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 mouth to anus, although the ileum, colon and perineum are most commonly involved. It is characterized by transmural granulomatous inflammation. Crohn's disease is thought to result from a complex interplay of multiple genetic and environmental factors. Alterations in the microbiota signature with reduced microbiota diversity are observed. Diarrhoea, abdominal pain, fatigue, weight loss and fever are hallmarks of Crohn's disease. Clinical features depend on the location and behaviour of disease in the gastrointestinal tract. Extra-gastrointestinal manifestations can involve the joints, skin, eyes and liver. Investigations are directed towards identifying the location, extent and severity/behaviour (inflammatory, stricturing, penetrating) of the disease. The goal of management should be to achieve clinical and endoscopic remission to avoid disease progression and surgical resections. Treatment usually features corticosteroids, immunomodulators (thiopurines, methotrexate), anti-tumour necrosis factor-α therapy or surgery. Newer biological agents included anti-integrin inhibitors and anti-interleukin-12/23 antibody. Patients with poor prognostic features may benefit from early treatment with immunomodulatory drugs and/or biological agents. Therapeutic drug monitoring can help physicians improve and personalize the management of Crohn's disease. Psychological support is also important in managing this chronic condition.

Keywords Anti-IL12/23; anti-integrin; anti-tumour necrosis factor-α; Crohn's disease; immunomodulators; inflammatory bowel disease; microbiota; MRCP

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Key points

- The incidence of Crohn's disease (CD) has been rising in newly industrialized countries in Africa, Asia and South America
- An altered microbiota signature with reduced microbiota diversity is observed in CD. Fewer *Clostridiales*, and increases in *Bacteroides*, *Proteus* and *Enterobacteriales*, are observed
- Diet, including artificial sweeteners and emulsifiers, alters the host–microbiome relationship and increases the risk of developing CD
- Management should take into account the site, extent and activity of CD, previous treatment and risk factors for poor prognosis
- Tight disease control, aiming to achieve mucosal healing, is associated with improved outcomes
- Multidisciplinary teamworking involving gastroenterologists, surgeons, radiologists, specialist nurses, dietitians and pharmacists aims to achieve optimal individualized patient management
- Psychological support is important
- Addressing symptoms such as continence issues, fatigue and pain is also an important part of overall management

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 mouth to anus, often in discontinuity. Common complications include intestinal strictures, fistulae and abscesses.

Epidemiology

The incidence of CD varies worldwide. Rates vary between 0.1 and 16 per 100,000 inhabitants, with the highest incidence recorded in Northern and Western Europe, North America and Oceania, and lower rates in Africa, South America and Asia (Table 1). Previously, CD was less commonly diagnosed than ulcerative colitis (UC), but in the late 20th century in the developed world diagnosis of CD has caught up and in several regions has surpassed that of UC. A recent systematic review showed that the incidence of CD has been stable or decreasing since 1990 in North America and Europe, but has been rising in newly industrialized countries in Africa, Asia and South America, including Brazil and Taiwan.[1] Living in an urban area is associated with increased risk of IBD. For instance, regions in Asia with a high population density had higher incidences of CD and UC.

Incidence rates of IBD worldwide[1]

	Incidence rate per 100,000 person–years	
	CD	UC
Oceania	12.96–29.30	7.33–17.4
Africa	5.87	3.29
North America	6.30–23.82	8.8–23.14
South America	0.0–3.50	0.19–6.76
Eastern Europe	0.40–14.6	0.97–11.9
Northern Europe	0–11.4	1.7–57.9
Southern Europe	0.95–15.4	3.3–11.47
Western Europe	1.85–10.5	1.9–17.2
Eastern Asia	0.06–3.2	0.42–4.6
South-Eastern Asia	0.14–0.41	0.15–0.68
Southern Asia	0.09–3.91	0.69–6.02
Western Asia	0.94–8.4	0.77–6.5

Table 1

Childhood-onset CD is also becoming more common, especially in children <10 years of age. Seniors with IBD are also a rapidly increasing population because of a combination of new diagnoses of IBD in elderly individuals and the advancing age of patients with IBD who were diagnosed earlier in adulthood. Estimates of prevalence vary depending on whether figures are derived from primary (200 per 100,000 population) or secondary/tertiary care settings (70–100 per 100,000 population). 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 men (the reverse is seen in Asian countries, where there is a male predominance). There is a notably high incidence among Ashkenazi Jewish populations.

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 per cent of patients with CD have a relative with either CD or UC, and the concordance rate in monozygotic twins is about 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. The inheritance of CD cannot be described by a simple Mendelian genetics model; instead, multiple genes are involved, with different genes conferring susceptibility, disease specificity and phenotype. Approximately one-third of patients with CD have mutations in *NOD2*, the first CD gene identified, on chromosome 16. Compared with the wild-type genotype, *NOD2* heterozygotes have a 2-fold 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 the activation of nuclear factor κB and downstream proinflammatory mediators by a poorly understood mechanism.

Genome-wide association studies 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. In addition, the interleukin (IL)-23 pathway is highlighted by association of variants in the IL-23 receptor gene. Overall, >200 IBD loci have been identified, most with small effect size, 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.

'Very early onset IBD' refers to children diagnosed with IBD before the age of 6 years and is rising in incidence. The diagnosis of monogenetic disorders should be suspected when IBD is diagnosed in infancy, particularly if there is a strong family history or a severe presentation such as perianal fistulae.

Genetics can predict the disease course; for instance, *NOD2* variants are particularly associated with ileal and stenosing CD and an earlier need for intestinal surgery. The presence of an ileal gene controlling extracellular matrix production has been associated with stricturing CD. However, despite advances in the field of CD genetics, there are currently no genetic tests that are routinely recommended for disease diagnosis.

Environmental factors

Smoking: smokers are more likely to develop CD than non-smokers (as opposed to UC, where smoking is protective). The disease also tends to be more difficult to manage in smokers with CD, who appear to need more immunosuppression and surgical intervention. Furthermore, there is an increased risk of relapse in smokers after surgery, but smoking cessation reduces the risk of relapse after surgery in non-smokers. In contrast, smoking is not a risk factor for CD in multiple countries across Asia, which highlights the heterogeneity of environmental risk factors in different regions of the world.

Early life events: meta-analyses show an inverse relationship between breastfeeding and IBD. For CD, there is an odds ratio of 0.45 (95% confidence interval 0.26–0.79). There is some evidence that a longer duration of breastfeeding might be associated with protection in the development of IBD, and that in Asian populations breastfeeding confers greater protection than it does in white populations. Epidemiological evidence does not support an association between mode of delivery (caesarean section versus vaginal delivery) and development of IBD.

Medications: oral contraceptive pills have been implicated in the development of CD, particularly among smokers, and in CD there is an increased risk of surgery in long-term oral contraceptive pill users. Non-steroidal anti-inflammatory drugs (NSAIDs), especially with longer duration of use, are associated with increased risk of IBD. There is a suggestion that selective cyclooxygenase-2 inhibitors are not associated with disease relapse.

Diet: dietary emulsifiers, such as carboxymethyl cellulose and polysorbate 80, have recently been shown to alter gut microbiota and promote colitis in mice.[2] Artificial sweeteners and food additives such as titanium dioxide nanoparticles alter the host–microbiome relationship, resulting in an unfavourable shift in the gut microbiome. Epidemiological studies have shown that the use of artificial sweeteners doubles the risk of CD. Lack of dietary fibre and frequent oscillations between fibre-rich and fibre-deprived diets lead to depletion of gut microbiota diversity and are associated with development of CD in epidemiological and animal studies.[2] There is some evidence that high dietary zinc concentrations and high (versus low) fish intake can be protective in CD. Elemental and polymeric diets are beneficial treatments for children and adults with CD and are associated with mucosal healing.

Psychosocial factors: emerging data suggest an association between psychiatric illness, development of IBD and worsening of prognosis in CD. Patients with IBD were more likely to suffer from depression and anxiety than healthy participants.

Microbiota: in CD, altered faecal microbiota signatures have been consistently reported, implicating a role for the microbiota in the pathogenesis of IBD. Bacterial diversity is decreased in patients with CD. Fewer *Clostridiales*, such as *Faecalibacterium prausnitzii* spp., and increases in *Bacteroides* and Enterobacteriales, such as *Escherichia coli* spp., are observed. *Ruminococcus* was shown to be associated with stricturing complications, while *Veillonella* was associated with penetrating complications. More recently, *Proteus* spp. have been identified as a potential pathogen in recurrence of CD after intestinal resection.

Diet is one of the most important factors influencing the gut microbiota. A 'Western' diet is associated with a decreased ratio of *Bacteroides* to *Firmicutes* and enhanced susceptibility to infection with adherent-invasive *E. coli* (AIEC). The presence of AIEC has been linked to the pathogenesis of CD. Smoking is associated with a decrease in gut microbial diversity and a different microbial composition. Recent studies have suggested that antibiotic use during childhood may predispose to disease development.

In terms of the gut mycobiota, several fungal species, including *Candida* spp., *Gibberella moniliformis*, *Alternaria brassicicola* and *Cryptococcus neoformans*, are increased in tissues from CD patients, while *Saccharomyces cerevisiae* are decreased. Fungal diversity is also decreased in CD. CD patients harbour increased numbers of bacteriophages in inflamed tissue and faeces, although no specific viruses have yet been associated with human IBD.

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 T-helper type 17 pathway. Expression of adhesion molecules is crucial to amplify the immune response, and targeting immune cell homing to the intestinal mucosa is an important pathway in CD therapeutics. Antibodies to either mucosal vascular addressin cell adhesion molecule (MAdCAM)-1 or its ligand $\alpha_4\beta_7$ (e.g. vedolizumab), or targeting the B7 subunit (e.g. etrolizumab (unlicensed drug)), prevent lymphocyte recruitment, reduce the severity of colonic inflammation and have been shown to be effective in clinical studies of CD. CD is characterized by dysregulation of both innate and adaptive immune responses, with perturbations in adaptive immunity more likely to be driving the long-term colitic change. IL-12 and IL-23 are major players in activating adaptive immunity and share the p40 subunit. Ustekinumab is a humanized monoclonal antibody against the p40 subunit of IL-12/23 that prevents interaction with the cell surface IL-12Rβ1 receptor, subsequently inhibiting IL-12- and IL-23-mediated cell signalling, activation and cytokine production in CD.

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 usually confined to the bowel and can be ileocaecal (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, plasma cells), focal crypt irregularity (discontinuous crypt distortion) and non-caseating granulomas (not related to crypt injury) are the generally accepted microscopic features that allow a diagnosis of CD (Table 2). Granulomas (Figure 1) occur in up to 60% of patients, particularly in distal and perianal disease.

Clinical features

These depend on the location and behaviour of the disease. CD has been subdivided 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.

Most patients have diarrhoea (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 fistulae (Figure 2) are a common complication of CD, occurring in around a third of patients. Some patients present with perianal fistulae before or at the time of diagnosis. Perianal disease (including skin tags, fissures, anal ulcers, fistulae, abscesses and anorectal strictures) generally denotes a more aggressive phenotype.

Macroscopic and microscopic features of CD

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

Table 2

Montreal classification of CD

Age at diagnosis (years)	Location	Behaviour
A1 <16	L1 ileal	B1 inflammatory
A2 17–40	L2 colonic	B2 stricturing
A3 >40	L3 ileo-colonic	B3 penetrating
	[a]L4 isolated upper gastrointestinal disease	[b]p perianal disease

[a] L4 is a modifier that can be added to L1–L3.
[b] p is a modifier that can be added to B1–B3.

Table 3

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

Extraintestinal manifestations (EIMs) of IBD

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 the joints being most commonly involved, followed by the 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 small bowel) is inflamed. Some EIMs, such as erythema nodosum, appear to be directly related to the activity of the 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 ileocaecal

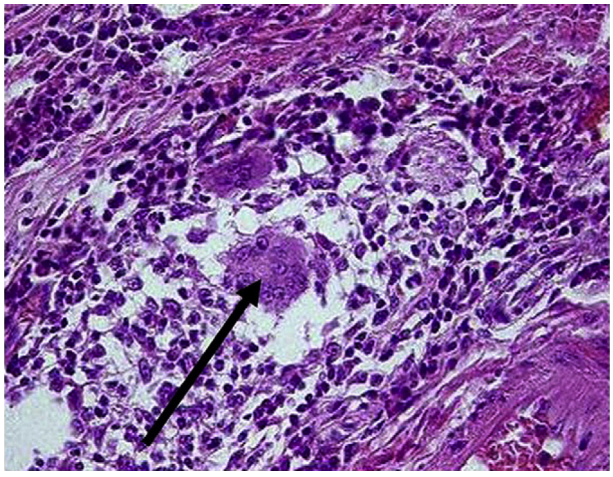

Figure 1 Histology from a patient with CD showing a granuloma (arrow).

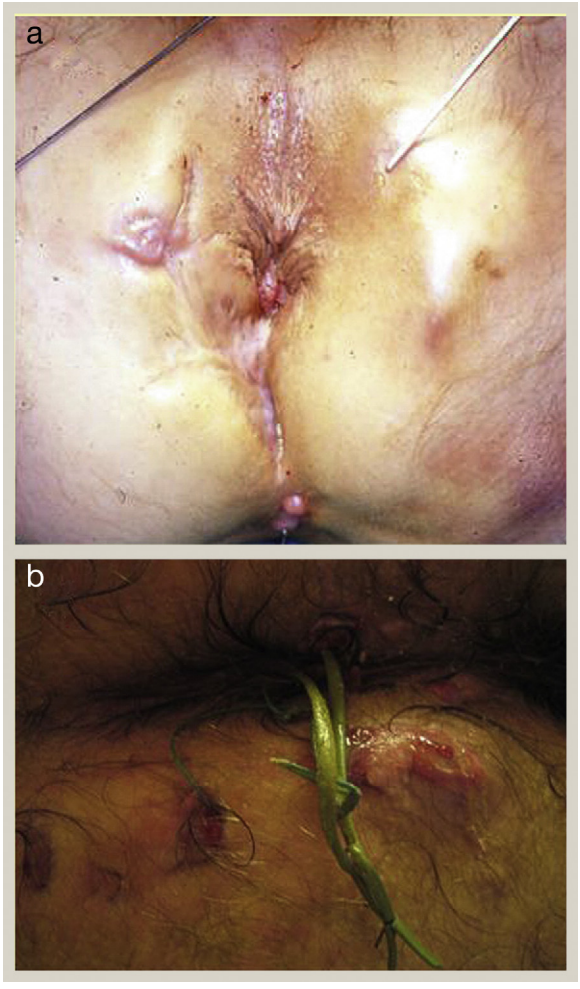

Figure 2 Perianal CD. (**a**) Anal skin tags, external fistula opening and scarred tissue from previous sites of surgery. (**b**) Multiple draining perianal fistula openings with a seton *in situ*.

resections). Additionally, there is an increased risk of gallstones in patients with CD, especially those with extensive ileal disease or extensive small bowel resections. The risk of thromboembolism 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 long-standing 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 the development of colorectal cancer. The optimal surveillance technique is pan-colonic chromoendoscopy with targeted biopsies of abnormal areas.

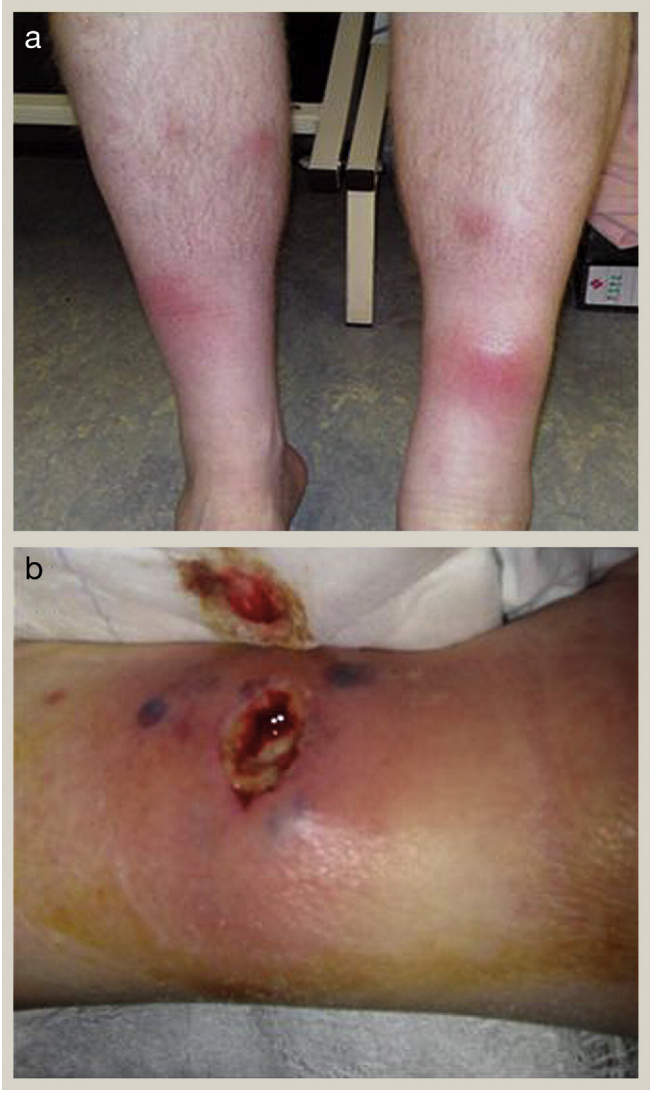

Figure 3 (**a**) Bilateral erythema nodosum. (**b**) Pyoderma gangrenosum.

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, NSAIDs), 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 rashes and digital rectal examination. The presence of perianal fissures or fistulae and anal induration is suggestive of CD. Physical examination can be normal in patients with mild or moderate CD, whereas those with severe disease present with fever, tachycardia or abdominal tenderness.

Investigations

Laboratory investigations involve initial blood tests including full blood count, renal function, liver function tests, serum albumin and inflammatory markers (serum C-reactive protein (CRP), erythrocyte sedimentation rate). Anaemia and thrombocytosis are common findings. Anaemia can be caused by iron deficiency (secondary to blood loss, malabsorption or chronic inflammation) or folate and vitamin B_{12} deficiency (after terminal ileal resection or malabsorption).

Stool tests, including *Clostridium difficile* toxin, to exclude known pathogens is recommended as routine. If there is a history of foreign travel, samples should be sent for ova, cysts and parasites. Faecal biomarkers such as calprotectin, lactoferrin and S100A12 are predominantly derived from neutrophils, easily detectable in the faeces and emerging as valuable markers of intestinal inflammation. Elevated faecal calprotectin (or lactoferrin) can be useful in distinguishing IBD from functional bowel disease. Calprotectin can also differentiate between active and inactive IBD, correlates with the severity of symptoms and endoscopic activity, and can 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 serological tests can have an adjunctive role. Genetic testing using *NOD2* is not routinely available or recommended for the diagnosis of CD. Serological tests, including anti-*S. cerevisiae* antibody or antineutrophil cytoplasmic antibody, have a high sensitivity but low predictive value. Therefore they are not useful in the routine diagnosis of CD but can be used as an adjunct.

Plain abdominal radiographs are not a diagnostic test for CD but can 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 can dilate to >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.

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,

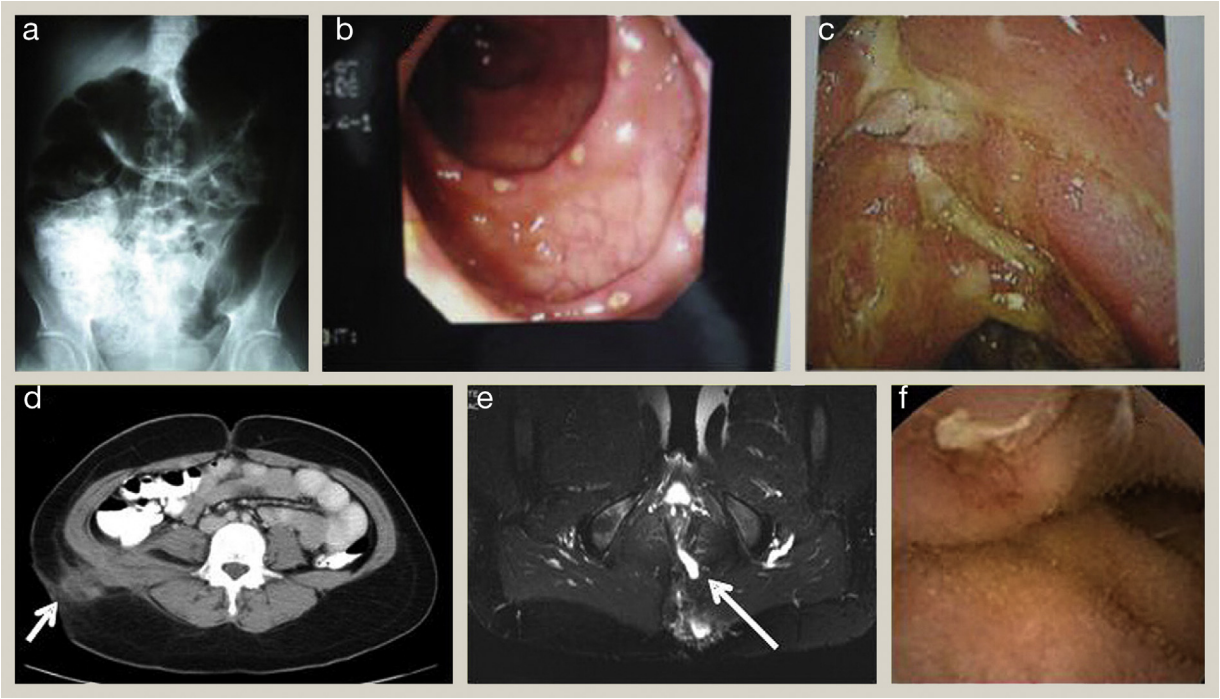

Figure 4 (**a**) Diluted transverse colon ('toxic megacolon') in a patient with colonic CD on plain abdominal X-ray. (**b**) Scattered aphthous ulcers in colonic CD on colonoscopy. (**c**) Deep ulceration and cobblestoning in severe ileal CD on ileoscopy. (**d**) Enterocutaneous fistula (arrow) in a patient with complex CD on a CT scan. (**e**) High-signal perianal fistula tract (arrow) on coronal pelvic MR imaging. (**f**) Jejunal aphthous ulcer on wireless capsule endoscopy.

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 ileo-colonoscopy results, photographs and biopsies should be taken of each bowel segment to map the disease accurately and act as a baseline for assessing the response to therapies. Representative biopsies should be taken to enable the histopathologist to assess any patchiness of disease. Particular care should be taken in describing the state of the rectum (endoscopically and histologically) as there can be implications for prognosis (proctitis worsens the prognosis for perianal disease) and future surgical management.

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

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

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 fistulas and abscesses (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 techniques are desirable, especially in young patients, to limit radiation exposure resulting from repeated examinations. CT and MR imaging 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 (Figure 4e) and useful in monitoring healing as radiological healing has been shown to lag behind clinical healing by 13 months, thus mandating prolonged therapy.

Wireless capsule endoscopy (WCE) and small bowel enteroscopy with biopsy using a push enteroscope or double-balloon enteroscope are useful in symptomatic patients in whom CD is highly likely but findings using other endoscopic and imaging techniques have been negative (Figure 4f). WCE is superior to small bowel follow-through, CT enterography and MR enteroclysis for diagnosing small 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. In general, the rate of capsule retention in patients with suspected CD is low, at around 0–5%.

Ultrasound scanning represents a non-ionizing imaging modality to evaluate 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 can be a useful option in young patients with a slender abdomen. Systematic reviews and meta-analysis have shown that bowel ultrasonography is as accurate as CT or MR enterography in assessing disease activity and complications, including abscesses and fistulae.

Differential diagnosis of CD

Infectious	
Bacterial	*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 whipplei*
Viral	Cytomegalovirus, herpes simplex (mainly proctitis), human immunodeficiency virus
Parasitic	*Entamoeba histolytica*, *Giardia lamblia*, *Strongyloides stercoralis*, *Cystoisospora belli*, *Cryptospora* spp., *Trichuris trichiura*
Mycotic	*Candida* spp., *Aspergillus* spp.
Non-infectious	
Inflammatory	UC (if only colonic disease), microscopic colitis, diverticulitis, eosinophilic gastroenteritis, sarcoidosis, Behçet's disease (if deep punched-out ulcers are present)
Vascular	Ischaemic colitis, vasculitis
Malignant	Colorectal cancer, small intestinal cancer, neuro-endocrine cancer, metastatic neoplasms, lymphoma
Iatrogenic	Radiation colitis, diversion colitis, drug-induced (NSAIDs, gold, penicillamine, oral contraceptive pill)

Table 4

Differential diagnosis

Infectious disease and non-infectious causes of colitis and enteritis should be excluded (Table 4). Intestinal tuberculosis is an important differential diagnosis for CD, especially in endemic regions. Tuberculosis can mimic CD endoscopically and most commonly involves the ileocaecal region. Behçet's disease can mimic CD and present with intestinal inflammation and EIMs. The presence of recurrent oral and genital ulcerations accompanied by uveitis and skin involvement should raise suspicion of Behçet's disease.

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 maintain remission, heal the mucosa and optimize the patient's quality of life. Table 5 summarizes current medical treatment for CD.

Localized ileocaecal 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 azathioprine, mercaptopurine (6-MP) or methotrexate to maintain it. Because immunomodulators can take up to 12 weeks to have a therapeutic effect, they are sometimes started concurrently with corticosteroids. Anti-tumour necrosis factor (TNF)-α therapy can be considered in patients with corticosteroid- and/or immunomodulator-refractory disease. Surgery is also an option (Table 6) and produces good results in localized disease. A recent study has demonstrated that laparoscopic resection in CD

Evidence-based medical treatment for CD

Drugs	Dose	Route	Induction of remission	Maintenance of remission
Prednisolone	20—40 mg daily	Oral	√	X
Budesonide	9 mg daily	Oral	√	X
Azathioprine	2—2.5 mg/kg daily	Oral	X	√
6-MP	1—1.5 mg/kg daily	Oral	X	√
Methotrexate	Induction 25 mg weekly Maintenance 15 mg weekly	i.m. (for induction)/oral (for maintenance)	√	√
Infliximab	Induction 5 mg at weeks 0, 2 and 6 Maintenance 5 mg (or 10 mg/kg) every 8 weeks	i.v.	√	√
Adalimumab	Induction 160 mg (or 80 mg) week 0, 80 mg (or 40 mg) week 2	s.c.	√	√
Vedolizumab	Induction 300 mg at weeks 0, 2 and 6 Maintenance 300 mg every 8 weeks	i.v.	√	√
Ustekinumab	Induction 260 mg (if ≤ 55 kg) 390 mg (if 55 kg to ≤85 kg) 520 mg (if >85 kg)	i.v.	√	X
	Maintenance 90 mg every 8 weeks	s.c.	X	√

6-MP, mercaptopurine; IM, intramuscular; IV, intravenous; SC, subcutaneous.

Table 5

Indications for surgery

- Localized or limited diseased segment causing severe symptoms and 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 fistulae

Table 6

patients with limited ileocaecal disease failing conventional therapy performed similarly to infliximab therapy.[3]

Extensive (>100 cm) small bowel disease

First-line treatment includes corticosteroids and concomitant immunomodulators. In patients with clinical markers of poor prognosis (e.g. age <40 years, significant weight loss at diagnosis, initial need for corticosteroids, perianal disease, extensive small bowel disease, stricturing), anti-TNF-α 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

Sulfasalazine can be used in mild disease but cannot be recommended in view of high incidence of adverse effects. There is no evidence that mesalazine is effective in active colonic CD, although it is sometimes used in mild CD. Corticosteroids (usually prednisolone) remain first-line therapy, with immunomodulators as corticosteroid-sparing agents. Anti-TNF-α therapy should be considered in patients with refractory disease. If patients fail to respond or lose response to anti-TNF-α therapy, another class of biological agent including vedolizumab, a monoclonal antibody against $\alpha_4\beta_7$ integrin, or ustekinumab, a monoclonal antibody against IL-12/23, should be considered. Surgery should be considered if patients fail to respond to medical therapy.

Crohn's proctitis

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

Perianal Crohn's disease

Antibiotics (metronidazole, ciprofloxacin) are widely used in patients with perianal fistulae. Perianal sepsis must be drained and seton(s) inserted if indicated. Complex fistulae should be treated with a combination of surgery and anti-TNF-α therapy. Overall, combining infliximab with surgical management produces clinical remission in 36–58% of patients. Mesenchymal stem cell therapy has recently been shown to be an effective treatment for complex perianal Crohn's fistula not responding to conventional or biological treatment.

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-TNF-α therapy is lower for severe or refractory upper gastrointestinal disease as the prognosis is often poor.

Postoperative recurrence of Crohn's disease

After curative resection of macroscopically diseased bowel, metronidazole can reduce postoperative recurrence. Patients should undergo colonoscopy at 6 months postoperatively to look for evidence of endoscopic recurrence as this predates clinical recurrence.[4] A thiopurine or anti-TNF-α agent should be considered for patients at high risk of disease recurrence, such as smokers and those with previous resection(s), fistulizing disease or residual inflammation after resection. Patients who smoke should be offered advice on smoking cessation. Faecal calprotectin can predict postoperative endoscopic recurrence of CD.

Specific drug therapy

Diet: a 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. Exclusive enteral nutrition (EEN) is recommended as the first line therapy for induction of remission in paediactric CD patients with active luminal disease due to its safety and its efficacy in induction of remission while limiting steroid exposure.

Corticosteroids: these 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 the femoral head, and growth retardation in children. Corticosteroids have been shown to increase the risk of infections, both independently and in combination with immunomodulatory or biological agents.

Budesonide, an alternative corticosteroid with an 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 ileocaecal disease. Budesonide MMX is a novel once-daily oral formulation of budesonide using MultiMatrix multimatrix system (MMX®) colonic delivery technology to allow the release of budesonide at a controlled rate throughout the colon, but this has not been studied in CD.

Supplementation with calcium and vitamin D is advocated if corticosteroid therapy is likely to continue for >3 months.

Sulfasalazine: a dose of 3–6 g daily is effective in mildly active colonic CD, but has no role in maintaining disease remission. Adverse effects are dose-related and commonly include headache, nausea and diarrhoea. Rarely, Stevens–Johnson syndrome, agranulocytosis or pancreatitis is seen. Because of this high incidence of adverse effects, sulfasalazine cannot be recommended for the management of CD.

Mesalazine (5-aminosalicylic acid (5-ASA)): meta-analysis has shown no benefit of 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 and ciprofloxacin, although commonly used, are 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, but 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. Checking thiopurine methyltransferase (TPMT) activity before the start of thiopurine therapy is recommended as low TPMT activity is associated with the development of leucopenia. Recently, *NUDT15* has been identified as a pharmacogenetic determinant for thiopurine-induced leucopenia and hair loss in diverse populations, especially in East Asia. Other adverse effects include nodular regenerative hyperplasia and lymphoma. It is currently unclear how long thiopurine therapy should be continued for, and these agents should be used with caution in elderly patients.

Methotrexate is an antimetabolite so concurrent folic acid supplementation is advisable. The toxic effects of methotrexate include rash, nausea, diarrhoea, leucopenia, stomatitis, pneumonitis, deranged liver function, bone marrow suppression and liver fibrosis. Thiopurines and methotrexate are often used in combination with anti-TNF-α agents, as immunogenicity is reduced.

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 anti-TNF-α agent depends on accessibility, route of administration, patient preference, cost and national guidelines. Some patients (especially those with poor prognostic features) appear to benefit from early treatment with immunomodulatory drugs and/or anti-TNF-α therapy. Episodic dosing is associated with immunogenicity so regular scheduled treatment is recommended. Recent evidence has shown that timely escalation with an anti-TNF-α agent on the basis of clinical symptoms together with biomarkers including CRP and faecal calprotectin in patients with CD results in better clinical and endoscopic outcomes than symptom-driven decisions alone.[5]

Proactive therapeutic drug monitoring, measuring drug concentrations and the development of antibodies towards therapeutic drugs, produces a personalized approach to optimized management in patients with CD. Therapeutic drug monitoring has shown to be associated with improved clinical and endoscopic outcomes. An infliximab trough concentration of $\geq$10.1 micrograms/ml is associated with healing of perianal fistulas.

Adverse effects include infusion and injection site reactions, delayed-type hypersensitivity reactions, drug-induced lupus, worsening heart failure, reactivation of latent tuberculosis and infections, lymphomas (including rare hepato-splenic T cell lymphomas) and possible solid tumours.

Anti-integrin inhibitors: vedolizumab is licensed for use in moderate to severe CD patients who have had an inadequate response with, lost response to, are intolerant to, or have contra-indications to either conventional therapy or a tumour necrosis factor alpha inhibitor. It binds to integrin $\alpha_4\beta7$and this blockage results in gut-selective anti-inflammatory activity. Natalizumab, a humanized anti-adhesion antibody, appears promising but has been associated with progressive multifocal leucoencephalopathy. Etrolizumab, which targets only the β_7 subunit of integrin $\alpha_4\beta_{7,}$ shows promise in the management of moderate to severe CD.

Anti-IL-12/23 antibody: ustekinumab, a monoclonal antibody against the p40 subunit shared by the proinflammatory cytokines IL-12 and IL-23, has recently been licensed for use in moderate to severe CD patients who have had an inadequate response with, lost response to, are intolerant to, or have contra-indications to either conventional therapy or a TNF-α inhibitor. The rate of active tuberculosis was significantly lower in patients given ustekinumab than in patients given anti-TNF-α agents.

Other agents: 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), antimycobacterial agents, cytapheresis and autologous stem cell transplantation is limited. Other biological agents under evaluation include anti-adhesion molecules, anti-inflammatory cytokines and granulocyte–macrophage colony-stimulating factor.

Faecal microbiota transplantation 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 than colonic CD. Approximately 50% of patients with CD require at least one intestinal resection within 10 years of diagnosis, and 40% require a further operation within 10 years of the first. Surgery is reserved for complications of disease and for severe limited disease unresponsive to medical therapy (Table 6). Recent study has shown that laparoscopic resection in CD patients with limited ileocaecal disease failing conventional therapy performed similarly to infliximab therapy and is an alternative choice in this group.[3] Multiple extensive small bowel operations can result in short bowel syndrome and intestinal failure, so 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. Careful perioperative management with attention to nutrition and timely cessation of therapies such as corticosteroids and biological drugs is helpful for optimizing outcomes.

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 fistulae (enteroenteric, enterocutaneous, enterovesical) also become more common.

In the first year after diagnosis, 50% of all patients with CD experience a flare of disease, irrespective of disease site. Of these, about one-third have a single flare and two-thirds 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 unaffected in quiescent disease. Active disease carries a risk of stillbirth, preterm delivery and low birthweight. 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-TNF-α drugs can cross the placenta in the second trimester, this treatment seems to be safe at least in the short term, however, it is wise to limit exposure during the last trimester of pregnancy and counsel the patient about risks and benefits. *In utero* exposure to immunomodulators and anti-TNF-α therapy also does not lead to developmental delay when compared with unexposed infants. However, women on combination therapy with thiopurines and anti-TNF-α agents have an increased rate of preterm deliveries and low birth weight.

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 pubertal delay, as well as psychosocial aspects, should be addressed. Both exclusive enteral nutrition and corticosteroids are effective in inducing remission irrespective of disease activity or location, but enteral nutrition has fewer adverse effects and promotes growth. Most patients with childhood-onset CD require immunomodulators 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-TNF-α-based top-down approach, i.e. early use of combination of anti-TNF- α and immunomodulators. Recent study has shown that children with CD who were given early anti-TNF-α therapy were less likely to have penetrating complications, but not stricturing complications. The goal is ultimately to optimize growth and limit the adverse effects of treatment. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 34-year-old woman presented with a 3-year history of recurrent abdominal pain. She also complained of recurrent oral ulcers and persistent vaginal discharge and ulceration. She did not have any fever, diarrhoea or weight loss. She had previously been well. Gynaecological examination showed multiple vaginal ulcers but no fistula opening.

Investigations

- Colonoscopy showed a 3 cm oval-shaped deep ulcer in the terminal ileum without any colonic lesions
- Chest X-ray was clear
- MR enterography and MRI of the pelvis showed normal small bowel and no fistulae

What is the most likely diagnosis?

A. Tuberculosis of the ileum
B. Crohn's disease of the ileum
C. Non-steroidal anti-inflammatory drug-related enteropathy
D. Beçhet's disease
E. Cytomegalovirus infection of the ileum

Question 2

A 28-year-old man presented with increasing abdominal pain, increasingly loose stool and weight loss. Three years previously, he had been found to have ileocaecal Crohn's disease and had undergone a limited right hemicolectomy for a pericaecal abscess. He had been started on infliximab and methotrexate after

the operation because of disease recurrence. He then presented again with fever and cough with whitish sputum. He was a chronic smoker. Chest X-ray showed left upper zone consolidation. Sputum showed positive acid-fast bacilli. Two months before his latest presentation, he had been started on anti-tuberculosis treatment, and infliximab and methotrexate had been stopped.

Investigations

- Serum C-reactive protein 75 mg/litre (<10)
- Colonoscopy showed multiple deep colonic ulcers

What is the best action to take?

A. Restart on infliximab
B. Switch to adalimumab
C. Switch to ustekinumab
D. Restart on methotrexate only
E. Refer to surgeons for consideration of colectomy

Question 3

A 32-year-old woman presented for review after an inpatient admission. She was asymptomatic. She had previously been found to have ileocaecal Crohn's disease with perianal involvement, and had been admitted with fever, abdominal pain and vomiting. Physical examination at that time showed a mildly distended abdomen with peritoneal signs over the lower quadrant and fever of 38.9°C. Blood tests showed leucocytosis and markedly elevated C-reactive protein (105 mg/litre). Urgent CT of the abdomen showed active inflammation over the terminal ileum, with an intra-abdominal collection. The patient was treated with ileocaecal resection of the terminal ileum after a course of antibiotics and radiological drainage of the collection.

Investigation

- Serum C-reactive protein 8 mg/litre (<10)

What is the most appropriate management at this review ?

A. Regular review for symptoms only
B. Review with monitor of blood inflammatory markers
C. Advise metronidazole for 3 months
D. Advise ciprofloxacin for 3 months
E. Perform colonoscopy 6 months after operation