Managing inflammatory bowel disease

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Inflammatory bowel diseases, comprising Crohn's disease and ulcerative colitis, usually take on a relapsing–remitting course. In most cases, they can be controlled successfully with medical therapy but sometimes surgery is necessary.

The incidence of inflammatory bowel disease (IBD) has increased considerably in developed Western countries since the Second World War, but is now starting to plateau. IBD can be divided into two major entities: ulcerative colitis and Crohn's disease. Ulcerative colitis involves only the mucosal layer and is limited to the colon, whereas Crohn's disease often results in transmural bowel wall inflammation and can affect any part of the gastrointestinal tract (GIT) from mouth to anus. These disorders have distinct clinical and pathological features, although significant degrees of overlap can make differentiation difficult. The term indeterminate colitis is sometimes used in the initial diagnosis of IBD to define colitis in the absence of specific features of Crohn's disease or ulcerative colitis. Some patients with indeterminate colitis eventually develop a pattern of disease that allows classification into Crohn's disease or ulcerative colitis.

Much research has been dedicated to clarifying the aetiology of IBD, but its pathogenesis remains poorly understood.

Clinical presentations of IBD

The diagnosis of IBD is based on suggestive features in the clinical presentation and relevant investigations. Clues from the patient's history can be missed, especially in the early phases of the disease due to misdiagnosis as irritable bowel syndrome, infective gastroenteritis or, in some cases, an eating disorder. Delay in diagnosis and treatment is not uncommon; the average time to diagnosis can be up to 7.7 years for Crohn's disease.[1] A high index of suspicion for IBD may help avoid such delays.

Ulcerative colitis in adults can have a variable presentation depending on the extent of disease and severity of inflammation. However, it is often easier to diagnose than Crohn's disease because

IN SUMMARY

- **IBD can be difficult to diagnose. The key is to suspect IBD when patients present with chronic gastrointestinal tract (GIT) symptoms that are not easily explained.**
- **The aim of management of IBD is to induce and maintain remission and prevent the long term consequences of GIT inflammation. This is usually achieved medically, but surgery can sometimes be the best option. The avoidance of long term corticosteroid treatment is important.**
- **The management of patients with severe and refractory IBD is changing with the advent of powerful new drugs such as the anti-tumour necrosis factor agents. Multinational, multicentre clinical trials are enrolling suitable patients in many Australian teaching hospitals to study these agents.**
- **IBD is chronic and can be complex. It is best managed in a multidisciplinary way by a gastroenterologist, GP, surgeon and dietitian.**

classically it affects the rectum and distal colon and ascends proximally. Patients with distal disease present with tenesmus, rectal bleeding and loose and frequent bowel motions. Typically, abdominal pain is colicky, focused in the lower abdominal region, associated with tenesmus, and relieved after passage of bowel motion.

Variable manifestations are typical of Crohn's disease, making diagnosis more difficult. Transmural inflammation, variability of extent and severity of disease, and, at times, the nonspecific nature of symptoms mean that the diagnosis of Crohn's disease is often delayed compared with that of ulcerative colitis. Fatigue, abdominal pain (often localised to the right iliac fossa), rectal bleeding, iron deficiency, anaemia, weight loss and fever are consistent with Crohn's disease. Diarrhoea is a feature if the inflammation is more widespread and/or involves the colon. Some patients may be detected initially when they develop a perianal abscess and/or fistula, and Crohn's disease is subsequently diagnosed by colonoscopy.

Patients with ulcerative colitis or Crohn's disease may present initially with extraintestinal manifestations such as arthritis. The typical pattern of bowel disease is one of relapse and remission. Nonresponse to conservative and supportive management should increase the suspicion for IBD. Physical examination may reveal oral ulcerations, abdominal tenderness, perianal disease (fistulae, anal tags or fissures), or a palpable abdominal mass caused by transmural inflammation resulting in a phlegmon in the case of Crohn's disease.

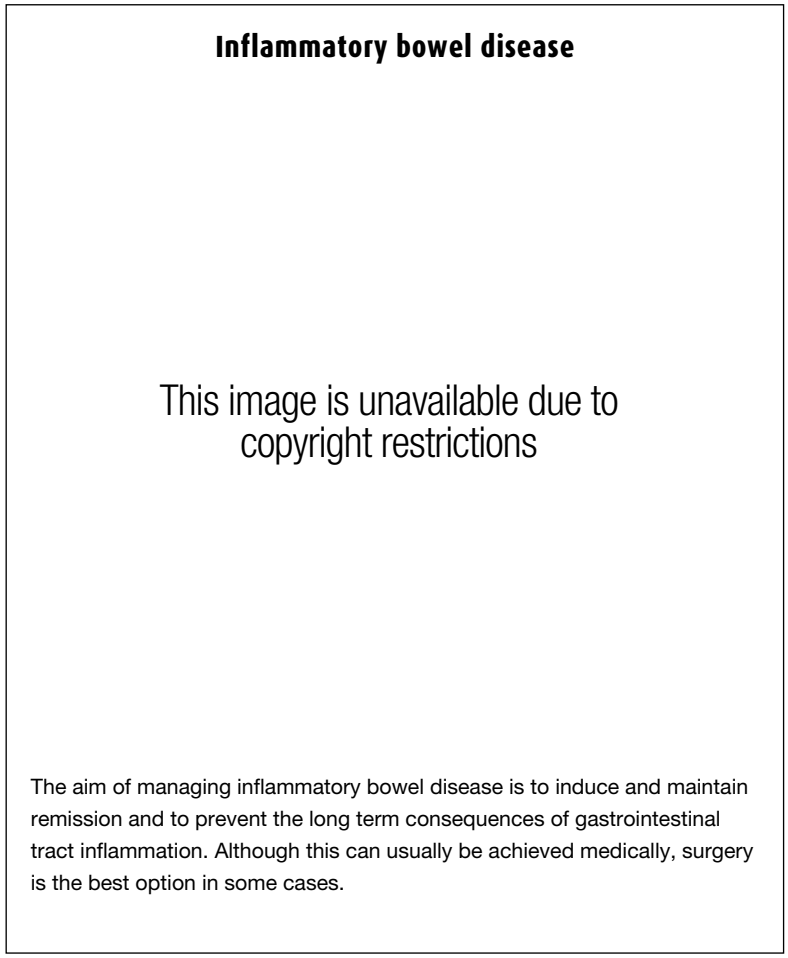
IBD in children and adolescents

There have been reports of an increasing incidence of IBD in the paediatric age group. In addition to the patterns of disease that occur in adults, children and adolescents can present with failure to thrive or significant weight loss.

Risk factors

Patients should be asked about their risk factors for IBD, including whether they have family history of either Crohn's disease or ulcerative colitis, and whether they smoke, which is relevant in the case of Crohn's disease. Appendicectomy, particularly at a young age, has been shown to protect against the development of ulcerative colitis, and probably also Crohn's disease, through unexplained mechanisms.

Inflammatory bowel disease



The aim of managing inflammatory bowel disease is to induce and maintain remission and to prevent the long term consequences of gastrointestinal tract inflammation. Although this can usually be achieved medically, surgery is the best option in some cases.

Investigations in patients suspected of having IBD

There is no single test or clinical presentation that conclusively diagnoses IBD. Investigations should be timely as spontaneous disease remission may result in a false negative test. Referral to a gastroenterologist helps expedite the diagnosis and management of patients with IBD.

Screening blood tests are very useful; abnormal results should alert the clinician to the possibility of IBD over more benign conditions such as irritable bowel syndrome. The presence of anaemia, elevated inflammatory markers (C-reactive protein and erythrocyte sedimentation rate) and iron deficiency in a patient with otherwise sufficient iron

Table 1. Investigations for IBD

Blood tests
- Inflammatory markers (erythrocyte sedimentation rate and C-reactive protein level)
- Full blood count (looking for anaemia and raised white cell count)
- Stool microscopy for erythrocytes and leucocytes

Endoscopy
- Colonoscopy and ileoscopy
- Upper GI endoscopy if appropriate

Histology
- Histological appearance of suspicious GIT mucosa

Imaging
- Plain abdominal x-ray
- Abdominal CT
- Abdominal MRI
- Small bowel enteroclysis
- White blood cell scintigraphy

consumption and without another source of blood loss, are features that support a diagnosis of IBD. Malabsorption associated with terminal ileitis can result in vitamin B_{12} deficiency. Evidence of inflammation is helpful, but its absence should not be a deterrent from further investigations if the clinical suspicion is high. Stool microscopy may reveal the presence of leucocytes and erythrocytes and stool culture should be negative for infectious agents.

Colonoscopy, including ileoscopy, should be performed in all patients suspected of having IBD. Contraindications for colonoscopy are intestinal obstruction and toxic megacolon, and in some cases a flexible sigmoidoscopy may be performed instead, with the colonoscopy postponed until patients improve clinically.

Characteristic endoscopic findings and biopsy histopathology can confirm the diagnosis of IBD, but the histological finding may not be able to differentiate Crohn's disease from ulcerative colitis. Further information regarding the extent and complications of IBD can be provided by imaging studies such as:
- abdominal CT
- MRI
- small bowel enteroclysis (that is, abdominal CT with the small bowel distended with a large amount of water to improve intestinal wall detail)
- white blood cell scintigraphy (in which radionucleotide labelled white blood cells 'home in' on areas of significant inflammation).

CT colonography (virtual CT scan) cannot detect superficial inflammation, erosion and ulceration and, therefore, is of little use in diagnosing IBD. The role of the wireless capsule endoscopy in diagnosing small bowel Crohn's disease remains to be defined but is contraindicated in patients with small bowel strictures.

Chronic ulcerative colitis and Crohn's colitis can result in the development of dysplasia and colorectal cancer. Colonoscopy and dysplasia screening is essential in patients with extensive IBD colitis, beginning eight to 10 years after the onset of symptoms. Only very short segment disease such as proctitis seems to be free of colorectal cancer risk. Chromoendoscopy (the use of dye spray during colonoscopy to highlight possible dysplastic lesions) can further increase the sensitivity of detecting colonic mucosal lesions in dysplasia screening.

Table 1 summarises the relevant investigations for IBD. Some of the characteristic endoscopic, histological and x-ray features of Crohn's disease and ulcerative colitis are show in Figures 1 to 4.

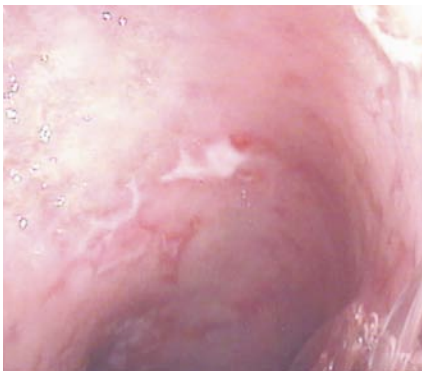


Figure 1. Crohn's disease endoscopy. Aphthoid ulceration on a background of mucosal erythema that tends to be discontinuous causing 'skip lesions'.

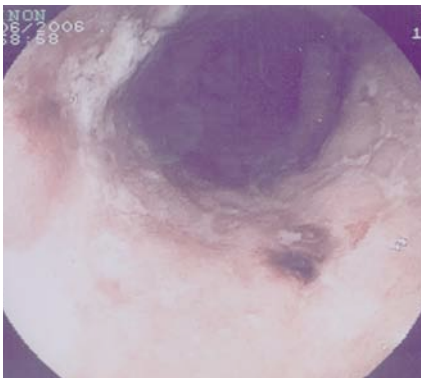


Figure 2. Ulcerative colitis endoscopy. Diffuse inflammation and ulceration of colonic mucosa, which can affect the entire large bowel.

Management of IBD

The three aims of IBD management are to:
- treat the inflammation (induction of remission)
- prevent the recurrence of inflammation (maintenance of remission)
- treat and prevent complications.

Treating the acute inflammation

The clinical manifestations of IBD relate predominantly to inflammation and ulceration of the GIT. Hence, treatment is aimed at controlling the inflammatory response. The approach in treating Crohn's disease and ulcerative colitis is similar.

5-aminosalicylate agents

The mainstay of therapy for ulcerative colitis is topical administration of mesalazine (5-aminosalicylate or 5-ASA) in large

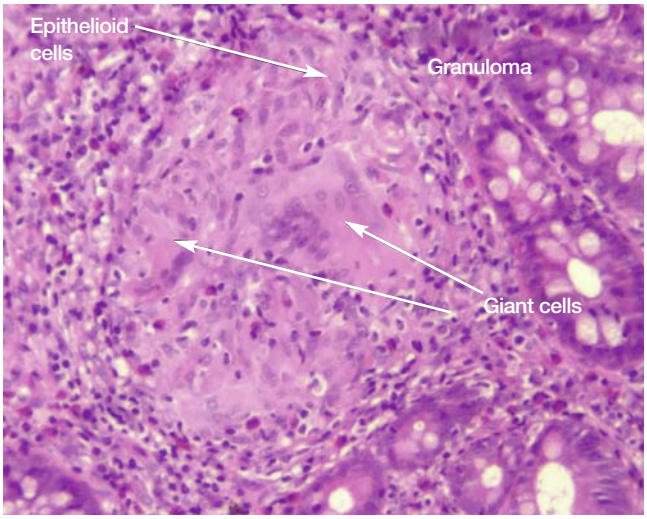


Figure 3. Typical granuloma of Crohn's disease. High powered light micrograph showing central giant cells surrounded by epithelioid cells.

Table 2. Sites of action of 5-ASA agents

Orally administered

- Colon: released by colonic bacterial action
  - mesalazine bound to a carrier molecule: sulfasalazine (Salazopyrin, Pyralin EN) and balsalazide (Colazide)
  - two mesalazine molecules bound together: olsalazine (Dipentum)
- Terminal ileum and proximal colon: pH dependent release
  - coated mesalazine preparations (Mesasal, Salofalk Granules and Tablets)

Rectally administered

- Rectum
  - suppository: mesalazine (Pentasa)
- Proximal sigmoid colon
  - foam: mesalazine (Salofalk Foam Enemas)
- Descending colon
  - enema: mesalazine (Pentasa, Salofalk Enemas)

quantities to the inflamed bowel surface. Mesalazine has broad anti-inflammatory effects, including inhibition of white cell adhesion and release of inflammatory cytokines. Orally ingested mesalazine is rapidly absorbed in the jejunum and, therefore, methods to deliver the drug to its site of action are required. The various preparations of the 5-ASA agents (mesalazine and its prodrugs) differ in terms of their delivery sites, as shown in Table 2.

Topical 5-ASA therapy via rectal administration is beneficial in patients with active distal ulcerative colitis. Again, various manufacturers have preparations that differ in their sites of actions. Use of a combination of oral and rectal 5-ASA agents is more effective than using either type alone in the treatment of distal disease.[2] These agents typically require about three to six weeks to exert their maximal effect.

In Crohn's disease, orally administered 5-ASA agents may be useful for patients with mild to moderate disease.

Corticosteroids

Conventional corticosteroids are very effective for the rapid induction of clinical remission but have no role in the maintenance of remission (Table 3). Intravenous corticosteroids are particularly useful for managing severe flares. Rectal corticosteroids have less systemic side effects than parenteral corticosteroids but are less efficacious than rectal mesalazine in the treatment of ulcerative colitis.[3]

Corticosteroid dosages are tapered slowly following the introduction of immunomodulators such as azathioprine and methotrexate (see below). In some patients, IBD may be controlled only by moderately high doses of corticosteroids; surgery should be considered in such patients (see below).

Treatment with oral budesonide capsules (Entocort), a corticosteroid with a high first pass metabolism and low systemic side effects,[4] can be considered in corticosteroid dependent patients. Budesonide has been shown to be almost as effective as conventional corticosteroids for induction of remission in patients with terminal ileal and/or ascending colon Crohn's disease but no better than placebo beyond one year's treatment.[5,6]

Other agents

- **Antibiotics.** Courses of antibiotics (metronidazole [Flagyl, Metrogyl, Metronide] and ciprofloxacin) are occasionally effective for subtypes of Crohn's disease, including perianal disease.

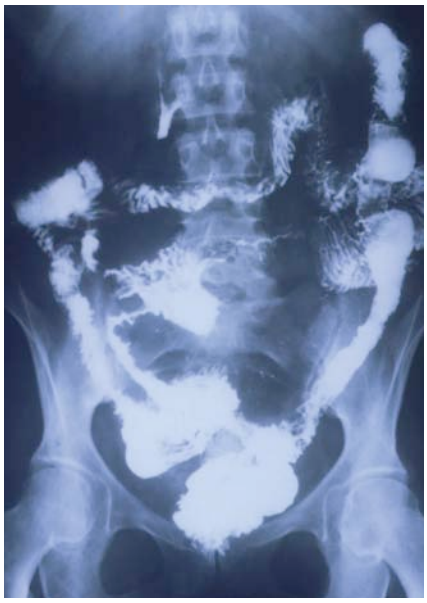


Figure 4. Abdominal barium x-ray showing small bowel strictures of Crohn's disease.

- **Anti-tumour necrosis factor (TNF) therapy.** New 'biologic' agents such as anti-TNF therapy (and in particular the monoclonal antibody infliximab [Remicade]) have markedly improved the ability to suppress inflammation in the GIT (Table 4). Infliximab, currently indicated for moderate to severe Crohn's disease refractory to traditional therapy and fistulising Crohn's disease, is not yet listed on the PBS. It is also effective in treating some extraintestinal manifestations of IBD and was shown recently to be effective in the treatment of ulcerative colitis. Infrequent severe adverse effects mean that such agents must be used cautiously in selected patients. Other anti-TNF agents, including adalimumab (Humira) and certolizumab, are currently undergoing clinical trials in patients with IBD.

Table 3. Corticosteroids for IBD: major features

Oral prednisolone or prednisone

- Rapidly shuts off the inflammatory cascade by attaching to glucocorticoid receptor
- Potent corticosteroid side effects (weight gain, osteoporosis, glucose intolerance, mental disturbance, hypertension)

Oral budesonide (Entocort)

- High affinity for glucocorticoid receptor but low systemic activity due to extensive first pass metabolism in the liver

Rectal prednisolone (Predsol) and hydrocortisone (Colifoam)

- Topical delivery of corticosteroid for distal disease
- Topical budesonide not yet available

Surgery

Surgery for ulcerative colitis represents an opportunity for 'cure' and involves removal of the entire colon and rectum, with the formation of an ileal pouch and reanastomosis with the anus (Table 5). The most common indications for surgery are:

- persistent symptoms despite high dose corticosteroids and corticosteroid dependence
- progression of disease despite maximal medical therapy
- colonic dysplasia (pre-cancer) or malignant transformation
- other complications, including failure to thrive and toxic megacolon.

Mortality and morbidity of surgery are low. Common long term complications include:

- day time incontinence that can affect daily activities
- pouchitis in about 30% of cases (this may be treated with antibiotics or probiotics and occasionally re-operation is needed)

Table 4. Infliximab for IBD

Features

- Chimeric monoclonal antibody (part human, part mouse)
- Inhibits binding of TNF to its receptor
- Treatment results in a rapid improvement in endoscopic and histological features of Crohn's disease

Main adverse effects

- Mortality of 1% secondary mainly to opportunistic infection
- Reactivation of tuberculosis or hepatitis B
- Development of autoantibodies
- Possible increased long term risk of malignancy, particularly lymphoma
- reduction in fecundity and impotence.

Most studies show that patients experience overall satisfactory long term functional outcomes and excellent quality of life.[7,8]

Crohn's disease can affect any part of the GIT. It often recurs at the site of intestinal anastomosis, and is not therefore curable by surgery. Surgery is reserved for patients with complications or symptoms refractory to medical therapy. Major indications for surgery are obstruction or perforation in small intestinal Crohn's disease. As little bowel as possible should be resected to avoid short bowel syndrome (Table 5). Laparoscopic techniques are being used increasingly, with good success and lower morbidity. In some patients, surgery may be the most efficient way of restoring quality of life and health.

Admission to hospital

Patients with severe ulcerative colitis can have frequent bloody stools (up to 10 to 15 per day), associated with weight loss, dehydration, fever and significant anaemia, and need to be managed in hospital. In a subset of these patients, the ulcerative colitis will progress to toxic megacolon, which is pathological dilatation of the colon with a high risk of perforation and mortality. Urgent treatment with fluid resuscitation, bowel rest, nutritional support including total parenteral nutrition, intravenous corticosteroids, cyclosporin (Cicloral, Cysporin, Neoral, Sandimmun), biologic therapies or colectomy may be required.

Patients with Crohn's disease may have similar complications to those with ulcerative colitis, but may also manifest with intestinal obstruction, perforation, fistulas and abscesses.

Maintaining remission

Smoking

It is now well established that smoking is detrimental to patients with Crohn's disease, and smoking cessation is a critical

component of effective therapy. Smoking doubles the risk of Crohn's disease.[9] Risk of disease recurrence is also increased in smokers, and some studies have suggested that there is a decreased risk of flares in smokers who quit smoking.[10,11] Smoking also reduces the efficacy of infliximab.

Azathioprine

Azathioprine and its metabolite 6-mercaptopurine (Puri-Nethol) can exert a steroid sparing effect (Table 6). They are useful in patients with chronically active disease who have frequent relapses despite adequate doses of 5-ASA agents. Both drugs have been used safely for many years in patients with IBD or various autoimmune disorders.

Methotrexate

Methotrexate administered by weekly intramuscular or subcutaneous injection is an alternative immunomodulator for patients who are unresponsive to or intolerant of azathioprine or 6-mercaptopurine. Oral methotrexate can have variable bioavailability. The results of liver function tests and full blood counts need to be monitored and referral to an appropriate specialist made if significant abnormalities occur. Folate replacement is required to reduce methotrexate toxicity but should be taken on a different day from the injection.

5-ASA agents

5-ASA agents reduce the chance of relapse by 60% in patients with ulcerative colitis and can be used long term. In addition, they exert a chemopreventative effect, reducing the risk of development of colorectal cancer. There is less evidence for their efficacy in maintaining remission from Crohn's disease.

Probiotics

Enteric flora may have a pathogenic role in bowel inflammation. However, more studies are required before probiotics can be recommended for the treatment of IBD. Limited data suggest a probiotic preparation (VSL#3) may be of benefit in primary and secondary prevention of pouchitis in patients with ulcerative colitis who have undergone total colectomy with ileal pouch formation.[12]

Table 5. Surgical procedures for IBD

Ulcerative colitis
• Colectomy and ileal pouch formation
• Proctocolectomy with ileostomy
• Colectomy with ileorectal anastomosis
Crohn's disease
Duodenal disease
• Stricturoplasty, duodenojejunostomy, endoscopic balloon dilatation
Small bowel disease
• Fistulas: resection and anastomosis of diseased segment
• Strictures: resection, stricturoplasty or balloon dilatation
Colorectal disease
• Segmental colectomy for limited disease
• Proctocolectomy for extensive, diffuse colorectal disease
Severe anorectal disease
• Abdominoperineal resection with permanent end-colostomy

Table 6. Azathioprine and 6-mercaptopurine for IBD

Features
• Azathioprine is prodrug that is converted to 6-mercaptopurine
• 6-mercaptopurine is metabolised by the liver to the active metabolite 6-thioguanine nucleotides
• Both inhibit purine synthesis and ultimately DNA and RNA synthesis
• Both inhibit proliferation of T and B lymphocytes
• Precise mechanism in IBD is unknown
Main adverse effects
• Dose dependent bone marrow depression and liver dysfunction
• Pancreatitis
• Drug fever or rash
• Pneumonitis
• Infections
• Cancer risk (low)

Treating and preventing complications

Nutrition

Good nutrition is essential in managing patients with IBD. Chronic IBD may result in malabsorption of vitamins (including vitamins D and B_{12}) and minerals, and iron deficiency and osteoporosis are common. Supplementation with vitamins and minerals may be required.

Dietary modifications in active disease may include a low lactose and fructose diet to reduce diarrhoea, and a low fibre diet in patients with Crohn's disease strictures and intestinal narrowing.

Fertility and pregnancy

Pregnancy outcomes are improved if conception and pregnancy occurs during maternal remission of IBD. Therefore, in women with difficult to manage IBD, maintenance medical therapy during pregnancy may be indicated. Referral of such patients to a gastroenterologist and obstetrician is highly recommended. Most studies do not show reduced fertility in men and women with IBD compared with that of the general population.[13] Modifications in therapy should be balanced against the risk of low birthweight infants in women who have active IBD during pregnancy.

- **5-ASA agents.** Sulfasalazine treatment

continued

IBD internet resources

Australian Crohn's and Colitis Association
www.acca.net.au
Gastroenterological Society of Australia
www.gesa.org.au

can be safely continued throughout pregnancy and nursing. Limited experience with newer 5-ASA agents suggests that they are safe in pregnancy. At therapeutic doses, 5-ASA agents result in very low serum concentrations and have not been associated with constriction of the ductus arteriosus.[14] Sulfasalazine causes oligospermia in more than 80% of males. This is reversible within two months of discontinuing treatment and is not seen with other 5-ASA agents.

- **Corticosteroids.** The risk associated with corticosteroid therapy during pregnancy is small, and these medications should not be withheld if clinically indicated. A very small amount of prednisolone and its metabolite prednisone is excreted in breast milk and is of little significance.
- **Azathioprine and 6-mercaptopurine.** Extensive favourable experience with azathioprine in renal transplant patients and pregnancy suggest that this immunomodulator can be continued during pregnancy if indicated. There are less data on 6-mercaptopurine, but clinical evidence supports its safety in pregnancy. As both of these agents are detectable at low levels in breast milk, mothers taking either of them should be discouraged from breastfeeding. A small study recently suggested paternal use of azathioprine or 6-mercaptopurine may be associated with an increase in congenital malformations.[15] Men should probably stop these agents three months before conception until this issue is clarified.
- **Methotrexate.** Methotrexate is a potent abortifacient and teratogen. Both men and women should cease this drug and delay conception for at least three months.
- **Infliximab.** Experience with infliximab during pregnancy is limited. Retrospective reviews of women given infliximab during pregnancy have not shown an increase in adverse outcomes compared with those of the general population.[16] Its excretion into breast milk is currently unknown.
- **Antibiotics.** Short courses of metronidazole are often used during pregnancy

and are safe. Ciprofloxacin can cause arthropathy in the fetus and should not be used during pregnancy. Both antibiotics are excreted in breast milk and are not recommended during nursing.

Colorectal cancer risk

Patients with IBD are at increased risk of colorectal cancer, and this is dependent on the duration and anatomical extent of the disease.[17,18] Patients with ulcerative colitis and primary sclerosing cholangitis have the highest risk of cancer, but colonic Crohn's disease probably has a comparable risk.[19] Although there is no clear evidence that surveillance colonoscopy prolongs survival, detection of early lesions leading to surgical resection decreases the risk of death from IBD associated colorectal cancer.[20] As mentioned previously, it is recommended that all patients with IBD have regular colonoscopic surveillance starting eight to 10 years from diagnosis and repeated every one to two years thereafter depending on histological findings.

Chemoprophylaxis with 5-ASA agents has been shown to reduce the risk of colorectal cancer by 50% in patients with ulcerative colitis,[21] thus reinforcing the need to maintain patients on such therapy. Some studies suggest folate supplementation may prevent colorectal cancer.

Conclusion

Patients with IBD are often young, and dealing with a chronic illness can be overwhelming. Disease education and ongoing support for patients is an integral part of treatment. Patients and families can be referred to organisations such as the Australian Crohn's and Colitis Association (ACCA) for support and educational material (see the box on page 22).

GPs are critical in first suspecting the disease, and subsequently in supporting patients in their lifelong journey. An experienced gastrointestinal surgeon becomes involved when complications requiring surgery develop and should be consulted early. A dietitian is essential, especially if patients have issues regarding malnutrition, dietary modifications and the prevention of osteoporosis. Management should be initiated and steered by a specialist experienced in IBD such as a gastroenterologist. Most patients should achieve a satisfactory and near-normal outcome under such a model of care. MT

A list of references is available on request to the editorial office.

DECLARATION OF INTEREST: None.

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References

1. Pimentel M, Chang M, Chow EJ, et al. Identification of a prodromal period in Crohn's disease but not ulcerative colitis. 2. Am J Gastroenterol 2000 95; 12: 3458-3462.
2. Marteau P, Gassul M, Befrits R, et al. Combined oral and enema treatment with Pentasa (mesalazine) is superior to oral therapy alone in patients with extensive mild/moderate active ulcerative colitis: a randomised, double blind, placebo controlled study. Gut 2005; 54: 960-965.
3. Marshall JK, Irvine EJ. Rectal corticosteroids versus alternative treatments in ulcerative colitis: a meta-analysis. Gut 1997; 40: 775-781.
4. Lofberg R, Danielsson A, Suhr O, et al. Oral budesonide versus prednisolone in patients with active extensive and left-sided ulcerative colitis. Gastroenterology 1996; 110: 1713-1718.
5. Otley A, Steinhart AH. Budesonide for induction of remission in Crohn's disease. Cochrane Database Syst Rev 2005; (4): CD0000296.
6. Hanauer S, Persson T, Sandborn W, Persson A. Budesonide as maintenance treatment in Crohn's disease: a placebo controlled trial. Aliment Pharmacol Ther 2005; 21: 363-371.
7. Fazio VW, O'Riordan MG, Lavery IC, et al. Long-term functional outcome and quality of life after stapled restorative proctocolectomy. Ann Surg 1999; 230: 575-584.
8. Michelassi F, Lee J, Rubin M, et al. Long-term functional results after ileal pouch anal restorative proctocolectomy for ulcerative colitis: a prospective observational study. Ann Surg 2003; 238: 433-441.
9. Silverstein MD, Lashner BA, Hanauer SB, Evans AA, Kirsner JB. Cigarette smoking in Crohn's disease. Am J Gastroenterol 1989; 84:31-33.
10. Cosnes J, Beaugerie L, Carbonnel F, Gendre JP. Smoking cessation and the course of Crohn's disease: an intervention study. Gastroenterology 2001; 20: 1093-1099.
11. Sutherland LR, Ramcharan S, Bryant H, Fick G. Effect of cigarette smoking on recurrence of Crohn's disease. Gastroenterology 1990; 98: 1123-1128.
12. Gionchetti P, Rizzello F, Venturi A. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. Gastroenterology 2000; 119: 305-309.
13. Ostensen M, Ramsey-Goldman R. Treatment of inflammatory rheumatic disorders in pregnancy: what are the safest treatment options? Drug Saf 1998; 19: 389-410.
14. Diav-Citrin O, Park YH, Veerasuntharam G, et al. The safety of mesalamine in human pregnancy: a prospective cohort study. Gastroenterology 1998; 114: 23-28.
15. Norgard B, Rasmussen SN, Sorensen HT, Pedersen L, Jacobsen J. The risk of congenital abnormalities in children fathered by men treated with azathioprine or mercaptopurine before conception. Aliment Pharmacol Ther 2004; 19: 679-685.
16. Smith D, Jacobs S, Antoni C, Keenan G, Lichtenstein G. Outcome of pregnancy in women receiving infliximab for the treatment of Crohn's disease and rheumatoid arthritis. Am J Gastroenterol 2005; 99: 2385-2392.
17. Ekbom A, Helmick C, Zack M, Adami HO. Ulcerative colitis and colorectal cancer: a population based study. N Engl J Med 1990; 323: 1228-1233.
18. Ekbom A, Helmick C, Zack M, Adami HO. Increased risk of large-bowel cancer in Crohn's disease with colonic involvement. Lancet 1990; 336: 357-359.
19. Softley A, Clamp SE, Watkinson G, Bouchier IA, Myren J, de Dombal FT. The natural history of inflammatory bowel disease: has there been a change in the last 20 years? Scand J Gastroenterol 1988; 144 (Suppl): 20-23.
20. Choi PM, Nugent FW, Scoetz DJ Jr, Silverman ML, Haggitt RC. Colonoscopic surveillance reduces mortality from colorectal cancer in ulcerative colitis. Gastroenterology 1993; 105: 418-424.
21. Velayos FS, Terdiman JP, Walsh JM. Effect of 5-aminasalicylate use on colorectal cancer and dysplasia risk: a systematic review and metaanalysis of observational studies. Am J Gastroenterol 2005; 100: 1345-1353.