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MANAGEMENT OF CROHN'S DISEASE

- **Crohn's Disease (CD) is a chronic inflammatory disease that can involve any part of the gut from the mouth to the anus**
- **The symptoms and signs depend on the affected site and the predominant pathological process; patients typically present with abdominal pain, diarrhoea and weight loss**
- **Corticosteroids are the mainstay for the induction of remission of CD; budesonide is the treatment of first choice for localised ileocaecal disease**
- **Maintenance treatment includes smoking cessation, immunomodulatory and/or biologic agents**
- **Surgery is a therapeutic option in some patients**

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD), which has shown increased incidence and prevalence, especially during the last 50 years in the western world.[1] Typically CD begins in young adulthood and follows a pattern of acute flare-ups alternating with periods of remission throughout life.[2] CD patients often have to deal with unpredictable and potentially debilitating symptoms and they require long-term treatment with frequent adverse effects, and the potential need for surgery and hospitalisation. Therefore CD patients report a lower quality of life compared with healthy individuals.[3]

According to a recent report, IBD (including CD and ulcerative colitis (UC)) affects approximately 20,000 Irish people today.[2] The IMPACT study on IBD from 2011 reported that only 36% of CD patients in Ireland were diagnosed within a year, although early diagnosis and early treatment are important.[4] In addition, 90% of those with IBD in that study had been hospitalised due to their disease, and more than half of those with CD had undergone surgery at least once. Therefore, CD places a huge burden on both patients and public health resources. A previous bulletin from the National Medicines Information Centre (NMIC) dealt with the management of UC in adults in Ireland.[5] This, the second of 2 bulletins on IBD, will outline the management options currently available for adults with CD.

PATHOPHYSIOLOGY AND CLINICAL FEATURES OF CROHN'S DISEASE

CD is a chronic inflammatory disease that can involve any part of the gut from the mouth to the anus. Table 1 outlines the possible causes and clinical features of CD.

Table 1: Main Features of Crohn's Disease[6-13]

Feature*	Crohn's Disease
Genetic factors	≈40% concordance for monozygotic twins (multiple gene involvement)
Environmental risk factors	Alteration in gut microbiota; cigarette smoking; use of processed food; high-fat diets in some ethnic groups (e.g. Japanese); some medicines
Site of disease	Any part of gut from mouth to anus (most commonly distal ileum and proximal colon - accounts for 40% of cases). Disease produces "skip" i.e. discontinuous gut lesions
Peak age of onset / Gender	20-40 years; smaller peak in older adults. Can occur at any age, including children. More common in females (20% more common)
Clinical features	Abdominal pain and diarrhoea. Nocturnal symptoms, weight loss, anorexia, fever and anaemia (due to deficiency of iron or folate or vitamin B12) and rectal bleeding may also occur. Strictures may lead to bowel obstruction
Natural history of the disease	Chronic disease, with symptoms dependent on extent of gut involvement, and disease pattern (i.e. penetrating or structuring). Disease waxes and wanes - 15% may have continuous symptoms
Extra intestinal manifestations**	Include: ↑ risk of TE, arthropathy, sacroileitis, ankylosing spondylitis, primary sclerosing cholangitis, uveitis, skin manifestations including erythema nodosum and pyoderma gangrenosum
Cancer risk	↑ risk of colorectal cancer with Crohn's colitis (↑ risk with ↑ extent, ↑ duration and ↑ inflammatory activity of colonic disease). ↑ risk of small bowel cancer (typically in ileal disease) after ≥8 years of active disease

*data taken primarily from studies in developed world. **more common in Crohn's colitis. TE=venous / arterial thromboembolism

The cause of CD is thought to **involve both genetic and environmental factors** which are associated with immune-mediated damage;[9,11,13] the **genetic component appears to be more important for CD** compared with UC.[13] Similar environmental factors to UC have been noted, particularly alteration of gut microbiota (so-called dysbiosis),[9] most likely associated with a western lifestyle and use of certain medicines (including oral hormonal contraceptives, antimicrobial agents and non-steroidal anti-inflammatory drugs).[10-13] Some studies have suggested an association between high-fat foods and CD in Japanese populations (Table 1).[13] No specific pathogen has been discovered, however an increase in adherent-invasive species of *E. coli* has been reported in patients with CD.[11] In contrast to UC, **prior appendicectomy and cigarette smoking are risk factors for CD**.[10]

Clinical Presentation: CD is a focal disease; it can begin with an ulcer(s) that may develop into strictures or fistulas (penetrating the gut wall), in any part of the gut.[6,7,10] Therefore, the symptoms and signs of CD depend on the affected site and the predominant pathological process in the individual patient.[10] **Patients with CD typically present with abdominal pain and diarrhoea and weight loss** (Table 1). A tender mass in the right iliac fossa (due to ileal disease) may be palpable. Pain tends to be constant with abscess or inflammation (with or without fever) but may be intermittent and colicky with small bowel stricture formation (due to subacute obstruction).[6] **Complications** include undernutrition, anaemia, short-bowel syndrome (due to extensive bowel resection), and an increased risk of cancer (especially with Crohn's colitis); extra-intestinal manifestations may also be present as listed in Table 1.

DIAGNOSIS OF CROHN'S DISEASE

A single gold standard for the diagnosis of CD is currently not available; therefore diagnosis is confirmed by clinical evaluation and a combination of endoscopic, histological, radiological and/or biochemical investigations.[6,10] The **clinical history** checks for the typical symptoms of CD (see Table 1) with particular attention paid to the well-proven risk factors (including smoking and family history); the **clinical examination** assesses general well-being (including vital signs and evidence of weight loss), abdominal tenderness, distension or palpable masses and should include an oral and perineal inspection. **Laboratory investigations** include a full blood count, ESR and C-reactive protein (to assess inflammatory activity), assessment of liver (LFTs) and renal function, vitamin B12 and iron.[10,14] Stool culture may be required to rule out infectious causes, and a faecal level of the enzyme calprotectin is a useful measure of non-specific gut inflammatory activity, if available. **Endoscopy and radiological examinations** are complementary techniques to define the site and extent of CD in order to optimise therapy.[10] Ileocolonoscopy is useful for diagnosing colonic and terminal ileal disease and enables histological diagnosis by multiple mucosal biopsies; upper GI endoscopy is also helpful for small bowel evaluation. MRI scanning (MR enterography / enteroclysis) is the recognised radiological standard for assessing small bowel disease.[10] Depending on the presentation, **differential diagnoses** include: UC, GI infection, appendiceal abscess, tuberculosis, malabsorption, gynaecological conditions such as ovarian cyst and (rarely) neoplasia.[6]

CLASSIFICATION OF CROHN'S DISEASE

CD may be classified according to the **age at diagnosis**, **location of disease** (ileal, colonic, ileocolonic, isolated upper GI disease) and **disease behaviour** (stricturing; penetrating; non-stricturing / non-penetrating).[15] Factors associated with a poor prognosis include age of onset <40 years, perianal (fistulating) disease at diagnosis, weight loss >5kg and stricturing disease.[16] In addition, disease may be classified according to disease activity; however, because of the heterogeneous presentation of CD, assessment of **disease activity** is more complicated than with UC.[10,16] There are several methods for calculating disease activity; the Crohn's Disease Activity Index (**CDAI**) is based on quantification of GI and systemic findings (http://www.ibdjohn.com/cdai/) and is most commonly used in clinical trials, while the Harvey-Bradshaw Index (**HBI**) for CD is a more simplified tool that is useful in clinical practice.[10,17] Studies have reported good correlation between the CDAI and HBI.[18] Table 2 outlines the HBI for CD. Table 3 outlines how the severity of disease activity may be assessed using the HBI.

Table 2: Harvey-Bradshaw Index (HBI) for Crohn's disease[17]

Clinical Variable	Scoring (points)
General well-being	0 (very well); 1 (slightly below par); 2 (poor); 3 (very poor); 4 (terrible)
Abdominal pain	0 (none); 1 (mild); 2 (moderate); 3 (severe)
Number of liquid stools / day	1 per occurrence
Abdominal mass	0 (none); 1 (dubious); 2 (definite); 3 (definite and tender)
Complications: arthralgia; uveitis; erythema nodosum; aphthous ulcer; pyoderma gangrenosum; anal fissure; new fistula; abscess	1 per item

Table 3: Severity of Disease Activity for Crohn's disease according to the Harvey-Bradshaw Index[17]

Remission	Mild	Moderate	Severe
<5	5-7	8-16	>16

MANAGEMENT OF CROHN'S DISEASE

The aims of treatment of CD are to induce and maintain remission of disease. Management involves a **multidisciplinary team (MDT)** approach including medical and surgical teams, experienced in the management of IBD, specialist nurses, nutritionists, pharmacists and patient support groups.[19] **Treatment modalities (in terms of medical, nutritional and surgical options) are much wider and more integrated for CD** compared with UC; their relative importance in the management plan varies according to the site and behaviour (i.e. stricturing or penetrating) of disease and the level of disease activity.[16] The **patient needs to be kept fully informed** about his or her illness and should be actively included in the therapeutic decision-making process.[19]

Before deciding on the treatment regimen, the predominant **location and behaviour of the disease**, the **severity of disease activity** (see Table 3) and the presence of **co-morbidities** (e.g. infection, abscess or fistula, stricture, symptoms related to prior surgery or therapy-related complications) must be determined.[16,19,20]

MEDICAL MANAGEMENT

The medicines used in CD are broadly similar to those used in UC with some exceptions. The pharmacological profiles of these agents have been discussed in the recent NMIC bulletin on UC;[5] full prescribing information, including information on monitoring requirements is available in the individual Summary of Product Characteristics (SmPC) for each medicine (www.hpra.ie; www.medicines.ie).

INDUCTION OF REMISSION

Mild to moderately active CD: Corticosteroids (CS) are recommended for use in the initial induction of mild to moderately active disease (see Table 3).[19] **Oral budesonide** 9mg/day is the preferred treatment for localised *ileocaecal disease* in this group.[19,21] Although the level of efficacy may be less than with prednisolone (40-60mg/day), budesonide is usually sufficient for this population and has a better safety profile (including less negative impact on bone metabolism and less adrenal suppression).[21,22] The full benefit of effect is usually achieved within 2-4 weeks. Overall study findings suggest that **5-aminosalicylates** (>3g/day 5-ASA) may be less effective than budesonide in CD patients without active colitis.[19,23,24] Patients with *more widespread small bowel disease or active colitis* may be treated with CS, with or without 5-ASA as appropriate.[25,26] CS therapy should generally be tapered slowly for the last 2-4 weeks of therapy.[19,21]

In moderate to severely active disease or in patients who have **failed initial induction therapy**, systemic CS, either **oral prednisolone or IV hydrocortisone** (300-400mg/day) if unable to eat, combined with an immunomodulatory agent is recommended.[19,24] The thiopurines **azathioprine** (AZA) or **6-mercaptopurine** (6-MP) may take several months to achieve full effect but are useful as adjunctive therapy and as steroid-sparing agents (unlicensed indication).[19,27-29] **Methotrexate** (MTX, the anti-folate immunomodulatory agent, **given once weekly**) may be used if thiopurines are

not tolerated (unlicensed indication).[24,30,31] All patients on immunomodulatory therapy must be closely monitored for evidence of toxicity.[27,28,30]

If the disease fails to respond to these treatment regimens or if the patient is intolerant of them, anti-Tumour Necrosis Factor alpha therapy (anti-TNFα therapy - **infliximab or adalimumab**) should be started.[19,32,33] Studies have reported increased efficacy with thiopurine plus anti-TNFα combination therapy with no incremental increase in toxicity.[34,35] If there is no response to one anti-TNFα, the patient may benefit from switching to another anti-TNFα.[20] Early introduction of anti-TNFα therapy with or without an immunomodulatory agent, so-called "**top-down" therapy,** may be warranted in severely active CD.[36] **Vedolizumab,** the gut-selective immunosuppressive biological agent may be used for those with moderately to severely active CD who have an inadequate response with, lost response to, or were intolerant to either conventional therapy or anti-TNFα therapy.[37] Prior to initiating anti-TNFα or vedolizumab therapy, patients must be evaluated for infections (including latent tuberculosis) and must be closely monitored during treatment for evidence of toxicity (See SmPCs for full information).[32,33,37]

Patients with moderate to severely active CD may also be at increased risk of thromboembolism, and may require **anticoagulant therapy**.[7]

ADJUNCTIVE THERAPIES IN INDUCTION OF REMISSION

Antimicrobial Therapy: Patients with CD may present with signs of septic complications (such as abscess with fistulating perineal disease).[6,10] **Metronidazole** and/or **ciprofloxacin** have shown varying efficacy in alleviating symptoms, when used typically for at least one month, in association with specific induction therapies.[16,24] Tolerability may be a problem particularly with metronidazole (gastrointestinal upset, or peripheral neuropathy with longer term use).[38]

Enteral Feeding: For patients with extensive small bowel involvement in CD, or in the case of undernutrition, a liquid formula diet may be used as primary therapy.[20] Although it has been shown to be less effective than CS it may also be used in patients who wish to avoid CS.[16,39] It is usually given for 4-6 weeks. It may be difficult to take because it has an unpleasant taste; in addition the route of administration (e.g. if administered by nasogastric tube) may be unacceptable to patients and/or the formulation may cause diarrhoea.[16,39] However, it is a valuable option for some patients.

MAINTENANCE OF MEDICALLY-INDUCED REMISSION

As with induction of remission, the choice of maintenance treatment must take into account the (1) extent of disease, (2) disease behaviour and course of disease to date and (3) effectiveness of prior therapies (Figure 1). **All patients should be encouraged to discontinue smoking** since studies have shown that continued smoking increases the need for CS, immunomodulatory agents and surgery.[19]

Remission from first presentation of CD: For these patients, no specific maintenance medication may be required. If maintenance therapy is needed, **AZA** is recommended, especially in the presence of extensive disease; studies have confirmed its efficacy in maintaining remission and reducing the need for CS.[40] 6-MP or MTX may be used if AZA is not tolerated.[40,41]

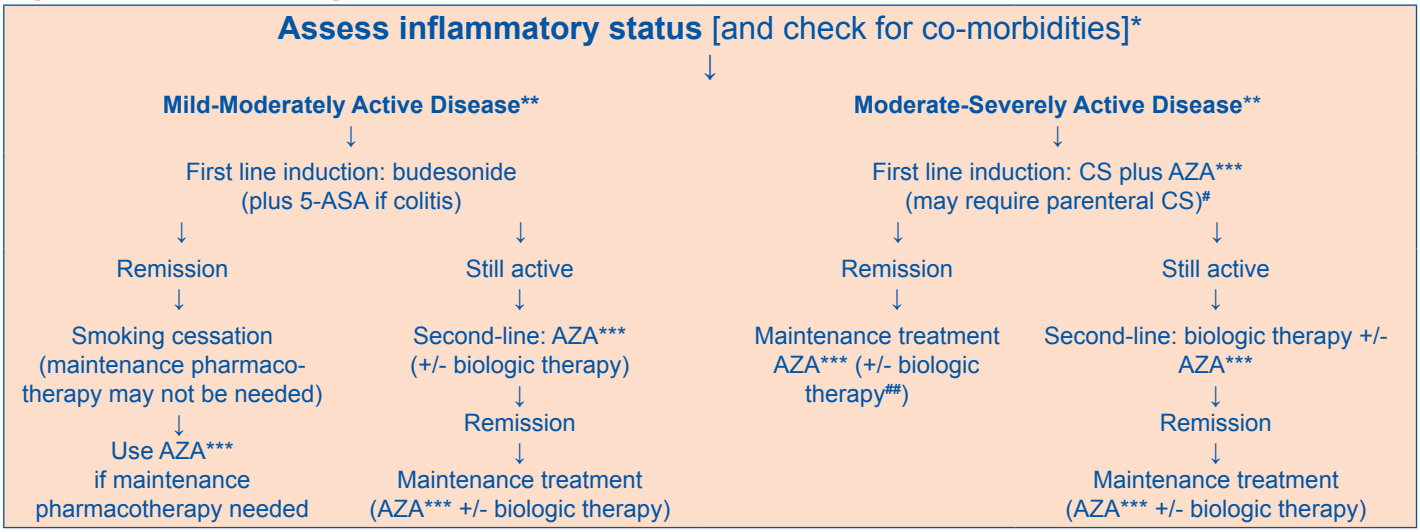
Steroid-dependent or steroid-refractory CD: if patients have steroid-dependent or steroid-refractory CD or if remission of disease was achieved with use of a biologic agent (either anti-TNFα or vedolizumab therapy), **maintenance treatment with a thiopurine or MTX and/or a biologic agent is recommended**.[16,19]

The duration of maintenance treatment must take into account the individual patient and disease characteristics; it is recommended that the patient is actively involved in the decision regarding maintenance therapy (including the possibility of surgery). **All patients receiving long-term immunomodulatory and biologic agents must be monitored regularly during treatment to check for the development of toxicity** (including regular FBC, LFTs and renal function).[14,16,24] An increased (albeit small) risk of lymphoproliferative disorders and other cancers has been reported with long-term usage of some agents.[27,28,32,33,37] Studies have shown that **5-ASA** have no role in the maintenance of medically-induced remission in CD.[16] Similarly, **CS are not suitable for maintenance of remission**; prednisolone cannot be recommended because of its toxicity profile (including osteoporosis, adrenal suppression) with longer-term use.[19] Budesonide modified release (6mg/day) is associated with less CS-related toxicity but has not been shown to reduce the relapse rate at one year.[16,19] Currently available clinical study data do not support the use of alternative therapies such as **probiotics** or **omega-3 fatty acids** in the maintenance of remission of CD.[19,42]

Disease Relapse on Maintenance Treatment: Patients who relapse while on immunomodulatory therapy should be evaluated to **check adherence** to therapy and to have their **dose optimised**.[19,20] A **change in therapy** to another immunomodulatory or to a biologic agent may be needed. **Surgery** may also be considered as an option in relapsed localised / fistulating perianal disease.[19]

Figure 1 summarises the medical management of CD.

Figure 1: Medical management of Crohn's disease[19,20,43]



*Co-morbidities and complications must be treated as appropriate. **Surgery may also be an option for localised / fistulating disease.
***6-mercaptopurine or methotrexate may also be used. #Biologic therapy may also be used as first-line induction therapy, so-called "top-down" therapy.
##If "top-down" therapy used for induction. CS=corticosteroids; 5-ASA=5-aminosalicylates; AZA=azathioprine

MANAGEMENT OF CO-MORBIDITIES / COMPLICATIONS

Patients with CD affecting the small bowel are at risk of **malabsorption** resulting in undernutrition and anaemia (related to deficiency of either iron or vitamin B12 with ileocaecal disease);[44] patients require regular monitoring (including weight and blood tests) and will require **dietary advice** (e.g. low residue diet) and **vitamin and mineral supplementation** as appropriate.[24] Frequent use of CS, malabsorption and repeated surgery may result in **metabolic bone disease** (reduced bone mineral density (BMD), osteoporosis); patients should be monitored and those with reduced BMD should receive **calcium and vitamin D supplements**.[44] Smoking cessation also helps to lessen the reduction in BMD. Although **bisphosphonates** are recommended for those with established fractures, their efficacy in preventing fractures in patients with CD has not been demonstrated.[44] **Colonic surveillance** is required for those with significant colonic involvement (see Table 1) and disease duration of ≥8 years.[43]

SURGERY FOR CROHN'S DISEASE

Surgery is indicated primarily for CD refractory to medical and/or nutritional therapy and to manage complications (including obstructive disease, abdominal mass and medically intractable fistulae).[7,45] Although the rate of surgery is decreasing, most patients with CD will require intestinal resection at some point in their disease and many may have repeat surgery.[7,20] Since the major principle of surgery for CD is to conserve as much bowel as possible, there is a risk of occurrence of CD at the site of surgical anastomosis.[19] Problems associated with extensive / repeated resection of the small bowel include **undernutrition** and **malabsorption**, due to the development of small bowel syndrome. **Bile-salt malabsorption** is a particular problem associated with removal of the ileocaecal area of bowel, potentially resulting in cholegenic diarrhoea, enteric hyperoxaluria (causing kidney oxalate stones) and gallstones.[7,45] **Colestyramine,** which binds bile salts, may be beneficial in these patients.[24]

Surgery and Medication: Management for CD is likely to involve both medical and surgical interventions during the course of the disease. There are very few studies looking at the potential impact of specific medicines on surgery and potential surgical complications.[44-7] The use of CS prior to surgery may increase the risk of surgical complications and therefore it is recommended to wean patients off CS prior to surgery if possible.[10] It has also been suggested that an interval of around 4 weeks be left between discontinuation of anti-TNFα therapy and surgery.[10] Following surgery, studies have shown that (a) **5-ASA** have modest benefits in maintaining remission (for small bowel CD only) (b) **anti-TNFα therapy** is useful in preventing relapse and (c) **thiopurines** appear to be especially useful in preventing relapse in aggressive CD.[16,20,46,47] Although **budesonide** is authorised for use post-surgery, longer term use of CS is not recommended because of toxicity with chronic use.[10,43,45]

CROHN'S DISEASE AND PREGNANCY

Female fertility is not impaired except in active CD and the outcome of pregnancy is normal in a women with quiescent CD.[44,48] The risk of relapse during pregnancy is similar to that for a non-pregnant woman with quiescent disease.[48] Women with CD, wishing to become pregnant are advised to achieve clinical remission before conception.[44] **Women who become pregnant with active CD or those who experience flare-ups of disease activity during pregnancy should receive appropriate treatment**, since active CD has been associated with foetal and maternal adverse effects.[49,50]

Pregnancy and Medication: Most medicines are not specifically authorised for use during pregnancy, due to the lack of clinical data available on such usage. Based on observational study data, guidelines recommend that **CS** and **5-ASA** may be used during pregnancy, if clinically indicated.[49,51] **AZA** (or **6-MP**) is also recommended for use during pregnancy when considered necessary.[49,51] **Anti-TNFα agents** are recommended for use only when other agents have failed. Studies have shown that **anti-TNFα agents may cross the placenta** when used in the second half of pregnancy.[49,51] In addition, anti-TNFα agents have been detected in the serum of infants for up to 6 months after treatment was discontinued in the mother, potentially putting the infant at increased risk of infection.[50] Therefore, it is recommended that anti-TNFα therapy be discontinued during the third trimester.[49,51] **Infants exposed to anti-TNFα therapy should not be immunised with a live vaccine for 5-6 months after the mother's last dose of treatment**.[32,33,49] **MTX** is teratogenic, therefore both male and female CD patients should use effective contraception during treatment and for up to 6 months post-discontinuation of MTX.[28]

Fertility and Medication: The 5-ASA **sulfasalazine** may cause oligospermia and reduced male fertility, which is reversible upon discontinuation of use.[25]

SUMMARY

- Crohn's disease is a chronic inflammatory disease, characterised by relapses and remissions which may impact on the quality of life of patients
- The increasing complexity and number of choices both in medical therapies and surgical options for patients with CD, require ongoing interaction between the members of the MDT involved in the patients' care
- Patients should be actively involved in the decision-making process in relation to their management plan
- The **Irish Society for Colitis and Crohn's Disease**, a patient support group has useful information booklets on IBD and links to international information sources on IBD on its website: **www.iscc.ie**.
- The **National Medicines Information Centre** can provide information about use of medicines in Crohn's disease, including use during pregnancy. Contact details are listed below

List of references available on request. Date of preparation: August 2015

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