Crohn’s disease
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Abstract
Crohn’s disease is a chronic inflammatory bowel disease that can affect any part of the gastrointestinal tract from the mouth to the anus, although the ileum, colon and perineum are most commonly involved. It is characterized by transmural granulomatous inflammation. Although the aetiology is unknown, Crohn’s disease is thought to result from a complex interplay of multiple genetic and environmental factors. There appears to be an immune dysregulation to microbiota in genetically predisposed individuals. Several genes involved in the interaction between microbiota and the host immune system, in particular the innate immune system, are defective in Crohn’s disease, including NOD2 and the autophagy genes ATG16L1 and IRGM. Diarrhoea, abdominal pain, fatigue, weight loss and fever are the hallmarks of Crohn’s disease. The clinical features depend on the location and behaviour of the disease in the gastrointestinal tract. Additionally there are extra-intestinal manifestations affecting joints, skin, eyes and the liver. Investigations are directed towards identifying the location, extent, and severity/behaviour (inflammatory, strictureting, penetrating) of disease. The goal of all therapies should be to achieve clinical and endoscopic remission in time to avoid disease progression and surgical resections. Treatment usually features corticosteroids, immunomodulators (thiopurines, methotrexate), anti-tumour necrosis factor-α (TNFα) therapy or surgery. Patients with poor prognostic features may benefit from early treatment with immunomodulator drugs and/or anti-TNFα therapy. Therapeutic drug monitoring can help physicians to improve and personalize the management of Crohn’s disease.

Keywords anti-tumour necrosis factor-α; autophagy genes (ATG16L1 and IRGM); corticosteroids; Crohn’s disease; immunomodulators; inflammatory bowel disease; NOD2

Introduction
Crohn’s disease (CD) is a chronic relapsing inflammatory bowel disease (IBD) of unknown cause (idiopathic). It is characterized by transmural granulomatous inflammation and typically involves the terminal ileum, colon and perianal region, although it can affect any part of the gastrointestinal tract from the mouth to the anus, often in discontinuity. Common complications include intestinal strictures, fistulas and abscesses.

What’s new?
• Incidence of Crohn’s disease (CD) is increasing particularly in children and in non-Western societies
• New CD-associated genes have increased understanding of the immunopathogenesis, especially the interplay between microbiota and the innate immune response and autophagy
• Magnetic resonance enterography and endoscopic techniques (wireless capsule endoscopy, double balloon enteroscopy) are useful to assess small bowel involvement
• Patients with poor prognostic features appear to benefit from early treatment with immunomodulator drugs and/or anti-tumour necrosis factor-α (TNFα) therapy
• Laparoscopic surgery is preferable where expertise is available
• Endoscopic mucosal healing is associated with better outcomes
• Drug concentration monitoring to adapt doses of immunomodulators and/or anti-TNFα antibodies can personalize patient management

Epidemiology
The incidence of CD varies worldwide. Rates vary between 0.1 and 16/100,000 inhabitants, with highest incidence recorded in Northern and Western Europe and North America, while lower rates are recorded in Africa, South America and Asia (Table 1). Overall, CD is less common than ulcerative colitis (UC). The number of people with CD has been steadily increasing, particularly among young people and in non-Western societies. Childhood-onset CD is also becoming more common, especially in those under 10 years of age. Estimates of prevalence vary depending on whether figures are derived from primary (200/100,000 population) or secondary/tertiary care settings (70–100/100,000 population). In a population-based study in Asia-Pacific, the incidence of CD varied across Asia but was still lower than the West. CD can be diagnosed at any age but most commonly presents between 10 and 40 years of age, with a smaller peak in the seventh decade. In Western countries, it is marginally more common in women than in men (the reverse is seen in Asian countries, where there is a male predominance). There is a notably high incidence among Ashkenazi Jews.

Aetiology
Although the cause of CD is unknown, there appears to be a dysregulated host immune response to intestinal microbiota (microbial flora harboured by healthy individuals) in genetically susceptible individuals. Indeed a common theme to emerge from genetic studies of CD is the importance of the innate immune response in handling intestinal microbiota.

Genetic determinants
Fifteen percent of patients with CD have a relative with either CD or UC and the concordance rate in monozygotic twins is about
Incidence rates of IBD worldwide

<table>
<thead>
<tr>
<th></th>
<th>Crohn’s disease</th>
<th>Ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>17.2</td>
<td>11.2</td>
</tr>
<tr>
<td>North America</td>
<td>20.2</td>
<td>19.2</td>
</tr>
<tr>
<td>Europe</td>
<td>12.7</td>
<td>24.3</td>
</tr>
<tr>
<td>Asia and Middle East</td>
<td>5.0</td>
<td>6.2</td>
</tr>
</tbody>
</table>

Table 1

45% (higher than for UC). Patterns of disease within families are similar.

There has been significant progress over the last decade in identifying susceptibility genes for CD. Approximately one-third of patients with CD have mutations in NOD2, the first CD gene identified, on chromosome 16. Compared with the wild type, NOD2 heterozygotes have a twofold increased risk of developing CD, whereas NOD2 homozygotes have a 17-fold increased risk. NOD2 variants are particularly associated with ileal CD. NOD2 encodes an intracellular receptor for bacterial muramyl dipeptide, and modulates activation of NFκB and downstream pro-inflammatory mediators by a poorly understood mechanism.

Genome-wide association scans in CD have highlighted several other important immune pathways: autophagy, a process involving the degradation of a cell’s own components and intracellular bacteria, is highlighted by association of the autophagy genes ATG16L1 and IRGM with CD; and the interleukin-23 (IL-23) pathway is highlighted by association of variants in the IL-23 receptor gene. Overall, there are 163 IBD loci that have been identified and about two-thirds of the genes are shared between CD and UC. There is particular overlap between IBD genes and genes implicated in ankylosing spondylitis and psoriasis.

Genetics can predict disease outcome; for instance, NOD2 variants are particularly associated with ileal and stenosing CD and earlier need for intestinal surgery. However, despite advances in the field of CD genetics, there are currently no genetic tests that are recommended routinely for disease diagnosis.

Environmental factors

Smoking: smokers are more likely to develop CD than non-smokers (as opposed to UC where smoking is protective) and the disease tends to be more difficult to manage in smokers, who appear to need more immunosuppression and surgical intervention.

Diet: although dietary factors are likely to be of key importance in CD, no dietary components consistently trigger a flare. Excess refined sugar or animal protein and low intake of fibre have been associated with CD, but dietary manipulation of sugars/fibre has had no demonstrable impact on disease presentation or disease course. Breastfeeding appeared to be protective. Elemental or polymeric diets are beneficial treatments for children and adults with CD and are associated with mucosal healing.

Microbiota: evidence implicating microbiota in the aetiology of CD comes from numerous animal models of inflammatory bowel disease, which remain healthy when kept in ‘germ-free’ conditions but develop colitis when colonized by commensal microbiota. In the closest analogous situation in humans, when the faecal stream of a patient with CD is diverted, the downstream inflammation resolves but reappears when continuity is restored. Many organisms have been suggested, including adherent, invasive Escherichia coli, measles virus, Mycobacterium paratuberculosis, listeria, Pseudomonas fluorescens and Bacteroides vulgatus. On the other hand, Faecalibacterium prausnitzii appears to be protective. However, as yet, there is no clear evidence for a single organism causing CD; instead, there appears to be an imbalance in the microbiota with altered diversity and richness. The impact of the genetic background, smoking and diet on the microbiota is poorly understood. Recent studies have suggested that antibiotic use during childhood may predispose to disease development.

Immunological factors

Genetic defects in CD have highlighted important immunological pathways, particularly involving the innate immune response, barrier function, defensins, macrophages, antigen-presenting dendritic cells and the Th17 pathway.

Pathology

CD can affect any part of the gastrointestinal tract, in contrast to UC, which affects the colon alone (with occasional backwash ileitis). CD is most often confined to the bowel and can be ileo-caecal (40%), exclusively ileal (30%) or exclusively colonic (25%). Perianal involvement occurs in about one-third of patients. Disease tends to be discontinuous, giving rise to ‘skip’ lesions, and affected bowel is oedematous and associated with fat wrapping on the serosal surface. Mucosal ulceration varies from scattered aphthous ulcers to deep serpiginous pleomorphic ulcers. These can burrow through the bowel wall, leading to fistula formation between the affected bowel and adjacent bowel, bladder, vagina or skin.

Histologically, transmural inflammation predominates although this is usually submucosal. Focal patchy chronic inflammation (lymphocytes and plasma cells), focal crypt irregularity (discontinuous crypt distortion) and non-caseating granulomata (not related to crypt injury) are the generally accepted microscopic features that allow a diagnosis of CD. (Table 2) Granulomata (Figure 1) occur in up to 60% of cases, particularly in distal and perianal disease.

Clinical features

The clinical features depend on the location and behaviour of the disease. CD has been sub-divided using the Montreal classification (Table 3), which takes into account the location of disease in addition to its behaviour (inflammatory; stricturing or penetrating) and the age at diagnosis.

Symptoms and signs

CD may present insidiously or acutely and symptoms can vary from vague gastrointestinal upset to severe systemic features of fever, malaise and tachycardia.

The majority of patients have diarrhea (70–90%), abdominal pain (45–66%) and/or weight loss (65–70%). Rectal...
bleeding is more common in patients with rectal involvement. Obstructive symptoms of nausea/vomiting and abdominal pain/fullness are more common in patients with ileal disease, when stricturing occurs. Perianal fistulas (Figure 2) are a common complication of CD, occurring in around a third of patients. Some patients present with perianal fistulas before or at the time of diagnosis. Perianal disease (including skin tags, fissures, anal ulcers, fistulas, abscesses, anorectal strictures) generally denotes a more aggressive phenotype.

The age at diagnosis may influence disease location, with jejuno-ileal disease being more common in children and adolescents, and colonic disease more common in adults.

**Extra-intestinal manifestations of IBD**

Extra-intestinal manifestations (EIMs) affect organs apart from the gut, such as the joints (peripheral arthritis, ankylosing spondylitis, sacroiliitis), skin (pyoderma gangrenosum, erythema nodosum — Figure 3), eyes (uveitis, episcleritis) and hepatobiliary system (primary sclerosing cholangitis; PSC). The overall incidence of such manifestations is about 30%, with joints being most commonly involved, followed by skin, eye and hepatobiliary system. The spectrum of EIMs seen in CD is similar to that seen in UC, with the exception that PSC is less common in CD. EIMs are most common when the colon (as opposed to the small bowel) is inflamed. Some EIMs, such as erythema nodosum, appear directly related to the activity of the disease.

### Table 2

<table>
<thead>
<tr>
<th>Macroscopic</th>
<th>Microscopic</th>
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</thead>
<tbody>
<tr>
<td>Whole gastrointestinal tract (commonly ileum)</td>
<td>Focal (discontinuous) crypt irregularity</td>
</tr>
<tr>
<td>Right &gt; left colon</td>
<td>Focal (discontinuous) chronic inflammation</td>
</tr>
<tr>
<td>Rectum typically spared</td>
<td>Transmural lymphoid aggregates</td>
</tr>
<tr>
<td>Segmental (discontinuous) involvement (skip lesion)</td>
<td>Serositis can be present</td>
</tr>
<tr>
<td>Aphthoid or confluent deep serpiginous pleomorphic ulcers</td>
<td>Non-caseating granulomas (not related to crypt injury) can be present (up to 60%)</td>
</tr>
<tr>
<td>Cobblestone-pattern</td>
<td>Focal crypt epithelial polymorphs</td>
</tr>
<tr>
<td>Deep fissures/fistulas/strictures</td>
<td>Neuronal hyperplasia</td>
</tr>
<tr>
<td>Increased wall thickness</td>
<td>Muscular hypertrophy</td>
</tr>
<tr>
<td>Fat wrapping</td>
<td>Pyloric gland metaplasia</td>
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</tbody>
</table>

### Montreal classification of Crohn's disease

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>Location</th>
<th>Behaviour</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1 &lt;16 years</td>
<td>L1 ileal</td>
<td>B1 inflammatory</td>
</tr>
<tr>
<td>A2 17–40 years</td>
<td>L2 colonic</td>
<td>B2 stricturing</td>
</tr>
<tr>
<td>A3 &gt;40 years</td>
<td>L3 ileo-colonic</td>
<td>B3 penetrating</td>
</tr>
<tr>
<td>L4 isolated upper GI disease</td>
<td>p perianal disease</td>
<td></td>
</tr>
</tbody>
</table>

* L4 is a modifier that can be added to L1–L3.
* p is a modifier that can be added to B1–B3.
bowel disease. Others, such as PSC and ankylosing spondylitis/sacroiliitis, appear to follow a distinct course.

Patients with CD have an increased risk of developing renal calculi (particularly urate stones in patients with ileostomy and proctocolectomy, and oxalate stones in patients with ileo-caecal resections). Additionally, patients with CD have an increased risk of gallstones, especially those with extensive ileal disease or extensive small bowel resections. The risk of thrombo-embolism is increased — particularly during active disease, compounded by dehydration, immobilization and sepsis. Osteoporosis/osteopenia is common in patients with CD owing to multiple factors, including underlying disease activity, therapy with corticosteroids, poor nutritional intake and/or absorption of vitamin D and calcium, low body mass index, smoking and low physical activity.

Colorectal cancer

Patients with longstanding Crohn’s colitis have an increased risk of colorectal cancer. Patients with risk factors for developing colitis-associated colorectal cancers are advised to have regular surveillance colonoscopies. The degree of colonic inflammation is now recognized as an independent risk factor for dysplasia and colorectal cancer development. Pancolonic chromoendoscopy with targeted biopsies of abnormal areas is the optimal surveillance technique.

Diagnosis

History and clinical examination

A full medical history should include a history of onset of symptoms, recent travel, family history of IBD, drug history (antibiotics and non-steroidal anti-inflammatory drugs), appendicectomy and smoking status. Physical examination should include general well being, temperature, blood pressure, heart rate, weight and height, abdominal tenderness or masses, inspection of the oral mucosa and perineum, assessment for any rashes and digital rectal examination. The presence of perianal fissures or fistulas and anal induration are suggestive of CD. In patients with mild or moderate CD, physical examination may be normal, whereas those with severe disease will present with fever, tachycardia or abdominal tenderness.

Investigations

Laboratory investigations. Initial blood tests include full blood count, renal function, liver function tests, serum albumin and inflammatory markers (serum C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR)). Anaemia and thrombocytosis are common findings. Anaemia may be due to iron deficiency (secondary to blood loss, malabsorption or chronic inflammation), or folate and vitamin B12 deficiency (following terminal ileal resection or malabsorption).

Stool tests. Routine stool testing, including Clostridium difficile toxin, to exclude known pathogens is recommended. Samples should be sent for ova, cysts and parasites if there is a history of foreign travel. Faecal biomarkers such as calprotectin, lactoferrin, and S100A12 are predominantly derived from neutrophils, are easily detectable in the faeces, and are emerging as valuable markers of intestinal inflammation. Elevated faecal calprotectin (or lactoferrin) can be useful in distinguishing inflammatory bowel disease from functional bowel disease. Calprotectin can also differentiate between active and inactive inflammatory bowel disease, correlates with the severity of symptoms and may predict relapse, especially in UC. It can be used as a surrogate marker for the response (including endoscopic response) to therapies, as a normal concentration of calprotectin is a reliable index of mucosal healing.

Genetic and serologic tests. Genetic testing using NOD2 is not routinely available or recommended for diagnosis of CD. Sero-logic testing, including anti-Saccharomyces cerevisiae antibody (ASCA) or anti-neutrophil cytoplasmic antibody (ANCA), have a high sensitivity but a low predictive value and are not useful in the routine diagnosis of CD but may be used as an adjunct.

Plain abdominal radiograph is not a diagnostic test for CD but may be used to assess the severity and extent of large bowel inflammation and small bowel dilatation in acutely unwell patients. In fulminant Crohn’s colitis, the colon may dilate to a diameter greater than 6.5 cm (‘toxic megacolon’) (Figure 4a). Complications of CD such as renal stones or sacroiliitis may be present on plain abdominal radiographs. Radiation-based
imaging should be used sparingly in view of the potential damage resulting from cumulative radiation.

**Ileo-colonoscopy** is the first-line procedure for establishing the diagnosis of CD. Typical endoscopic features include isolated aphthous ulcers with intervening normal mucosa, cobblestoning, anal lesions and/or ileal ulceration (Figure 4b and c). The presence of deep ulceration or mucosal detachment indicates severe disease, and post-inflammatory polyps (‘pseudopolyps’) suggest previous severe inflammation. When reporting ileocolonoscopies, photographs and biopsies should be taken of each bowel segment in order to map the disease accurately and to act as a baseline for assessing response to therapies. Representative biopsies should be taken to enable the histopathologist to assess any patchiness of the disease. Particular care should be taken in describing the state of the rectum (endoscopically and histologically) as there may be implications for prognosis (proctitis worsens the prognosis for perianal disease) and for future surgical management.

**Gastroduodenoscopy** is recommended in patients with upper gastrointestinal symptoms, and in children, in whom there is a greater burden of upper gastrointestinal disease.

Once CD is assessed on ileo-colonoscopy and confirmed on histology, further investigations are recommended to assess the extent, severity and the site of small bowel disease.22

**Magnetic resonance (MR) and computed tomography (CT) enterography or enteroclysis** have a high diagnostic sensitivity in detecting small bowel involvement and extraluminal complications of CD, including internal fistula and abscess (Figure 4d). Both techniques are helpful in assessing disease activity and extent, based on wall thickness and intravenous contrast enhancement. CT is widely available, less time consuming and inexpensive, whereas MR is more desirable, especially in young patients, to limit radiation exposure resulting from repeated examinations. CT and MR require oral luminal contrast to ensure adequate small bowel distension. Enteroclysis involves the placement of a nasojejunal tube to administer luminal contrast for better small bowel distension and stricture assessment. MR scanning of the pelvis is important to assess the anatomical extent of perianal CD and may be useful in monitoring healing (Figure 4e).

**Barium follow through** can be used to assess the extent of small bowel disease, but has a lower sensitivity compared with CT or MR. The main features apparent include thickening of valvular conniventes, ulcers and fissuring, bowel oedema, luminal narrowing and strictures, prestenotic dilatation and fistulas. Barium follow through performed in expert hands can be particularly useful in mapping any strictures and fistulating disease.

**Wireless capsule endoscopy (WCE) and small bowel enteroscopy** — WCE and enteroscopy with biopsy using a push enteroscope or a double-balloon enteroscope are useful in symptomatic patients with a high clinical suspicion of CD but negative findings using other endoscopic and imaging techniques (Figure 4f). WCE is superior to small bowel follow through, CT enterography, and MR enteroclysis in the diagnosis of small

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**Figure 4 a** Diluted transverse colon (‘toxic megacolon’) in a patient with colonic Crohn’s disease on plain abdominal X-ray. **(b)** Scattered aphthous ulcers in colonic Crohn’s disease on colonoscopy. **(c)** Deep ulceration and cobblestoning in severe ileal Crohn’s disease on ileoscopy. **(d)** Entero-cutaneous fistula (arrow) in a patient with complex Crohn’s disease on a CT scan. **(e)** High signal perianal fistula tract (arrow) on coronal pelvic MRI. **(f)** Jejunal aphthous ulcer on wireless capsule endoscopy.
bowel Crohn’s lesions, but lesions seen on WCE are non-specific and about 10% of healthy individuals have mucosal breaks and erosions in their small bowel. Contraindications to WCE include intestinal obstruction, stenosis or strictures, and pacemakers.

Ultrasound scanning represents a non-ionizing imaging modality to evaluate the site, extent and disease activity in CD, especially for inflammation limited to the terminal ileum, and to exclude abscesses. It is widely available and inexpensive, but is operator dependent and has wide interobserver variability. It may be a useful option in young patients with slender abdomens.

Leucocyte scans – Indium-111-labelled or technetium-99 HMPAO-labelled white blood cell scans may be helpful to detect the location and extent of bowel inflammation but lack specificity.

Sinography or fistulography is useful to delineate the anatomy of fistulizing disease. Contrast medium is injected into a sinus tract or external fistula tracts (e.g. enterocutaneous fistulas).

Differential diagnosis

Infectious disease and non-infectious causes of colitis and enteritis need to be excluded (Table 4).

**Table 4**

<table>
<thead>
<tr>
<th><strong>Differential diagnosis of Crohn’s disease</strong></th>
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<tbody>
<tr>
<td><strong>Infectious</strong></td>
</tr>
<tr>
<td><strong>Bacterial</strong></td>
</tr>
<tr>
<td>Shigella spp, Salmonella spp, Campylobacter jejuni, Clostridium difficile, Escherichia coli, Yersinia spp (if only the terminal ileum is inflamed), Actinomyces, Mycobacterium tuberculosis, atypical mycobacteria, Neisseria gonorrhoeae (mainly proctitis), Chlamydia trachomatis (mainly proctitis), Tropheryma whippelii</td>
</tr>
<tr>
<td><strong>Viral</strong></td>
</tr>
<tr>
<td>Cytomegalovirus, herpes simplex (mainly proctitis), human immunodeficiency virus</td>
</tr>
<tr>
<td><strong>Parasitic</strong></td>
</tr>
<tr>
<td>Entamoeba histolytica, Giardia lamblia, Strongyloides stercoralis, Isosporidia belli, Cryptospora spp, Trichuris trichiura</td>
</tr>
<tr>
<td><strong>Mycotic</strong></td>
</tr>
<tr>
<td>Candida spp, Aspergillus spp</td>
</tr>
<tr>
<td><strong>Non-infectious</strong></td>
</tr>
<tr>
<td><strong>Inflammatory</strong></td>
</tr>
<tr>
<td>Ulcerative colitis (if only colonic disease), microscopic colitis, diverticulitis, eosinophilic gastroenteritis, sarcoidosis, Behçet’s disease (if deep punched-out ulcers are present)</td>
</tr>
<tr>
<td><strong>Vascular</strong></td>
</tr>
<tr>
<td>Ischaemic colitis, vasculitis</td>
</tr>
<tr>
<td><strong>Malignant</strong></td>
</tr>
<tr>
<td>Colorectal cancer, small intestinal cancer, neuroendocrine cancer, metastatic neoplasms, lymphoma</td>
</tr>
<tr>
<td><strong>Iatrogenic</strong></td>
</tr>
<tr>
<td>Radiation colitis, Diversion colitis, Drug-induced (non-steroidal anti-inflammatory drugs, gold, penicillamine, oral contraceptive pill)</td>
</tr>
</tbody>
</table>

**Management**

Management of CD depends on the site, extent and activity of disease, and the presence of complications. The therapeutic goal is to induce and to maintain remission, heal the mucosa and optimize quality of life for the patient. Table 5 summarizes current medical treatment for CD.15

**Localized ileo-caecal Crohn’s disease**

In mild disease, budesonide (9 mg daily) or primary nutritional therapies can be used to induce remission; mesalazine is of little benefit. In moderate to severely active disease, the recommended treatment is corticosteroids to induce remission followed by zathioprine, 6-mercaptopurine (6-MP) or methotrexate, to maintain remission. Since the immunomodulators may take up to 12 weeks to have a therapeutic effect, they are sometimes started concurrently with corticosteroids. Anti-tumour necrosis factor-α (TNFα) therapy can be considered in patients with corticosteroid- and/or immunomodulator-refractory disease. Surgery is also an option and produces good results in localized disease (Table 6).

**Extensive small bowel disease (> 100 cm)**

First-line treatment includes corticosteroids and concomitant immunomodulators. In patients with clinical markers of poor prognosis (e.g. <40 years and/or significant weight loss at diagnosis, initial need for corticosteroids, perianal disease, extensive small bowel disease, strictureting behaviour), anti-TNFα therapy should be initiated early in the disease course as it is more likely to be effective at this stage. Adjunctive nutritional support is important.

**Colonic Crohn’s disease**

Sulphasalazine can be used in mild disease. Corticosteroids (usually prednisolone) remain first-line therapy, with immunomodulators as corticosteroid-sparing agents. Anti-TNFα therapy should be considered in patients with refractory disease.

**Crohn’s proctitis**

Topical mesalazine or corticosteroids can be considered in Crohn’s proctitis. There is an increased risk of rectal stricture formation in cases of marked anal involvement.

**Perianal Crohn’s disease**

Antibiotics (metronidazole or ciprofloxacin) are widely used in patients with perianal fistulas. Perianal sepsis must be drained and seton(s) inserted if indicated. Complex fistulas should be treated using thiopurines with early introduction of anti-TNFα to achieve fistula closure.

**Oesophageal and gastroduodenal Crohn’s disease**

Treatment includes systemic corticosteroids, with thiopurines or methotrexate, combined with a proton pump inhibitor. The threshold for starting anti-TNFα therapy is lower for severe or refractory upper gastrointestinal disease as prognosis is often poor.

**Postoperative Crohn’s recurrence**

After curative resection of macroscopically diseased bowel, metronidazole can reduce postoperative recurrence. In patients at high risk of disease recurrence, such as smokers, and those with previous resection(s), fistulizing disease, and residual inflammation after...
Evidence-based medical treatment for Crohn’s disease

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose</th>
<th>Route</th>
<th>Induction of remission</th>
<th>Maintenance of remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone</td>
<td>40 mg daily</td>
<td>Oral</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Budesonide</td>
<td>9 mg daily</td>
<td>Oral</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>2–2.5 mg per kg daily</td>
<td>Oral</td>
<td>X</td>
<td>✓</td>
</tr>
<tr>
<td>6-Mercaptopurine</td>
<td>1–1.5 mg per kg daily</td>
<td>Oral</td>
<td>X</td>
<td>✓</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Induction 25 mg weekly</td>
<td>SC/IM/Oral</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Maintenance 15 mg weekly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infliximab</td>
<td>Induction 5 mg at weeks 0, 2 and 6</td>
<td>IV</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Maintenance 5 mg (or 10 mg/kg) every 8 weeks</td>
<td></td>
<td></td>
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<tr>
<td>Adalimumab</td>
<td>Induction 160 mg (or 80 mg) week 0, 80 mg (or 40 mg) week 2</td>
<td>SC</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>Maintenance 40 mg every other week or weekly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Certolizumab</td>
<td>Induction 400 mg at weeks 0, 2 and 4</td>
<td>SC</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td></td>
<td>Maintenance 400 mg every 4 weeks</td>
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</table>

SC, subcutaneous; IM, intramuscular.

Table 5

Indications for surgery

- Localized or limited diseased segment causing severe symptoms not responding to medical therapy
- Abdominal abscess not controlled by antibiotics or percutaneous drainage
- Obstructive symptoms not relieved by medical therapy
- Perianal sepsis requiring drainage and seton insertion
- Symptomatic enterocutaneous or enterovesical fistulas

Table 6

Specific drug therapy

Diet

Liquid diet (elemental and polymeric) orally or via nasogastric feeding can be effective in treating active CD, but compliance is an issue. Exclusion diets are of unproven value in inducing or maintaining remission in CD. Probiotics are not useful for maintaining remission or preventing recurrence after surgery in CD. Existing data do not support the use of omega-3 fatty acids.

Corticosteroids

They are effective in inducing remission in active CD. The optimal initial dose for acute episodes is oral prednisolone 40 mg daily. Patients with severe disease may need intravenous corticosteroids (hydrocortisone 100 mg four times daily or methylprednisolone 20 mg three times daily). Long-term corticosteroid use is not recommended because of serious adverse effects, including osteoporosis, osteonecrosis of femoral head, and growth retardation in children. Corticosteroids have been shown to increase the risk of infections, both independently and in combination with immunomodulator or biologic agents. Budesonide, an alternative corticosteroid with extensive first-pass metabolism and limited systemic bioavailability, delivers treatment to the right colon and ileum. It is associated with fewer adverse effects and is preferred to prednisolone in patients with ileal or ileo-caecal disease. Supplementation with calcium and vitamin D is advocated if corticosteroid therapy is likely to continue for longer than 3 months.

Sulphasalazine

Sulphasalazine (3–6 g daily) is effective in patients with mildly active colonic CD, but has no role in maintaining disease remission. Adverse effects are dose-related and commonly include headache, nausea, diarrhoea and, rarely, Stevens–Johnson syndrome, agranulocytosis or pancreatitis.

Mesalazine (5-aminosalicylic acid)

Meta-analysis showed no benefit from 5-ASA in active ileal or colonic CD and no benefit in maintaining remission. Diarrhoea, nausea, headache, rash, thrombocytopenia and renal impairment have been reported with mesalazine.

Antibiotics

There is little evidence that metronidazole or ciprofloxacin, although commonly used, is effective in CD except in patients with septic complications and perianal disease. Metronidazole may help to prevent postoperative recurrence but long-term use is associated with peripheral neuropathy. Ciprofloxacin is associated with tendon damage.

Immunomodulators

Azathioprine and 6-MP have a corticosteroid-sparing effect. Azathioprine is metabolized to 6-MP, and is largely a pro-drug; its
mode of action is unclear. Both drugs have a slow mode of action and the maximum effect may not be seen for up to a few months. Approximately 10% of patients are intolerant of these drugs because of nausea or vomiting, flu-like symptoms, fever, myalgia, pancreatitis or bone marrow suppression. Regular blood monitoring is essential. Other adverse effects include nodular regenerative hyperplasia and lymphoma. It is currently unclear for how long thiopurine therapy should be continued. Methotrexate is an anti-metabolite and concurrent folic acid supplementation is advisable. The toxic effects of methotrexate include rash, nausea, diarrhoea, leucopenia, stomatitis, pneumonia, deranged liver function, bone marrow suppression and liver fibrosis.

**Anti-TNFα therapy**

All anti-TNFα therapies (infliximab, adalimumab, certolizumab) have comparable efficacy in inducing and maintaining remission in CD, especially in patients with severe disease refractory to conventional corticosteroids and immunomodulators. The choice of an anti-TNFα agent depends on accessibility, route of administration, patient preference, cost and national guidelines. Some patients (in particular those with poor prognostic features) appear to benefit from early treatment with immunomodulator drugs and/or anti-TNFα therapy. Episodic dosing is associated with immunogenicity and regular scheduled treatment is recommended. Adverse effects include infusion reactions, delayed-type hypersensitivity reactions, injection site reactions, drug-induced lupus, worsening heart failure, reactivation of latent tuberculosis and infections, lymphomas (including rare hepatosplenic T cell lymphomas) and possible solid tumours. Serum drug concentrations and antibodies to drugs can guide therapy particularly in the context of loss of response to anti-TNFα drugs.

**Other agents**

Vedolizumab is licensed for use in moderate-to-severe CD. It binds to integrin α4β7 and blocking the α4β7 integrin results in gut-selective anti-inflammatory activity. Natalizumab, a humanized anti-adhesion antibody, appears promising but was associated with progressive multifocal leucoencephalopathy. Thalidomide, although effective in some patients with luminal and fistulizing CD, is commonly associated with toxicities (neuropathy, drowsiness, teratogenicity). Evidence supporting calcineurin inhibitors (ciclosporin, tacrolimus), anti-mycobacterial agents, cytapheresis and autologous stem cell transplantation is limited. Other biologic agents under evaluation include anti-adhesion molecules, anti-inflammatory cytokines and granulocyte-macrophage colony-stimulating factor (GM-CSF).

Faecal microbiota transplant (FMT) is safe and has shown variable efficacy in cohort and case–control studies, but randomized controlled studies are needed.

**Surgical management**

Intestinal resection is more likely to be required for ileal CD than for colonic disease. Approximately 50% of all patients with CD will require at least one intestinal resection within 10 years of diagnosis, and 40% will require a further operation within 10 years of the first. Surgery is reserved for complications of disease, or for severe limited disease unresponsive to medical therapy (Table 4). Multiple extensive small bowel operations can result in short bowel syndrome and intestinal failure, and limited resections or stricturoplasty should be performed where possible. A laparoscopic approach is preferred for ileo-colonic resections in CD where appropriate expertise is available.

**Clinical course and prognosis**

Whereas disease location usually remains stable, there can be a significant change in disease behaviour over time, with progression from inflammatory to stricturing to penetrating disease; complications such as strictures, perforations, abscesses and fistulas (entero-enteric, enterocutaneous, enterovesical) become more common.

In the first year after diagnosis, 50% of all patients with CD will experience a flare of disease, irrespective of the site of disease. Of these about one-third will have a single flare and two-thirds will have at least two relapses. The life expectancy of patients with CD is slightly reduced.

**Special groups**

**Crohn's disease and fertility/pregnancy**

Fertility is reduced in patients with active CD but is unaffected in quiescent disease. Active disease is a risk for stillbirth, pre-term delivery and low birth weight. Most medications used to treat CD are safe in pregnancy, with the exception of methotrexate and thalidomide. The overarching principle is to control the mother's disease effectively as in general the risks of active disease outweigh any adverse effects of drug treatment. Caesarean section is recommended in the context of active perianal disease.

Although anti-TNFα drugs can cross the placenta in the second trimester of gestation, this treatment seems to be safe at least in the short term, but it is wise to limit exposure during the last trimester of pregnancy and counsel the patient about risks and benefits. In utero exposure to immunomodulator and anti-TNFα therapy also does not lead to developmental delay when compared with unexposed infants.

**Crohn's disease in children and adolescents**

The course of disease and treatment principles in children/adolescents are the same as in adults, but growth retardation and puberal delay as well as psychosocial aspects need to be addressed. Both exclusive enteral nutrition and corticosteroids are effective for induction of remission irrespective of disease activity or location, but enteral nutrition has fewer adverse effects and promotes growth. Most patients with childhood-onset CD require immunomodulator to maintain disease remission, whereas those with severe perianal fistulizing disease, severe stricturing/penetrating disease, severe growth retardation or panenteric disease, may benefit from an anti-TNFα-based top-down approach. Ultimately the goal is to optimize growth and limit the adverse effects of treatment.

**REFERENCES**

2. Ng SC, Tang W, Ching JY, et al. Incidence and phenotype of inflammatory bowel disease based on results from the Asia-pacific...

**Practice points**

- Ileo-colonoscopy with biopsies is the first-line investigation to establish the diagnosis of Crohn's disease (CD)
- Magnetic resonance enterography is recommended to establish the extent of small bowel disease and extramural complications
- Management should take into account the site, extent and activity of CD, previous treatment and risk factors for poor prognosis
- Disease monitoring using blood tests, faecal calprotectin, endoscopy and small bowel imaging should be incorporated in routine practice
- Multidisciplinary team working with gastroenterologists, surgeons, radiologists, specialist nurses, dietitians and pharmacists aims to achieve optimal individualized patient management