Common questions in inflammatory bowel disease

Alan Fraser MBChB FRACP

Alan Fraser is Associate Professor of Medicine at the University of Auckland. He works as a gastroenterologist at Auckland Hospital and also in private practice. His main research interests are inflammatory bowel disease and Helicobacter pylori infection.

Ulcerative colitis and Crohn's disease are chronic inflammatory diseases of the gastrointestinal tract. They are identified by characteristic endoscopic/radiological and histological appearances.

Ulcerative colitis and Crohn's disease have many clinical features in common but are best considered as separate disease entities rather than being two ends of a spectrum.

What is the cause of inflammatory bowel disease (IBD)?

A genetic susceptibility for IBD has been known for many years. There are three main lines of evidence. Firstly, IBD is more or less common in some ethnic groups. For example, in New Zealand, IBD is very uncommon in Maori or Pacific Islanders. Secondly, there is familial clustering of disease. About 20% of patients with IBD know of another family member with IBD. The lifetime risk of IBD for a first-degree relative is 10%. Thirdly, the most compelling evidence comes from identical twin studies. These studies show a concordance rate of 33% if the first affected twin has Crohn's disease. The magnitude of the genetic effect is greater for Crohn's disease – there is only 7% concordance for ulcerative colitis.

One gene called NOD2 has been defined and appears to be involved in the immune response to 'normal' bacteria in the bowel. There is likely to be a complex interaction between genetics and environment. One environmental factor of significant interest is smoking. Smoking increases the risk of Crohn's disease but decreases the risk of ulcerative colitis. For patients with Crohn's disease, smoking doubles the risk of disease recurrence after surgery.

What is the appropriate treatment for a patient with an acute flare of ulcerative colitis?

The immediate question to be resolved is the need for hospital admission. This depends on the severity of the colitis.

A severe attack is suggested by the following features: >6 BMs/day, fever >37.5°C, ESR >30 m/hr, albumin <30g/L. Hospital admission will usually be required with two or more of these features. Any significant abdominal pain or tenderness is suggestive of a severe flare of colitis.

Intravenous hydrocortisone is required for severe colitis but only 60–70% will achieve remission and failures of treatment will require urgent colectomy. This outcome can be improved with the use of cyclosporine (if hydrocortisone fails), however this needs careful specialist supervision because of the risks of toxicity.

If hospital admission is not required what changes to oral treatment will be effective?

Increasing the dose of 5-ASA medication is only of modest benefit and will not usually be enough to resolve a relapse. However any benefit is achieved with only minimal risk of side-effects. The usual maintenance dose of mesalazine can be increased from 2g to 3g daily (for Pentasa) or from 1.6 to 2.4g daily (for Asacol). Salazaopyrin can be increased from 2g to 3g daily but will often result in headaches or gastrointestinal side-effects. Further dose increases are unlikely to be beneficial. Higher doses of Pentasa (4g/day) are occasionally used in Crohn's disease.

Most relapses will require a course of oral prednisone. The starting dose should be 40mg daily. Lower doses are often not enough to induce remission and higher doses are not usually required. The dose should be decreased only when clinical improvement is seen.

This may take two to three weeks. There should then be a gradual reduction in dose – hopefully stopping completely after six to eight weeks. Steroids have no role as maintenance treatment but some patients will relapse as the steroids are decreased. Sometimes multiple 'short' courses can result in a higher cumulative exposure to steroids (compared to a single 'effective' course).

Relapse during dose withdrawal or relapse soon after stopping prednisone usually implies the need for immunosuppressive treatment or surgery.

Sometimes more intensive use of 5-ASA drugs and regular use of 'per rectal' treatments can be enough to maintain remission. Occasionally slower withdrawal of prednisone is successful, particularly if there has been long-term use of steroids. Some of the symptoms on withdrawal of steroids can relate to adrenal suppression rather than relapse of the inflammation.

What are the hazards of immunosuppression treatment?

Azathioprine was first used in the treatment of inflammatory bowel disease over 30 years ago. The initial evidence for efficacy was mixed largely because trials did not continue treatment for long enough. It is now clear that it can take up to six months for azathioprine to have the maximal effect. The overall treatment duration is now usually at least five years. About 15% of patients cannot tolerate azathioprine (or 6-mercatopurine) mainly because of nausea or allergic-type symptoms. If the medication can be tolerated then there is usually sustained efficacy with minimal side-effects in the longer term. The main risks are not those of infective complications (this is surprisingly uncommon). The main problems are the small risk of neutropenia and liver disease (this risk is effectively managed with regular blood tests). The only other theoretical concern with long durations of treatment is the risk of malignancy.

Two major reviews have concluded that there is no evidence of an increased risk of malignancy in patients treated with azathioprine.

There is definitely no increased risk of colon cancer. The risk of lymphoma is still debated. The problem is the small numbers in reported studies and a larger meta-analysis is required.

Does proctitis require a different approach?

Yes, this condition presents some different treatment issues. Proctitis is chronic inflammation (of the ulcerative colitis type) confined to the rectum. Diarrhoea is generally not the problem – the patient is most troubled by rectal bleeding, tenesmus and urgency.

The treatment should concentrate on 'per rectal' medication. There are a variety of formulations available that have different levels of patient acceptability. The easiest (and most acceptable) method of delivering drug is by suppositories (e.g. Asacol suppositories). This results in good delivery of 5-ASA to the rectum and perhaps sigmoid. Colifoam enemas are also convenient to use. Many patients alternate between these two types of medication or, by trial and error, find that one is better for them. Liquid enemas are difficult to use. They may be the most effective form of treatment and are able to treat inflammation extending up to the splenic flexure (Pentasa and Asacol enemas) however few patients are able to manage more than short-term treatment.

Continuation of medication during pregnancy is usually the safest approach because of the greater risk to the foetus of uncontrolled disease activity

Oral 5-ASA medication (Asacol, Pentasa or Dipentum) does have an additive benefit to 'per rectal' treatment. Dipentum has some theoretical advantages (and some supporting trial data) for proctitis or distal colitis. This medication needs to be introduced slowly and should be taken with meals to lessen the chance of diarrhoea. Oral prednisone and/or azathioprine are rarely required.

What is the long-term cancer risk with ulcerative colitis?

There is an increased risk of colorectal cancer for ulcerative colitis (mainly for pan-colitis but also, to a lesser extent, for left-sided colitis). There is no increased risk for proctitis alone. The cancer risk (over and above that of the general population) becomes apparent after 10 years of disease. The reported magnitude of the risk varies widely in different countries. After 30 years of pan-colitis the risk may be up to 10%. This risk can be managed with colonoscopic surveillance but this is costly and not accepted by all patients. Recommendations from USA and Europe suggest two-yearly colonoscopy after eight years of pan-colitis. This level of surveillance is not always achieved in New Zealand. In practice, many gastroenterologists feel the risk of colorectal cancer is over-emphasised but there is no local data.

The risk of colorectal cancer can be reduced by 50% with maintenance 5-ASA compounds.

Most patients should continue maintenance 5-ASA drugs to reduce the risk of relapse. It is difficult to know if we should insist on maintenance 5-ASA for those patients with quiescent disease. Our patients should be informed of this data and will need to decide for themselves.

What medications can be used during pregnancy?

Giving good advice to a pregnant patient with IBD involves balancing the risk of treatment with the risk of untreated disease. There is a large amount of data to support the continued use of 5-ASA and steroids (if required) during pregnancy. Azathioprine treatment can be continued during pregnancy if required to maintain remission.

Continuation of medication during pregnancy is usually the safest approach because of the greater risk to the foetus of uncontrolled disease activity.

There is a large collective experience from patients with renal transplants (and other diseases) showing that azathioprine has no teratogenicity, no increased risk of abortion and no decrease in fertility. There was some

concern regarding fathers taking azathioprine. This came from one small study but other data is reassuring.

Does Crohn's disease have a worse prognosis compared with ulcerative colitis?

Yes and No.

No: Both conditions have a highly variable course. Patients do tend to have more fear of Crohn's disease but the majority of patients with Crohn's disease do achieve an excellent quality of life with a combination of medical and surgical treatment.

Yes: There is the potential for more complicated disease with Crohn's disease. The complications are more diverse and severe because of the transmural nature of the inflammation (intestinal obstruction, perforation and fistulae). Diffuse small bowel disease may have prominent abdominal pain, weight loss and nutritional deficiencies. Perianal disease may lead to abscess and fistulae leading to troublesome peri-anal pain and discharge.

What is the role of diet?

The role of diet is surprisingly limited. Nutritional deficiencies need to be identified and treated. The cause is usually multi-factorial – inadequate intake is often more important than malabsorption. Supplemental oral feeding with polymeric liquid defined diet may be helpful, particularly to enhance growth in children. A complete switch to an elemental diet (containing only low molecular weight nutrients) has been shown to be as effective as steroids, but practicalities have limited the use of this approach (the diet is unpalatable – often needing nasogastric nocturnal feeding). Some patients feel better with some dietary exclusions (e.g. wheat-free or dairy-free diet) but this is a non-specific effect.

What about alternative treatments?

Most patients have tried alternative treatments. There is no evidence of any harm from the commonly used approaches. Some treatments have been studied in randomised trials. Omega-3 fatty acids (in the form of fish oil) have been shown to be effective in some trials (mostly for ulcerative colitis) but have had no effect in other studies. There is continued research into acceptable formulations ('non-fishy!'). Aloe vera, evening primrose oil and bovine colostrum have minimal supporting evidence. Probiotics are likely to be an emerging field. There is evidence of efficacy for probiotics in mild to moderate ulcerative colitis. The most effective preparations are currently expensive and have limited availability in NZ.

Many patients feel in retrospect that they waited too long before embarking on surgery. If the symptoms are obstructive in nature then surgery is the preferred option

Can anti-inflammatory drugs aggravate IBD?

Yes, non-steroidal anti-inflammatory drugs are definitely a problem for some patients with ulcerative colitis. They are clearly associated with a higher risk of relapse. There is also an association with perforation of the colon. The use of NSAIDs should be discouraged. Salazopyrin has a role for joint disease associated with IBD and is a preferred approach. The safety of COX2-inhibitors in IBD remains uncertain.

Is medical treatment the same for ulcerative colitis or Crohn's disease?

There are many similarities in approaches. Steroids and 5-ASA compounds are the mainstay of medical treatment for both diseases. Maintenance treatment with 5-ASA is less effective in Crohn's disease compared with ulcerative colitis but is widely used because of the good side-effect profile.

For patients with small bowel Crohn's the formulation of 5-ASA is important. The slow release formulation of Pentasa is preferred for small bowel disease. Asacol is a pH-dependent formulation that gives good delivery of 5-ASA to the terminal ileum.

Budesonide is a steroid with minimal systemic side-effects. This was developed for ileo-caecal Crohn's disease. This has some efficacy as maintenance treatment but is not funded for this indication. Antibiotics have a role in rectal and peri-anal Crohn's disease. Azathioprine has similar efficacy for Crohn's or ulcerative colitis. Methotrexate is probably more effective for Crohn's disease. Infliximab (a monoclonal antibody against TNF-alpha) appears to be much more effective for Crohn's disease but further trials in ulcerative colitis are planned.

Should surgery for Crohn's disease be delayed as long as possible?

Many patients feel in retrospect that they waited too long before embarking on surgery. If the symptoms are obstructive in nature then surgery is the preferred option.

This usually involves a resection (with a conservative approach to resections margins) to maintain as much functional bowel as possible. Another option in some patients with short segments of diseased bowel is stricturoplasty.

The need for surgery in ileocolonic Crohn's disease (the most common site) is approximately 45% at seven years and 80% at 15 years. A symptomatic recurrence after surgery occurs in 35–65% of patients after five years. Endoscopic recurrence occurs much earlier – 70% have ulceration at the anastomosis after 12 months. Azathioprine, high dose 5-ASA (Pentasa) and metronidazole (for two months after surgery) have all been shown to reduce the recurrence rate after surgical resection. However only some patients will benefit from prophylactic treatment,

but the selection of patients in greatest need is difficult as the course of the disease is unpredictable. For patients with severe disease then azathioprine may be the most effective option. For colonic disease the surgical choices are more difficult. Proctocolectomy and ileostomy may be required and is often preferred to segmental excision.

The timing of surgery in ulcerative colitis is a matter of clinical judgement and the personal choice of an informed patient. Sometimes this decision can be unduly delayed. The critical issue is the expected quality of life following surgery compared with quality of life with ongoing medical treatment. The increasing use of azathioprine for ulcerative colitis is tending to decrease the colectomy rate in NZ although exact data is not available.

What is the future of treatment for IBD?

Infliximab (anti-TNF monclonal antibody) is effective treatment for Crohn's disease. There is a clinical response observed in two-thirds of patients but the benefit usually only lasts for two to three months. Sometimes this response is dramatic – this is the only medication that can induce complete endoscopic healing. Maintenance treatment is being advocated in some countries. This may be a way for the future but the cost will need to come down significantly for this to be a viable option in New Zealand. Other monoclonal antibodies look to have significant activity and will become available over the next five to 10 years. A possible view in future will be the use of a range of monoclonal antibodies with the selection of the best option determined by genetic studies.

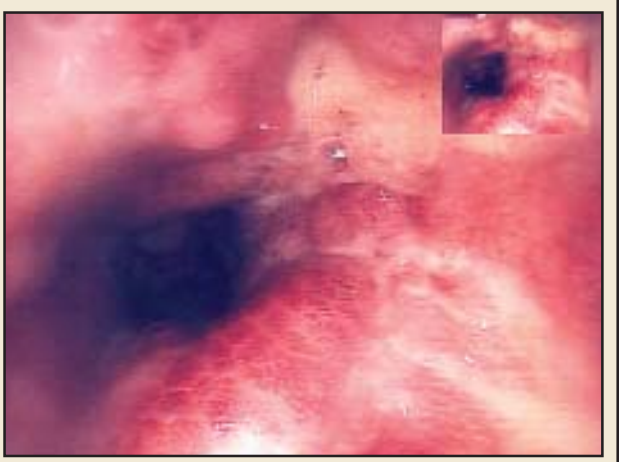
Overall there has been a steady improvement in our use of conventional medication treatment, combined with judicious use of newer agents and surgery, resulting in a better quality of life for our patients.

Case 1

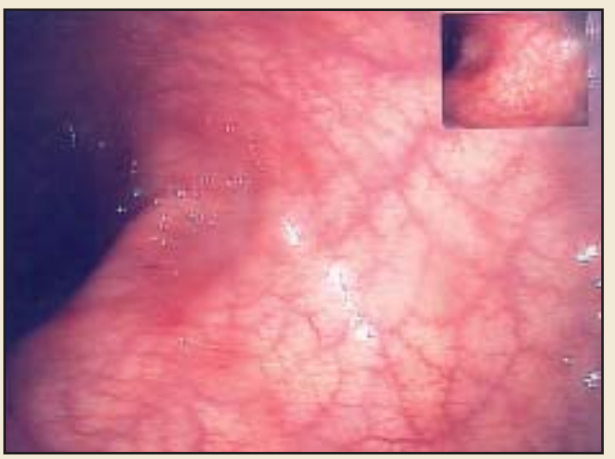
A 35-year-old man known to have ulcerative colitis presents with diarrhoea up to 10 times per day with blood and mucus. He had lower abdominal pain prior to passing a bowel motion. An abdominal examination shows tenderness in the left iliac fossa. Blood tests showed a Hb of 105g/L, ESR 82mm/hr, serum albumin 28g/L. He was admitted to hospital for treatment with intravenous hydrocortisone. There was no response after five days of treatment.

The following endoscopy photos are from his limited colonoscopy during admission. The rectum is relatively normal (the vascular pattern is easily observed). The sigmoid and descending colon show severe inflammation. There is some pseudopolyposis in the sigmoid. There is some deep ulceration in the descending colon - this is only seen in ulcerative colitis when there is severe inflammation and 'sloughing of mucosa'.

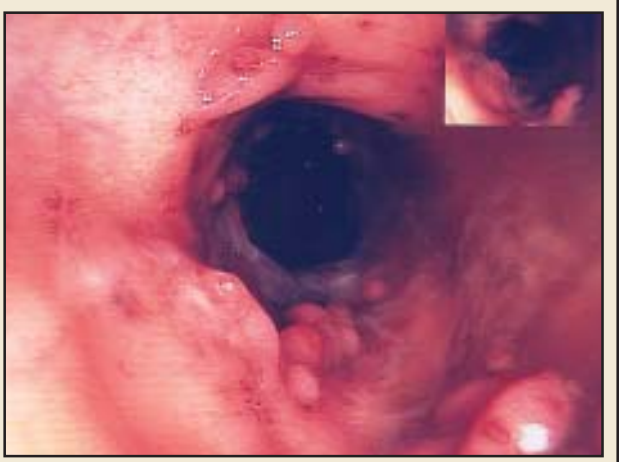
He was treated with cyclosporine for six weeks and changed to azathioprine 150mg daily as long-term maintenance treatment. He has been well without any further relapse for four years.



Descending colon



Rectum

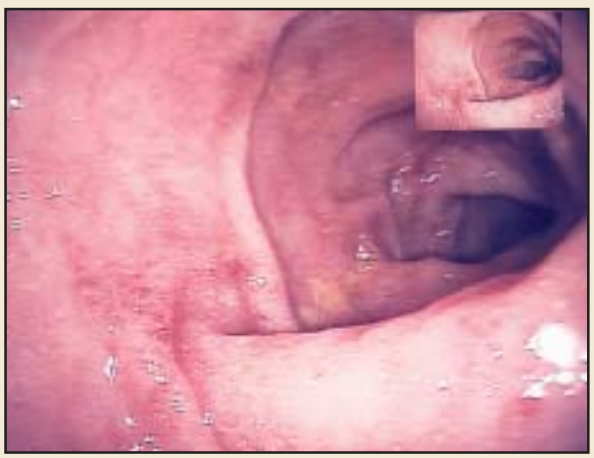


Sigmoid colon

Case 2

A 25-year-old female presents with urgency and increased bowel frequency – passing three to four bowel motions per day with some blood and mucus – over the last three months. The bowel motions are of relatively normal consistency. The abdominal examination is normal. Routine blood tests are normal.

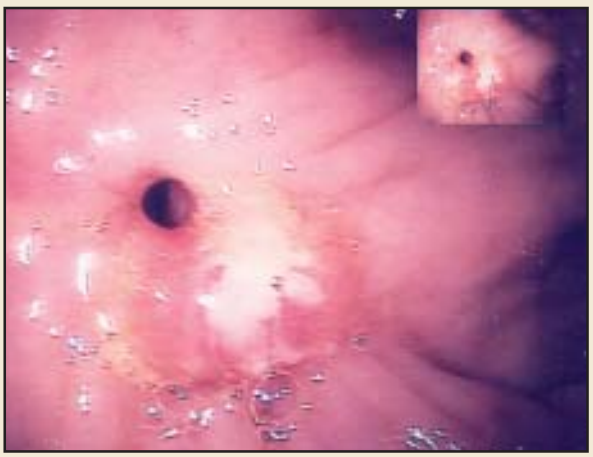
Colonoscopy shows mild inflammation of the rectum only (the photo shows loss of normal vascular pattern and mild patchy erythema). She has an excellent response to the intermittent use of Asacol suppositories and occasional use of Colifoam enemas.



Case 3

A 45-year-old man with Crohn's disease with a previous resection of the terminal ileum and caecum seven years ago presents with central cramping abdominal pain that comes on one hour after meals. The pain is worse with larger meals and usually last for 30–60mins.

The abdominal examination is normal. Blood tests are normal apart from an elevated ESR at 35mm/hr and a raised platelet count at 487x109 (consistent with some activity of the Crohn's disease). Colonoscopy shows a normal colon but at the anastomosis there is recurrent Crohn's disease with stricture formation causing the symptoms of subacute obstruction. The lumen was less than 5mm. Usually this situation requires a further resection of the abnormal segment of small bowel. However for this patient the symptoms were completely resolved with balloon dilatation at the time of colonoscopy.



References

1. Su C, Lichtenstein GR. Recent developments in inflammatory bowel disease. Med Clin Nth Amer 2002; 86:1497–523.
2. Fraser AG, Orchard TR, Robinson EM et al. Long-term risk of malignancy after of inflammatory bowel disease with azathioprine. Aliment Pharmacol Ther 2002; 16:1225–32.
3. Fraser AG, Orchard TR, Jewell DP. The efficacy of azathioprine for the treatment of inflammatory bowel disease. Gut 2002; 50:485–89.
4. Kane S. Inflammatory bowel disease in pregnancy. Gast Clin Nth Amer 2003; 32:323–40.
5. Bone DK, Cho JH. Genetics of inflammatory bowel disease. Gastroenterology 2003; 124:521–6.

General practice and clinical research

'Despite their Cinderella status, most Australian general practice academic units have actively pursued research for over 25 years. But what are the outcomes? Unless research leads to publication, its quality is essentially unknown. Through exposure to public scrutiny, individual research can be independently assessed. If deemed rigorous and relevant, it joins the living literature and may change clinical practice; if deemed inadequate or irrelevant, it lies buried in the grave of the silent literature.'

– Van Der Weyden MB. General practice research in Australia: a timely reality check. MJA 2000; 173:569–570.

'Up until the 1970s, the United Kingdom was internationally recognised for its contribution to characterising diseases by careful examination and testing in patients. However, the development of methods to investigate the molecular and genetic basis of disease has since shifted research away from the bedside and into the laboratory. The surge in activity in molecular science has led to a substantial reduction in both research and researchers in clinical science. Pressure on NHS beds and facilities in teaching hospitals is also pushing out clinical research so that the NHS now has limited capacity to evaluate the new tools that are emerging from academia and industry.'

– Bell J. Resuscitating clinical research in the United Kingdom. BMJ 2003; 327:1041–1043.