The role of budesonide in the management of Crohn's disease

Abstract

Inflammatory bowel disease encompasses two main conditions: ulcerative colitis (UC) and Crohn's disease (CD). These are chronic debilitating conditions, characterised by relapsing inflammation of the gastrointestinal tract. Approximately 620 000 people in the UK are affected by these conditions. The management of CD can be complex, which presents challenges to both patients and clinicians. Treatment of CD is evolving in tandem with an improved understanding of the disease. However, there is currently no cure for this disease. The mainstay of treatment is to induce and maintain clinical remission. Steroid therapies are used in the induction of remission. Current European Crohn's and colitis Organisation (ECCO) guidelines recommend the use of budesonide as the first-line treatment of mild to moderate ileo-caecal CD. This article provides an overview of CD and the current strategies used in its pharmacological management, placing specific focus on the role of budesonide in the treatment pathway.

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Key words

- Crohn's disease
- Budesonide
- Induction of remission
- Clinical nurse specialists
- Inflammatory bowel disease

This article has been subject to double-blind peer review

Inflammatory bowel disease (IBD) consists of two main conditions, ulcerative colitis (UC) and Crohn's disease (CD), which are generally characterised by chronic relapsing inflammation of the gastrointestinal (GI) tract (Molodecky et al, 2012). In the UK, around 620 000 people are affected by these conditions (IBD Standards Group, 2013), although it has been recognised that there is no accurate UK-wide IBD database. The development of the IBD Registry may give clinicians a better insight into the disease prevalence (Munro, 2014).

CD can affect any section of the GI tract from the mouth to the anus (Laass et al, 2014), as opposed to the limited colonic activity seen in UC. The most common site of the disease is the distal (terminal) ileum, although the reason for this is unclear (Caprilli, 2008). CD is distinguished by the presence of patchy, transmural inflammation of the intestine (Mowat et al, 2011). Endoscopically, these discontinuous patches of inflammation are commonly referred to as 'skip lesions' (Laass et al, 2014). Entirely colonic disease is often termed Crohn's colitis.

The pathogenesis of CD is still not well understood, but it is thought to be multi-factorial (Wehkamp et al, 2004). It is suggested that an interaction between environmental and genetic factors may lead to a predisposition to develop the disease (Travis et al, 2006). However, recent genetic research has identified over 160 genes that may contribute to the risk of IBD (either CD or UC) (Cleynen and Vermeire, 2015); therefore, heritability is complex. A positive association has been found with a higher prevalence of disease diagnosis in Western industrialized society, but again, the significance of this is unclear (Soon et al, 2012). Given that the precise cause of the disease is unknown, there is no cure. CD may present at any age, but typical presentation is most common between the ages of 15 and 30 years (Laass et al, 2014). Disease prevalence is equally distributed between the sexes (Travis et al, 2006). Tobacco smoking is a recognised risk factor for poor disease control and complications (Parkes et al, 2014). Familial history of IBD is also recognised as a risk factor (Mowat et al, 2011).

Patients can present with symptoms of diarrhoea (with or without the presence of blood and mucous), abdominal pain, weight loss and fever, as well as a possible clinical indication of bowel obstruction (Baumgart and Sandborn, 2012). Micronutrient deficiencies, such as B12 deficiency, vitamin D deficiency, folate and iron are common

in CD (Hwang et al, 2012), which may occur as a result of malabsorption and active disease (Bermejo et al, 2013). Extra-intestinal manifestations of CD can occur, and it has been suggested that up to 30% of patients can be affected (Caprilli et al, 2006). Common complications include uveitis, joint arthropathies and cutaneous developments, such as erythema nodosum or pyoderma gangrenosum (Caprilli et al, 2006). Patients with disease of the rectum can be susceptible to perianal abscesses and fistula formation (Lichtenstein et al, 2009).

How is Crohn's disease diagnosed?

Many patients can present with progressively worsening symptoms over weeks or months. Investigation may be delayed, as patients or their doctors can attribute symptoms to irritable bowel syndrome (IBS). A recent case study suggests that patients with IBD are three times more likely to have been misdiagnosed with IBS (Card et al, 2014). However, symptoms lasting longer than 6 weeks with weight loss and bleeding or abnormal first-line investigations should prompt further investigations (Mozdiak et al, 2015).

The initial investigations, usually carried out in primary care, are likely to include blood count, (FBC), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Coeliac disease should be excluded by tissue transglutaminase (TTG) testing (National Institute for Health and Care Excellence (NICE), 2008). Faecal calprotectin is a protein released in the bowel in the presence of inflammation. An excess measurement of calprotectin is useful in distinguishing between inflammatory and noninflammatory conditions, such as IBD and IBS (NICE, 2013). A raised faecal calprotectin may be used to help stratify referrals to secondary care.

Colonoscopy is widely regarded as the 'gold standard' in the diagnosis of IBD (Schreyer et al, 2005). Colonoscopy with ileal intubation is recommended for all patients with a high index of suspicion of CD (Laass et al, 2014). Small bowel imaging should be performed in patients in whom small intestinal disease is likely, such as individuals with suspected stenosis, proximal symptoms, or a mass in the right iliac fossa and/or a low serum B12 level (Mowat et al, 2011).

Table 1. Montreal classification for Crohn's disease

Age at diagnosis	Location of disease	Behaviour of disease
A1: Below 16 years	L1: Disease isolated to ileum	B1: Not causing strictures or perforations
A2: 17–40 years	L2: Disease isolated to large bowel	B2: Causing strictures
A3: Over 40 years	L3: Disease involving ileum and colon	B3: Causing perforations

Source: Satsangi et al, 2006

Types and severity

The Montreal classification (Satsangi et al, 2006) was designed to sub-classify the varying phenotypes of CD by age, disease location and behaviour (*Table 1*)

A typical new patient in the early twenties with CD of the ileum will be classified as A2L1B1. This type of classification enables clinicians to rapidly summarise a patient's disease type. This classification is often used when recruiting patients to research studies. Although the site of disease tends to be constant, in some patients additional areas of the bowel may become involved over time. The behaviour of CD using the Montreal classification can vary substantially as the disease progresses (Baumgart and Sandborn, 2012). B1 disease may develop into B2 if inflammation is not controlled. B1 may turn into B3 when ulceration is aggressive.

There are multiple disease-severity grading systems. Recently, clinical trials have used the Crohn's Disease Activity Index (CDAI) (Best et al, 1976) (*Table 2*), which has some limitations, particularly the need to collect diary data for several days prior to assessment. The system can also be time consuming to calculate a final score. Values of less than 150 represent quiescent disease, moving through the spectrum until 450, which is associated with severe disease (Best et al, 1976).

The Harvey-Bradshaw Index (HBI) (Harvey and Bradshaw, 1980) (*Table 3*) is a user-friendly scoring tool that can be applied in the clinic and that does not require patients to keep a diary prior to the assessment. NICE (2010) recommends the HBI tool when selecting patients to be treated with anti-tumour necrosis factor (Anti-TNF) agents. A score of 3 or less on the HBI indicates remission from CD, while a score of 8 to 9 or higher is indicative of severe disease. It has been suggested that, given the complexity of the CDAI, the HBI may be favourable for use in clinical practice as it is simpler to use (Vermeire et al, 2010).

Management of Crohn's disease

Therapeutic treatment of CD has evolved as the understanding of the inflammatory cascade, and the natural progression of the disease becomes better understood (Baert and Rutgeerts, 1999). Current practice employs the use of serological markers and endoscopic assessment to determine disease progression, but there are no validated clinical prediction rules for CD (Bouguen et al, 2013).

It is recognised that treatments used in CD are reasonably well tolerated and are thought to be generally safe. These treatments are used to induce and maintain clinical remission. Various strategies have been used, but the most widely recognised are the 'step-up' and 'top-down' approaches.

The traditional approach to treatment involves treating clinical symptoms as they develop, to maintain clinical remission (Rogler, 2013). This usually involves a step-up approach to therapy. As clinical symptoms worsen and become refractory to the current treatment, the patient traditionally requires a course of treatment, usually corticosteroids, before escalation to other therapies, such as immunosuppressant and biological therapies (Hanauer, 2006).

In recent times, there has been a shift to focus on more proactive and early intervention (Bouguen et al, 2013). The top-down approach employs the early introduction of biological and immunosuppressant therapies as a first-line treatment, and aims to induce mucosal healing at an early stage to reduce the risk of complications at a later stage (Vos and Hommes, 2012). It is proposed that this quick induction of clinical remission reduces the risk of hospitalisation and requirement for surgery, as well as improving general quality of life.

There remains an ongoing debate as to the best strategy to employ; however, it is generally accepted that a blanket top-down approach is not appropriate for all patients (Ordás et al, 2011). With more aggressive treatments, there is a risk of over-treating patients who may have a benign disease course (Fascì-Spurio et al, 2012). An individualised risk/benefit approach has been advocated to attempt to identify patients who are at high risk of complicated disease progression (Ordás et al, 2011). It is suggested that it is this patient group who would most benefit from early intervention of biological therapy.

Risks of therapy must be addressed and discussed with patients prior to commencement,

Table 2. Crohn's Disease Activity Index

Variable	Scale	Weight
Liquid or very soft stool	Daily stool count is calculated for 7 days	2
Abdominal pain	Sum of 7 days of daily ratings as: 0 = none, 1 = mild, 2 = moderate, 3 = severe	5
General wellbeing	Sum of 7 days of daily ratings as: 0 = generally well, 1 = slightly below par, 2 = poor, 3 = very poor, 4 = terrible	7
Features of extraintestinal disease	Presence of any of the following in the previous 7 days: Arthritis or arthralgia Skin or mouth lesions (erythema nodosum, aphthous ulcers, pyoderma gangrenosum) Iritis or uveitis Anal fissures, fistulas, perianal abscess Other external fistulas Fever >100° F	20 each
Opiates for diarrhoea	0 = no, 1 = yes	30
Abdominal mass	0 = none, 2 = questionable, 5 = definite	10
Hematocrit	Men: 47% hematocrit Women: 42% hematocrit	6
Body weight	100 × [1–(body weight/standard weight)]	1

Source: Parray et al, 2011

Table 3: Harvey Bradshaw Index

Variable	Scale	Weight
General wellbeing	Very well	0
	Slightly below par	1
	Poor	2
	Very poor	3
	Terrible	4
Abdominal pain	None	0
	Mild	1
	Moderate	2
	Severe	3
Diarrhoea		1 for each liquid stool/day
Abdominal mass	None	0
	Dubious	1
	Definite	2
	Definite and tender	3
Complications	Artralgia	1 for each item
	Uveitis	
	Erythema nodsum	
	Pyoderma gangrenosum	
	Aphthous ulcers	
	Anal fissure	
	New fistula	
	Abscess	

Source: Harvey and Bradshaw, 1980

as steroid-sparing, biological therapies and immunomodulators carry inherent risk. Biological therapies are known to induce quick remission, but have been linked with rare cases of hepatosplenic T-cell lymphoma (Feldman et al, 2007), paresthesia and demyelination (Kaltsonoudis et al, 2014). Immunomodulators carry rare complications of myelosuppression, hepatotoxicity, lymphoma and skin cancer. These are perceived as slow acting and are not useful in inducing clinical remission (Prefontaine et al, 2009). Both biologicals and immunomodulators carry the risk of opportunistic infection (Rahier et al, 2009), and require intense monitoring through serological markers and clinical review.

Inducing remission

Steroids (or more accurately, glucocorticoids) are a class of drugs with anti-inflammatory and immunosuppressive properties, widely used to treat a range of inflammatory and autoimmune disorders. They have saved countless lives, but have significant potential to do harm. Traditional drugs, such as prednisolone, are associated with a number of side effects, the most common being weight gain, the 'moon face' (Kuenzig et al, 2014), severe mood changes (toward either mania or depression), insomnia and poor concentration. In addition, there are medical complications, such as osteoporosis, hypertension, cataracts and infection (De Cassan et al, 2012).

Patients with active disease are typically treated initially with steroid preparations. The options are prednisolone and budesonide, both of which begin to control symptoms in many patients within 2–3 weeks. They should be prescribed at a recommended initial dose with a planned taper. In clinical practice, prednisolone is typically used at 40 mg daily for the first week, then tapered by 5 mg/week over an 8-week period. Budesonide is used at a dose of 9 mg for 8 weeks, reducing to 6 mg for a week, and then 3 mg for a final week (Forbes et al, 2013).

Recently, views have been expressed that steroids may not promote mucosal healing in many patients (Travis et al, 2006). Although it is recognised that corticosteroids should not be used for maintenance, they continue to be of value in the induction of remission in Crohn's disease (Travis et al, 2006). A Cochrane meta-analysis (Kuenzig et al, 2014) concluded that budesonide was an effective treatment in the induction of remission of CD, particularly when disease is limited to the distal ileum and right colon. Furthermore, recent European Crohn's and Colitis Organisation (ECCO) consensus statements (Dignass et al, 2010) recommend the use of budesonide as a first-line treatment in mild to moderate ileo-caecal CD. A treatment algorithm in line with ECCO guidelines has been developed by Dr Falk Pharma (*Figure 1*).

In comparison to prednisolone, which carries a high systemic adverse effect profile, budesonide is a locally acting glucocorticosteroid . Following oral ingestion, the active drug undergoes extensive first-pass metabolism in the liver (Greenberg et al, 1996). It is rapidly absorbed and broken down by the protein cytochrome P450 (Rutgeerts et al, 1994). This lowers the systemic bioavailability of the budesonide, resulting in 90% of the drug being converted into inactive metabolites (Edsbäcker and Andersson, 2004). Thus budesonide is associated with significantly fewer adverse effects than prednisolone (Bar-Meir et al (1998). This advantage is of particular use when treating patients in whom normal use of steroids would be of concern, such as the elderly, or diabetics.

Budesonide is commercially available in two preparations. One preparation is Budenofalk (Dr Falk Pharma), which uses pH-dependent delivery, with the drug's coating dissolving at a pH of 6.4, and comes as either capsules (3 mg) or granules (9 mg), given once daily or in divided doses. The other preparation is Entocort (AstraZeneca) (3 mg capsules given as a once daily dose of 9 mg), which has a controlled-release formation that dissolves at a pH of 5.5. The pH-dependent delivery is designed to release the drug as the pH in the terminal ileum changes (Edsbäcker and Andersson, 2004).

For decades, 5-aminosalicylic acid (5-ASA, or mesalazines) preparations have been used to treat patients with mild CD. However, there is much debate over the continued use of 5-ASA therapy in the management of CD. Although initial data promoted the use of these treatments (Hanauer and Strömberg, 2004), more recent studies detract from their use. Recent European Crohn's and Colitis Organisation (ECCO) consensus statements have indicated that their use is little more effective than placebo (Dignass et al, 2010). Long-term colitis is a risk factor for colorectal cancer, and many studies suggest that 5-ASA reduces the risk of cancer in patients with UC

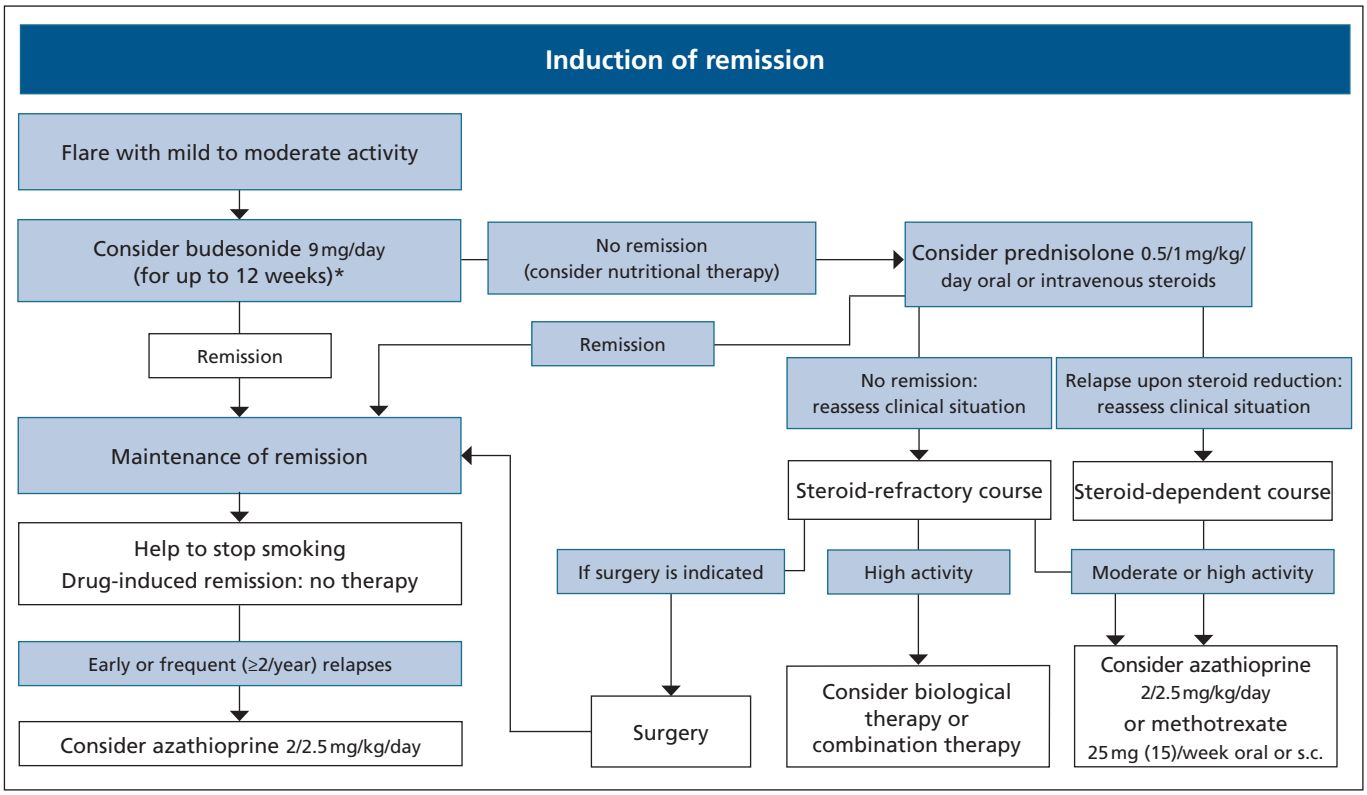

Figure 1. Therapy algorithm for mild to moderate ileocaecal Crohn's disease (adapted from Forbes et al, 2013)

(Velayos et al, 2005). Some clinicians extrapolate this and use 5-ASA to reduce the risk of cancer in patients with Crohn's colitis.

Antibiotics (metronidazole and ciprofloxacin) may be used to treat rectal and perianal disease. However, careful evaluation is crucial to look for penetrating disease and its complications—abscess and fistulisation (Baumgart and Sandborn, 2012). Examination under anaesthetic (EUA) and pelvic magnetic resonance imaging (MRI) are recommended (Gecse et al, 2014). Abscesses should be managed by a multidisciplinary team, with timely surgery by an appropriate colorectal surgeon. Many abscesses will require surgical drainage. Fistulas may require the insertion of a draining seton (Gecse et al, 2014).

A moderate-severe relapse of CD is likely to be treated initially with prednisolone. However, in established disease, especially when the patient is on maintenance medication, a moderate–severe relapse may be treated with a biological agent (NICE, 2010). There are currently two classes of biologic agents for CD: the anti-TNFs (infliximab, adalimumab and golimumab) and an anti-integrin (vedolizumab). A detailed discussion of these drugs is beyond the scope of this article.

Maintaining remission

Many patients will achieve symptomatic remission with steroids, but most will relapse (Rutgeerts et al, 1999). Patients should be considered for maintenance medication after receiving a second course of steroids, at the latest. However, maintenance medication may be started sooner in patients with a severe attack at presentation, or in those with a high-risk phenotype, such as classifications B2 and B3. Thiopurines (azathioprine and mercaptopurine) are first choice for most European clinicians. Patients should be screened for immunity to Varicella zoster virus (and vaccinated if necessary), and screened for infection by hepatitis B and C and HIV infection. Patients should be counselled about the risk of pancreatitis, skin cancer and lymphoma, and undergo regular blood monitoring. Methotrexate (oral, intramuscular or subcuteanous) is an alternative that appears to have fewer complications, although it cannot be given to women planning a pregnancy given the risk of teraterogenicty and miscarriage (Lloyd et al, 1999).

Thiopurines and methotrexate are effective in maintaining remission for CD in many patients (Plevy, 2002). If they are inappropriate, biological agents or surgery should be considered. Steroids

Crohn's disease case study

Patient M, a 19-year-old female, was referred via her GP to the gastroenterologists and reported a 6-month history of right-sided abdominal pain, diarrhoeal symptoms (bowel opening 5–6 times/day), loss of appetite, and weight loss of 8 kg. Her father had a 20-year diagnosis of Crohn's disease (CD). There was a high index of suspicion of inflammatory bowel disease (IBD), and an outpatient colonoscopy was organised. Serological, inflammatory, micronutrient markers and thiopurine methyltransferase (TPMT) were carried out.

The colonoscopy showed evidence of apthous ulceration and terminal ileitis with moderate erythema. Disease was isolated to the terminal ileum (TI) with the rest of the colonic mucosa normal. TI biopsies were performed. Patient M was commenced on 40 mg oral prednisolone on a reducing dose of 5 mg per week. She was referred onto the IBD nurses for follow-up.

Patient M was reviewed at a rapid-access clinic to discuss treatment options. Histopathology confirmed evidence of chronic inflammatory infiltrate, mild–moderate severity and evidence of epithelioid granulomas, in keeping with a new diagnosis of CD. Inflammatory indices were conforming to uncontrolled disease with elevation of C-reactive protein (CRP), white cell count, erythrocyte sedimentation rate (ESR) and platelets. Vitamin B12 deficiency was noted. The patient was keen to continue with medical therapy and the risk and benefits of thiopurines were discussed.

Symptomatic improvement was noted on prednisolone over a 2-week period. Stool frequency reduced and abdominal pain subsided. However, the patient reported side effects, including sleep disturbance, irritability and headache. Steroid therapy was switched to oral budesonide (9 mg/day) and azathioprine. Vitamin B12 supplementation was organised via the GP.

At the 3-month review, it was felt that Patient M had achieved remission. Steroid therapy was completed and azathioprine was therapeutic. There were no adverse events associated with steroids following commencement on budesonide.

should not be used to maintain remission—they are not effective in the medium to long term and their side effects are cumulative (Rutgeerts, 2001).

Like most chronic disease processes, there are issues that stem from both adherence to and tolerability of medication. Some studies have indicated that as many as 40% of patients with CD adhere poorly to treatments (Robinson, 2008; Horne et al, 2009). It has been suggested that patients who are involved in decision making and with good levels of education are more likely to adhere to therapy (Červený et al, 2007). Nurse specialists are in a favourable position to help educate patients and address any issues that may detract from adherence (Norton and Kamm, 2002).

The landscape of the management of IBD has changed over the past 15 years, particularly owing to the emergence of IBD nurse specialists (Belling et al, 2009). Nurses now contribute to the overall management of patients with CD. The role and responsibility of the nurse practitioners is varied. Nurses can offer more traditional roles, such as education and support (Smith et al, 2002), but the role has evolved. Many IBD nurse specialists have developed autonomous advanced practice roles and are involved in clinical decision making, providing expert clinical care and independently prescribing therapies (Greveson and Woodward, 2013). Nurses are often the first point of contact for patients via telephone triage and rapid access clinics, where the IBD nurses skills and knowledge allow for the application of effective intervention (Squires et al, 2015) and ultimately improve patient outcomes.

Conclusion

CD is a debilitating, lifelong disease and affects a large number of patients. The management of CD can be complex, and this in itself offers challenges to both patients and clinicians. There have been significant advances in the medical management of IBD with the use of immunomodulating and biological therapies, and although there is debate over the best pathway of treatment, it is generally agreed that treatments are effective and well tolerated.

Overall, management of CD has changed, and nurses now play an integral role in disease diagnosis, investigation and management. Many nurses now possess non-medical prescriber qualifications and contribute to the prescription management of patients.

Steroid therapy remains a mainstay of therapy for the induction of remission of CD. Although not used for maintenance, these treatments continue to have their place in any treatment pathway. The choice of steroid therapy is generally guided on the severity of disease. As demonstrated, current ECCO guidelines recommend the first-line use of budesonide in the treatment of mild to moderate ileo-caecal CD.

From a clinical perspective, efficacy of treatment is paramount. From a patient perspective, there are obvious considerations to be made, primarily side effects and tolerability of treatment. Owing to its relatively low side-effect profile, it is reasonable that budesonide would be a good clinical choice over traditional prednisolone in the treatment of mild to moderate ileo-caecal CD. GN

Declaration of interest *This article has been supported by Dr Falk Pharma UK*

Baert FJ, Rutgeerts PR (1999) Anti-TNF strategies in Crohn's disease: mechanisms, clinical effects, indications. *Int J Colorectal Dis* **14**(1): 47–51

Bar-Meir S, Chowers Y, Lavy A et al (1998) Budesonide versus prednisone in the treatment of active Crohn's disease. *Gastroenterology* **115**(4): 835–40

Baumgart DC, Sandborn WJ (2012) Crohn's disease. *Lancet* **380**(9853): 1590–605

Belling R, McLaren S, Woods L (2009) Specialist nursing interventions for inflammatory bowel disease. *Cochrane Database Syst Rev* (4): CD006597. doi: 10.1002/14651858.CD006597.pub2

Bermejo F, Algaba A, Guerra I et al (2013) Should we monitor vitamin B12 and folate levels in Crohn's disease patients? *Scand J Gastroenterol* **48**(11): 1272–7. doi: 10.3109/00365521.2013.836752

Best WR, Becktel JM, Singleton JW, Kern F Jr (1976). Development of a Crohn's disease activity index. *Gastroenterology* **70**(3): 439–44

Bouguen G, Levesque BG, Feagan BG et al (2013) Treat to target: a proposed new paradigm for the management of Crohn's disease. *Clin Gastroenterol Hepatol* **13**(6): 1042–50. doi: 10.1016/j.cgh.2013.09.006

Caprilli R (2008) Why does Crohn's disease usually occur in terminal ileum? *J Crohns Colitis* **2**(4): 352–6. doi: 10.1016/j.crohns.2008.06.001

Caprilli R, Gassull MA, Escher JC et al (2006) European evidence based consensus on the diagnosis and management of Crohn's disease: special situations. *Gut* **55**(Supp 1): i36–58

Card TR, Siffledeen J, Fleming KM (2014) Are IBD patients more likely to have a prior diagnosis of irritable bowel syndrome? Report of a case-control study in the General Practice Research Database. *United European Gastroenterol J* **2**(6):505-12. doi: 10.1177/2050640614554217

Cervený P, Bortlík M, Kubena A, Vlcek J, Lakatos PL, Lukás M (2007) Nonadherence in inflammatory bowel disease: results of factor analysis. *Inflamm Bowel Dis* **13**(10): 1244–49

Cleynen I, Vermeire S (2015) The genetic architecture of inflammatory bowel disease: past, present and future. *Curr Opin Gastroenterol* **31**(6): 456–63. doi: 10.1097/MOG.0000000000000215

De Cassan C, Fiorino G, Danese S (2012) Second-generation corticosteroids for the treatment of Crohn's disease and ulcerative colitis: more effective and less side effects? *Dig Dis* **30**(4): 368–75. doi: 10.1159/000338128

Dignass A, Van Assche G, Lindsay JO et al (2010) The second European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. *J Crohns Colitis* **4**(1): 28–62. doi: 10.1016/j.crohns.2009

Edsbäcker S, Andersson T (2004) Pharmacokinetics of budesonide (Entocort™ EC) capsules for Crohn's disease. Clin Pharmacokinet **43**(12): 803–21

Forbes A, Orchard T, Travis S, Greveson K (2013) Therapy algorithm: Mild to moderate ileocaecal Crohn's disease. Dr Falk Pharma UK

Hanauer SB (2006) Clinical perspectives in Crohn's disease. Turning traditional treatment strategies on their heads: current evidence for "step-up" versus "top-down". *Rev Gastroenterol Disord* **7**(Suppl 2): S17–22

Hanauer SB, Strömberg U (2004) Oral Pentasa in the treatment of active Crohn's disease: a meta-analysis of double-blind, placebo-controlled trials. *Clin Gastroenterol Hepatol* **2**(5): 379–88

Harvey RF, Bradshaw JM (1980) A simple index of Crohn's-disease activity. *Lancet* **1**(8167): 514

Horne R, Parham R, Driscoll R, Robinson A (2009) Patients' attitudes to medicines and adherence to maintenance treatment in inflammatory bowel disease. *Inflamm Bowel Dis* **15**(6): 837–44. doi: 10.1002/ibd.20846

Hwang C, Ross V, Mahadevan U (2012) Micronutrient deficiencies in inflammatory bowel disease: from A to zinc. *Inflamm Bowel Dis* **18**(10): 1961–81. doi: 10.1002/ibd.22906

Fascì Spurio FF, Aratari A, Margagnoni G, Doddato MT, Papi C (2012) Early treatment in Crohn's disease: do we have enough evidence to reverse the therapeutic pyramid? *J Gastrointestin Liver Dis* **21**(1): 67–73

Feldman PA, Wolfson D, Barkin JS (2007) Medical management of Crohn's disease. *Clin Colon Rectal Surg* **20**(4): 269–81. doi:10.1055/s-2007-991026

Gecse KB, Bemelman W, Kamm MA et al (2014) A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn's disease. *Gut* **63**(9): 1381–92. doi: 10.1136/gutjnl-2013-306709

Greenberg GR, Feagan BG, Martin F et al (1996) Oral budesonide as maintenance treatment for Crohn's disease: a placebo-controlled, dose-ranging study. Canadian Inflammatory Bowel Disease Study Group. *Gastroenterology* **110**(1): 45–51

Greveson K, Woodward S (2013) Exploring the role of the inflammatory bowel disease nurse specialist. *Br J Nurs* **22**(16) 952–8

IBD Standards Group (2013) Standards for the Healthcare of People who have Inflammatory Bowel Disease (IBD). http://tinyurl.com/m5ypc8h (accessed 30 November 2015)

Kuenzig ME, Rezaie A, Seow CH et al (2014) Budesonide for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* (8): CD002913. doi: 10.1002/14651858.CD002913.pub3

Kaltsonoudis E, Voulgari PV, Konitsiotis S, Drosos AA (2014) Demyelination and other neurological adverse events after anti-TNF therapy. *Autoimmun Rev* **13**(1): 54–8. doi: 10.1016/j.autrev.2013.09.002

Laass MW, Roggenbuck D, Conrad K (2014) Diagnosis and classification of Crohn's disease. *Autoimmun Rev* **13**(4): 467–71. doi: 10.1016/j.autrev.2014.01.029

Lichtenstein GR, Hanauer SB, Sandborn WJ (2009) Management of Crohn's disease in adults. *Am J Gastroenterol* **104**(2): 465–83. doi: 10.1038/ajg.2008.168

Lin MV, Blonski W, Lichtenstein GR (2010) What is the optimal therapy for Crohn's disease: step-up or top-down? *Expert Rev Gastroenterol Hepatol* **4**(2): 167–80. doi: 10.1586/egh.10.4

Lloyd ME, Carr M, McElhatton P, Hall GM, Hughes RA (1999) The effects of methotrexate on pregnancy, fertility and lactation. *QJM* **92**(10): 551–63

Molodecky NA, Soon S, Rabi DM et al (2012) Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* **142**(1): 46–54. doi: 10.1053/j.gastro.2011.10.001

Mowat C, Cole A, Windsor AL et al (2011) Guidelines for the management of inflammatory bowel disease in adults. *Gut* **60**(5): 571–607. doi: 10.1136/gut.2010.224154

Mozdiak E, O'Malley J, Arasaradnam R (2015) Inflammatory bowel disease. *BMJ* **351**: h4416. doi: 10.1136/bmj.h4416.

Munro C (2014) The IBD Registry: a patient management system to improve practice. *Gastrointestinal Nursing* **12**(2): 20–7. doi: 10.12968/gasn.2014.12.2.20

National Institute for Health and Care Excellence (2008) NICE Guidelines [CG61] Irritable bowel syndrome in adults: diagnosis and management. http://tinyurl.com/jmhw7zz (accessed 30 November 2015)

National Institute for Health and Care Excellence (2010) NICE technology appraisal guidance [TA187] Infliximab (review) and adalimumab for the treatment of Crohn's disease. http://tinyurl.com/jhdstrx (accessed 30 November 2015)

National Institute for Health and Care Excellence (2013) NICE diagnostics guidance [DG11] Faecal calprotectin diagnostic tests for inflammatory diseases of the bowel. http://preview.tinyurl.com/zlz5dus (accessed 30 November 2015)

Norton C, Kamm MA (2002) Specialist urses in gastroenterology. *J R Soc Med* **95**(7): 331–5

Ordás I, Feagan BG, Sandborn WJ (2011) Early use of immunosuppressives or TNF antagonists for the treatment of Crohn's disease: time for a change. *Gut* **60**(12): 1754–63

Parkes GC, Whelan K, Lindsay JO (2014) Smoking in inflammatory bowel disease: Impact on disease course and insights into the aetiology of its effect. *J Crohns Colitis* **8**(8): 717–25. doi: 10.1016/j.crohns.2014.02.002

Parray FQ, Wani ML, Bijli AH, Thakur N, Irshad I, Nayeem-ul-Hassan (2011) Crohn's disease: a surgeon's perspective. *Saudi J Gastroenterol* **17**(1): 6–15. doi: 10.4103/1319-3767.74430

Plevy SE (2002) Corticosteroid-sparing treatments in patients with Crohn's disease. *Am J Gastroenterol* **97**(7): 1607–17

Prefontaine E, Sutherland LR, MacDonald JK, Cepoiu M (2009) Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* (1): CD000067. doi: 10.1002/14651858.CD000067.pub2

Rahier JF, Ben-Horin S, Chowers Y et al (2009) European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* **3**(2): 47–91. doi: 10.1016/j.crohns.2009.02.010

Robinson A (2008) Review article: improving adherence to medication in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* **27**(Suppl 1): 9–14. doi: 10.1111/j.1365-2036.2008.03604.x

Rogler G (2013) Top-down or step-up treatment in Crohn's disease? *Dig Dis* **31**(1): 83–90. doi: 10.1159/000347190

Rutgeerts P, Löfberg R, Malchow H et al (1994) A comparison of budesonide with prednisolone for active Crohn's disease. *N Engl J Med* **331**(13): 842–5

Rutgeerts P, D'Haens G, Targan S et al (1999) Efficacy and safety of retreatment with anti–tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. *Gastroenterology* **117**(4): 761–9

Rutgeerts PJ (2001) The limitations of corticosteroid therapy in Crohn's disease. *Aliment Pharmacol Ther* **15**(10): 1515–25

Satsangi J, Silverberg MS, Vermeire S, Colombel J (2006) The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* **55**(6): 749–53

Schreyer AG, Rath HC, Kikinis R et al (2005) Comparison of magnetic resonance imaging colonography with conventional colonoscopy for the assessment of intestinal inflammation in patients with inflammatory bowel disease: a feasibility study. *Gut* **54**(2): 250–6

Soon S, Molodecky NA, Rabi DM, Ghali WA, Barkema HW, Kaplan GG (2012) The relationship between urban environment and the inflammatory bowel diseases: a systematic review and meta-analysis. *BMC Gastroenterol* **12**(1): 51. doi: 10.1186/1471-230X-12-51.

Smith GD, Watson R, Roger D, Luman W, Palmer K (2002) Impact of a nurse Led counselling service on quality of life in patients with Inflammatory Bowel Disease. *J Adv Nurs* **38**(2): 152–60

Squires SI, Boal AJ, Naismith GD (2015) The financial impact of a nurse-led telemedicine service for inflammatory bowel disease in a large district general hospital. *Frontline Gastroenterol.* doi:10.1136/flgastro-2015-100630

Travis SP, Stange EF, Lémann M et al (2006) European evidence based consensus on the diagnosis and management of Crohn's disease: current management. *Gut* **55**(Supp 1): i16–35

Velayos FS, Terdiman JP, Walsh JM (2005) Effect of 5-aminosalicylate use on colorectal cancer and dysplasia risk: a systematic review and meta-analysis of observational studies. *Am J Gastroenterol* **100**(6): 1345–53

Vermeire S, Schreiber S, Sandborn WJ, Dubois C, Rutgeerts P (2010) Correlation between the Crohn's disease activity and Harvey–Bradshaw indices in assessing Crohn's disease severity. *Clin Gastroenterol Hepatol* **8**(4): 357–63. doi: 10.1016/j.cgh.2010.01.001

Vos ACW, Hommes DW (2012) Step-Up vs. Top-down approach in medical management of inflammatory bowel disease. In: Baumgart DC, ed. *Crohn's Disease and Ulcerative Colitis: From Epidemiology and Immunobiology to a Rational Diagnostic and Therapeautic Approach*. Springer, New York: 535–47

Wehkamp J, Harder J, Weichenthal M et al (2004) NOD2 (CARD15) mutations in Crohn's disease are associated with diminished mucosal alpha-defensin expression. *Gut* **53**(11): 1658–64