Crohn's disease: a clinical update

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***Abstract*:** Crohn's disease is increasing in prevalence worldwide. It arises from a complex interplay between both genetic predisposition and environmental influence. A search of databases and clinical practice guidelines was performed to provide the most up-to-date evidence-based approach for diagnosing and managing patients with Crohn's disease. No single gold standard investigation exists. Whilst full ileocolonoscopy with biopsies remains the mainstay for diagnosis, other less invasive imaging modalities are being actively considered in the workup, as well as the use of serological markers. Management should incorporate dietary and lifestyle modifications where necessary, the use of medications in induction and remission of disease, and consideration of surgical intervention where medical therapy has failed.

Keywords: Crohn's disease, diagnosis, inflammatory bowel disease, investigations, management, colorectal cancer, risk factors

Introduction

Crohn's disease (CD) is a chronic relapsing inflammatory bowel disease (IBD). It is characterized by a transmural granulomatous inflammation which can affect any part of the gastrointestinal tract, most commonly the ileum, colon or both [Thia *et al.* 2010]. Its prevalence has continually increased over the past 50 years with the highest incidence being reported in northern Europe, the United Kingdom and North America [Cosnes *et al.* 2011]. Despite biological treatment being associated with an improved health-related quality of life [van der Have *et al.* 2014], patients still report significant impediment on lifestyle and daily activities during both flares and remissions [Devlen *et al.* 2014]. The mortality amongst patients with CD has been persistently higher than the general population with a meta-analysis showing a pooled estimate for the standardized mortality ratio of 1.52 [Canavan *et al.* 2007]. No statistically significant change has occurred for this estimate over the past 30 years and thus CD remains relevant to a broad spectrum of clinicians involved in the multidisciplinary care of affected patients.

Methods

This evidence-based review derives from a comprehensive search of several databases including: Ovid Medline, Cochrane library and PubMed. MeSH terms used were "Crohn disease", "Inflammatory Bowel Diseases" with other search terms including "epidemiology", "risk factors", "diagnosis", "investigations", "management" and "colorectal cancer".

Clinical features

CD is a clinical diagnosis formed by correlation of clinical signs and symptoms, objective data from imaging including endoscopic with histologic information as well as laboratory studies [Baumgart and Sandborn, 2012]. Chronic diarrhoea, defined as a decrease in faecal consistency for more than 4 weeks [Juckett and Trivedi, 2011], is the most common presenting symptom [Sands, 2004]. Abdominal pain (70%), weight loss (60%) and blood, mucus or both in stools (40–50%) are also common findings in CD [Lennard-Jones and Shivananda, 1997]. Extraintestinal manifestations affect approximately a third of patients with IBD [Trost and McDonnell, 2005; Lourenco *et al.* 2010]. The most commonly observed extraintestinal manifestation is primary peripheral arthritis (33%); aphthous stomatitis, uveitis, erythema nodosum and ankylosing spondylitis can be seen whilst pyoderma gangrenosum, psoriasis and primary sclerosing cholangitis are relatively uncommon [Bernstein *et al.* 2001; Vavricka *et al.* 2011]. Fistulae, a complication of CD, occurs in up to 35% of patients with CD, with

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perianal fistula occurring in 20% [Schwartz *et al.* 2002]. These clinical features associated with disease activity were found to contribute to 37% of health-related quality-of-life (HRQOL) in a systematic review analysing determinants of HRQOL in CD [van der Have *et al.* 2014]. According to a patient-reported qualitative analysis [Devlen *et al.* 2014], there is impact on lifestyle in regards to taking regular medication, restricting diet and avoiding certain trigger foods, as well as impact on daily activities where patients report absence from employment or school during acute flares due to pain and fatigue.

Risk factors

CD has a peak age prevalence of 30–39 years old and gender influence differs in various demographics. In a Canadian and New Zealand population, females are 10–30% more likely to acquire the disease than males [Bernstein *et al.* 2006; Gearry *et al.* 2006], whereas males with CD are reported as up to three times more likely in Japan and Korea [Yao *et al.* 2000; Kim *et al.* 2015]. Although the exact aetiology remains unknown, it is a complex interaction between genetic predisposition, environmental risk factors and immune dysregulation to intestinal microbiota [Sartor and Muehlbauer, 2007]. A co-twin British cohort study showed concordant monozygotic twins with CD had similar disease location, disease behaviour and a moderate agreement for age at diagnosis [Ng *et al.* 2012]. This genetic influence is consistent with previous findings from another co-twin German study [Spehlmann *et al.* 2008]. Familial aggregation has been shown with most children acquiring the disease at an earlier time in life compared with their parents [Bengtson *et al.* 2009]. High prevalence has also been found amongst Jewish populations although varying prevalence in different geographic locations suggests the influence of environmental factors as well [Fireman *et al.* 1989]. Other inflammatory diseases have been implicated with CD including asthma, psoriasis, pericarditis, ankylosing spondylitis, atopic dermatitis and primary sclerosing cholangitis [Bernstein *et al.* 2005; Lees *et al.* 2011].

Moreover, environmental risk factors have attributed to the rising incidence of CD worldwide [Thia *et al.* 2008]. Their impact tends to be most influential during childhood [Feeney *et al.* 2002. Smoking has been confirmed to influence the phenotype of CD [Halfvarson *et al.* 2006; Bengtson *et al.* 2009; Ng *et al.* 2012] and a meta-analysis found that smoking increased the risk of CD by more than twice [Calkins, 1989]. Previous history of symptomatic mumps [Ng *et al.* 2012] and a high dietary intake of fats, polyunsaturated fatty acids, omega-6 fatty acids and meats have both been associated with an increased risk of CD, whilst a high fibre and fruit diet has been seen to be protective [Hou *et al.* 2011]. The oral contraceptive pill has also been associated with the development of CD; a meta-analysis [Cornish *et al.* 2008] assessing quantitative risk of the oral contraceptive pill (OCP) in the aetiology of CD found a pooled relative risk for women currently exposed to the OCP was 1.51 (95%CI 1.17–1.96, $p = 0.002$).

Diagnosis and investigations

No single definitive diagnostic investigation exists for the diagnosis of CD [Dignass *et al.* 2010]. Full ileocolonoscopy with biopsies is currently the most widely used diagnostic investigation [Baumgart and Sandborn, 2012]. This can demonstrate noncaseating granulomas, though may only be detected in up to 60% of resected specimens and even less so in biopsy samples [Nikolaus and Schreiber, 2007]. Cross-sectional imaging studies have been increasingly involved in the diagnostic evaluation of CD. This includes ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI). A systematic review [Panes *et al.* 2011] comparing the accuracy of each cross-sectional imaging modality in the diagnosis of CD found US had a sensitivity and specificity of 85% (95% CI 83–87%) and 98% (95% CI 95–99%), respectively. This was superior to MRI which had an overall sensitivity and specificity of 78% (95% CI 67–84%) and 85% (95% CI 76–90%) respectively. Another systematic review comparing the diagnostic accuracy of magnetic resonance enterography (MRE) and computed tomography (CTE) found MRE had a diagnostic yield comparable with CTE, but does not carry the same risks of radiation exposure, especially to younger patients [Qiu *et al.* 2014].

A normal finding on ileocolonoscopy is not sufficient to exclude the diagnosis of CD as 27% of patients have disease localized to the terminal ileum [Cleynen *et al.* 2013], which can prove difficult to diagnose [Doherty *et al.* 2011]. Capsule endoscopy is a relatively new, simple, noninvasive imaging technique that is gaining recognition for small bowel exploration [Munoz-Navas, 2009]. The investigation involves consumption of a

disposable, small, wireless camera within a capsule which passes through the gastrointestinal tract allowing direct visualization of the mucosa [Nakamura and Terano, 2008]. A meta-analysis comparing the diagnostic yield of capsule endoscopy to other imaging modalities found an increased diagnostic rate of 15% over colonoscopy with ileoscopy [Dionisio *et al.* 2010].

Disease heterogeneity and atypical presentations of IBD have highlighted the need for new diagnostic tools in addition to ileocolonoscopy with biopsy and other imaging studies. This has led to research of serological markers with the two most intensively studied serological markers being atypical perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) and anti *Saccharomyces cerevisiae* antibodies (ASCA) [Bossuyt, 2006]. pANCA are antibodies formed against proteins in the nuclear lamina of neutrophils, whilst ASCA are antibodies against mannose epitopes from the yeast *Saccharomyces cerevisiae* [van Schaik *et al.* 2013]. The generation of antibodies occurs most likely from abnormal response of mucosal immune system to commensal intestinal flora in genetically susceptible patients [van Schaik *et al.* 2013]. A systematic review of the role of serological antibodies in diagnosing IBD found the most sensitive and specific test for CD was sera with positive ASCA and negative pANCA, 52–64% and 92–94%, respectively [Prideaux *et al.* 2012]. The identification of these markers can help differentiate CD from ulcerative colitis where diagnosis remains ambiguous following clinical, histological and endoscopic grounds as well provide the opportunity for early intervention given their ability to predict development of CD [van Schaik *et al.* 2013].

Management

Decisions in the management of CD should always be made through discussion between the multidisciplinary team and patients themselves. Risk factors such as smoking should be ceased due to its harmful impact on the course of disease and potentially the OCP depending on the patient's circumstances. A balanced diet of high fibre and fruits have been shown to be protective against CD and should be encouraged [Hou *et al.* 2011].

Pharmacological management

Medications are intended to suppress the inflammatory response and a host of therapeutic agents are now available to treat CD [Seow *et al.* 2008]. The conventional approach to managing active disease has been derived from progressive intensification of drug therapy, with the focus on inducing and maintaining clinical remission. However, there is evidence to suggest the use of aggressive treatment early to improve clinical outcomes in patients with risk factors predisposing to increased disease severity [D'haens *et al.* 2014]. These include smoking [Lees *et al.* 2011], initial requirement of steroid use, age below 40 years and presence of perianal disease [Beaugerie *et al.* 2006]. Usually medications such as corticosteroids, budesonide or mesalazine are prescribed initially for induction of remission [Dignass *et al.* 2010]. Anti-tumour necrosis factor (TNF) immunosuppressive therapies are also used in patients refractory to conventional therapy. Medical management of CD is reliant upon compliance and patient education is crucial, with patient age and follow up by a gastroenterologist being independently associated with nonadherence [Zelante *et al.* 2014].

Corticosteroids are widely prescribed for the induction but not the maintenance of remission due to increasing resistance over time, patient dependence and adverse side effects with long-term use [Kuenzig *et al.* 2014]. Budesonide is an alternate enteral glucocorticoid used for induction with limited systemic bioavailability due to extensive first-pass hepatic metabolism by cytochrome p-450 enzymes [Kuenzig *et al.* 2014]. A systematic review evaluating use of budesonide for the induction of remission in CD showed budesonide to be significantly superior to placebo up to 8 weeks with a relative risk (RR) of 1.96 (95% CI, 1.19–3.23) [Seow *et al.* 2008]. Although budesonide was shown to be inferior to conventional steroids for the induction of remission in active CD (RR 0.85; 95% CI 0.75–0.97), it had significantly fewer corticosteroid-related adverse events compared with those treated with conventional corticosteroids (RR 0.64; 95% CI 0.54–0.76) [Seow *et al.* 2008].

5-Aminosalicylates also have a long established use in IBD [Akobeng and Gardener, 2005], initially as sulfasalazine, a compound consisting of 5-aminosalicylic acid and sulfapyridine. More recently, 5-aminosalicylic acid has been isolated as a single agent being the active component without sulfapyridine, which was responsible for the majority of adverse side effects [Ford *et al.* 2011]. However, a systematic review assessing the efficacy of 5-aminosalicylates in CD found insufficient evidence for their definitive use in either

inducing remission or preventing relapse in CD [Ford *et al.* 2011].

Purine antimetabolites azathioprine and 6-mercaptopurine have both been used in patients with active CD, although evidence has been conflicting and controversial. A Cochrane review found 48% of patients receiving antimetabolites achieved remission compared with 37% of placebo patients, with no statistically significant difference between the two groups [Chande *et al.* 2013]. Evidence remains sparse in regards to whether purine analogues are superior to placebo for maintenance of surgically-induced remission in patients with CD [Gordon *et al.* 2014]. Methotrexate, another antimetabolite with antagonistic action against folic acid, was superior to placebo in maintenance of remission at 40 weeks; 65% of patients receiving intramuscular methotrexate maintained remission compared to 39% in the placebo group (RR 1.67 95% CI 1.05–2.67) [Patel *et al.* 2014].

Anti-TNF immunosuppressive therapies, most commonly infliximab and adalimumab, are another group of agents generally reserved for patients refractory to conventional therapies. A randomized controlled trial [Colombel *et al.* 2010] evaluating the efficacy of infliximab monotherapy, azathioprine monotherapy and combination of both found 56.8% of patients receiving combination therapy achieved corticosteroid-free clinical remission at week 26 compared with 44.4% receiving infliximab alone ($p = 0.02$) and 30.0% receiving azathioprine alone ($p < 0.001$). Superiority of combination therapy compared with monotherapy of adalimumab remains unclear.

More recently, the novel agent vedolizumab, a monoclonal antibody targeting α4β7 [Bryant *et al.* 2015], has shown efficacy in a randomized controlled trial for the induction of remission of CD compared with placebo (14.5% and 6.8%, respectively, $p = 0.02$) as well as maintenance of remission [Sandborn *et al.* 2013]. Vedolizumab has also demonstrated similar efficacy to natalizumab, another anti-α4 integrin, although it does not pose the risk of progressive multifocal leukoencephalopathy as natalizumab does. However, a network meta-analysis found adalimumab to be superior to vedolizumab in maintenance of remission and its role in the stepwise management of CD still needs to be defined in further trials [Hazlewood *et al.* 2015]. Ustekinumab, a monoclonal antibody against interleukin-12, has also demonstrated a role in maintenance of remission of CD [Sandborn *et al.* 2012] and these biologic agents are likely to change the approach to medical management in the near future.

Surgical management

The majority of patients diagnosed with CD will have a surgical resection within 10 years of their diagnosis [Bernell *et al.* 2000]. Surgical treatment is required for failed medical therapy, recurrent intestinal obstruction, malnutrition and for septic complications such as perforations and abscesses [Dasari *et al.* 2011]. It has a role in limiting other complications including complex perianal disease and internal fistulas [Baumgart and Sandborn, 2012] as well as improving quality of life [Delaney *et al.* 2003]. However, the underlying pathology still persists resulting in high recurrence of disease, ranging from 28 to 45% at 5 years and 36 to 61% at 10 years [Buisson *et al.* 2012]. Surgical admissions account for more than half of all hospitalizations and accounts for almost 40% of total financial costs to patients [Cohen *et al.* 2000].

Laparoscopy has been widely accepted in gastrointestinal surgery over open surgery in CD [Duepree *et al.* 2002]. Whilst laparoscopy offers certain advantages of smaller abdominal wounds, lower risk of hernia and decreased rate of small bowel obstruction, there are concerns that occult segments of disease and severe strictures can be missed due to limited tactile ability [Dasari *et al.* 2011]. However, a meta-analysis on perioperative complications and long-term outcomes between open surgery and laparoscopic surgery found a nonsignificant difference in rate of surgical recurrence and a decreased risk of perioperative complications in the laparoscopic group compared to the open surgery group (12% to 18%, RR = 0.71 CI = 0.58–0.86, $p = 0.001$) [Patel *et al.* 2013]. The overall cost including hospital stay costs and costs associated with lost working days between laparoscopic-assisted bowel resection and open surgery was no different [Scarpa *et al.* 2009]. Despite the evidence for the advantages of laparoscopic surgery, further randomized controlled trials with adequate follow up are required prior to firm recommendations being made [Patel *et al.* 2013].

Malignancy

The association between CD and malignancy is well documented, although the risk of colorectal cancer is decreasing [Soderlund *et al.* 2009]. A meta-analysis of population-based cohort studies

found a pooled standardized incidence ratio (SIR) of 1.7 amongst patients with CD in the general population (95% CI 1.01–2.5) and a pooled SIR of 4.4 in referral centres (95% CI 1.5–7.2) [Lutgens *et al.* 2013]. For patients with chronic perianal fistula, there is possibility of malignant transformation and it should not be overlooked by the treating clinician [Thomas *et al.* 2010]. There is a lack of consensus in regards to the frequency of colonoscopic surveillance. The American Gastroenterological Association (AGA) recommends surveillance intervals of 1–3 years for a maximum of 8 years after diagnosis [Farraye *et al.* 2010] whilst the British Society of Gastroenter-ology (BSG) recommends yearly, 3-yearly or 5-yearly intervals depending on risk factors after ten years [Cairns *et al.* 2010]. Chromoendoscopy is also a relatively recent technique that uses topical application of dyes or pigments to improve detection of subtle mucosal aberrations compared with usual white light endoscopy. A meta-analysis showed that, although chromoendoscopy had a 7% increase in dysplasia detection (95% CI 3.2–11.3) compared with white light endoscopy, it is uncertain as to whether this confers a survival benefit in patients given most were low grade dysplasia [Subramanian *et al.* 2011]. The SCENIC consensus statement (Surveillance for Colorectal Endoscopic Neoplasia Detection and Manage-ment in Inflammatory Bowel Disease Patients: International Consensus Recommendations) nevertheless recommends chromoendoscopy as the preferred technique for surveillance for dysplasia in IBD [Laine *et al.* 2015].

Conclusion

There are still certain gaps in the evidence regarding the diagnosis and management of CD. Each patient must be assessed individually to determine which investigation is most appropriate, taking into consideration age, suspected location of disease, disease severity and likelihood of recurrence. Numerous diagnostic techniques, be it serological markers or imaging modalities, have assisted both diagnosis and monitoring of CD. Further research is needed to assess the efficacy of certain novel therapeutic agents including vedolizumab and ustekinumab, and their role in active CD compared with classic anti-TNF therapy.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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