Management of inflammatory bowel disease

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Inflammatory bowel disease (IBD), which encompasses both Crohn disease and ulcerative colitis, is a chronic, relapsing condition of the gastrointestinal tract. Children, adolescents and young adults are most commonly affected. This condition has an impact on quality of life and is associated with an increased risk of hospitalisation and surgery. The past decade has seen major improvements in the management of IBD; these improvements have evolved from a better understanding of the disease pathophysiology, the availability of new diagnostic tools and the expanding therapeutic armamentarium. The aim of treatment has moved beyond symptom control only and is based on a “treat to target” approach, with clear objective measures to ensure the target, usually mucosal healing, is reached.

This review provides an update on IBD pathogenesis and approach to diagnosis. We summarise recent developments in therapeutics and indicate potential emerging treatment options, while highlighting the importance of holistic and multidisciplinary care for patients with IBD.

Methods

We performed a PubMed review of original articles, review articles and society publications, guidelines and recent conference abstracts to formulate an evidence-based overview of the topics as applied to clinical practice. Articles from early 1990s to present were reviewed.

Natural history and epidemiology

IBD has been on the rise in developed countries over the past half century, with Australia having one of the highest incidence rates in the world at 29.3 per 100,000. However, this rapid rise has plateaued in the past decade in developed countries. A dramatic rise in incidence is now being observed in developing parts of the world such as Asia. The natural history of Crohn disease and ulcerative colitis is variable, from mild forms with infrequent symptoms to debilitating disease that can result in hospitalisation, surgery and disability. For most patients, IBD follows a relapsing and remitting course. A relapse is characterised by symptoms with objective signs of inflammation. It is now understood that even during periods of remission, subclinical inflammation often persists, particularly in Crohn disease, increasing the risk of progression to stenosing or penetrating complications. Such structural bowel damage frequently requires surgery (Box 1). For this reason, treatment is now set beyond symptom control only and targeted at preventing all inflammation.

Recent population-based studies show that disease course is overall more optimistic compared with older studies. Hospitalisation rates are highest during the first year in both ulcerative colitis and Crohn disease, but drop off in the following years. Surgery rates have declined, with a 5-year risk of 33% and 12% in Crohn disease and ulcerative colitis, respectively.

Summary

- Australia has one of the highest incidence rates of inflammatory bowel disease (IBD) in the world.
- Early diagnosis and treatment for IBD is critical. For Crohn disease, in particular, this may change the natural history of disease and reduce disability.
- Faecal calprotectin is a sensitive test that can be used by primary care physicians to assist in determining which patients with gastrointestinal symptoms may have IBD. This allows for prompt identification of patients who may benefit from endoscopy.
- Regular re-evaluation of disease status with strategies that can safely, readily and reliably detect the presence of inflammation with faecal biomarkers and imaging is important. To avoid the risks of cumulative radiation exposure, magnetic resonance imaging and/or intestinal ultrasound, rather than computed tomography scanning, should be performed when possible.
- Drug treatments for IBD now include five biological drugs listed by the Pharmaceutical Benefits Scheme: adalimumab, infliximab, golimumab, vedolizumab and ustekinumab. Such developments offer the possibility for improved disease control in selected patients.

Pathogenesis of inflammatory bowel disease

IBD results from an inappropriate immune response against environmental factors in genetically predisposed individuals (Box 2). Genome-wide sequencing and other genetic analyses have culminated in the discovery of 163 published susceptibility loci in IBD. These loci are involved in an aberrant immune response to intestinal microbiota. However, given the rapid raise of the disease incidence and studies that have shown a concordance of less than 50% in monozygotic twins, a genetic predisposition is not enough on its own to explain the cause of the disease.

The diversity and composition of gut microbiota are major factors influencing gut homeostasis. An imbalance in the composition of the gut microbiome (dysbiosis) has been associated with IBD. Profiling studies of the microbiome, which are now possible due to new technologies, have identified certain shifts in intestinal microbiota composition in patients with IBD compared with healthy controls. These results have created an interest in microbial manipulation, including faecal microbiota transplantation (FMT), as a potential therapy for IBD.

Environmental factors including diet, smoking and antibiotic use are of great interest and are all likely to affect the gastrointestinal microbiota, and may have a role in the development of disease. The rapid rise in incidence of IBD in eastern countries with the increasing adoption of westernised lifestyles has increased the focus on diet in particular as having a role in disease pathogenesis. To date, no specific diet has been shown to directly cause, prevent or treat IBD, but certain associations have been made. Epidemiological studies have shown that high fibre intake and fruit intake may be protective against developing IBD, while diets high in fats (specifically omega-6 polyunsaturated fatty acids) increase the risk.
Diagnosis of inflammatory bowel disease

The diagnosis of IBD can be separated into two distinct phenotypes: Crohn disease and ulcerative colitis. General practitioners have an important role in facilitating the early diagnosis of IBD in order to prevent the development of severe disease and complications. In Crohn disease, delayed diagnosis leads to cumulative bowel damage, fibrosis and disability. In ulcerative colitis, early diagnosis and effective treatment reduces the long term risks of colorectal cancer and the need for surgery.

Clinical assessment

The initial assessment of patients with possible IBD is summarised in Box 3. Clinical symptoms that may alert the GP to possible IBD include abdominal pain and/or diarrhoea (often with blood or mucous). These symptoms may fluctuate and can be present for weeks to months, compared with the symptoms of infectious gastroenteritis which are present usually only for days. Symptoms may continue at night, as distinct from most functional gastrointestinal disorders, in which symptoms are mostly only present during the day. There may be loss of weight and fever. A history of perianal fissures, fistulas or abscesses raises the possibility of Crohn disease. The presence of associated non-gut symptoms such as rash, iritis, mouth ulcers and arthralgia may also be a clue to a diagnosis of IBD as is a family history of the condition.

Blood and stool tests

Blood tests may show raised white cell counts, C-reactive protein levels or erythrocyte sedimentation rates, but may also be normal. Faecal calprotectin, a cytoplasmic product released from neutrophils, is a relatively new and useful test for differentiating IBD from functional gastrointestinal disorders, offering improved sensitivity and specificity for the diagnosis of IBD over C-reactive protein level alone. Performing a faecal calprotectin test should be considered as part of the initial investigation of a patient with gastrointestinal symptoms. An elevated faecal calprotectin level (> 50 μg/g) identifies patients who are more likely to have IBD and should have a colonoscopy performed. A faecal calprotectin level < 50 μg/g makes a diagnosis of IBD very unlikely. Although not reimbursed by the Medicare Benefits Schedule as yet, this test is likely to be included in the schedule in the coming months. At present, faecal calprotectin is an inexpensive, readily available and clinically useful test lending itself perfectly to use in the primary care setting.

Imaging

Regular re-evaluation of the disease status with imaging that can safely, readily and reliably detect the presence of inflammation, particularly in Crohn disease, is important. To avoid the risks of cumulative radiation exposure, magnetic resonance imaging (MRI) and/or intestinal ultrasound, rather than computed tomography (CT) scanning, should be performed when possible. MRI is usually requested by the treating gastroenterologist as part of the more detailed assessment of Crohn disease location. Intestinal ultrasound is an imaging modality that presents several advantages compared with MRI and CT scan, including low financial cost, portability, availability, reproducibility, real-time assessment and the absence of radiation exposure and potentially nephrotoxic contrast agents. This technique is increasingly being embraced by IBD centres across Australia as a point of care test performed by gastroenterologists at the time of outpatient review. Formal training programs for gastroenterologists in bedside intestinal ultrasound are in development.
Colonoscopy remains the gold standard for the diagnosis and assessment of IBD. Colonoscopy is critical for dysplasia surveillance in patients with ulcerative colitis. All patients who have had a diagnosis of ulcerative colitis extending proximal to the sigmoid colon or colonic Crohn disease involving more than one-third of the colon should be enrolled in an endoscopic surveillance program with their gastroenterologist for the screening of colonic dysplasia. Screening is universally recommended for these patients, with surveillance intervals depending on time since diagnosis, severity of disease, endoscopic appearance, history of previous dysplasia, presence or absence of primary sclerosing cholangitis and a family history of colorectal cancer.

Treatment
The treatment of IBD aims to first induce and then maintain remission. Drug treatment in IBD must control mucosal inflammation rather than just improve symptoms. Induction of remission must happen promptly, ideally by 3 months, in order to minimise intestinal damage. Monitoring to ensure that inflammation is controlled long term is central to the treatment strategy.

A recommended approach to treatment is shown in Box 4. Available treatment options for patients with IBD are discussed below and summarised in Box 5.

Corticosteroids
Corticosteroids are the most important treatment for remission induction in active disease, but they must be used as part of a treatment strategy. For patients with IBD, prednisolone is prescribed at a dose of 40–60 mg per day and tapered over 4–8 weeks. There is no role for long term steroids in the treatment of IBD.

5-Aminosalicylic acids
5-Aminosalicylic acid (5-ASA)-based drugs, including sulfasalazine and mesalazine, are the mainstay of treatment in mild to moderate ulcerative colitis, for which they are effective and safe (when administered at appropriate doses) for both inducing remission of active disease and preventing relapse of quiescent disease. For the induction of remission, a dose of at least 3 g daily is optimal; however, for the maintenance of remission, doses of as low as 1 g daily appear efficacious when compared with placebo. Rectally administered 5-ASA is efficacious in left-sided colitis and proctitis and can be used either alone or in combination with oral 5-ASA drugs.

Failure to achieve remission with 5-ASA drugs must prompt the clinician to ensure that the prescribed dose is optimal and that the patient is compliant with the therapy. If the dose has been optimised and disease remains active, escalation of therapy to include an immunomodulator is indicated.

Unlike ulcerative colitis, 5-ASA therapies have limited efficacy for the treatment of Crohn disease, for which this therapy is only likely to be beneficial in mild ileal disease and only at sufficiently high doses (3–4 g daily). However, even in this setting, the benefit is modest at best.

Immunomodulators
Immunomodulators including thiopurines (azathioprine and 6-mercaptopurine) are the mainstay of treatment for the maintenance of remission for moderate to severe Crohn disease and ulcerative colitis that remain active despite optimally dosed 5-ASA therapy. The efficacy of thiopurines in the treatment of IBD is well established. Methotrexate is generally reserved only for patients who fail to respond to or are intolerant of thiopurines. Its efficacy in Crohn disease has been demonstrated, but in ulcerative colitis the evidence is less conclusive.

The use of thiopurines is limited by poor tolerability for some patients, but the majority of patients will not experience significant side effects to the therapy. The toxicities of thiopurine therapy concern both doctors and patients. Risks include leucopenia and infectious complications, particularly viral infections and a small, but definite, increased risk of lymphoma and non-melanoma skin cancer. In most cases, such risks do not contraindicate the use of these agents if...
clinically required, but patient education is important. There are tools that have been developed to communicate some of these risks, including the risk of lymphoma (online Appendix).\(^{30}\)

**Biologics**

Escalation to biological drug therapy for both the induction and maintenance of remission is indicated when a patient’s disease has not been adequately controlled by immunomodulator therapy alone. The Pharmaceutical Benefits Scheme (PBS) requires patients to have clinically active disease despite immunomodulator use for at least 3 months and 6 weeks of corticosteroid therapy before a biological drug can be approved for use.

**Anti-tumour necrosis factor \(\alpha\) drugs.** The anti-tumour necrosis factor \(\alpha\) (TNF-\(\alpha\)) monoclonal antibodies, adalimumab and infliximab, are safe and efficacious and have revolutionised the treatment of IBD. Golimumab has recently been approved by the PBS for the treatment of ulcerative colitis. Their use is indicated in moderate to severe luminal Crohn disease (adalimumab and infliximab) and ulcerative colitis (adalimumab, infliximab and golimumab). In order to prevent the development of long term complications, treatment should be intensified to include a biological drug promptly if there is evidence of active inflammation despite immunomodulator therapy.\(^{31}\) Combination therapy — when an anti-TNF-\(\alpha\) monoclonal antibody is used in combination with thiopurines — is probably superior to treatment with anti-TNF-\(\alpha\) monotherapy in Crohn disease and ulcerative colitis.\(^{32,33}\)

In ulcerative colitis, infliximab is listed in the PBS for the treatment of acute severe colitis in hospitalised patients who have failed to achieve an adequate response to high dose corticosteroid. This treatment, when administered in a timely fashion, is surgery sparing for many patients in the short and medium term.\(^{34}\)

However, treatment failures do occur with anti-TNF-\(\alpha\) therapy in the form of loss of response, usually related to immunogenicity. Rates of loss of response in the first 12 months of therapy range from 23% to 46%, with loss of response rates after this time being estimated at about 13% per year.\(^{35}\)

Anti-TNF-\(\alpha\) therapy is associated with the reactivation of serious infections, including tuberculosis and hepatitis B.\(^{36}\) Hepatosplenic T-cell lymphoma is a rare but often fatal condition usually affecting young males. Cases have been reported in patients with IBD who are receiving combination therapy and thiopurine monotherapy, but never in patients who are using anti-TNF-\(\alpha\) drugs alone.\(^{37}\)

Treatment with anti-TNF-\(\alpha\) drugs is associated with a small increased risk of melanoma,\(^{38}\) but otherwise, the risk of malignancies in patients with no prior history of cancer is not increased.\(^{39}\)

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### 5 Current treatments for inflammatory bowel disease: dose and indication

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indication</th>
<th>Dose</th>
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</thead>
<tbody>
<tr>
<td><strong>Crohn disease</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroid (prednisolone)</td>
<td>Induction of remission</td>
<td>50 mg daily (wean over 6–8 weeks)</td>
</tr>
<tr>
<td>Oral 5-ASA (sulfasalazine, mesalazine)</td>
<td>Induction and maintenance of remission for mild ileal disease only</td>
<td>3–4 g daily</td>
</tr>
<tr>
<td>Thiopurines (AZA, 6-MP)</td>
<td>Maintenance of remission</td>
<td>AZA, 2–2.5 mg/kg daily 6-MP, 1–1.5 mg/kg daily</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Maintenance of remission</td>
<td>20–25 mg (oral, subcutaneous)</td>
</tr>
<tr>
<td>Adalimumab/infliximab</td>
<td>Induction and maintenance of remission</td>
<td>As per PBS Treatment of perianal disease</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>Induction and maintenance of remission</td>
<td>As per PBS</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>Induction and maintenance of remission</td>
<td>As per PBS</td>
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<p>| <strong>Ulcerative colitis</strong> | | |</p>
<table>
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</tr>
<tr>
<td>Topical corticosteroid</td>
<td>Left-sided colitis and proctitis</td>
<td>Suppository, 5 mg daily Enema, 5 mg daily</td>
</tr>
<tr>
<td>Oral 5-ASA (sulfasalazine, balsalazide, mesalazine)</td>
<td>Induction and maintenance of remission</td>
<td>3–4 g daily (induction of remission) 2 g daily (maintenance of remission)</td>
</tr>
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</tr>
<tr>
<td>Adalimumab/infliximab-golimumab</td>
<td>Induction and maintenance of remission</td>
<td>As per PBS</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>Induction and maintenance of remission</td>
<td>As per PBS</td>
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</tbody>
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5-ASA – 5-aminosalicylic acid. AZA – azathioprine. 6-MP – 6-mercaptopurine. PBS – Pharmaceutical Benefits Scheme. \(^{30}\)
Vedolizumab. In 2015, the PBS listed vedolizumab — a monoclonal antibody — for induction of remission and maintenance therapy for Crohn disease and ulcerative colitis after trials showed efficacy for these indications.40,41 Vedolizumab inhibits leucocyte trafficking in the gut by blocking the α4 β7 integrin, resulting in gut-selective anti-inflammatory activity. This drug has an improved safety profile when compared with anti-TNF-α drugs due to its gut-selective immunosuppressive effect. The use of vedolizumab has not been associated with an increased risk of malignancy.

Ustekinumab. Ustekinumab is a monoclonal antibody with efficacy in the treatment of moderately to severely active Crohn disease42 and was approved for this indication by the PBS in 2017. The safety of ustekinumab has been well established in the population with psoriasis. The serious adverse event rate in ustekinumab-treated patients with Crohn disease in clinical trials is equivalent to that of placebo. Open-label experiences with ustekinumab in Crohn disease have reported almost no serious adverse events, in particular no increased risk of malignancy.43

Faecal microbiota transplantation

A 2013 study showing that the infusion of donor faeces for recurrent Clostridium difficile infection was superior to the use of vancomycin44 transformed the global perspective on the therapeutic role of FMT in gastrointestinal disease.

A recent Australian randomised controlled trial and a meta-analysis have supported the use of FMT for induction of remission in patients with ulcerative colitis,45,46 but there are no data to support the use of FMT for remission maintenance. Both studies were small, with less than 100 patients in each. There are no such studies in Crohn disease. Suitable donor selection, preparation technique and administration have varied across the published studies, making extrapolation of these results into routine clinical practice difficult.

The approach to FMT in IBD is in its infancy. Practical considerations and access to this therapy remain challenging. At the time of writing, FMT is not available for the treatment of IBD at any public hospital in Australia outside of clinical trials.

Managing the patient with inflammatory bowel disease in primary care

GPs have an important role in the management of patients with IBD. Attention needs to be directed towards the maintenance and optimisation of nutrition, psychological wellbeing, bone health, vaccination against preventable diseases and screening for malignancy.

Patients with IBD should have iron, vitamin B12, folate and vitamin D levels tested every 6 months — supplementation is recommended if these are deficient. Dual-energy x-ray absorptiometry scans are recommended if there has been prolonged corticosteroid exposure.

Symptoms of IBD have a substantial impact on psychological wellbeing and quality of life. Anxiety and depression are more common in patients with IBD compared with the general population.47 Screening for depression and anxiety and referral to a psychologist or psychiatrist when appropriate is important.

Vaccination is important and should be coordinated by the GP. Recommended vaccinations for patients with IBD include hepatitis A and B, tetanus, diphtheria, pertussis, human papillomavirus, influenza, pneumococcal and meningococcal, and can be given at any time.48 Live vaccines must not be given to any patient taking an immunomodulator or a biological drug or any person who will commence these therapies within 3 months of the date of vaccination.49

Patients receiving a thiopurine therapy should have a skin check performed yearly because of the increased risk of non-melanoma skin cancer.49 Adequate sun protection must be encouraged.

Dietary advice for patients with IBD should focus on a healthy, balanced diet comprising fresh foods. It may be beneficial to avoid highly processed foods and foods high in preservatives and emulsifiers. In patients with intestinal strictures or active colitis, a low fibre diet is recommended, as it will help to reduce symptoms, especially abdominal pain. To date, there are no specific diets (other than the use of exclusive enteral nutrition) that have been shown to reduce intestinal inflammation in patients with Crohn disease, although there is ongoing research in this area.49

Smoking is strongly associated with negative disease outcomes in Crohn disease.50 Cessation should be actively encouraged and consideration be given to using pharmaceutical and psychological approaches.

Conclusion

The management of IBD is increasingly complicated as we strive for tougher treatment targets, including the elimination of intestinal inflammation and normalisation of quality of life. Improved diagnostic and imaging tests and safer and more effective therapies offer the possibility of better long term outcomes for patients. The emphasis on prompt diagnosis and treatment is of the utmost importance and offers the possibility of altering the natural history of disease and reducing disability. The future of strategies in the management of IBD will be towards personalising management according to host genotype, serology, and gastrointestinal microbial profile. Public IBD clinics should offer complete, multidisciplinary care for patients and should include gastroenterologists, surgeons, nurses, psychologists and dietitians. The role of the GP is critical in assisting with prompt diagnosis, appropriate referral, preventive health care, health promotion and care coordination.

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