Graham Morrison
MBBCh, MRCP, is IBD Fellow, Department of Gastroenterology, Box Hill Hospital, Melbourne, Victoria. gmorrison2001@hotmail.com

Belinda Headon
is IBD nurse specialist, Department of Gastroenterology, Box Hill Hospital, Melbourne, Victoria.

Peter Gibson
MBBS, is Professor of Medicine and Gastroenterology, Department of Gastroenterology, Box Hill Hospital and Department of Medicine, Monash University, Melbourne, Victoria.

Update in inflammatory bowel disease

Background
Inflammatory bowel disease (IBD) is a common disease in Australia and frequently encountered in primary care. Major developments in investigation and management have taken place.

Objective
This article aims to review some recent breakthroughs in IBD investigation and management.

Discussion
Diagnosis involves a changing combination of enhanced traditional techniques with new diagnostic tools, typically blood and stool testing with improved endoscopy and new radiological tests. Management has seen the introduction of new powerful biologic therapies, greater understanding in the way we use older therapies, and a focus on preventing complications such as malignancy or infection. Treatment philosophy now attempts to alter the natural history of the disease and prevent long term complications. The importance of associated, previously overlooked factors is being increasingly recognised. Only by taking a long term, patient centred multidisciplinary approach will an optimal outlook for the majority of patients with IBD be achieved.

Inflammatory bowel disease (IBD) refers to a group of conditions characterised by inflammation in the intestinal tract. Crohn disease (CD) and ulcerative colitis (UC) account for the majority of these conditions. The aim of this article is to review recent breakthroughs in IBD investigation and management. Several other comprehensive reviews and position statements are also available.[1–4]

How common is IBD?

Inflammatory bowel disease is common and increasing in prevalence. Recent population studies indicate it is as common in Australia and New Zealand as other parts the world[5,6] and prevalence is increasing in Asia.[7] What this means to general practice is that IBD is more common than epilepsy or road traffic accidents, and as common as type 1 diabetes or schizophrenia. It is a major workload burden for the health care system and a global economic burden.[8]

The changing face of investigation

A combination of noninvasive testing with endoscopy and/or imaging is usually required and how these tests are being performed is changing.

Noninvasive tests

Blood tests provide clues but are not specific for IBD. Many new or not so new serological tests, such as anti-saccharomyces cerevisiae antibody (ASCA) and atypical perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) are being used.[9] However, they cannot differentiate UC from CD alone and can be considered at best as 'supportive evidence' when the diagnosis is uncertain.

A good marker of inflammation is needed. C-reactive protein (CRP) levels have been shown to correlate with clinical, endoscopic and histologic disease activity and persistent elevation is associated with a higher relapse rate and better response to infliximab.[10] However, some patients will not mount a CRP response to intestinal

inflammation[11] so CRP is a useful marker if elevated, but care must be taken in interpreting a normal value when clinical suspicion of active inflammation exists. Calprotectin and lactoferrin (neutrophil derived proteins in the stool as a result of inflammation) are faecal markers that show promise as a way of excluding intestinal inflammation.[9]

Endoscopy – keeps getting better

Ileocolonoscopy and biopsy remain the gold standard for diagnosis of colonic and terminal ileal disease, and will usually confirm the diagnosis. The instruments themselves have considerably improved over recent years, both in their ease of use and ability to provide good mucosal images. The vast majority of colonoscopies now include visualisation of the terminal ileum, of key diagnostic importance if IBD is suspected and monitoring patients with known IBD. Further improvements in the quality and diagnostic ability of the endoscopic image have been the subject of many technological developments (*Table 1*). In IBD, only chromoendoscopy has entered routine practice in surveillance for preneoplastic lesions.[12]

Techniques to endoscope the last frontier of the gut – the small intestine, have moved ahead considerably. Wireless capsule endoscopy (WCE or 'pillcam'), where patients swallow a capsule that provides images as it passes through the small bowel, is now available and experience in interpreting findings is growing. Double balloon enteroscopy offers the possibility of complete diagnostic and therapeutic access to the entire small bowel. Currently, the availability of both these techniques is limited by high costs.

Imaging – what's in and what's out

Barium imaging of the gut is now rarely used in IBD and has been replaced by colonoscopy. Small bowel barium studies are too insensitive and unreliable and have been replaced by enterography (where contrast is swallowed) or enteroclysis (where the contrast is infused via a nasogastric tube) with imaging via computerised tomography (CT) (*Figure 1, 2*)[13] or magnetic resonance (MRI).[14] Enteroclysis is probably superior, but many patients do not tolerate the nasogastric tube.[13]

Table 1. Endoscopic image enhancing techniques used in IBD colonoscopic surveillance

Technology	Principle	Indication	Advantages	Disadvantages
Chromoendoscopy	Application of dye (eg. indigo carmine) during endoscopy	Highlight dysplastic tissue	Evidence supporting dysplasia pick up	• Time consuming • Preparation of dye
Narrow band imaging	Reflected light of varying wavelength used (via optical filter) to visualise structure and vasculature within mucosa	Highlight dysplastic tissue	• Noninvasive • No dye • Ease of use ('push button on endoscope')	• Conflicting evidence to date • Expense of new equipment
FICE®/iScan®	Similar to NBI but no filter required	Highlight dysplastic tissue	• Noninvasive • No dye • Ease of use	• Limited evidence • Expense • New technique
Confocal laser endoscopy (An Australian invention)	Imaging microscope in tip of scope or via working channel	'Real time' histology – a 'virtual biopsy'	Immediate histologic assessment	• Limited evidence • Expense • Additional training • Only able to visualise small areas at once

Figure 1. Coronal CT enteroclysis showing small bowel thickening and Crohn stricture

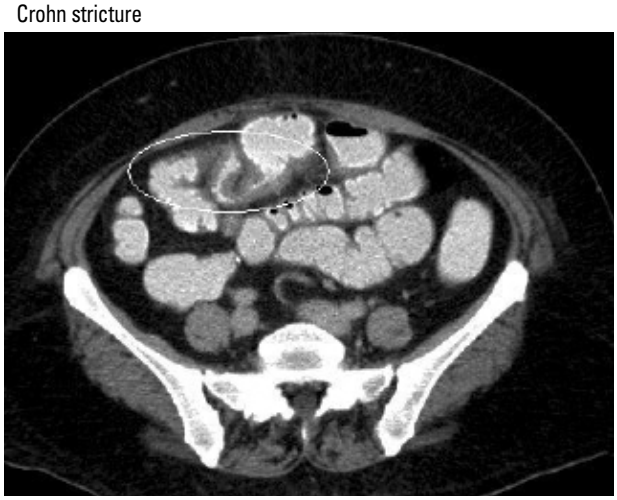
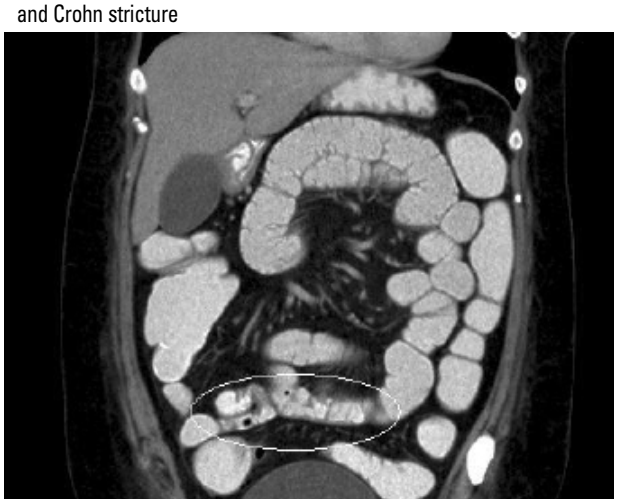


Figure 2. Sagittal CT enteroclysis showing inflamed distal small bowel and Crohn stricture



Medical management – the old and the new

Old drugs used better

Aminosalicylates

5-amino salicylic acid drugs (*Table 2*) are the standard treatment for induction and maintenance of remission in mild to moderate UC.[1,3] Their place in the management of intestinal inflammation in CD is controversial.[15] They are well tolerated by most people with a low rate of adverse events. Comparative trials have not clearly defined which preparation should be used in specific situations and choice largely comes down to clinician experience or patient preference.

Rectally administered 5-ASA is more effective than rectal corticosteroid or oral 5-ASA for proctitis and left sided UC.[16] When used orally, it is generally believed there is a dose dependent response for 5-ASA drugs, particularly for active disease. However, the evidence base for this is small and involves preparations not marketed in Australia. Nevertheless, higher oral doses are anecdotally effective when efficacy is inadequate on standard doses.

The drugs certainly work better if actually taken; studies show 5-ASA drugs (especially in maintenance) have a relatively low compliance rate.[17] Recent trials have clearly demonstrated that, for UC, once daily delivery is as effective as twice daily, which may improve compliance.[18–20] An additional reason for using 5-ASA drugs is the concept of chemoprevention of colorectal cancer.[21]

Immunomodulators

The main immunomodulators in use in IBD patients are thiopurines (azathioprine, 6-mercaptopurine) and methotrexate. They are the mainstay of treatment in maintenance therapy for patients with more than mild CD and for chronically active or frequently relapsing UC where 5-ASA drugs have failed.[4] The slow escalation of therapeutic effects of the drugs (at least 3 months for each) is an essential factor in decision making, and optimal use should be ensured before moving to new expensive therapies.

Figure 3. Thiopurine metabolite reference ranges and interpretation

Thiopurine metabolite measurement

Metabolite	Reference range (units: pmol/8 x 10^8 RBCs)
6-thioguanine nucleotide (6-TGN)	235–450
6-methylmercaptopurine (6-MMP)	<5700

Thiopurine metabolite result interpretation

Metabolite result	Very low/absent 6-TGN Very low/absent 6-MMP	Low 6-TGN Low 6-MMP	Low 6-TGN High 6-MMP	Therapeutic 6-TGN Therapeutic 6-MMP
Interpretation	Noncompliance	Under dosing	Thiopurine resistance	Thiopurine refractory

Table 2. 5-ASA drug preparations available via the PBS in Australia

Generic name	Brand name	Formulation	Oral/rectal	Strength	Daily dose	Site of delivery	Authority
Sulfasalazine	Salazopyrin®	Tablet	Oral	500 mg	2–4 g	Colon	No
Balsalazide	Colazide®	Capsule	Oral	750 mg	4.0–6.75 g	Colon	Streamlined
Olsalazine	Dipentum®	• Capsule • Tablet	Oral Oral	250 mg 500 mg	1–3 g	Colon	Streamlined
Mesalazine	Mesasal®	Tablet	Oral	250 mg	1.5–3.0 g	Ileum and colon	Streamlined
	Pentasa®	• Granules • Granules • Tablet • Enema • Suppository	 Oral Rectal Rectal	1 g 2 g 500 mg 1 g 1 g	 2–4 g 1 g 1 g	Duodenum, jejunum, ileum and colon Recto-sigmoid Rectal	Streamlined Streamlined No
	Salofalk®	• Granules • Granules • Granules • Tablet • Enema • Enema • Foam	 Oral Rectal 	500 mg 1 g 1.5 g 500 mg 2 g 4 g 1 g	 1.5–3.0 g 2 g 4 g 1 g	 Ileum and colon Recto-sigmoid 	 Streamlined Streamlined

Table 3. TNFα antagonists used in inflammatory bowel disease

Drug	Brand name	Class	Administration	Dose	Induction	Maintenance
Infliximab	Remicade®	Anti-TNF (chimeric)	Intravenous infusion	5 mg/kg	0, 2 and 6 weeks	Every 8 weeks
Adalimumab	Humira®	Anti-TNF (fully humanised)	Subcutaneous injection	See induction and maintenance	Week 0, 160 mg Week 2, 80 mg	40 mg fortnightly from week 4
Certolizumab (not available in Australia)	Cimzia®	Anti-TNF (pegylated humanised)	Subcutaneous injection	400 mg	0, 2 and 4 weeks	Every 4 weeks

Getting the dose right is key to optimal efficacy. Traditionally, weight based dosing with regular checks on toxicity (neutrophil count and liver function tests) has been used to guide dosage. Measuring thiopurine metabolites (*Figure 3*) has enabled the heterogeneity in the metabolism of these drugs across individuals to be taken into account and has improved the fine tuning of dosage to achieve better efficacy and safety.[22]

Methotrexate is now being increasingly used in patients with IBD. Its efficacy in CD has been demonstrated.[4] In UC however, the appropriate randomised controlled trials have yet to be done and evidence for efficacy is based upon observational studies only.[23] Because absorption after oral dosing is highly variable, the preferred route of administration is subcutaneous, usually commencing with 25 mg/week, adjusted accordingly.[23]

New drugs – the biologic therapies

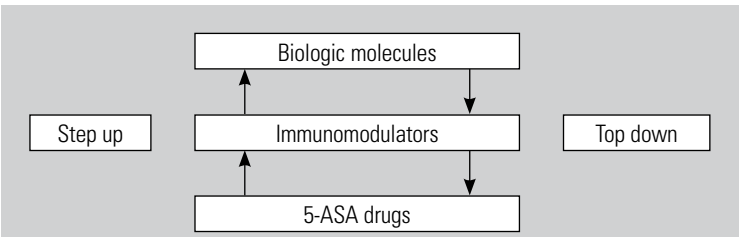
Biologic therapies are drugs directed against specific molecules in the inflammatory pathways involved in IBD. While many are under development, two are available via the Pharmaceutical Benefits Scheme (PBS) for Crohn disease (*Table 3*). Both bind tumour necrosis factor alpha (TNF) and have efficacy for luminal, perianal and fistulising CD.[4] Infliximab has efficacy in UC[24] but is not funded by the PBS. In general, they are used for induction (to get disease under control) and long term maintenance of moderate to severely active disease which has not responded to conventional treatment. Current controversies in their use evolve around the need for concurrent immunomodulatory therapy which, on the one hand, increases the risk of serious infection (though still uncommon), but on the other, improves efficacy and the likelihood of durable response. Decisions rest with each patient's circumstances, but most clinicians continue concurrent immunomodulators for the first 6 months of therapy.

Treatment philosophy and keeping it safe

Planning treatment for patients with IBD now looks toward long term outcomes not just acute care. This implies changing the natural history of the disease by preventing disease progression and avoiding treatment complications.[4,25] For example, steroid use has changed dramatically. Steroids are rapidly effective for inducing remission in IBD, and are cheap and readily available. However, they are not effective or recommended for maintenance therapy and are associated with several serious complications in the short and long term.[26] Yet, in CD, it has been 'traditional' to use steroids as monotherapy and observe the behaviour of the individual's disease. After 2–3 relapses (treated with steroids) immunomodulators would be introduced, the 'step up' approach (*Figure 4*). The outcome of this approach was to have a high proportion of patients dependent on, or unable to stop taking, steroids at 12 months. This led to the concept of using immunomodulators as 'steroid sparing agents'. It is now known that the disease is more responsive to therapy early in its time course and relative resistance to therapies increases with time. This has led to 'top down' therapy – the initiation of efficacious long term strategies from a diagnosis of CD.[27] The idea is that controlling the disease process early (when it is more amenable to treatment) prevents resistance to therapy and subsequent escalation, complications, and the need for surgery. Such an approach will alter the natural history of the disease and reduce the need for steroids (and their adverse effects). There is short term evidence that such strategies are successful.[28,29]

However, more aggressive therapy introduces risk from the drugs used (especially infection and malignancy), and this must be considered in balance with the risk from ongoing disease activity

Figure 4. Top down versus step up strategies in IBD management



What the 'top' of the top down approach should be is still under debate but usually implies use of biological molecules from the outset. This means starting biologics on first presentation in an attempt to change the history of the disease and ensure healing. It is not currently in widespread practice and most patients are managed by starting at the bottom of the treatment pathway (step up) and moving to stronger therapy based on poor symptom control and/or evidence of active disease. The main use of top down is in the first presentation of acute severe disease where biologic therapy can be used as a 'bridge' to maintenance therapy (usually an immunomodulator)

Rapid escalation of therapy to gain effective disease control should be the strategy from the point of diagnosis

for each patient. There has been a major push to upgrade the efforts by clinicians to prevent infection in patients on immunomodulating drugs. This was prompted by poor outcomes (including death) from reactivation of serious infections, particularly tuberculosis, and opportunistic infections in patients on anti-TNF drugs.[30,31] Patients and health care staff must be aware of the need for prompt medical attention and investigation if the suspicion of infection arises while on biologic therapy. Combination drug therapy, particularly where steroids are used in moderate or high doses, carries the greatest risk of severe infection.[30]

Given the risks of infection, vaccination and screening have become important issues in IBD (*Table 4*). This includes:

- screening for tuberculosis and hepatitis B infection before initiating therapy
- checking immunisation/past infection status of relevant viruses (eg. varicella zoster)
- ensuring vaccination for influenza and pneumococcus, and
- advice regarding travel (eg. avoid travelling to areas where tuberculosis is endemic if taking an anti-TNF agent).

Emerging evidence suggests women with IBD on immunosuppression have a higher risk of an abnormal Pap smear associated with human papillomavirus (HPV) infection.[32] Vaccination should be offered to suitable patients and consideration given to screening immunocompromised individuals with yearly Pap tests.[33]

Table 4. Infection prevention and screening strategies for IBD patients on immunomodulating drugs

Infection	Prevention and screening strategy
Tuberculosis	Screen with chest X-ray and QuantiFERON gold before therapy Avoid travel to TB endemic areas Active TB – anti-TNF contraindicated Latent TB – assess need for therapy. May proceed if concomitant prophylactic TB treatment given (seek specialist advice)
Hepatitis	Check hepatitis B and C serology and immunise against hepatitis B if seronegative (some suggest all IBD patients should be immunised)
Influenza	Annual flu vaccination
Herpes zoster virus	Check VZV serology before therapy and vaccinate if negative
Pneumococcus	Pneumococcal vaccine every 5 years
Cytomegalovirus	No action required
Herpes simplex virus	No action required
Epstein-Barr virus	No action required
Human papillomavirus	Regular Pap smears HPV vaccination should be offered
Note: Live attenuated vaccines should not be given to IBD patients on immunomodulator therapy. These include MMR, live typhoid vaccine, live attenuated influenza, varicella, oral polio and bacille calmette-guerin (BCG)	

Table 5. The overlooked issues in IBD patient care

Issue	Comment
Employment	The ACCESS report[8] revealed over three-quarters of patients noticed a change in work life as a result of IBD. This included time off, restriction of duties, travel restriction and loss of income
Education	Similar findings to above, as well as a lack of understanding or not being believed about their illness[8]
Quality of life	Many studies have shown a lower quality of life in IBD patients and this has been associated with disease activity[34]
Anaemia	Common in IBD and often multifactorial. Iron deficiency is common and responds poorly to oral iron.[35] Intravenous iron is particularly useful in this situation
Psychological health	Stress, depression and poor psychological health are associated with chronic disease and increased disease activity.[34] Many new psychological therapies may help, although evidence on the use of antidepressants is conflicting
Sexual dysfunction	The potential for incontinence and wind, and a resistance to discuss sexual health concerns makes these issues common and challenging[8]
Functional GI symptoms	Common in IBD and require careful assessment. Dietary interventions (via a specialist dietician) have proven useful[36]
Smoking	Strongly associated with negative disease outcomes in CD.[37] Cessation should be actively encouraged and awareness of available help and resources given
Nutrition and development	Key priorities in all patients, but should be particularly focused on children, adolescents and young adults[38]

The other feared complication of immune modulating therapy is malignancy. This can be limited to an increased risk of skin cancer (related to long term thiopurines) through to the development of nasty hepatosplenic T-cell lymphoma (HSTCL).[34] Fortunately the latter is rare. The risks lie with all immunomodulators (perhaps with the exception of methotrexate) and correlates to a 2–3 fold increased risk compared to the non-IBD population.[30,31,35]

While investigation and management is important in treatment decision making, many other issues are important to patients. These are best managed by a multidisciplinary team (*Table 5*).

Conclusion

While our ability to diagnose, evaluate and manage patients with IBD continues to improve, it remains a challenging and complex disease. Treatment philosophy is moving toward altering the natural history of the disease while aiming for as normal a quality of life as possible. Inflammatory bowel disease is no longer an illness managed by the gastroenterologist. It requires a multidisciplinary approach with many key players. Only by taking a long term approach in treatment decisions, delivering a patient centred multidisciplinary approach, and adopting a chronic disease pathway to management will an optimal outlook for the vast majority of patients with IBD be achieved.

Conflict of interest: none declared.

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AFP CORRESPONDENCE afp@racgp.org.au