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Inflammatory bowel disease

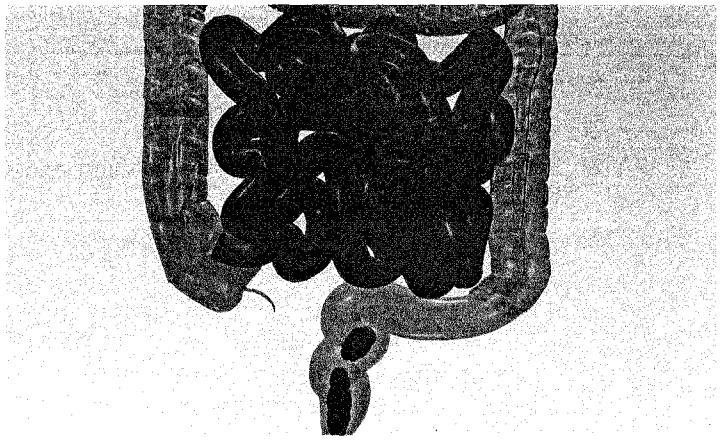
By Ella Jeffrey and Dr Luke Bereznicki

Learning objectives

After reading this article, you should be able to:

- Describe the symptoms that differentiate inflammatory bowel disease (IBD) from other gastrointestinal complaints
- Identify the goals of IBD treatment, and
- Recognise the role of various treatments in IBD.

Competencies addressed: 3.1.2, 3.2.2, 4.2.1, 4.2.2, 6.1.1



IBD is thought to result from inappropriate and ongoing activation of the mucosal immune system, driven by intolerance to normal gut flora.

Introduction

Inflammatory bowel disease (IBD) refers to a group of disorders characterised by chronic, relapsing inflammation in the gut. The main forms of IBD are Crohn's disease (CD) and ulcerative colitis (UC). The clinical course of both diseases can range from a mild form, in which the patient reaches long term remission without taking permanent medication, to a chronic active form, in which remission is only reached by permanently taking immunosuppressives and/or biologicals.[1] Approximately 61,000 Australians have IBD, with 1600 new cases diagnosed each year.[2] IBD can be diagnosed at any age, but has a peak onset between 15 to 40 years.[2]

Aetiology

IBD is thought to result from inappropriate and ongoing activation of the mucosal immune system, driven by intolerance to normal gut flora.[3,4] Genetic and environmental factors also play an important role. First degree relatives of people affected by IBD have a four to 20 times greater risk of developing IBD than the background population.[3] It is thought that multiple genes contribute to a person's risk of IBD.[3]

A number of factors are associated with either an increased or decreased risk of IBD. Non-steroidal anti-inflammatory drugs (NSAIDs) are thought to alter the intestinal barrier and lead to disease flares, while an early appendectomy is associated with a reduced incidence of UC.[5,6] Cigarette smoking and nicotine play an intriguing role in these diseases. It is thought that smoking may modify the phenotype associated with IBD as it protects against UC but increases the risk of CD three- to four-fold.[7,8]

Features

CD can affect any part of the gastrointestinal tract, whereas UC by definition affects only the colon.[4] UC is a mucosal disease, characterised by uniform, continuous inflammation extending from the rectum variable distances towards the caecum.[9] CD, on the other hand, appears patchy, with ulcerations separated by segments of normal mucosa.[9] The inflammation of CD extends transmurally, involving several layers of the gastrointestinal lumen, and commonly results in the development of fissures, fistulas and strictures.[9]

Symptoms/diagnosis

Almost all patients with IBD have intestinal symptoms, such as abdominal discomfort or pain and/or change of bowel habits (usually manifesting as diarrhoea).[10] These symptoms are non-specific; the vast majority of patients presenting with these symptoms will have irritable bowel syndrome (IBS). Unfortunately, many patients with IBD are subjected to a long diagnostic process while their symptoms are treated as IBS.[2,10] Features that distinguish IBD from IBS are 'alarm' symptoms and signs, such as rectal bleeding, weight loss, abdominal mass, fever, nocturnal symptoms, pallor or tachycardia.[10] Blood tests may also be useful in providing

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clues to suggest IBD. These include elevated C-reactive protein, white cell and/or platelet count, or erythrocyte sedimentation rate.[10]

Endoscopic examination is also a useful tool in determining the type of disease and the most appropriate course of treatment.[11] For UC, differentiation is easier because inflammation only involves the colon.[1] Around 20% of CD cases are also confined to the colon, making them more difficult to distinguish from UC.[9]

Treatment

Overview

The treatment of IBD is a rapidly expanding area. The introduction of infliximab, an anti-tumour necrosis factor alpha (TNF-α) medication almost a decade ago, has been the most significant addition to the spectrum of therapeutic options in IBD. For many years treatment was primarily limited to aminosalicylates, antibiotics, steroids and immunomodulators.[4] Medications may be used either to induce or maintain remission. Choice of therapy depends largely on the severity of disease, and may also be influenced by such factors as disease location, adverse effects and cost.

'Step-up' vs 'Top-down' therapy

Traditional treatment of IBD is based on a 'step-up' approach where therapies with the least toxicity are utilised early with further treatments being added due to a lack of response or development of toxicity.[11,12] This may lead to agents with low efficacy being used for prolonged periods of time, while inflammation continues uncontrolled, which may result in tissue damage.[11] Corticosteroids are important agents in this method of management.[11–14] Mucosal healing the key indicator that inflammation is controlled and the bowel is normalising, as tissue damage may continue to occur in the absence of symptoms.[11]

More recently a 'top-down' approach has been explored on the premise that biological therapies can heal the mucosa and potentially alter the progression of disease.[11,12] This approach aims to rapidly induce remission in a steroid-free environment and promote mucosal healing.[11,12] The disadvantage of this approach is that it assumes all patients with IBD have a similar disease course. However, approximately 50% of patients with IBD will never require corticosteroids, and this approach may be considered unnecessary in these patients.[11,12] It has been suggested that the key to 'top-down' management of IBD is to recognise the effectiveness of therapies in a structured time frame, and to evaluate their place in treating each patient against defined therapeutic goals.[11]

There are multiple therapeutic goals for IBD which can be evaluated at regular intervals to assess the effectiveness of treatments.[11] These goals are:

- Induction of rapid response
- Maintenance of remission without steroids
- Achieving and maintaining complete mucosal healing
- Avoiding complications, hospitalisation and surgery
- Preventing disease-related mortality, and
- Improving patient quality of life.[11]

1. 5-Aminosalicylates (5-ASA)

Aminosalicylates are among the oldest and most commonly used drugs for IBD.[15] They are bowel-specific drugs metabolised in the gut where their predominant actions occur.[1] Taken orally, these drugs are delivered intact to the colon where they are degraded by colonic bacteria into 5-ASA.[15] The original aminosalicylate, sulfasalazine, is still widely used, though many newer formulations have been developed to optimise drug delivery and minimise adverse effects, particularly those associated with the sulfa-component.[15]

Mesalazine is 5-ASA (the active component of sulfasalazine), which needs to be delivered to the large bowel mucosa to exert its effect.[16] To achieve this, 5-ASA can be bound to a carrier molecule (e.g. sulfapyridine in the case of sulfasalazine, another 5-ASA molecule in the case of osalazine, or an inert carrier molecule in the case of balsalazide) or coated with a pH dependent substance to ensure its release in the terminal ileum and proximal colon.[10,17,18] Alternatively, 5-ASA can be delivered directly to the rectum via a suppository, foam, or enema.[10,18] Rectal preparations are usually used in conjunction with oral aminosalicylates, as these preparations have additive efficacy in distal disease through increasing mucosal concentrations of 5-ASA.[3,15,18–20] The exact mode of action of these agents is unknown, but they are likely to have multiple anti-inflammatory effects, including inhibition of cyclooxygenase and several inflammatory cytokines.[4]

Aminosalicylates remain the standard treatment for induction and maintenance therapy in UC.[4] In contrast to UC, the use of aminosalicylates for the maintenance of remission is not consistently recommended in CD as clinical studies have not shown their success in remission maintenance.[21,22] Their use is of most benefit in patients with colonic disease.[15]

2. Antibiotics

Despite a lack of evidence, antibiotics are frequently used in CD, especially with colonic and perianal disease.[4] Metronidazole and ciprofloxacin are the most common agents used, especially in post-operative management and the treatment of perianal fistulae, though this therapy is based on expert opinion rather than clinical trials.[1,4,15] The role of antibiotics in the treatment of active disease, as well as a safe and effective dose schedule in the post-operative setting, remain to be established.[4]

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3. Corticosteroids

Conventional steroids induce remission for both CD and UC but are often reserved for patients with moderate-severe disease or for those who have failed first line therapy.[1,4]

While these agents are effective in inducing remission, they are not suitable for maintenance therapy because of lack of efficacy, and because their long term use is sometimes associated with severe and irreversible side effects.[11] Additionally, some patients may become corticosteroid dependent, while others may become refractory to steroid treatment.[11] After the induction of remission, the steroid dose should be tapered.[1]

Budesonide has the advantage of reducing the typical systemic steroid side effects associated with prednisolone, due to a high first pass metabolism of around 90%.[23] Budesonide is effective as a first-line agent for ileal and/or right colonic CD, although maintenance benefits remain to be proven, especially in the presence of long-term adverse effects.[4] Because it is released in the distal ileum and proximal colon, the role of budesonide in the treatment of UC is limited.[4]

4. Immunomodulators

Immunomodulators such as 6-mercaptopurine (6-MP), azathioprine (AZA), and methotrexate (MTX), are effective steroid-sparing and maintenance therapies.[4] These agents are used in patients with chronically active disease (where remission cannot be achieved) and in patients where relapses occur more commonly despite appropriate aminosalicylate maintenance therapy.[10]

The thiopurine immunosuppressive agents (6-MP and AZA) have been shown to be effective in the control of inflammation and maintenance of remission in both UC and CD, and work by interfering with the proliferation of activated lymphocytes and inducing apoptosis.[24,25]

The onset of benefit typically takes several weeks, sometimes up to a few months, so these drugs are not useful in the control of acute disease, and should only be given when prolonged treatment is planned.[3] Treatment with AZA or 6-MP is usually of an 'indefinite' duration for patients who have responded.[4]

Methotrexate has multiple anti-inflammatory effects, including inducing lymphocyte apoptosis.[26] MTX is recommended as long-term therapy in patients with CD who do not respond to or cannot tolerate AZA or 6-MP.[15]

Other immunomodulators

Cyclosporin may be effective for severe or refractory UC.[4] Cyclosporin is reserved for the treatment of severe steroid-refractory UC.[1] It is associated with significant morbidity, including opportunistic infections, and neurologic and renal toxicity.[27] Due to its toxicity, use should be carefully considered and it should only be used in severe active disease cases to avoid a colectomy.[1,28]

Tacrolimus and mycophenolate mofetil have also shown promise in the treatment of patients with IBD.[3] Mycophenolate mofetil has been shown to have an equivalent action to AZA in patients with moderately active CD, and greater efficacy in those with highly active disease.[29] Tacrolimus is thought to have local effects on the intestine and has showed promising results in fistulising disease, unresponsive CD and UC, and during extra-intestinal manifestations.[30] Thalidomide has a potential role in maintaining infliximab-induced remission in CD.[31]

5. Biological agents

Biological therapies, especially anti-TNFα agents, play a pivotal role in the treatment of chronic active IBD and fistulising disease.[32–35] They have been shown to be effective for patients with moderate-severe IBD, independent of concomitant medications.[4]

The first anti-TNFα agent on the market was infliximab. Infliximab has been shown to induce and maintain remission in IBD when given regularly (e.g. 8 to 12 weekly). Patients with steroid-refractory or chronically active IBD who do not respond to immunosuppressive therapy alone should also receive treatment with infliximab.[1,36–43] Other anti-TNF agents, such as adalimumab, have also shown efficacy in these conditions.[1,35]

6. Other treatment options

a. Surgery

Surgery provides a chance of 'cure' for patients with UC.[10] Here the rectum and entire colon is removed, followed by possible ileal pouch formation.[10] Surgery is indicated for patients suffering from severe, unresponsive disease, chronically active disease which impacts negatively on quality of life, and those with neoplastic changes in the large bowel.[10] Surgery may also be an option for patients with CD, particularly those with refractory disease, intestinal obstruction, fistula formation, or other complications.[44] While around 80% of CD patients will need intestinal surgery at some time,[45] this treatment is not curative as it is in UC, and disease frequently reappears at the site of surgery.[46,47]

b. Nicotine

Smoking may decrease the risk of developing UC, but the evidence to support the use of nicotine in the treatment of UC is lacking.[48] Patients with moderately active UC may improve with nicotine intake, however nicotine is not effective for maintenance.[15] There is however, strong evidence to support the discontinuation of smoking as an important treatment strategy for CD. In fact, smoking cessation is probably the most important factor in maintaining

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remission.[49] Cigarette smoking in CD is significantly associated with a more aggressive course of disease and an increased risk of relapse.[50,51] It also increases the need for immunosuppressants and corticosteroids and the risk of relapse post operatively.[50,52] Smoking cessation is a valuable treatment option in CD and can reduce the risk of relapse by up to 65%.[7]

c. Diet

Nutrition has an important role in the management of IBD.[53] In active CD nutritional therapy in the form of enteral feeding can be used as primary therapy for many patients, and is particularly beneficial in paediatric patients to minimise the need for corticosteroids.[53,54] There is no evidence to support the role of enteral nutrition in UC.[53,55,56] All IBD patients should be encouraged to maintain a diet adequate in energy, protein, and micronutrients through diet where possible, and supplements where necessary.[53,55] Patients may also benefit from dietary advice directed at minimising symptoms, including avoiding foods that exacerbate symptoms, and reducing fibre intake for symptomatic relief of diarrhoea.[10,55]

d. Antidiarrhoeals

Antidiarrhoeals, such as loperamide, may be useful in the management of diarrhoea in both forms of IBD.[49,55] Patients need to be warned to use these agents with caution in UC and only to use them in controlling the symptoms of mild disease, as their use may precipitate toxic megacolon in severe cases of UC.[49,55] Diarrhoea in CD may be associated with bile salt malabsorption, steatorrhoea, or active disease.[55] It is important to distinguish between the causes of diarrhoea as bile salt diarrhoea may be controlled by cholestyramine, while steatorrhoea will be worsened by cholestyramine and should be managed with a low-fat diet.[55]

e. Fish oils

There are some promising studies on the use of fish oils in IBD. Possible benefits include a reduced risk of relapse in CD and a steroid sparing effect in UC.[57,58] The evidence for long term effectiveness is currently lacking.[15]

f. Probiotics

The theory of dysbiosis maintains that a decrease in 'good' bacteria and a concomitant increase in 'bad' bacteria contribute to the pathogenesis of IBD.[4,59] While this appears to be a promising treatment option, especially for remission maintenance in UC and prevention of pouchitis, current evidence suggests that the benefits are strain-specific and cannot be generalised to all probiotics.[49,59–62] More studies are needed to better establish the safety and efficacy of probiotic treatment in IBD.[59,63]

g. Curcumin

Derived from turmeric, curcumin appears to possess anti-inflammatory, antimicrobial and tumour suppressing characteristics.[4] One study has shown a reduced rate of relapse in patients who took a combination of 5-ASA and curcumin copared to those who took 5-ASA and placebo.[64]

Conclusion

Even though there is currently no cure for IBD, current medical therapy has improved the health and quality of life of most people living with IBD. The therapeutic options to treat IBD continue to expand. A number of new agents directed against TNFα are in various stages of development, as are other drugs that inhibit the recruitment of inflammatory cells. The development of these agents and future research into these conditions will lead to further improvements in the medical and surgical treatment of IBD.

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