HOW TO TREAT

inflammatory bowel disease

The cause of IBD remains unknown, despite the identified genetic and environmental components to its aetiology. While there is no cure, the GP is in an important position and can help the patient achieve more time in remission, with greater quality of life. This article was written by Richard Gearry, Department of Medicine, University of Otago; Department of Gastroenterology, Christchurch Hospital; and Gastroenterology and Endoscopy Specialists, Christchurch; and Andrew Day, Department of Paediatrics, University of Otago and Christchurch Hospital.

IBD is complex and on the increase

Inflammatory bowel disease (IBD) comprises Crohn's disease (CD), ulcerative colitis (UC) and indeterminate colitis (IC). These are idiopathic conditions characterised by inflammation of the gut mucosa leading to symptoms such as diarrhoea, rectal bleeding, abdominal pain and weight loss.

Over the last 50 years there has been an exponential increase in the number of people diagnosed with IBD. The significant patient morbidity now places a major burden on the healthcare system.

IBD is a lifelong disease with no cure. It is characterised by periods of relapse and remission. The aim of management is to prolong remission while minimising disease and treatment complications and maximising quality of life.

Recent studies from Canterbury show New Zealand to have one of the highest incidences of IBD, particularly CD, ever described. Extrapolating the Canterbury IBD Project nationally, at least 15,000 New Zealanders are likely to have IBD.

While people of all ages may be diagnosed with IBD, peak incidence is between 15 and 35 years of age (Figure 1). This is an important time of life and IBD may have a negative impact on adolescence, education, new relationships and employment.

IBD is one of a number of inflammatory or autoimmune diseases that have increased rapidly over the last 50 years; others include type 1 diabetes, multiple sclerosis, rheumatoid arthritis and asthma. The causes for this changing epidemiology are poorly understood.

IBD is complex. The strongest identified risk factor is a positive family history, and many genes have been found to be associated with CD in particular. However, most IBD patients do not have a family history of IBD, and none of the genes found to be associated with IBD have an established role in disease prediction or any clinical utility. Most of these genes encode for proteins involved in the interaction of gut microflora with the host immune system.

In healthy people, the gut immune system faces an enormous volume and variety of microbes but develops tolerance to these. This tolerance is lost in patients with IBD, leading to uncontrolled mucosal inflammation.

Environmental aetiologies are of immense interest due to the increasing incidence of IBD. Cigarette smoking doubles the risk of developing CD but, paradoxically, reduces the risk of UC. However, people who cease smoking are at increased risk of subsequently developing UC.

Continued smoking also has a negative impact on the course of CD (see later). Other environmental factors that

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Forms of IBD have distinctive features

The location and type of inflammation distinguishes CD from UC. UC is characterised by continuous mucosal inflammation extending proximally from the anus and CD more often affects the terminal ileum and/or colon with inflammation being transmural and discontinuous (Table 1).

The diagnosis of IC, now more correctly known as IBD-type unspecified (IBD-U), is made when the colon is inflamed but there are no features that allow CD or UC to be definitively diagnosed. In general, this does not affect the choice of drug therapy but has major implications if a colectomy is required because the option of reconstruction with an ileal pouch anal anastomosis is less favourable in CD patients. Many individuals initially labelled as IBD-U are subsequently reclassified as CD or UC.

Inflammation, cancer risks and malnourishment

Histologically, chronic UC features a mixed acute and chronic inflammatory cell infiltrate in the lamina propria with architectural distortion of the crypts and villi. Crypt abscesses are common.

In severe fulminant colitis, patients may present with severe systemic symptoms. Gross dilatation of the colon (>5cm diameter) occurs and there is a high risk of perforation. This is a medical emergency that requires urgent medical therapy and close consultation with a colorectal surgeon.

Patients who have had pancolitis for more than eight years (15 years for left-sided colitis) are at increased risk of colorectal cancer compared with the general population. Those with proctitis alone have no increased risk of colorectal cancer.

Carcinogenesis is different in this group of patients compared with the classic polyp–carcinoma sequence of the general population. Typically, dysplasia occurs in flat mucosa due to chronic inflammation. Those at increased risk include those with a family history of colorectal cancer, those with early-onset UC and those with coincident primary sclerosing cholangitis (PSC). While not proven effective in randomised controlled trials, two or three yearly surveillance colonoscopy is recommended in those with pancolitis after eight years, left-sided disease after 15 years and from diagnosis of UC in those with concomitant PSC. 5-Aminosalicylic acid (5-ASA) drugs may also have a chemopreventive role for cancer (discussed later).

The inflammation of CD differs from UC. It is often transmural leading to either stricturing disease with partial or complete bowel obstruction and anorexia, weight loss, pain, bloating and nausea; or penetrating disease leading to intra-abdominal abscesses or fistulae to adjacent loops of intestine or structures such as the bladder or vagina. Perianal disease can be a devastating example of penetrating CD leading to marked morbidity and impaired quality of life.

Anaemia is common in IBD patients and may be due to iron deficiency from blood loss or poor oral intake, chronic inflammation, drugs or folate/vitamin B12 deficiency. Patients may also become deficient in other vitamins, such as vitamin D.

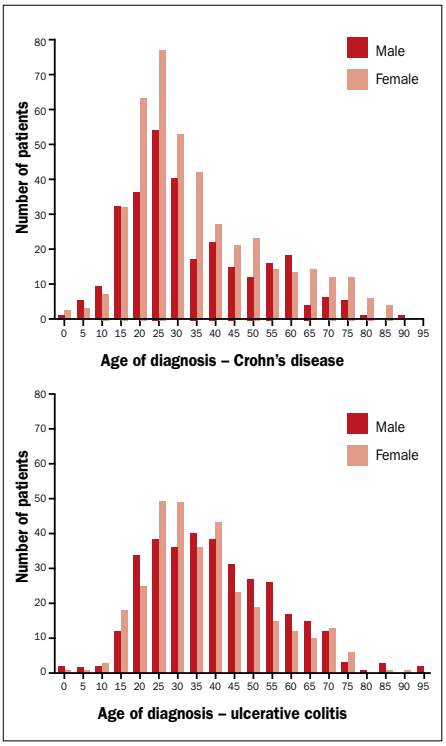

Figure 1. Age of diagnosis of 1420 IBD patients in Canterbury (Gearry R et al, Inflamm Bowel Dis *2006;12[10]:936–43)*

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have been associated with IBD include appendicectomy (protective in UC patients), antibiotic usage (more common in CD patients) and having been breastfed (less common in CD patients).

IBD is frequently confused with IBS (irritable bowel syndrome). Although both can display similar symptoms, IBD is characterised by intestinal inflammation while IBS is a functional disorder with endoscopic and microscopically normal intestinal mucosa. Patients with suspected IBD need to be assessed appropriately and start treatment as soon as possible.

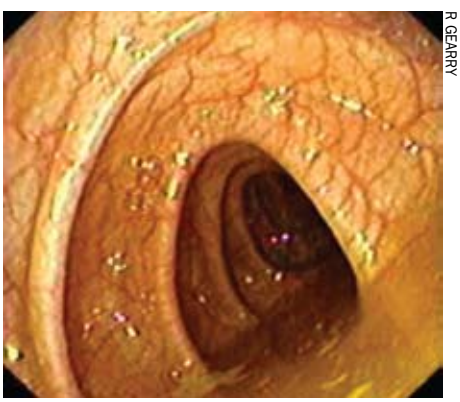
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Figure 2. Normal colonic mucosa

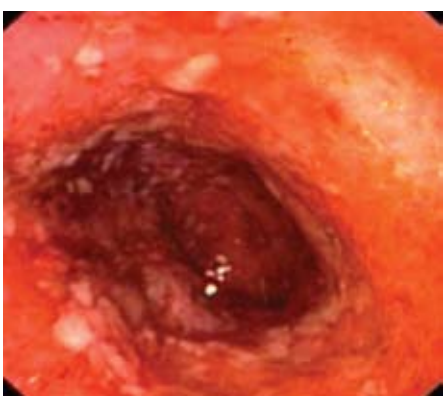
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Figure 3. Severe colitis

Diagnosis can bring unavoidable delays

There is no single test to diagnose IBD. Typically, a combination of clinical, endoscopic, histologic and (occasionally) radiologic information is required. This commonly leads to diagnostic delay for patients for a number of reasons.

- Patients may delay seeking medical attention due to embarrassment about the nature of their symptoms.
- The patient's presenting symptoms and signs may not immediately suggest IBD.
- The GP may not consider a diagnosis of IBD.
- Access to a gastroenterologist and specialist tests may be limited.
- Occasionally, time is required for a patient's disease to become more overt and allow accurate diagnosis.

Symptoms and history need documenting

Presenting symptoms depend on the location and behaviour of the inflammation. Typically, colitis presents with diarrhoea, rectal bleeding and urgency. These tend to be most severe with rectal inflammation (proctitis) where urgency, tenesmus and incontinence are common.

Small bowel inflammation seen in CD is more likely to present with pain, bloating, anorexia, weight loss and nausea as there is frequently some stricturing and obstruction. Perineal pain or discharge through visible fistulae is seen with perianal manifestations of CD. Less specific features, such as fever, lethargy and pallor, may be a manifestation of systemic inflammation or anaemia.

Extra-intestinal manifestations are seen in up to one in five IBD patients and include erythema nodosum (Figure 4), pyoderma gangrenosum (Figure 5), peripheral or axial arthritis, episcleritis, iritis, conjunctivitis, PSC, kidney stones and gallstones. Occasionally, these features may precede intestinal symptoms. In general (apart from PSC and kidney or gallstones), they respond to treatment of intestinal IBD.

Relevant patient medical history may include mouth ulcers (more common in CD), previous extra-intestinal manifestations and smoking (particularly the timing of commencement or cessation relative to symptoms onset).

Excluding other diagnoses is also important as is careful questioning about symptom duration. (IBD is a chronic condition and invasive investigation of diarrhoea is often not helpful within one month of onset.)

Recent and current medications of relevance include: antibiotics (associated with diarrhoea), anti-inflammatories (NSAID enteropathy), antihypertensives, colchicines, theophylline, antacids and acid-reducing drugs.

NSAID enteropathy is an increasing problem. The addictive nature of codeine can lead to the ingestion of very large quantities of both codeine and NSAID, leading to small and large intestine mucosal ulceration and inflammation. Combination codeine and NSAID

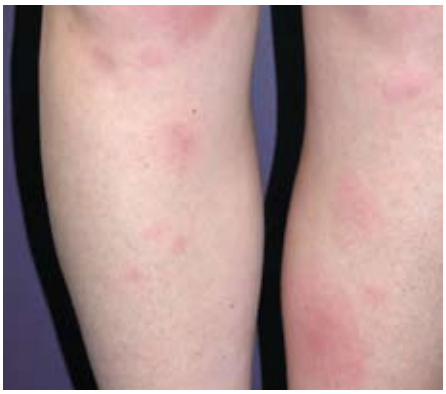

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Figure 4. Erythema nodosum in a young woman

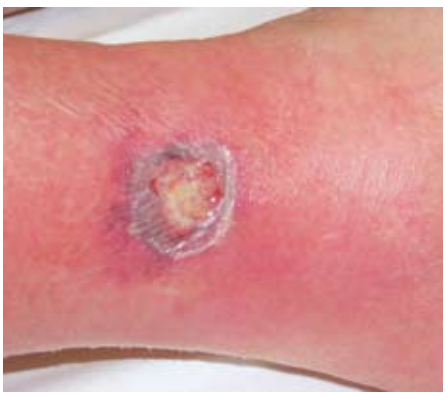

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Figure 5. Pyoderma gangrenosum

Distinctive features of Crohn's disease and ulcerative colitis (Table 1)

Characteristic	Crohn's disease	Ulcerative colitis
Location	anywhere in the GI tract	colon only
Pattern	skip lesions or continuous	continuous from anus
Inflammation	transmural (abscesses/fistulae in up to 50 per cent)	mucosal
Histology	granulomas (~50 per cent)	frequent crypt abscesses
Perianal disease	present (~20 per cent)	absent
Smoking	worsens course	protective

preparations are soon to be more tightly regulated.

Infectious contacts and travel history may signal possible infectious diarrhoea. A family history of colorectal cancer (particularly at a young age), IBD, coeliac disease or other gastrointestinal disease may also be relevant.

IBS can lead to similar symptoms as IBD in some patients. A positive diagnosis of IBS can be made in most patients, without referral and colonoscopy, using the Rome III Criteria (Panel 1).

Examination should look beyond abdomen

Physical examination may provide useful clues to the diagnosis of IBD. These may include signs of anaemia or focal abdominal findings, particularly right iliac fossa pain with a mass in patients with terminal ileal CD. Occasionally, this leads to psoas muscle irritation or abscess and limitation of hip flexion.

It is mandatory to examine the perineum for abscesses, fistula openings and fissures.

Patients with severe disease may be systemically unwell with fever, tachycardia and hypotension and require hospitalisation for urgent assessment and treatment.

Extra-intestinal manifestations such as erythema nodosum (painful, red, subcutaneous lumps that fade to appear as a bruise, often found over the anterior tibia) and peripheral arthritis may also be visible. Digital clubbing can present in long-standing disease. Pallor, peripheral oedema and changes in the oral mucosa may be present.

Investigations to exclude differentials first

An initial panel of investigations to consider for patients presenting with GI symptoms suggestive of IBD is summarised in Table 2. If any of these tests are abnormal, an organic diagnosis must be considered (eg, coeliac disease, infectious gastroenteritis), or a colonoscopy with ileoscopy may be indicated.

If the tests are normal but there is still a high index of suspicion for GI inflammation then a faecal calprotectin test may be useful. Calprotectin is a protein that comprises 50 per cent neutrophil cytosolic protein. In patients with undifferentiated diarrhoea it outperforms CRP and ESR testing and has an excellent negative predictive value for IBD.

In these suspected patients, a negative faecal calprotectin (<50µg/L) makes IBD extremely unlikely and may prevent the need for further investigation.

Colonoscopy best chance of positive diagnosis

Colonoscopy is the single test most likely to diagnose IBD as it allows direct visualisation of the colonic and terminal ileal mucosa with biopsy to confirm the diagnosis.

Radiology (eg, CT colonography) provides insufficient mucosal detail for accurate diagnosis of IBD.

Colonoscopy is the single test most likely to diagnose IBD as it allows direct visualisation

Patients undergoing colonoscopy need to maintain adequate hydration during bowel preparation, which, together with diarrhoea, may lead to dehydration.

A small proportion of patients may have small intestinal CD proximal to the reach of a colonoscope. Such patients may be investigated with capsule endoscopy or CT/MRI of the small intestine. Capsule endoscopy provides direct visualisation of the small intestine and is most sensitive, while cross-sectional imaging diagnoses penetrating disease most easily.

Patients with perianal disease may have this assessed with MRI of the perineum or endoanal ultrasound with examination under anaesthetic, depending on local expertise.

If IBD is confirmed, testing for nutritional deficiencies is indicated, specifically iron studies, vitamin B12, folate and vitamin D.

Rome III Criteria for IBS
(Panel 1)

Recurrent abdominal pain or discomfort at least three days/month in last three months associated with two or more of:

- improvement with defecation
- onset associated with a change in frequency of stool
- onset associated with a change in form (appearance) of stool.

Criteria fulfilled for the last three months with symptom onset at least six months prior to diagnosis.

Lower GI alarm symptoms
(Panel 2)

- Rectal bleeding
- Anaemia (not related to menstruation in women)
- Unintentional weight loss > 4.5kg
- Recent major change in bowel habit (age > 50 years)
- First-degree relative with colorectal cancer at a young age, CD or UC
- Nocturnal symptoms
- Severe unremitting symptoms.

Differential diagnosis should include cancer

The differential diagnoses to consider are shown in Table 3. In older patients, it is important to consider colorectal cancer as a cause of significantly altered bowel habit or rectal bleeding, and this should be investigated with a colonoscopy.

New Zealanders have a one in 18 lifetime risk of developing colorectal cancer – the greatest risk factor is age over 50 years. A family history of colorectal cancer in multiple relatives at a young age is an important risk factor for familial polyposis syndromes.

In younger patients, IBS is more common (one in six women, one in nine men) than IBD and may be diagnosed positively by symptoms alone (see Panel 1).

In patients presenting with lower GI

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Remaining hydrated is important in disease flares

Goals are symptom control, remission

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symptoms, the most important question facing a GP is usually: "Does this patient require referral to a gastroenterologist with/without a colonoscopy?"

If IBS can be diagnosed positively (see Panel 1) with no alarm symptoms (Panel 2), abnormal physical findings or abnormal basic laboratory tests in a patient aged less than 50 years, then colonoscopy for the assessment of new lower GI symptoms usually is not indicated. However, gastroenterological advice can be sought for the management of troublesome functional symptoms.

There is currently no cure for IBD. The aim of treatment is to induce and then maintain remission. Clinical remission can be defined as the ability of the patient to perform age-specific everyday activities without limitation by symptoms.

Many therapies are available – drugs, nutritional treatments (particularly for children) and surgery. The decisions regarding modality are based on patient wishes, disease severity and disease location.

In general, the treatments for patients with IBD are divided into those that induce remission and those that maintain remission (Table 4). The standard medical treatments can also be considered in terms of the groups of drugs, described here.

5-Aminosalicylates and sulphasalazine

The 5-ASA drugs are the mainstay for induction and maintenance of remission from UC. There is emerging evidence that long term use of these highly efficacious, relatively safe drugs is associated with a reduced risk of IBD-associated dysplasia and colorectal cancer.

The 5-ASA drugs have various delivery systems that allow delayed release of the 5-ASA active moiety to the distal small bowel and colonic mucosa, maximising mucosal drug concentrations and minimising systemic absorption.

In New Zealand, there are four drugs available in this class: sulphasalazine, olsalazine, and two formulations of mesalazine. Sulphasalazine comprises a

Initial laboratory testing (Table 2)

For patients with a differential diagnosis including IBD	
Full blood count	possible anaemia; leucocytosis and thrombocytosis may suggest inflammation
Erythrocyte sedimentation rate (ESR)	systemic marker of inflammation
C-reactive protein (CRP)	a non-specific marker of inflammation
Coeliac markers*	exclusion of coeliac disease
Faecal sample	exclusion of GI infection

* Endomysial (EMA) or tissue transglutaminase (tTG) antibodies with total IgA depending on local laboratory practice

Differential diagnosis of GI symptoms suggestive of IBD (Table 3)

Diagnosis	Characteristics
Irritable bowel syndrome	see Panel 1
Infectious diarrhoea	infectious contacts/travel history and stool sample
Drug-associated diarrhoea	history of appropriate drug use
Coeliac disease	positive coeliac markers
Colorectal cancer	usually older patients, unremitting symptoms, family history of colorectal cancer
Small intestinal bacterial overgrowth	history suggestive of small bowel abnormality
Ischaemic colitis	often sudden onset of rectal bleeding in a patient with vascular disease
Diverticulitis	usually older patients, left iliac fossa abdominal pain, fever with diarrhoea

sulphapyridine molecule bound to a 5-ASA molecule. Colonic bacterial enzymes cleave the bond, releasing active 5-ASA into the colon. The discovery and use of this drug was a major advance in IBD therapy but the sulphur moiety can cause adverse effects that make it poorly tolerated. There are further severe haematologic, pulmonary and dermatologic side effects not seen with newer 5-ASAs, meaning sulphasalazine is now used less.

Olsalazine is two 5-ASA molecules similarly bound together by the same azo bond. It is better tolerated than sulphasalazine but, paradoxically, may cause diarrhoea.

Mesalazine is available in two formulations in New Zealand. Pentasa (mesalazine 500mg ethylcellulose-coated) provides delayed 5-ASA release through the small and large intestine. Asacol (mesalazine 400mg coated with Eudragit-S) gives drug release in the terminal ileum and colon.

In addition, topical formulations of Asacol and Pentasa are available – suppositories for rectal disease and enemas for disease distal to the splenic flexure. Topicals offer the advantage of delivering high drug doses directly to the inflamed mucosa while minimising systemic exposure. Where oral or topical therapy alone is not effective for distal disease, combining both is shown to be effective in randomised trials.

The standard dose to induce remission of UC is Asacol 3.2g/day or Pentasa 4g/day (ie, eight tablets of each). The daily dose for sulphasalazine is also 4g/day (eight tablets) – usually the dose needs increasing slowly to reduce the risk of intolerance.

While the 5-ASA drugs have traditionally been given in divided doses, a recent study demonstrated improved efficacy when Pentasa was given as a single dose (4g once daily), presumably because of improved patient compliance. 5-ASA drugs are less effective in CD than UC but are often used before corticosteroids or immunomodulators as they have a better safety profile.

Corticosteroids useful in more severe IBD

While 5-ASA drugs are usually effective for mild to moderate disease, patients with moderate to severe disease require more powerful therapy, and oral corticosteroids are typically used.

There are no strict guidelines for their use but typically IBD patients commence on prednisone 40mg/day and wean the dose over about eight weeks (reducing by 5mg/week).

While steroids are efficacious – inducing remission 85 per cent of patients – they have no role in maintenance therapy. Patients should be warned of the many side effects when corticosteroids are commenced. Care should be taken in those with diabetes where blood glucose control may become problematic and in those with profuse diarrhoea where hypokalaemia can occur.

Osteoporosis prophylaxis should be initiated with oral steroids ensuring adequate calcium and vitamin D intake

Common drug therapies in IBD (Table 4)

Treatment	Crohn's disease		Ulcerative colitis	
	Induce remission	Maintain remission	Induce remission	Maintain remission
5-ASA/sulphasalazine	+	+	++	++
Corticosteroids	++	–	++	–
Immunomodulators	+	+++	+	++
Biologics	++	++	+	+
Antibiotics	±	–	–	–

** Symbols – and + denote degree of efficacy*

Common IBD drug adverse event monitoring (Table 5)

Drug	Side effects	Monitoring
5-ASA	marrow suppression (rare), diarrhoea	annual full blood count, urea and electrolytes, urinalysis
Sulphasalazine	allergy, headache, reduced sperm count	annual full blood count, urea and electrolytes, urinalysis
Azathioprine/6-mercaptopurine	marrow suppression, nausea, hepatotoxicity, immunosuppression, sun sensitivity, pancreatitis	three-monthly full blood count, liver function tests
Methotrexate	marrow suppression, nausea, hepatotoxicity, immunosuppression, sun sensitivity	three-monthly full blood count, liver function tests
Steroids	osteopenia, immunosuppression, adrenal suppression, fluid retention, mood changes, (and others)	blood sugar level monitoring, bone mineral density

or bisphosphonate therapy if this is indicated.

Budesonide is an oral steroid with very high first-pass metabolism. It is effective for mild to moderate ileal and right colonic CD but can only be prescribed on Special Authority by a gastroenterologist for patients with specific side effects to corticosteroids.

Where oral steroids are ineffective, after seven to 10 days depending on the clinical context, patients may require admission for intravenous (IV) steroids and possibly IV cyclosporine (UC) or Infliximab (UC and CD), and the patient should be discussed with a gastroenterologist.

Immunomodulators can help some IBD patients

Immunomodulators are indicated where 5-ASA is ineffective and patients require repeated corticosteroids or are steroid dependent. These comprise the thiopurines (azathioprine and 6-mercaptopurine) and methotrexate.

Immunomodulators should be started by a gastroenterologist after a full discussion of their important features:

- the 25 per cent adverse event rate (Table 5) leading to cessation
- the three to six-month delay in onset of action
- the slightly increased risk of infection, and
- the small increase in risk of lymphoma and skin cancer.

While target doses of 2–2.5mg/kg azathioprine (1–1.5mg/kg 6-mercaptopurine) are aimed for, dosing is guided by patient tolerance and thiopurine methyltransferase (TPMT) activity. This enzyme is involved in drug metabolism and about one in 250 people are deficient. TPMT-deficient patients develop severe bone marrow toxicity on standard doses of thiopurines while those with intermediate activity require about 1mg/kg azathioprine. Measuring concentrations of azathioprine metabolites can help ensure optimal dosing.

Methotrexate is generally a second-line agent if the thiopurines are ineffective or poorly tolerated. Methotrexate is given once weekly and has enhanced efficacy and a decreased side effect profile when provided subcutaneously rather than orally. This drug also has a slow onset of action (at least six weeks) and numerous potential side effects and requires regular monitoring (Table 5).

Two biologics available in New Zealand

Two biologic agents are currently available in New Zealand for IBD – infliximab (Remicade) and adalimumab (Humira). Both act on the cytokine tumour necrosis factor-α (TNFα) but differ in administration and pharmacokinetics.

Studies show both drugs efficaciously induce and maintain remission of CD. Infliximab is also indicated for inducing and maintaining remission of UC, as well as treating perianal CD.

The drugs have various side effects and are considered only following individual assessment of risk and benefit by the gastroenterologist with the patient. At present, only adalimumab is funded on Special Authority application by a gastroenterologist, although GPs can prescribe ongoing drug once a patient has responded.

Antibiotics have a limited role

Some data support the use of antibiotics, namely metronidazole and ciprofloxacin, to induce remission, particularly for perianal CD and possibly luminal CD. Metronidazole also has a proven role in preventing recurrences after an intestinal resection. Antibiotics have no role in maintaining remission in CD and no role in managing UC.

Risks of immunosuppression

Many of the drugs used to induce or maintain IBD remission have side effects of immunosuppression. An increased risk of infection is seen with corticosteroids, thiopurines, methotrexate and the biologic drugs.

Particular concern has focused on the increased risk of reactivation of tuberculosis following use of the biologics: screening for tuberculosis is undertaken before commencing these drugs. Patients on biologics should in general not receive live vaccines.

Vitamin D deficiency is common in IBD patients

Surgery for patients with IBD

Surgical procedures are required in some patients with CD and many with UC.

Indications for surgical consultation in CD include medically unresponsive or stricturing disease. Resections in CD are not curative: disease recurs postoperatively.

In UC, colectomy may be required acutely in fulminant colitis, perforation or megacolon. Colectomy is also required electively in many individuals with UC. Colectomy in UC can be considered curative; however, other morbidities (such as pouchitis) can occur afterwards.

Nutrition and nutritional deficiencies

Patients with CD and UC can have macro and/or micronutrient deficiencies. Weight loss or difficulties maintaining weight are common complaints, especially in CD.

Common micronutrient deficiencies include iron, vitamin B12 and vitamin D; less common are deficiencies of vitamin K, zinc and folate. Attention to diet and nutrition is therefore an important part of management. Nutritional deficiencies should be corrected with available supplements and levels monitored over time.

Nutritional therapies can have a role in managing CD, especially in young people. However, there are no current data to support particular dietary changes for all people with CD and UC. Some people with IBD who have coincident IBS can have improvements in some functional symptoms with careful supervised diet adjustments.

Patient follow-up a key role for GP

As with all incurable chronic diseases, IBD management requires a long term perspective to achieve the best sustainable results for patients. Notably, an IBD patient interacts with numerous professionals in managing their disease, including: GPs; gastroenterologists; IBD, stoma therapy and outpatient nurses; colorectal surgeons; other specialists (eg, rheumatologists, dermatologists, and ophthalmologists); pharmacists; researchers; dietitians; IBD support groups; and friends and family. As always, the GP has a central role in coordinating services and overseeing the patient's wider health.

IBD has a relapsing-remitting course. Therefore, patients may have long periods feeling well and variable periods of illness with significant morbidity.

The peak age of incidence is 15 to 35 years and many patients are affected at a vital time in their development, education, employment and formation of relationships. Patients often require support through this time and the role of support groups, friends and family cannot be underestimated.

Local research shows depression is twice as common in IBD patients as age-matched controls and that, on average, IBD patients have more time away from normal activities.

Sexuality and fertility

Other important issues facing young people with IBD are sexuality, fertility and reproductive health. IBD and its treatments can have significant effects on these aspects. CD is diagnosed more commonly in women than men.

IBD patients are often less sexually active due to the nature of IBD and its symptoms and may even avoid relationships. Confidence and self-image are easily hampered in the course of IBD and its treatment, making intimate relationships difficult.

The systemic inflammation with IBD can disturb menstruation and female fertility. Furthermore, previous surgery (particularly in the pelvic area) may lead to female fertility problems. For example, women with UC undergoing a pan-proctocolectomy with ileal pouch anal anastamosis reconstruction have three times the risk of infertility as women with UC without a pouch formation (15 *v* 48 per cent).

While there are limited data on the effects of drugs on female and male fertility, sulphasalazine is associated with oligospermia and defects in sperm form and motility. These effects are secondary to the non-therapeutic sulphapyridine moiety of sulphasalazine, are fully reversible upon drug cessation and are not seen with the newer 5-ASA agents.

Pregnancy and breastfeeding

As a rule, the risks of uncontrolled IBD outweigh the risk with most drug therapies. The notable exception is methotrexate, which causes miscarriage, is highly teratogenic and is contra-

Young teen with IBD (Case study 1)

History and presentation

Katie is 14 years old. She presents, with her mother, with a history of diarrhoea, rectal bleeding, abdominal pain and poor growth. Diarrhoea and pain have occurred for more than three years, with rectal bleeding over the last two months. She has gained no weight in 12 months, and has actually lost weight in the last three. Katie has also shown minimal height gain this year and no signs of puberty. She had intermittent mouth ulcers and decreasing exercise tolerance (pulling out of school sports in the last six months). There is no family history of IBD or other GI condition.

Examination

Katie weighs 40.6kg (10th centile) and stands 146.7cm (<3rd centile). Previous charts show her at the 25th centile three years earlier. She has mild conjunctival pallor but no clubbing, oedema or skin changes. Her abdomen and perianal region are unremarkable. She is Tanner Stage 0 (no pubertal changes evident).

Investigation

Initial blood tests show elevated ESR (26), low albumin (29), thrombocytosis (625) and microcytic anaemia (Hb100). Stool cultures show no pathogens and microscopy for faecal white cells is negative.

Management

As there is concern about possible IBD, Katie undergoes upper GI endoscopy and a colonoscopy, which show scattered aphthoid ulcers in the antrum and proximal duodenum, with ulcers in the ileo-caecal region, along with increased friability and narrowing of the ileocaecal valve. Histologically, mucosal biopsies show focal enhanced gastritis, acute duodenitis and ileocaecitis, and granulomata in the ileal biopsies. There are also scattered acute and chronic inflammation changes in additional colonic biopsies. With the histology assessed, all of the results are discussed with the family who are told the diagnosis of CD and its nature, and given initial education about CD and the prognosis. Management options are outlined and discussed in detail. Commencing exclusive enteral nutrition to induce remission is agreed. Following dietetic consultation, Katie starts a polymeric formula with volumes increased to supply full nutritional requirements. Within 10 days she has greater energy and wellbeing with improving gut symptoms. Blood and diarrhoea resolve by two weeks and pain completely resolves by three weeks. Repeat blood tests at four weeks show normalised CRP, platelets and ESR with improved albumin. Also at four weeks, Katie commences standard protocol azathioprine, with dose optimisation after initial monitoring tests show no changes. After eight weeks, she recommences a normal diet following a standard protocol, with some ongoing oral supplemental formula. By now, she has gained 6.3kg. Ongoing follow-up continues in a paediatric IBD clinic setting.

indicated in women not using adequate contraception (FDA Category X).

While patients often have concerns about using the other immunomodulators, steroids and 5-ASA agents in pregnancy, there are no data to suggest these drugs increase the incidence of poor birth outcomes. Likewise, drugs used for IBD (methotrexate excluded) have no associations with adverse events in breastfed babies whose mothers are receiving the drugs. This includes the thiopurines whose use is often questioned in breastfeeding. However, recent data from Christchurch show azathioprine metabolites cannot be detected in the blood of exclusively breastfed babies whose mothers are receiving therapeutic thiopurine doses.

Drugs used for IBD (methotrexate excluded) have no associations with adverse events in breastfed babies whose mothers are receiving the drugs

Cancer risk

IBD is associated with a small but statistically significant increased risk of cancer – some associated with disease activity and some with treatment.

IBD management requires a long term perspective to achieve the best sustainable results for patients

Patients with UC that extends proximal to the rectosigmoid junction (or those with pan-colonic CD) have an increased risk of developing colorectal cancer. Such patients should be informed of this risk during the course of their disease and again eight years after diagnosis when strategies to reduce the risk of advanced colorectal cancer should be discussed.

While surveillance colonoscopy is recommended after eight years of pancolitis or 15 years of left-sided disease, there are no randomised controlled trials to prove this strategy prevents advanced colorectal cancer. Patients should be warned of the possibility of interval cancers and careful colonoscopy should be undertaken by an experienced gastroenterologist.

Colorectal cancer risk is reduced by long term use of 5-ASA and this may provide additional motivation for patient compliance with 5-ASAs.

There is an increased risk of small intestine adenocarcinoma in patients with extensive small bowel CD but this diagnosis remains exceedingly rare.

The association between immunosuppressive therapy and cancer is well described across a number of diseases. The thiopurines are associated with a modest increase in the risk of lymphoma and probably skin cancer as well. At this stage, it is too early to be sure whether infliximab and adalimumab confer an increased risk of cancer.

IBD in children and adolescents

IBD can present in children of any age, from the first weeks or life. It is, however, most common in the middle of the second decade of life. The most common symptoms in CD are pain, weight loss and diarrhoea, while bloody diarrhoea is most common with UC. Children can also have atypical symptoms – these may include isolated chronic abdominal pain and short stature.

As many children with IBD develop symptoms around or during puberty, normal pubertal development is commonly interrupted. Weight loss and impaired linear growth are very common features, especially in CD. Pubertal delay and growth impairment together often lead to adverse psychological effects.

The patterns of childhood IBD differ in many regards, especially in terms of disease site (eg, high rates of upper GI involvement in children) and disease behaviour. Ileo-colonoscopy and upper GI endoscopy are required for initial assessment, along with definition of small bowel involvement (such as by MRI).

The principles of management in children are similar to that in adults. The primary aims are to induce and maintain remission.

Nutritional therapy (see Case study 1) has proven efficacy in inducing remission, while also improving nutrition and resulting in very high rates of mucosal healing. Supplementary nutrition can also contribute to maintenance of remission. Early use of immunomodulators (as in Case study 1) can be most efficacious in moderately severe disease, especially to avoid steroid-related adverse events and to prolong remission.

Ongoing monitoring of growth and normal development (eg, puberty), along with reassessment of the inflammatory markers, is required. Long term it is important to avoid complications (such as impaired linear growth) and to ensure normal daily activities (school, education, sports and social) can be conducted. Multi-disciplinary inputs are required. IBD in a child can impact adversely on the child's quality of life and also adversely affects their siblings and parents.

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Tradesman cannot work

(Case study 2)

History and presentation

Jim, a 42-year-old electrician, presents to his GP with increasing diarrhoea, rectal bleeding and urgency. He has been unable to work for one week due to marked urgency and an embarrassing episode of incontinence. He has felt lethargic for three weeks. His medical history is notable for a diagnosis of UC at the age of 20, asthma and depression (a single episode age 24 years). Jim uses no medications, has no known drug allergy. He is married with three schoolage children. His father was successfully treated for colorectal cancer aged 59 years. Further questioning reveals Jim's diagnosis of UC at age 20 was left-sided colitis, made by colonoscopy at another centre. He was initially managed with sulphasalazine but stopped this when he and his partner wished to conceive 15 years ago. Subsequently, he has had significant episodic diarrhoea requiring two or three courses of oral steroids per year.

Examination

Jim appears pale and has a pulse of 90bpm. Apart from mild left abdominal tenderness and blood on the glove following a rectal examination, no other abnormalities are identified.

Investigation

Faecal samples are sent, and they exclude infective gastroenteritis. Blood tests reveal a microcytic anaemia (Hb 113g/L, MCV 79), raised platelets (623) and raised CRP (23mg/L). Liver function tests are also abnormal (bilirubin normal, ALP 245, GGT 347, AST 34, ALT 54, INR normal).

Management

Mesalazine 4g/day orally and 1g rectal enemas are commenced. Jim is reviewed one week later. He has improved with bowel frequency reduced and rectal bleeding stopped. Oral corticosteroids are therefore avoided. Jim is then referred to a gastroenterologist for follow-up.

Follow-up

The mesalazine enemas are weaned over a six-week period and Jim is maintained on oral mesalazine 4g alone. Magnetic resonance cholangio-pancreatography (MRCP) is ordered – it demonstrates subtle biliary changes consistent with primary sclerosing cholangitis. Surveillance colonoscopy is performed three months later – the colonoscopy reveals macroscopically quiescent disease. Random biopsies taken to exclude dysplastic change are negative. Jim remains in remission on oral 5-ASA alone.

Further support and resources

IBD support groups play a vital role in patient education and support. Regional groups in New Zealand have recently merged to form a national support group: Crohn's and Colitis New Zealand with a national website under development.

Crohn's and Colitis New Zealand – www.crohnsandcolitis.org.nz

Other national organisation websites:

- Crohn's and Colitis Australia – www.acca.net.au
- Crohn's and Colitis Foundation of America – www.ccfa.org
- National Association for Colitis and Crohn's Disease – www.nacc.org.uk
- Crohn's & Colitis Foundation of Canada – www.ccfc.ca
- European Federation of Crohn's & Ulcerative Colitis Associations (EFCCA) – www.efcca.org

Specific websites for children and young people:

www.ucandcrohns.org
www.kidsibd.org
www.naspghan.org
www.reachoutforyouth.org