Crohn's disease for the general physician: presentation and investigations

Crohn's disease presents to general physicians in a variety of ways. This article outlines the clinical features and initial investigation of suspected Crohn's disease. The accompanying article reviews treatment strategies.

Crohn's disease is an inflammatory condition presenting most often in young adulthood, with European incidence still rising (12.7 new cases per 100 000/year), and prevalence as high as 322/100 000 (Molodecky et al, 2012). Inflammation in patients with Crohn's disease is thought to arise from an aberrant immune response to commensal gut microbes in genetically susceptible individuals. Despite more than 160 genetic loci being identified (Cleynen et al, 2016), this still accounts for only a small part of the risk of developing Crohn's disease.

Cigarette smoking is the best recognized environmental risk factor, increasing the risk of Crohn's disease, and with cessation improving the course of the disease. Conversely cigarette smoking appears to be protective against developing ulcerative colitis and may ameliorate its clinical course. Other environmental factors are shown in *Table 1*. Many susceptibility loci are shared by both Crohn's disease and ulcerative colitis, while others are linked with either disease specifically. Phenotypically Crohn's disease presents in a far more varied way than ulcerative colitis, as it can affect any part of the gastrointestinal tract, often with skip lesions (segments of inflammation separated by normal bowel). Non-caseating granulomas on biopsy histology are characteristic, but occur in less than a third of patients with Crohn's disease (Heresbach et al, 2005). Other histological features suggestive of Crohn's disease include inflammation and crypt distortion that is patchy or focal (rather than continuous) and ileal inflammation (Feakins, 2013). However, isolated colonic involvement can be endoscopically and histologically indistinguishable from ulcerative colitis, and is described as inflammatory bowel disease unclassified, or after colectomy (when definitive histology is available) as indeterminate colitis.

Table 1. Environmental factors increasing the risk of Crohn's disease

Smoking
Diet (high animal protein, high n6 fatty acids, low n3 fatty acids)
Antibiotics in childhood
High latitude or low sunlight exposure
Not receiving breast-feeding

From Ng et al (2013)

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There is enormous interest in the role of the gut microbial flora (microbiota) in the aetiology of Crohn's disease (and the potential for therapeutic manipulation). There is strong evidence of reduced bacterial diversity in the gut of patients with Crohn's disease, and growing evidence that this is a primary event, rather than a consequence of diseased gut (based on similar findings in healthy siblings of patients with Crohn's disease; Hedin et al, 2015). Broad-spectrum antibiotics, such as metronidazole or ciprofloxacin, can improve symptoms of Crohn's disease, particularly for those with perianal fistulizing disease, but also in luminal disease. Evidence that manipulation of the microbiota (either by use of prebiotics, probiotics or by faecal microbial transplantation from healthy donors) can improve symptoms or alter the natural history are as yet lacking in Crohn's disease (although evidence is a little further forward in treatment of ulcerative colitis).

The social costs of Crohn's disease are considerable with European direct health-care costs alone estimated at €4.6–5.6 billion per year (Burisch et al, 2013).

Clinical presentation

Crohn's disease can affect any part of the gut. Population-based studies show colonic distribution (37–42%) and ileocolonic distribution (37–38%) are commonest, with ileal disease but no colonic involvement in 15–23% (Wolters et al, 2006; Henriksen et al, 2007). In the past ileocaecal disease would have been the most typical presentation, but colonic involvement is much more common now (Gunesh et al, 2008). Upper gastrointestinal involvement (jejunal or oesophagogastroduodenal) occurs in 6%. Perianal involvement occurs in 10–15%. Children

and young adults have more extensive and often more aggressive disease (Ruemmele et al, 2014). Disease location has a strong genetic association, whereas disease behaviour tends to vary over time (Cleynen et al, 2016). Behaviour can be classified as inflammatory, stricturing or penetrating. A goal of therapy is to prevent progression to stricturing or penetrating complications, although many patients present initially with these patterns, presumably having had a short subclinical inflammatory phase.

Inflammatory disease

Inflammatory Crohn's disease presents with diarrhoea, often also with abdominal pain and perhaps weight loss, but this depends on the location and extent of disease. The main differential diagnosis here lies between Crohn's disease and irritable bowel syndrome, and infection needs excluding. Ulcerative colitis usually (but not always) presents with bloody diarrhoea. Family history of inflammatory bowel disease, smoking and travel history are important. Examination is often unremarkable unless there are signs of significant weight loss, finger clubbing or angular cheilitis (*Figure 1*). An abdominal mass is unusual, and a rectal examination is mandatory to exclude perianal skin tags, fistulae or pain which could be the result of anal fissure. A classical presentation would be with erythema nodosum and asymmetrical oligoarthropathy, but this is uncommon (*Figure 2*). Stool cultures are needed to rule out giardiasis. Blood tests (anaemia, raised platelet count, C-reactive protein, low albumin, low ferritin, vitamin B_{12} or folate) can give important clues to an inflammatory or malabsorptive condition, but if these are normal and the differential between Crohn's disease and irritable bowel syndrome is still unclear then measurement of faecal calprotectin is useful (*Table 2*), with progression to imaging if significantly raised.

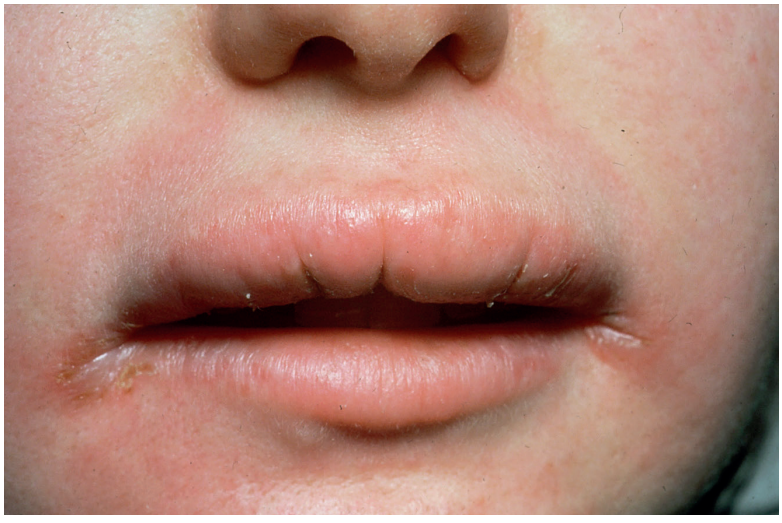
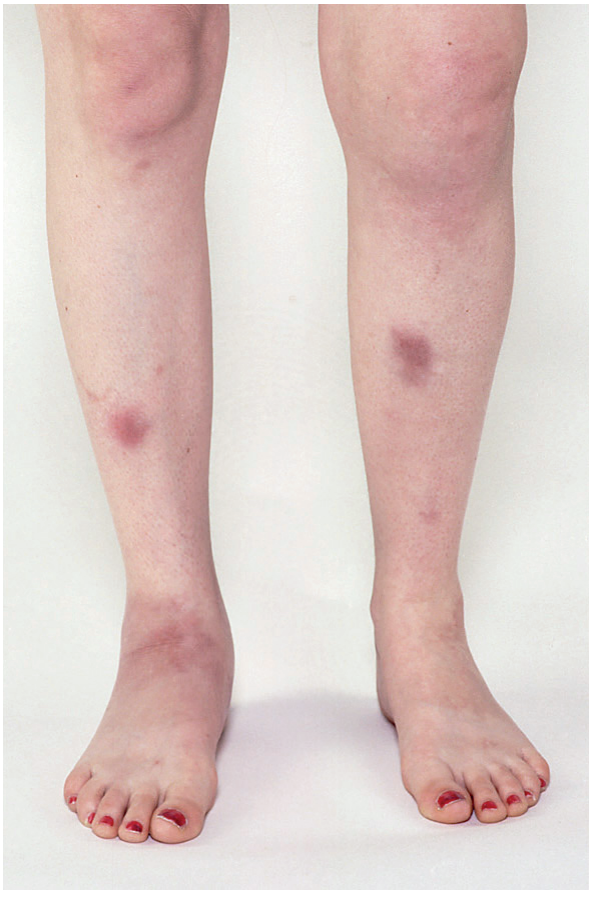


Figure 1. Angular cheilitis in a patient with lip swelling and circumoral erythema suggestive of orofacial granulomatosis.

Figure 2. Erythema nodosum with arthropathy of left knee and right ankle.



Diagnosis is confirmed by ileocolonoscopy and biopsy. Although ileal intubation will establish whether Crohn's disease extends into the distal 15 cm of ileum, small bowel imaging (preferably by magnetic resonance enterogram) is important to exclude more widespread ileal or jejunal involvement. Capsule endoscopy will detect small bowel lesions in more than half of patients with established Crohn's disease, and jejunal lesions are associated with a slightly higher risk of relapse (Flamant et al, 2013). If ileocolonoscopy is normal, then isolated proximal ileal

Table 2. Faecal calprotectin

Faecal calprotectin is a stable neutrophil protein used as a non-specific marker for gut inflammation. The usual assay 'normal range' is <50 ug/g stool
It is used in patients with recent onset diarrhoea to distinguish inflammatory bowel disease from irritable bowel syndrome
Although usually normal, a mildly raised value (50–200 ug/g stool) occurs in 10–15% of patients with irritable bowel syndrome (poor specificity)
A normal value (<50 ug/g stool) rules out active Crohn's disease (high negative predictive value)
This test should not be used in acute diarrhoea (levels are raised in gastroenteritis), bloody diarrhoea (invasive tests are required regardless of calprotectin value) or in patients over 50 years of age (poor discriminant value for advanced polyps or cancer)

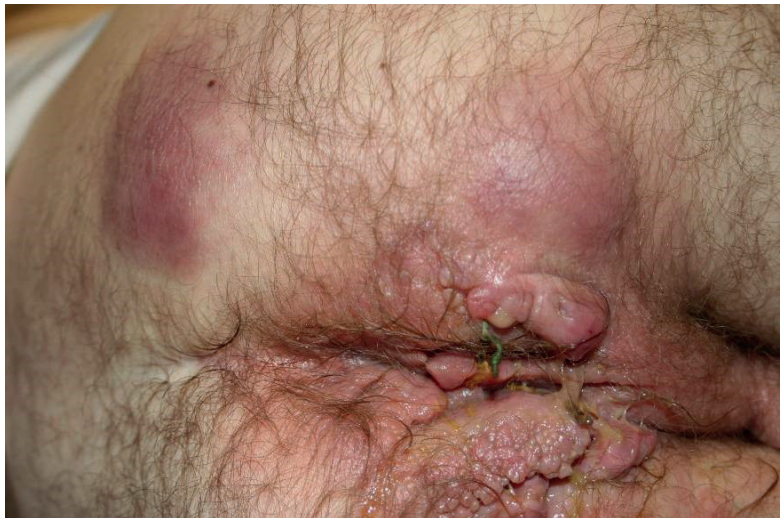


Figure 3. Anal skin tags and perianal abscesses.

or jejunal Crohn's disease is very unusual, but should be sought if calprotectin levels are significantly raised. In this situation, magnetic resonance enterogram is probably the best test. Small bowel ultrasound is much more operator-dependent, but a skilled ultrasonographer can assess small and large bowel for areas of inflammation. Capsule endoscopy has high sensitivity and negative predictive value, but low positive predictive value (Argüelles-Arias et al, 2014). If small bowel strictures are possible, then capsule use is contraindicated unless a dissolvable patency capsule is passed first. If a capsule does become lodged in the small bowel, a course of prednisolone is worthwhile as many will then pass as inflammation subsides and the lumen becomes wider.

Obstructive symptoms

Patients presenting with progressive abdominal pain related to eating, with weight loss and a history of abdominal distension, raises suspicion of a fibrostenotic lesion of the bowel. In young people ileocaecal Crohn's disease is the commonest cause, but in older patients colorectal cancer must also be considered. Other causes include lymphoma, intussusception or adhesion band obstruction (if they have had previous surgery). Loose stool may or may not be present in this situation.

Examination sometimes reveals a right iliac fossa mass, distended abdomen or obstructive, tinkling bowel sounds, but these findings are often not present. Blood tests are important, but imaging is mandatory (even with normal bloods) to exclude a mechanical problem, particularly ileocaecal stricture caused by Crohn's disease. Imaging with magnetic resonance enterogram and/or ileocolonoscopy is needed. If an ulcerated or stricturing area is found at ileocolonoscopy then histology can be obtained to confirm a diagnosis of Crohn's disease. If, however, the very distal ileum is not involved, the abnormal area of ileum may not be reached and the diagnosis is based on the radiological appearance. Magnetic resonance enterography and ultrasound can discriminate between inflammatory and non-inflammatory stricturing, and this can help in decision making regarding treatment, as initial management can be surgical or medical. Patients with more obstructive symptoms, and localized terminal ileal or ileocaecal disease are best dealt with by laparoscopic ileocaecal resection. However, if diarrhoea predominates, or a longer segment is involved, with less stricturing and no evidence of pre-stenotic dilatation of the ileum, then corticosteroids should be given initially, as discussed in the accompanying article (https://doi.org/10.12968/hmed.2017.78.2.77).

Fistulizing disease

In patients with Crohn's disease, 20% or more will have anorectal fistulae (more commonly in the presence of colonic disease), and at least half of these present with this feature at diagnosis. The commonest presentation is with perianal abscess. This usually presents with a painful swelling adjacent to the anus on either side (*Figure 3*). Other anorectal features include anal fissures, oedematous skin tags (often mistaken for haemorrhoids) and anal stenosis. After drainage and antibiotic therapy (ciprofloxacin or metronidazole), the patient requires ileocolonoscopy to look for Crohn's colitis. After the abscess has healed, a pelvic magnetic resonance scan will map the extent of fistulae and any high collections, followed by examination under anaesthetic to identify and probe any fistulae in order to pass stitches (setons) to prevent blockage of the fistula track, which can precipitate further abscess formation. Further medical therapy can then be started.

Other presentations

Crohn's disease presents in a range of other ways. This can be with extraintestinal features rather than obvious bowel symptoms (*Table 3*). Examples would include liver disease resulting from primary sclerosing cholangitis, occurring in 2–4% of patients with inflammatory bowel disease. All have colonic disease, but nearly half of these have Crohn's disease (Lunder et al, 2016) contrary to older studies linking this mostly with ulcerative colitis. Screening studies using magnetic resonance cholangiography show that 9% of patients with inflammatory bowel disease develop radiological signs of primary sclerosing cholangitis over 20 years of follow up. There is a male preponderance in primary sclerosing cholangitis. Investigations include magnetic resonance cholangiography (or endoscopic retrograde cholangiopancreatogram, *Figure 4*), but a small percentage have small-duct primary sclerosing cholangitis (which has better prognosis), requiring liver biopsy for diagnosis. Primary sclerosing cholangitis increases the risk of colorectal carcinoma significantly (requiring early and more frequent colonoscopy surveillance) and increases the risk of cholangiocarcinoma, gallbladder cancer and (if the patient develops cirrhosis) hepatocellular carcinoma.

Patients presenting with an inflammatory arthropathy can have underlying Crohn's disease (or ulcerative colitis), and there should be a low threshold for investigating these patients if they have diarrhoea, weight loss or anaemia. Other extraintestinal manifestations are shown in *Table 3*.

A small number of children and young people present with oral manifestations of Crohn's disease (aphthous ulceration, angular cheilitis, glossitis, oral candida or orofacial granulomatosis. Orofacial granulomatosis has similar pathology to inflammatory bowel disease and often presents in children and young adults (*Figure 1*). Features include lip swelling, circumoral erythema, buccal fissuring and cobblestoning, with mucosal tags. Although orofacial granulomatosis can present in isolation, if investigated thoroughly over half will have endoscopic or histological evidence of intestinal Crohn's disease. Younger patients respond to a benzoate and cinnamon-free diet, but many require immunosuppressive treatments as for other forms of Crohn's disease.

Small bowel Crohn's disease can present with weight loss and may be mistaken for anorexia nervosa, particularly in adolescent girls. Gastrointestinal symptoms may be less obvious, with early satiety, nausea and malaise resulting in poor appetite and progressive malnutrition. In contrast to anorexia nervosa, however, blood tests usually suggest organic disease with low albumin levels, raised platelet counts suggesting inflammation, and iron, folate, vitamin D or zinc deficiency.

Conclusions

Crohn's disease is a disease of urbanized societies whose incidence continues to rise. Aetiology is thought to be partly genetic with numerous genes causing an aberrant immune response to commensal gut organisms. Important environmental factors are yet to be identified but attention is focused on the gut microbiota. Ileocolonic distribution is the most common, but it can affect any part of the gut, and a variety of extraintestinal manifestations occur as part of the disease process. The next article (https://doi.org/10.12968/hmed.2017.78.2.77) discusses management strategies. **BJHM**

Conflict of interest: none.

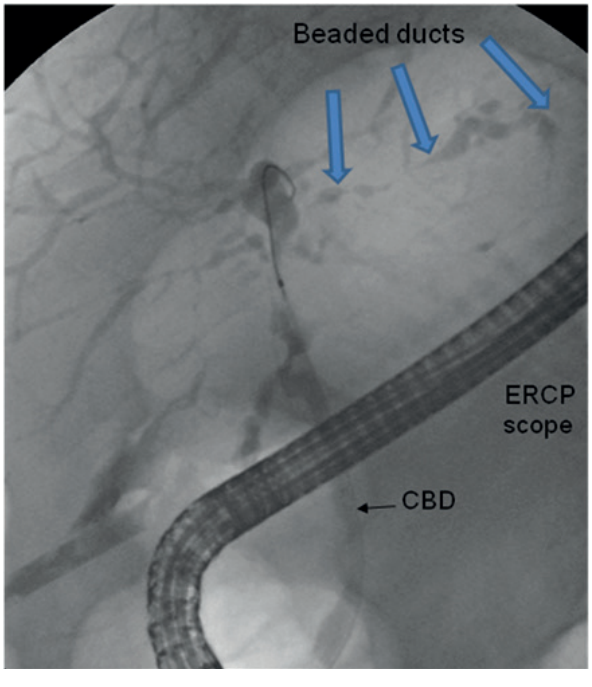
KEY POINTS

- The incidence of Crohn's disease continues to rise.
- It presents in a variety of clinical patterns.
- Faecal calprotectin is a useful screen for gut inflammation to distinguish possible Crohn's disease from irritable bowel syndrome.
- New imaging modalities including capsule endoscopy, ultrasound and magnetic resonance enterography make it easier to detect and assess small bowel disease.

Table 3. Extraintestinal manifestations of inflammatory bowel disease

Site	Common		Associated with active disease
Joints	Axial arthropathy	Sacroilitis	No
		Ankylosing spondylitis	
	Peripheral arthropathy	Type 1 – asymmetrical oligoarthropathy (*Figure 2*)	Yes
		Type 2 – small joints arthropathy	No
Eyes	Uveitis, episcleritis, iritis		Yes
Skin	Erythema nodosum, pyoderma gangrenosum		Yes
Vascular	Arterial and venous thromboembolism		Yes
Renal	Renal stones		No
Bone	Osteoporosis		No
Haematological	Anaemia (iron or vitamin B_{12} deficiency, anaemia of chronic disease)		Yes
Liver and biliary tree	Primary sclerosing cholangitis, gallstones		No

Figure 4. Primary sclerosing cholangitis shown at endoscopic retrograde cholangiopancreatogram (ERCP). CBD = common bile duct.



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