schreiber et al, 2005).

Although infliximab is now well established for use in moderate to severe CD, treatment is governed by the National Institute of Health and Clinical Excellence (NICE), according to guidelines first drawn up in 2002. Clinical experience however, suggests that it might be more effective, and prevent much of the tissue destruction if it was given earlier in a ‘top down’ approach with immunomodulators, such as azathioprine, rather than the more traditional ‘step up approach’. Unlike steroids, it actually has an affect on the underlying disease process (D’Haens, 2006). This is likely to be viewed with caution given the post-marketing reports of an increased incidence of hepatosplenic T-cell lymphoma (Mackey et al, 2007), which is rare but usually fatal, and also a rise in cases of tuberculosis associated with treatment (Rampton, 2005). This is likely to apply to all anti-TNF treatments and perhaps for the time being, they should be reserved for the most severe cases following full counselling of the risks and benefits involved.

Nutritional support and primary dietary therapy
Many patients with IBD are malnourished, often owing to the effects of the underlying disease process but also because they avoid certain foods perceived to be contributing to symptoms or food altogether, in an effort to reduce pain (Razack and Seidner, 2007). It is therefore essential that a full nutritional assessment be performed by a specialist dietitian with appropriate supplementation instituted as indicated.

Diet
Elemental liquid diets have proved very effective as primary treatment of active CD and are at least as effective as oral steroids, but treatment does require considerable motivation and dietetic support (Riordan et al, 1993). The exact mechanism of action is unclear but it appears to have an anti-inflammatory effect in addition to restoring optimum nutritional status (O’Sullivan and O’Morain, 2001). Although many patients relapse on return to normal eating, remission
can be maintained if followed by an exclusion diet and subsequent programmed food reintroduction with avoidance of those foods found to provoke symptoms. A reduction in dietary fat and fibre seem to have a positive effect as demonstrated by the success of a low fat, fibre-limited exclusion (LOFFLEX) diet (Woolner et al, 1998). The most common intolerances include wheat, yeast, dairy products and caffeine.

Primary dietary treatment provides a safe and effective alternative to drug treatment and unlike corticosteroids, does not lead to osteoporosis (Dear et al, 2001). It is not effective in UC however, and patients are simply advised to eat a wide-ranging diet so long as it does not appear to consistently trigger symptoms.

**Antibiotics, probiotics and prebiotics**

Antibiotics such as ciprofloxacin and metronidazole, are used to treat diarrhoea owing to bacterial overgrowth of the small intestine resulting from strictures or scarring because of long-standing disease. They are also used to treat active CD as well as septic complications (Guslandi, 2007). They appear to have an anti-inflammatory as well as antibacterial action, but their use in UC is less well documented, apart from prophylaxis in acute severe UC before the exclusion of an infective cause. Conversely, in view of the association of bacteria and inflammation with the development of IBD, probiotics, and even prebiotics, are creating much interest and have, perhaps, been more successful in colitis than in CD. Further investigation is needed before these can be widely adopted into clinical practice successfully (Sartor, 2004).

**Adjunctive treatments**

Antidiarrheal agents, such as codeine phosphate and loperamide, may be used with caution but should be avoided in active disease. Although diarrhoea may resolve, underlying inflammation remains unaffected and complications such as perforation may arise. Resection of the terminal ileum can result in diarrhoea owing to malabsorption of bile salts and is usually treated with colestyramine (Questran). Concomitant medication needs to be taken an hour before, or at least 4 hours after, a dose as absorption may be affected. Supplements of fat-soluble vitamins are also recommended if used long-term.

**Surgery**

It is beyond the realms of this article to discuss the surgical options in detail. Suffice to say removal of the colon (colectomy) in the case of medically refractory UC provides the only permanent cure (Travis, 2004), whereas surgical management of CD involves limited resection of the most diseased intestine and management of sepsis, i.e. drainage of abscesses and fistulae. Strictureplasty can sometimes be performed, thereby preserving intestinal length in the case of short strictures (Roy and Kumar, 2004).

**Complementary therapies**

Poor response, or unacceptable side-effects associated with conventional therapy, can cause many patients to turn to complementary or homeopathic therapies (Langmead and Rampton, 2006). Although the evidence base for their use and potential efficacy is sparse and may simply lie in stress reduction, anti-inflammatory benefits have been associated with preparations such as aloe vera, essential oils and acupuncture. Awareness that a patient might be taking these treatments is important as they might adversely interact with conventional therapy.

**Education and support**

Support and education are essential to improve concordance with treatment. Patients with UC are five-times more likely to relapse if they fail to take their 5-ASA therapy (Kane, 2005) and those requiring hospitalization owing to relapse and subsequent treatment of disease complications cost the NHS 20-times more than patients in remission (Bassi et al, 2004). IBD nurse specialists, where present, have been able to make a significant impact on care delivery and optimize treatment outcomes providing telephone support, continuity and early access to prompt, effective treatment and advice when symptoms recur, with
improved patient satisfaction (Nightingale et al, 2000). Preliminary findings from the ongoing National IBD Audit support this.

**Everyday Living support service**

Companies such as Procter & Gamble Pharmaceuticals UK are also working closely with health professionals to improve support for patients and have recently developed the *Everyday Living* patient support service (Figure 1). Aimed at newly diagnosed patients with UC taking 5-ASA (mesalazine) treatments, this will be an invaluable resource for patients and their families, especially in centres where there is no IBD nurse specialist. The resource should also complement services where posts already exist.

Although it is of the utmost importance that patients take their medication regularly and appropriately, a holistic approach to management is essential in dealing effectively with a disease that impacts on many aspects of the lives of both the patients and their families. Patients often have issues relating to altered body image, not only resulting from the effects of the disease or surgery, but also from the treatments themselves, particularly oral steroids. Many fear or suffer actual incontinence and are too embarrassed to talk about their problems with friends and family, which often leads to social isolation and a poor quality of life. Support groups such as The National Association for Colitis and Crohn's Disease (NACC) help to raise the profile of IBD and offers an extensive range of services including information booklets, counselling and peer support (see *Further information*). They work in partnership with health professionals to campaign for improvements in services for patients, raising funds to further research.

**Conclusion**

Inflammatory bowel disease is complex and multifactorial, generally requiring a multidisciplinary team approach to management, involving the gastroenterologist, nurse specialist and dietitian, supported by radiological and histological services. Close collaboration with the colorectal surgeons is also essential to ensure appropriately timed surgery. Patients need to take regular medication even when well, or follow specific advice, which often requires considerable lifestyle adaptations in order to reduce the incidence of relapse and prevent complications. Regular follow-up and periodic investigations are also necessary to monitor the effects of treatment, especially immunomodulatory, biological therapy and colonic surveillance, in order to detect early changes of colorectal cancer, all of which can be intrusive to normal day-to-day life.

Education regarding disease management and self-help strategies are paramount to improve concordance and achieving optimal outcomes. This might be best

The *Everyday Living* support service, supported by Procter & Gamble Pharmaceuticals, aims to enhance the patient experience, improve patients' well-being and provide education on the long-term management of ulcerative colitis. It has many different but complementary components including:

- A telephone support service
- Intermittent letters and disease awareness leaflets
- Quarterly lifestyle magazines
- Dedicated patient website.

Website: www.everyday-living.co.uk
Telephone: 0800 234 6389

**Figure 1. The Everyday Living patient support service.**

provided by IBD nurse specialists, although equity of such roles throughout the UK remains a concern for patients and is the subject of a major campaign by NACC. Significant advances in knowledge and understanding of the disease process have greatly extended the range of more specific treatment options for IBD, and gives new hope to patients suffering from these debilitating conditions.

**References**


Clinical focus

Key Points
- The management of inflammatory bowel disease (IBD) is complex and multifactorial and requires a multidisciplinary team approach.
- Significant advances in research into IBD have led to the development of more specific and effective treatments.
- Primary dietary therapy offers a safe and effective alternative to drug treatment in the management of CD.
- Patients who are non-concordant in taking their medications and following appropriate advice are at significant risk of relapse.
- Education and support are essential in helping patients to better understand their disease and develop self-management strategies.
- IBD nurse specialists are associated with improved management outcomes and increased patient satisfaction.
- IBD is an unpredictable chronic relapsing and remitting disease that has a huge impact on many aspects of the lives of patients and their families and therefore, a holistic approach to care is likely to be more effective.

Useful information
For more information contact the NACC information line on 0845 130 2233 (weekdays 10.00–13.00). Alternatively call 0845 130 3344 to talk to someone who has colitis or Crohn’s disease (weekdays 18.30–21.00) or visit www.nacc.org.uk


The Wellcome Trust, (2007) Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls, Eur J Hum Genet 13: 877–88