Crohn's Disease

Synonyms: regional ileitis, terminal ileitis, regional enteritis or granulomatous enteritis

Crohn's disease is a chronic relapsing inflammatory bowel disease (IBD). It is characterised by a transmural granulomatous inflammation which can affect any part of the gastrointestinal tract, most commonly the ileum, colon or both. Unlike ulcerative colitis, there may be unaffected bowel between areas of active disease (skip lesions). The clinical course is characterised by exacerbations and remission.[1]

Crohn's disease has several extra-intestinal manifestations, including iritis, arthritis, erythema nodosum and pyoderma gangrenosum[2].

Epidemiology[3]

- The incidence and prevalence of Crohn's disease is increasing worldwide, with a systematic review reporting the highest incidence in Australia (29.3 per 100,000 population), Canada (20.2 per 100,000 population) and northern Europe (10.6 per 100,000).
- The prevalence in the UK is about 145 per 100,000 population[2].
- Crohn's disease is more likely in those with a strong family history (first-degree relatives).
- Crohn's disease affects both sexes equally and is associated with excess mortality compared with the general population, with a standardised mortality ratio of 1.38.
- The onset of Crohn's disease has two age peaks: the first and largest peak occurs between the ages of 15-30 years; the second smaller peak is between 50-70 years. People over the age of 60 contribute to 10-15% of IBD diagnoses, compared to 5-25% made in children or adolescents[4].
- However, Crohn's disease is also rapidly increasing in children. The vast majority of affected children will need immunosuppressant treatment and around 20% will need treatment with biological agents[5].

Risk factors

- There is a genetic element (15-20% will have an affected family member with IBD; 70% concordance in identical twins).
- Smoking increases risk three- to four-fold and smokers tend to have more aggressive disease and an earlier postoperative relapse.
- Other exacerbating factors include intercurrent infections (eg, upper respiratory tract infection (URTI) or enteric infection) and non-steroidal anti-inflammatory drugs (NSAIDs).

Presentation

Symptoms[1, 3]

- Symptoms are variable but often include diarrhoea (which may be bloody and become chronic - ie present for more than six weeks), abdominal pain and/or weight loss. Such symptoms should raise the suspicion of Crohn's disease, especially in patients of young age.
- Typically, there will be periods of acute exacerbation, interspersed with remissions or less active disease.
- Systemic symptoms of malaise, anorexia, or fever are common.
- The history should include enquiry about possible extra-intestinal manifestations involving the mouth, skin, eyes and joints and episodes of perianal abscess or anal fissure.
- Children may present with poor growth, delayed puberty, malnutrition and bone demineralisation.
Examination
- General ill health with signs of weight loss, fluid depletion and anaemia.
- There may be hypotension, tachycardia and pyrexia during acute exacerbations.
- Abdominal tenderness or distension, palpable masses.
- Anal and perianal lesions (pendulous skin tags, abscesses, fistulae) are characteristic.
- Mouth ulcers.

Extra-intestinal features
- Clubbing, erythema nodosum, pyoderma gangrenosum.
- Conjunctivitis, episcleritis, iritis.
- Large joint arthritis, sacroilitis, ankylosing spondylitis.
- Fatty liver, primary sclerosing cholangitis (rare), cholangiocarcinoma (rare).
- Granulomata may occur in the skin, epiglottis, mouth, vocal cords, liver, nodes, mesentry, peritoneum, bones, joints, muscle or kidney.
- Renal stones.
- Osteomalacia.
- Malnutrition.
- Amyloidosis.

Investigations [3]
- The diagnosis is confirmed by clinical evaluation and a combination of endoscopic, histological, radiological and biochemical investigations.
- Initial investigations are FBC, CRP, U&Es, LFTs, stool culture and microscopy. Serum levels of CRP are useful for assessing a patient's risk of relapse. High CRP levels are indicative of active disease or a bacterial complication. CRP levels can be used to guide therapy and follow-up.
- Faecal calprotectin:
  - Calprotectin is a small calcium-binding protein. The concentration of calprotectin in faeces has been shown to correlate well with the severity of intestinal inflammation [6].
  - Faecal calprotectin testing is recommended as an option when considering the differential diagnosis of inflammatory bowel disease or irritable bowel syndrome [7].
  - One study looking at children and teenagers found that a diagnostic strategy of using clinical assessment in combination with a positive faecal calprotectin result increased the specificity to detect IBD and reduced the need for referral to a paediatric gastroenterology centre, with a very low risk of missing cases [8].
  - Microbiological testing for infectious diarrhoea including *Clostridium difficile* toxin is recommended. Additional stool tests may be needed for patients who have travelled abroad. See separate Traveller's Diarrhoea article.
- For suspected Crohn's disease, ileocolonoscopy and biopsies from the terminal ileum as well as each affected colonic segment, to look for microscopic evidence of Crohn's disease, are first-line procedures to establish the diagnosis.
- Ileocolonoscopy defines the presence and severity of morphological recurrence and predicts the clinical course, so is recommended in all patients where recurrence is suspected.
- Although evaluation of the bowel has traditionally included imaging using barium fluoroscopic techniques to assess the portions of the small bowel that are inaccessible to endoscopic visualisation, cross-sectional imaging techniques (CT and MR) are being increasingly used to assess both mural and extramural manifestations of IBD [9].
- Radionuclide scanning may be used for patients too ill to undergo colonoscopy or barium studies.
- Gastroduodenoscopy and biopsy are recommended in patients with upper gastrointestinal symptoms.
- For perianal disease:
  - Pelvic MRI should be the initial procedure because it is accurate and non-invasive, although it is not needed routinely in simple fistulae.
  - Examination under anaesthetic is considered the gold standard but only in the hands of an experienced surgeon. It may permit concomitant surgery.
  - As the presence of concomitant rectosigmoid inflammation has prognostic and therapeutic relevance, proctosigmoidoscopy is used routinely in the initial evaluation.
- Laparoscopy may be necessary in selected patients and research into its effectiveness compared to laparotomy is ongoing. It is especially useful where the differential diagnosis of intestinal tuberculosis is being considered, and is also frequently employed in paediatric patients.

Differential diagnosis
- Infectious gastroenteritis.
- Tuberculosis.
- Ulcerative colitis.
- Actinomycosis.
- Carcinoid.
- Amyloidosis.
- Intestinal lymphoma.
- Behçet's disease.
- Bowel carcinoma.
- Ischaemic colitis.
- Radiation or drug-induced colitis (eg, NSAIDs).
- Diverticulitis.
Staging

Various staging systems are in use, principally to assess response to treatment and for research purposes. They all rely on a combination of the patient's history, physical findings and laboratory data. Two in common use are the Crohn's Disease Activity Index (CDAI)\(^{[11]}\) and the Pediatric Crohn's Disease Activity Index (PCDAI)\(^{[12]}\).

Management

- Prompt referral is indicated for any patient with abdominal pain and diarrhoea associated with weight loss, iron deficiency, or raised inflammatory markers.
- Urgent hospital admission for a patient known to have Crohn's disease is required if\(^{[13]}\):
  - There is severe abdominal pain, especially if there is tenderness on palpation.
  - There is severe diarrhoea (frequency eight or more times per day), with or without rectal bleeding.
  - There is bowel obstruction.
  - The patient has fever and is systemically unwell.
- If the patient does not require admission, assess disease activity by thorough history and examination and blood tests (FBC, CRP, renal function and electrolytes, LFTs).

National Institute for Health and Care Excellence (NICE) guidance\(^{[14]}\)

**Inducing remission in Crohn's disease**

- **Monotherapy:**
  - Offer monotherapy with a conventional glucocorticosteroid (prednisolone, methylprednisolone or intravenous hydrocortisone) to induce remission in people with a first presentation or a single inflammatory exacerbation of Crohn's disease in a 12-month period.
  - Consider enteral nutrition as an alternative to a conventional glucocorticosteroid to induce remission for children in whom there is concern about growth or side-effects, and young people in whom there is concern about growth.
  - In people with one or more of distal ileal, ileocaecal or right-sided colonic disease, who decline, cannot tolerate or in whom a conventional glucocorticosteroid is contra-indicated, consider budesonide for a first presentation or a single inflammatory exacerbation in a 12-month period. Budesonide is less effective than a conventional glucocorticosteroid but may have fewer side-effects.
  - In people who decline, cannot tolerate or in whom glucocorticosteroid treatment is contra-indicated, consider 5-aminosalicylate (5-ASA) treatment for a first presentation or a single inflammatory exacerbation in a 12-month period. 5-ASA is less effective than a conventional glucocorticosteroid or budesonide but may have fewer side-effects than a conventional glucocorticosteroid.
  - Do not offer budesonide or 5-ASA treatment for severe presentations or exacerbations. Do not offer azathioprine, mercaptopurine or methotrexate as monotherapy to induce remission.

- **Add-on treatment:**
  - Consider adding azathioprine or mercaptopurine to a conventional glucocorticosteroid or budesonide to induce remission of Crohn's disease if there are two or more inflammatory exacerbations in a 12-month period, or the glucocorticosteroid dose cannot be tapered.
  - Assess thiopurine methyltransferase (TPMT) activity before offering azathioprine or mercaptopurine. Do not offer azathioprine or mercaptopurine if TPMT activity is deficient (very low or absent). Consider azathioprine or mercaptopurine at a lower dose if TPMT activity is below normal but not deficient.
  - Consider adding methotrexate to a conventional glucocorticosteroid or budesonide to induce remission in people who cannot tolerate azathioprine or mercaptopurine, or in whom TPMT activity is deficient, if there are two or more inflammatory exacerbations in a 12-month period, or the glucocorticosteroid dose cannot be tapered.
  - Infliximab and adalimumab\(^{[15]}\):
    - Infliximab and adalimumab block the action of the cytokine tumour necrosis factor alpha (TNF-α), which mediates inflammation in Crohn's disease.
    - Infliximab or adalimumab is recommended by NICE for the treatment of severe active Crohn's disease that has not responded to conventional therapy (including corticosteroids and other drugs affecting the immune response) or when conventional therapy cannot be used because of intolerance or contra-indications.
    - Infliximab is recommended for the treatment of fistulating Crohn's disease that has not responded to conventional therapy (including antibacterials, drainage and other drugs affecting the immune response) or when conventional therapy cannot be used because of intolerance or contra-indications.
    - Infliximab or adalimumab should be given as a planned course of treatment for 12 months or until treatment failure, whichever is shorter.
    - Treatment should be continued beyond 12 months only if there is evidence of active disease. The need for treatment should then be reviewed at least annually. If the disease relapses after stopping treatment, adalimumab or infliximab can be restarted.

- Vedolizumab is recommended by NICE as an option for treating moderately to severely active Crohn's disease only if a TNF-α inhibitor has failed or a TNF-α inhibitor cannot be tolerated or is contra-indicated\(^{[16]}\).
Severe active Crohn's disease is defined as very poor general health and one or more symptoms such as weight loss, fever, severe abdominal pain and usually frequent (3-4 or more) diarrhoeal stools daily. People with severe active Crohn's disease may or may not develop new fistulae or have extra-intestinal manifestations of the disease.

Maintaining remission in Crohn's disease

- When people choose not to receive maintenance treatment, discuss plans for follow-up, including the frequency of follow-up and who they should see to ensure they know which symptoms may suggest a relapse and should prompt a consultation with their healthcare professional (especially unintended weight loss, abdominal pain, diarrhoea, general ill-health).
- **Smoking cessation** is very important.
Maintenance treatment for those who choose this option:
  - Offer azathioprine or mercaptopurine as monotherapy to maintain remission when previously used with a conventional glucocorticosteroid or budesonide to induce remission. Also consider azathioprine or mercaptopurine to maintain remission in people who have not previously received these drugs (particularly those with adverse prognostic factors such as early age of onset, perianal disease, glucocorticosteroid use at presentation and severe presentations).
  - Consider methotrexate to maintain remission only in people who needed methotrexate to induce remission, or have tried but did not tolerate azathioprine or mercaptopurine for maintenance or have contra-indications to azathioprine or mercaptopurine.
  - Do not offer a conventional glucocorticosteroid or budesonide to maintain remission.

Maintaining remission in Crohn's disease after surgery:
  - Consider azathioprine or mercaptopurine to maintain remission after surgery in people with adverse prognostic factors such as more than one resection, or previously complicated or debilitating disease (eg, abscess, involvement of adjacent structures, fistulising or penetrating disease).
  - Consider 5-ASA treatment to maintain remission after surgery.
  - Do not offer budesonide or enteral nutrition to maintain remission after surgery.

Surgery

Crohn's disease limited to the distal ileum:
  - Consider surgery as an alternative to medical treatment early in the course of the disease for people whose disease is limited to the distal ileum.
  - Consider surgery early in the course of the disease or before or early in puberty for children and young people whose disease is limited to the distal ileum and who have growth impairment despite optimal medical treatment and/or refractory disease.

Managing strictures: consider balloon dilation particularly in people with a single stricture that is short, straight and accessible by colonoscopy. Ensure that abdominal surgery is available for managing complications or failure of balloon dilation.

Monitoring for osteopenia and assessing fracture risk
Crohn's disease is a cause of secondary osteoporosis. Consider monitoring for changes in bone mineral density in children and young people with risk factors, such as low body mass index, low trauma fracture or continued or repeated glucocorticosteroid use. See also separate Osteoporosis Risk Assessment and Primary Prevention article.

Fistulating Crohn's disease
  - Treatment may not be necessary for simple, asymptomatic perianal fistulas. Metronidazole or ciprofloxacin can improve symptoms of fistulating Crohn's disease but complete healing is rare.
  - Other antibacterials should be given if specifically indicated, such as for sepsis associated with fistulas and perianal disease, and for managing bacterial overgrowth in the small bowel.
  - Fistulas may also require surgical exploration and local drainage.
  - Either azathioprine or mercaptopurine can be used used as a second-line treatment for fistulating Crohn's disease and continued for maintenance.
  - Infliximab can be used for fistulating Crohn's disease refractory to conventional treatments. Adalimumab can be used if there is intolerance to infliximab.

Other treatments
  - Antidiarrhoeals such as loperamide are contra-indicated during episodes of active colitis, as they may cause toxic megacolon. However, they can be prescribed for the control of chronic diarrhoea in patients with stable disease.
  - Bile acid sequestrants such as colestyramine and colestipol may be useful to control secretory diarrhoea in patients with terminal ileal disease causing bile acid malabsorption.
  - Abdominal cramps may be controlled by antispasmodics such as dicycloverine, or hyoscymamine, providing intestinal obstruction has been excluded.
Elemental or polymeric diets[18].

Elemental or polymeric diets are less effective than corticosteroids but may be used to induce remission in selected patients with active disease who are unable or unwilling to take corticosteroid therapy, or as an adjunctive therapy.

There is limited evidence indicating potential benefits of elemental nutrition against no intervention in the maintenance of remission and prevention of relapse in adult patients with Crohn's disease[19].

Many early studies used elemental formulae. The difference between polymeric and elemental formulae is that the protein fraction in polymeric formula is in its whole form rather than as individual amino acids or peptides, which is the case in elemental formulae.

Elemental formulae tend to have a low total fat content. Polymeric formulae have been shown to be as effective as elemental at inducing disease remission. Polymeric formulae are thought to be more palatable and therefore better tolerated and have improved compliance.

Total parenteral nutrition is appropriate adjunctive therapy in complex, fistulating disease.

Treatment of extra-intestinal manifestations

Oral Crohn's disease: topical steroids, topical tacrolimus, intralesional steroid injections, enteral nutrition and infliximab may have a role in management but there are no randomised controlled trials.

Arthritis and arthropathy: there is some general support for use of sulfasalazine, simple analgesics, local corticosteroid injections and physiotherapy. In axial arthritis, the arguments in favour of intensive physiotherapy, sulfasalazine, methotrexate or infliximab are somewhat stronger.

Erythema nodosum: systemic corticosteroids are usually required.

Pyoderma gangrenosum: topical and systemic corticosteroids, with the more toxic ciclosporin and tacrolimus reserved for resistant cases. Data support the use of infliximab.

Uveitis is treated with topical and/or systemic corticosteroids.

Primary sclerosing cholangitis: responds to ursodeoxycholic acid. Endoscopic retrograde cholangiopancreatography (ERCP) may be used to treat dominant strictures by dilatation and/or stenting.

Advanced liver disease may necessitate transplantation.

Complications

Bowel:
- Strictures causing subacute or acute obstruction.
- Fistulae between loops of bowel and other bowel, bladder, vagina, or skin.
- Perforation, acute dilatation and massive haemorrhage can occur.
- Crohn's colitis is associated with an increased risk of colonic carcinoma. Colonoscopic surveillance should be offered[20].

Clinical Editor’s comments (October 2017)

Dr Hayley Willacy recently read a paper looking at lifetime risks of cancer in children who are diagnosed as having inflammatory bowel disease in childhood[21]. This group has an increased risk of cancer, especially gastrointestinal cancers, both in childhood and later in life. The increase persists into adulthood, and has not fallen since the introduction of modern drug therapies for inflammatory bowel disease. However, the researchers stress that absolute risks are low - corresponding to one extra case of cancer for every 556 patients with inflammatory bowel disease followed for a year, compared with healthy individuals.

Osteoporosis (especially with steroid therapy):
- Weight bearing, isotonc exercise, stopping smoking, avoiding alcohol excess and maintaining adequate dietary calcium are beneficial.
- Consider assessing for changes in bone mineral density in children who have low body mass index, unexpected fracture or high levels of corticosteroid use[14].
- Regular use of bisphosphonates and raloxifene may reduce or prevent further bone loss.

Renal disease (secondary to obstruction of the right ureter by ileocaecal disease).

Iron, folate and vitamin B12 deficiency.

Gallstones and renal stones (usually oxalate) especially when there has been a previous right hemicolecotomy.

Crohn's disease may cause a delay in growth and puberty in children[14].

If Crohn's disease in a pregnant patient is in remission, there is no effect on the prognosis for pregnancy. Women with active disease are more likely to have complications such as spontaneous abortions, miscarriages, stillbirths and exacerbation of the disease[22, 23]. Treatment of pregnant women with infliximab does not increase the incidence of adverse outcomes[24].
Prognosis

- The natural history and clinical course of IBD is very variable. More than 50% of patients with Crohn's disease need surgery within 10 years of diagnosis.
- Furthermore, 30% of people with Crohn's disease will have a fairly indolent disease course without the need for immunosuppression or surgery.
- Clinical indicators of a poor prognosis at diagnosis include perianal or strictureing disease, weight loss >5 kg, or the need for steroids.

Further reading & references

- Inflammatory bowel disease; NICE Quality Standard, February 2015
- Standards of Healthcare for People who have Inflammatory Bowel Disease (IBD); The IBD Standards Group, 2013

2. Crohn's disease; NICE CKS, April 2015 (UK access only)
7. Fecal calprotectin diagnostic tests for inflammatory diseases of the bowel; NICE Diagnostics Guidance (Oct 2013)
11. Adult CDAI (Crohn's Disease Activity Index) Calculator; IBD Support Australia, 2011
12. Pediatric Crohn's Disease Activity Index Calculator; Cincinnati Children's Hospital Medical Center, 2007; online calculator
15. Infliximab (review) and adalimumab for the treatment of Crohn's disease; NICE Technology Appraisal Guidance, May 2010
16. Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy; NICE Technology Appraisal Guidance, August 2015
17. British National Formulary; NICE Evidence Services (UK access only)
20. Colon cancer surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas; NICE Clinical Guideline (March 2011)

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