BMJ 2014;349:g6670 doi: 10.1136/bmj.g6670 (Published 19 November 2014)

CLINICAL REVIEW

Crohn's disease

Rahul Kalla *clinical research fellow*, Nicholas T Ventham *clinical research fellow*, Jack Satsangi *professor of gastroenterology*, Ian D R Arnott *consultant gastroenterologist*

Gastrointestinal Unit, Centre for Molecular Medicine, Institute of Genetics and Molecular Medicine, Western General Hospital, Edinburgh EH4 2XU, UK

Crohn's disease is a chronic inflammatory disorder that can affect any part of the gastrointestinal tract. Although the disease most commonly presents at a young age, it can affect people of all ages. Patients often present with persistent diarrhoea, abdominal pain, and weight loss. Crohn's disease has a global impact on patients' education, work, and social and family life. High quality multidisciplinary care, of which primary care is a key aspect, can attenuate relapse, prevent long term complications, and improve quality of life. In this review we provide a practical approach to the diagnosis, management, and long term care of patients with Crohn's disease.

How common is it?

Crohn's disease is an idiopathic, chronic relapsing immune mediated disease, the pathogenesis of which remains incompletely understood, although the condition is thought to arise from environmental priming and triggering events in a genetically susceptible patient.[1] The incidence and prevalence of Crohn's disease is increasing worldwide, with a recent systematic review reporting the highest incidence in Australia (29.3 per 100 000), Canada (20.2 per 100 000 population), and northern Europe (10.6 per 100 000).[2] Crohn's disease is more likely in those with a strong family history (first degree relatives) of the condition and often presents in the second to fourth decades of life, affecting both sexes equally.[2 3] Crohn's disease is associated with excess mortality compared with the general population, with a standardised mortality ratio of 1.38 (95% confidence interval 1.23 to 1.55).[4]

What are the clinical features?

Diagnosing Crohn's disease can be a challenge because of its widespread and often cryptic manifestations. The clinical features vary according to disease location (table 1⇓) but include chronic diarrhoea (>4 weeks with or without blood and mucus),[5] abdominal pain, and weight loss; patients presenting with this triad of symptoms should initially have blood tests (fig 1⇓). Nocturnal defecation often occurs; this symptom is not a feature of irritable bowel syndrome and indicates the need for urgent investigations. Non-specific symptoms such as malaise, fever, and anorexia commonly occur and some patients may present with extraintestinal manifestations (fig 2⇓). The presence of aphthous mouth ulcers, pyoderma gangrenosum, or erythema nodosum can be especially suggestive of inflammatory bowel diseases. The course of Crohn's disease is typified by periods of relapse and remission with recurrent cycles of inflammation leading to development of complications such as strictures and fistulas. Distinguishing Crohn's disease from irritable bowel syndrome can be difficult. The prodromal period is often considerable and can be up to 10 years before the diagnosis is established.[6]

How is it diagnosed?

Crohn's disease is diagnosed by a combination of clinical, laboratory, radiological, endoscopic, and histological findings (fig 1). Initial blood tests include a full blood count, haematinics, inflammatory markers, and vitamin D level. Typical findings suggestive of Crohn's disease include increased levels of inflammatory markers (C reactive protein and erythrocyte sedimentation rate), iron deficiency anaemia, and nutritional deficiencies such as low vitamin B_{12} and folate levels. These tests can help differentiate inflammatory bowel diseasses from irritable bowel syndrome. Stool cultures should be performed for *Clostridium difficile*, parasites or their ova, and in all patients presenting with diarrhoea.

Faecal calprotectin, a neutrophil cytosolic protein, is an effective marker for the presence of intestinal inflammation. A meta-analysis of six studies (670 adults) found that the faecal calprotectin test had a pooled sensitivity of 0.93 (95% confidence interval 0.85 to 0.97) and a pooled specificity of 0.96 (95% confidence interval 0.79 to 0.99) for inflammatory bowel diseases.[8] The test is a simple and cost effective way of identifying those with probable inflammatory bowel diseases that require urgent investigation. In the United Kingdom, the National Institute for Health and Care Excellence provides guidelines on the use of faecal calprotectin testing in primary care,[9] but this test is not always available. As classic features

Correspondence to: I D R Arnott ian.arnott@nhslothian.scot.nhs.uk

Extra material supplied by the author (see http://www.bmj.com/content/349/bmj.g6670?tab=related#datasupp)
Overview of remission and disease flare

The bottom line

- The incidence and prevalence of Crohn's disease is increasing worldwide
- Crohn's disease can have a major impact on patients' education, work, and social and family life
- To induce early remission and prevent long term complications, early diagnosis of Crohn's disease is a priority
- Adequate clinical and biochemical (for example, faecal calprotectin level) or endoscopic assessment of disease activity is needed to guide further decisions about treatment
- Drugs such as thiopurines, methotrexate, and anti-tumour necrosis factor are often used to maintain remission in patients with Crohn's disease
- Adverse pregnancy outcomes are associated with active Crohn's disease, and disease flares should be treated aggressively in pregnancy
- A systematic programme of surveillance to monitor long term sequelae should be in place to ensure the best outcomes for patients with Crohn's disease

Sources and selection criteria

We carried out an electronic search of PubMed, the Cochrane Library, and Ovid databases for articles using the term "Crohn's disease". We limited studies to those in adults and focused on high quality randomised control trials, meta-analyses, and systematic reviews.

of Crohn's disease are not always present and blood test results can be normal, referral should be considered in those who have persisting symptoms atypical for irritable bowel syndrome.[10]

Any patients with a suspected diagnosis of inflammatory bowel disease should be referred urgently to specialist services for further investigation.

In secondary care, ileocolonoscopy and biopsies are desirable when diagnosing Crohn's disease. Findings include discontinuous colonic or ileal inflammation or ulceration, a "cobblestone" appearance, and rectal sparing. Characteristic histology shows focal or patchy chronic inflammation, focal crypt irregularity, and granulomas.[11] In 5% of cases it can be difficult to differentiate histologically between Crohn's disease and ulcerative colitis, and the term inflammatory bowel disease type-unclassified is used.[12] Although a diagnosis based on histology is preferred, this can be challenging when Crohn's disease affects the small bowel. Magnetic resonance imaging of the small bowel is becoming the preferred imaging modality for such cases, and specific sequences can give information on the presence of active complications. Other investigations include computed tomography for extraluminal complications such as abscesses and fistulas, small bowel ultrasonography in specialist centres, and small bowel capsule endoscopy. Small bowel enteroscopy, including double balloon enteroscopy, is often used in those in whom a histological diagnosis is important.[13]

How is it managed?

Crohn's disease has a global impact on patients' health. To ensure the best outcomes for patients, a multidisciplinary approach is important. Patients with active disease often have a poor quality of life and may experience repeat hospital admissions, multiple operations, poor nutrition, and malignancy. Therefore early diagnosis and regular and objective assessment of disease activity is essential to support continued wellbeing. Local services responsive to the needs of patients are vital. Key features are the provision of telephone access to specialist care, expedited review in the event of a relapse, rigorous monitoring of treatment, and a systematic programme of disease surveillance. A range of follow-up options, such as nurse led clinics and guided self management has also been implemented.

Patients should undergo nutritional screening that assesses body mass index and unplanned weight loss, such as the Malnutrition Universal Screening Tool (MUST), which can be completed by all healthcare professionals.[14] Those at high risk of malnutrition require appropriate dietician review. Micronutrient assessment must also be undertaken such as for vitamin B_{12}, folate, iron, calcium, and vitamin D, and patients should receive supplementation where appropriate. Smoking cessation can be as effective as immunomodulatory therapy and can reduce the risk of relapse by 65% compared with continued smoking.[15-18] Patients should be offered the full remit of smoking cessation services. Non-steroidal anti-inflammatory drugs should be discontinued.[19 20]

The choice of drug treatment is influenced by factors such as efficacy, the need for inducing or maintaining remission, side effect profile, long term risks, and patient choice (table 2⇓). Patients with predictors of a severe disease phenotype (box) should be targeted for early, arguably combined, immunosuppressive therapy.[29-31]

Treatment of disease flare

Induction of remission

Crohn's disease is characterised by cycles of inflammation that cause disease flares, with periods of relapse and remission in between. Symptoms of flare vary by disease location (fig 1). Management depends on the severity of symptoms (fig 3⇓). If patients are systemically unwell, doctors should consider seeking urgent specialist advice and arranging hospital admission. Patients without systemic problems should be seen in specialist clinics. While awaiting clinic review, primary care doctors can consider initiating a tapered course of corticosteroids once infection is definitively ruled out, with reassessment before and after treatment. Steroid initiation in primary care should be avoided in patients taking dual immunomodulators or anti-tumour necrosis factor agents.

Corticosteroids—Two randomised controlled trials showed the efficacy of corticosteroids at inducing remission in 60-83% of patients with active Crohn's disease compared with placebo (NNT 3).[26 27] For disease flares, guidelines recommend 30-40 mg of prednisolone or 9 mg of budesonide, tapered over 6-8 weeks.[12] Steroids should not be used to maintain remission and are associated with important short term and long term side effects.[26 32 33] Budesonide acts locally in the gut and consequently has fewer side effects. It is indicated in patients with mild to moderate disease confined to the small bowel or the proximal colon, but it is ineffective in maintaining remission.[34]

Biological treatments—Anti-tumour necrosis factor alpha monoclonal antibodies are effective at inducing remission in patients with moderate to severe Crohn's disease compared with

Risk factors for a severe Crohn's disease phenotype[29-31]

- Younger age of onset (<40 years)
- Perianal disease
- Stricturing, and penetrating disease (perforation, intra-abdominal abscess, abdominal fistulas)
- Presence of upper gastrointestinal lesions
- Need for steroids for treating first flare
- Female sex

placebo (remission rates of 81% *v* 17%, respectively at week 4 for infliximab, 35.5% *v* 12% at week 4 for adalimumab)[22 35] and for treating perianal disease (response in 68% *v* 26% with infliximab median 12 weeks; 33% *v* 13% at week 56 for adalimumab).[22 36] Early use of anti-tumour necrosis factor alpha agents (top-down approach) is associated with increased remission rates over three years of treatment.[37-39] NICE guidelines recommend the step-up approach: using anti-tumour necrosis factor agents for patients in whom conventional immunomodulatory therapies have failed.[40] A rapid step-up therapy in those with predictors of a severe phenotype should be considered (box).[29-31]

Enteral nutrition—In adults, guidelines recommend exclusive enteral nutrition as an adjunct to improve nutritional status or as the preferred treatment in those who decline conventional drugs.[11] A Cochrane review of six randomised controlled trials that included 196 adults treated with exclusive enteral nutrition for active Crohn's disease concluded that corticosteroid treatment was superior to exclusive enteral nutrition in inducing remission (odds ratio 0.33, 95% confidence interval 0.21 to 0.53).[41]

Maintenance of remission

Once patients are in remission, maintenance treatment should be considered, aiming to avoid repeated use of corticosteroids and reduce long term complications.[11 12] Symptoms can be a poor guide to the attainment of complete remission, and clinical, biochemical (including faecal calprotectin test), and endoscopic findings should be used to determine deep remission and guide further treatment decisions.[42]

Immunomodulators—Immunomodulatory drugs used to treat Crohn's disease include the thiopurines (azathioprine, mercaptopurine) and methotrexate. These drugs are effective at maintaining remission in patients with moderate to severe Crohn's disease and in those who are steroid dependent. The odds ratio for maintenance of remission with azathioprine was 2.32 (95% confidence interval 1.55 to 3.49, number needed to treat (NNT) 6) and for mercaptopurine was 3.32 (40 to 7.87, NNT 4).[23] The onset of action of the thiopurines is slow (up to 17 weeks) and induction treatments (corticosteroids or anti-tumour necrosis factor agents) are often needed.[11] Methotrexate is also effective at maintaining remission in Crohn's disease compared with placebo (65% *v* 39%, NNT 4)[24]; however, it is teratogenic, often poorly tolerated, and guidelines recommend its use only in patients who are intolerant or refractory to thiopurines or anti-tumour necrosis factor agents.[12 43] The optimal time for drug withdrawal has been debated, although expert opinion suggests discontinuation once patients have been in clinical remission for four years.[44] Such decisions are often made on an individual basis, taking into account the risk of relapse against the long term risks of treatment.[45]

Biological treatment—Anti-tumour necrosis factor agents are effective at maintaining remission in patients with Crohn's disease.[22 25] They can be used as monotherapy or as combination therapy with immunomodulators. Combination therapy is superior to monotherapy in maintaining steroid-free clinical remission (56.8% *v* 30%, P<0.001), with evidence of better mucosal healing (43.9% *v* 16.5%, P<0.001).[45 46] Compared with monotherapy, combination therapy carries the risks of non-melanoma skin cancer and other cancers: standardised incidence ratio 3.46 (95% confidence interval 1.08 to 11.06) and 2.82 (1.07 to 7.44), respectively.[47]

The optimal time for withdrawal of anti-tumour necrosis factor agents is currently unknown, but an expert panel review identified low risk groups where timed withdrawal may be considered.[44 48]

When should surgery be considered?

Failure of medical treatment is the most common reason for resectional surgery.[49] This includes treatment of fibrostenotic disease and penetrating disease (perforation, intra-abdominal abscess, abdominal fistulas). Crohn's disease with perianal involvement may require surgery either to drain sepsis or to control fistulas. Ileoceacal resection can be first line treatment for discrete terminal ileal disease,[50-52] although anastomotic recurrence remains common. The role of medical treatment to prevent postoperative recurrence is currently being investigated by the Trial of Prevention of Postoperative Crohn's disease (ISRCTN89489788), Postoperative Crohn's Endoscopic Recurrence (NCT00989560) study, and infliximab (NCT01190839) trial.

The main principle of surgery is to preserve bowel length to avoid short bowel syndrome and intestinal failure. Stricturoplasty can effectively treat strictures without the need for resection. Ileorectal anastomosis is not often indicated owing to the high risk of disease recurrence in proximal small bowel and the risk of anastomotic leaks.[52 53]

What is the long term care for patients with Crohn's disease?

A complete vaccination history is vital before starting immunomodulator therapy in patients with Crohn's disease. Ensuring adequate titres of antihepatitis B surface antigen, that antivaricella zoster virus antibodies are present, and screening for latent tuberculosis is essential. Patients who are carriers of hepatitis B virus are at risk of hepatic failure, whereas those with latent tuberculosis are at risk of reactivation if exposed to immunomodulatory therapies. Live vaccines should only be administered before the start of treatment. Table 2 provides a summary of live, inactivated, and conjugate vaccines. Patients receiving immunomodulatory therapy are at an increased risk of severe influenza and pneumococcal infections and should be vaccinated against these pathogens every year and every five years, respectively.[54] Patients receiving triple immunosuppression are at an increased risk of *Pneumocystis*

jivoreci pneumonia and should be given cotrimoxazole prophylaxis.[54]

Fertility

Infertility in men and women with inflammatory bowel diseases is common and often due to voluntary childlessness based on inaccurate beliefs about pregnancy outcomes in Crohn's disease.[55] Fertility in patients with inactive Crohn's disease is similar to that in those without Crohn's disease but is lower in those with active disease. Preconception planning to minimise disease activity is important to ensure the best possible pregnancy outcomes.[56]

Patients who have had pelvic surgery are at a threefold increased risk of infertility and may benefit from fertility counselling.[57] Patients taking methotrexate should be informed of the risk of teratogenicity and offered detailed contraception counselling, and should stop treatment for 6-9 months before conception.[12]

Pregnancy and breast feeding

Inflammatory bowel diseases often affect people of childbearing age, and patients should be counselled about the risks and benefits of treatment during pregnancy. The risk of flares is similar between pregnant and non-pregnant women and disease activity at conception influences the disease course during pregnancy.[58 59] Only a third of women will achieve remission during pregnancy if Crohn's disease was active at conception.[60 61] Adverse pregnancy outcomes are associated with active disease and flares should be treated aggressively to reduce fetal and maternal complications. Neonates born to mothers receiving immunosuppressive and anti-tumour necrosis factor drugs are considered to be immunosuppressed and should not receive live vaccines for at least six months after exposure.[54] Women who have undergone pelvic surgery or have extensive perianal disease should be scheduled for elective caesarean to limit potential anal sphincter damage.

Cancer

Patients with Crohn's disease have an increased risk of small bowel (standard incidence ratio 40.6, 95% confidence interval 8.4 to 118) and colorectal malignancy (1.9, 0.7 to 4.1).[62] Surveillance usually begins 10 years after the diagnosis of inflammatory bowel disease, and patients are risk stratified to determine the frequency of ongoing surveillance. Patients with concurrent primary sclerosing cholangitis are at greatest risk and should undergo annual surveillance after diagnosis. The American Society of Gastrointestinal Endoscopy has also produced guidelines for surveillance of colorectal cancer.[63]

Patients receiving thiopurines are at a slightly increased risk of non-melanoma skin cancer (0.66 per 1000 patient years) and B cell lymphoma (0.9 per 1000 patient years) and should undergo dermatological surveillance and use protection, such as clothing and sunscreens against ultraviolet A light to minimise the risk of skin cancer.[64 65] Treatments with anti-tumour necrosis factor carry a small risk of B cell lymphoma and a rare, often fatal hepatosplenic T cell lymphoma.[66 67] In contrast, the use of thiopurines is associated with a lower risk of colorectal cancer (relative risk 0.71, 95% confidence interval 0.54 to 0.94; P=0.017).[68] The aforementioned findings may be overwhelming for some patients and the appropriate information should be provided to facilitate an informed decision.

Osteoporosis

Patients with Crohn's disease are at risk of osteoporosis from intermittent steroid use and altered micronutrient absorption. Calcium and vitamin D supplementation during steroid treatment is beneficial. The British Society of Gastroenterology has produced guidelines for the management of osteoporosis risk,[69] including the recommendation that all patients taking steroids for more than three months should have a bone mineral density scan. The guidelines also recommend that patients aged less than 65 with a T score of less than 1.5 should start bisphosphonates, as should those aged more than 65 who take corticosteroids.

Psychosocial health

Depression is an independent risk factor for a poor health related quality of life and is associated with adverse outcomes in patients with Crohn's disease.[70-72] A study found that the incidence of depression was higher in a cohort with inflammatory bowel diseases than in a control population (odds ratio 2.2, 95% confidence interval 1.64 to 2.95).[73] The fear of incontinence and its impact seems to inhibit social interaction and can lead to missed life events.[74] Doctors must be alert to the psychosocial burden of Crohn's disease and provide support for patients. Patient groups may be a useful source of support.

Contributors: RK wrote the initial draft of the manuscript. All authors amended the manuscript and approved the final version.

Competing interests: We have read and understood the BMJ policy on declaration of interests and declare the following interests: none.

Provenance and peer review: Commissioned; externally peer reviewed.

1 Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. *Nature* 2007;448:427-34.
2 Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 2012;142:46-54.e42; quiz e30.
3 Orholm M, Munkholm P, Langholz E, Nielsen OH, Sørensen TI, Binder V. Familial occurrence of inflammatory bowel disease. *N Engl J Med* 1991;324:84-8.
4 Bewtra M, Kaiser LM, TenHave T, Lewis JD. Crohn's disease and ulcerative colitis are associated with elevated standardized mortality ratios: a meta-analysis. *Inflamm Bowel Dis* 2013;19:599-613.
5 Fine KD, Schiller LR. AGA technical review on the evaluation and management of chronic diarrhea. *Gastroenterology* 1999;116:1464-86.
6 Pimentel M, Chang M, Chow EJ, Tabibzadeh S, Kirit-Kiriak V, Targan SR, et al. Identification of a prodromal period in Crohn's disease but not ulcerative colitis. *Am J Gastroenterol* 2000;95:3458-62.
7 Baumgart DC, Sandborn WJ. Crohn's disease. *Lancet* 2012;380:1590-605.
8 Van Rheenen PF, Van de Vijver E, Fidler V. Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis. *BMJ* 2010;341:c3369.
9 National Institute for Health and Care Excellence. Faecal calprotectin diagnostic tests for inflammatory diseases of the bowel (DG11). NICE, 2013. www.nice.org.uk/guidance/dg11/chapter/5-outcomes.
10 National Institute of Health and Care Excellence. Inflammatory bowel disease: quality standard (GID-QSD70). NICE, 2014. www.nice.org.uk/guidance/indevelopment/gid-qsd70/documents.
11 Dignass A, Van Assche G, Lindsay JO, Lémann M, Söderholm J, Colombel JF, et al. The second European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. *J Crohns Colitis* 2010;4:28-62.
12 Mowat C, Cole A, Windsor A, Ahmad T, Arnott I, Driscoll R, et al. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2011;60:571-607.
13 Sidhu R, Sanders DS, Morris AJ, McAlindon ME. Guidelines on small bowel enteroscopy and capsule endoscopy in adults. *Gut* 2008;57:125-36.
14 Screening for Malnutrition A Multidisciplinary Responsibility. Development and USe of the Malnutrition Universal Screening Tool (MUST) for Adults. Malnutrition Advisory Group (MAG) BAPEN.
15 Seksik P, Nion-Larmurier I, Sokol H, Beaugerie L, Cosnes J. Effects of light smoking consumption on the clinical course of Crohn's disease. *Inflamm Bowel Dis* 2009;15:734-41.
16 Johnson GJ, Cosnes J, Mansfield JC. Review article: smoking cessation as primary therapy to modify the course of Crohn's disease. *Aliment Pharmacol Ther* 2005;21:921-31.
17 Dam AN, Berg AM, Farraye FA. Environmental influences on the onset and clinical course of Crohn's disease-part 1: an overview of external risk factors. *Gastroenterol Hepatol (N Y)* 2013;9:711-7.
18 Mahid SS, Minor KS, Soto RE, Hornung CA, Galandiuk S. Smoking and inflammatory bowel disease: a meta-analysis. *Mayo Clin Proc* 2006;81:1462-71.
19 Takeuchi K, Smale S, Premchand P, Maiden L, Sherwood R, Thjodleifsson B, et al. Prevalence and mechanism of nonsteroidal anti-inflammatory drug-induced clinical relapse in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2006;4:196-202.

Additional educational resources

Resources for healthcare professionals

British Society of Gastroenterology guidelines (www.bsg.org.uk)—Provides evidence based guidelines on the diagnosis and management of Crohn's disease

European Crohn's and Colitis Organisation. Inflammatory bowel diseases (www.ecco-ibd.eu)—Provides European evidence based guidelines on the diagnosis and management of Crohn's disease

Inflammatory Bowel Disease Standards (www.ibdstandards.org.uk)—National UK standards for the care of patients with inflammatory bowel diseases

National Institute for Health and Care Excellence. Crohn's disease: management in adults, children and young people (www.nice.org.uk/guidance/cg152)

InnovAiT CD review (http://ino.sagepub.com/content/7/1/43.full)—A review on the diagnosis and management of Crohn's disease tailored for general practitioners

BAPEN: Malnutrition Universal Screening Tool (MUST) (www.bapen.org.uk/must/)—A nutritional screening tool for healthcare professionals to assess patients at risk of malnutrition

Resources for patients

Crohn's and Colitis UK (www.crohnsandcolitis.org.uk) and Crohn's and Colitis Foundation of America (www.ccfa.org)—UK and US based charities that raise awareness of inflammatory bowel diseases and provide information and support for patients and fund research into the diseases

CORE: fighting gut and liver disease (www.corecharityorg.uk)—A UK based charity that raises awareness and funds research in gut and liver diseases

EFCCA: the European Federation of Ulcerative colitis and Crohn's Associations (hwww.efcca.org)—An umbrella organisation representing 28 national patients' associations from 27 European countries

IA: The ileostomy and internal pouch Support Group (www.iasupport.org) and UOAA: United Ostomy Associations of America (www.ostomy.org)—UK and US based support groups for patients with ileostomy and internal pouch

Questions for future research

Can new stool, tissue, blood, and serum biomarkers be identified to allow the early diagnosis and risk stratification of the course of inflammatory bowel diseases?

Can genetic analysis and gene expression profiling allow us to better prognosticate for patients and to personalise treatments?

How effective will be new treatments such as "biosimilars" and novel drugs that target specific immunological pathways, such as tofacitinib (Jak 1/3 antagonist) and ustekinumab (targets interleukin 12/23)?

20 Meyer AM, Ramzan NN, Heigh RI, Leighton JA. Relapse of inflammatory bowel disease associated with use of nonsteroidal anti-inflammatory drugs. *Dig Dis Sci* 2006;51:168-72.
21 Evans JM, McMahon AD, Murray FE, McDevitt DG, MacDonald TM. Non-steroidal anti-inflammatory drugs are associated with emergency admission to hospital for colitis due to inflammatory bowel disease. *Gut* 1997;40:619-22.
22 Hanauer SB, Sandborn WJ, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh D, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology* 2006;130:323-33; quiz 591.
23 Prefontaine E, Sutherland LR, Macdonald JK, Cepoiu M. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2009;1:CD000067.
24 Patel V, Wang Y, MacDonald JK, McDonald JWD, Chande N. Methotrexate for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2014;8:CD006884.
25 Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;359:1541-9.
26 Truelove SC, Willoughby CP, Lee EG, Kettlewell MG. Further experience in the treatment of severe attacks of ulcerative colitis. *Lancet* 1978;2:1086-8.
27 Malchow H, Ewe K, Brandes JW, Goebell H, Ehms H, Sommer H, et al. European Cooperative Crohn's Disease Study (ECCDS): results of drug treatment. *Gastroenterology* 1984;86:249-66.
28 Van der Woude CJ, Kolacek S, Dotan I, Oresland T, Vermeire S, Munkholm P, et al. European evidenced-based consensus on reproduction in inflammatory bowel disease. *J Crohns Colitis* 2010;4:493-510.
29 Beaugerie L, Sokol H. Clinical, serological and genetic predictors of inflammatory bowel disease course. *World J Gastroenterol* 2012;18:3806-13.
30 Travis SPL, Stange EF, Lémann M, Oresland T, Chowers Y, Forbes A, et al. European evidence based consensus on the diagnosis and management of Crohn's disease: current management. *Gut* 2006;55(Suppl 1):i16-35.
31 Blonski W, Buchner AM, Lichtenstein GR. Clinical predictors of aggressive/disabling disease: ulcerative colitis and crohn disease. *Gastroenterol Clin North Am* 2012;41:443-62.
32 Lichtenstein GR, Feagan BG, Cohen RD, Salzberg BA, Diamond RH, Price S, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREATTM registry. *Am J Gastroenterol* 2012;107:1409-22.
33 Summers RW, Switz DM, Sessions JT, Becktel JM, Best WR, Kern F, et al. National Cooperative Crohn's Disease Study: results of drug treatment. *Gastroenterology* 1979;77:847-69.
34 Benchimol EI, Seow CH, Otley AR, Steinhart AH. Budesonide for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2009;1:CD002913.
35 Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med* 1997;337:1029-35.
36 Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, van Hogezand RA, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999;340:1398-405.
37 Schreiber S, Reinisch W, Colombel JF, Sandborn WJ, Hommes DW, Robinson AM, et al. Subgroup analysis of the placebo-controlled CHARM trial: increased remission rates through 3 years for adalimumab-treated patients with early Crohn's disease. *J Crohns Colitis* 2013;7:213-21.
38 D'Haens G, Baert F, van Assche G, Caenepeel P, Vergauwe P, Tuynman H, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet* 2008;371:660-7.
39 Schreiber S, Colombel J-F, Bloomfield R, Nikolaus S, Schölmerich J, Panés J, et al. Increased response and remission rates in short-duration Crohn's disease with subcutaneous certolizumab pegol: an analysis of PRECiSE 2 randomized maintenance trial data. *Am J Gastroenterol* 2010;105:1574-82.
40 Infliximab (review) and adalimumab for the treatment of Crohn's disease. Guidance and guidelines. NICE. 2014. www.nice.org.uk/guidance/TA187.
41 Zachos M, Tondeur M, Griffiths AM. Enteral nutritional therapy for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2007;1:CD000542.
42 Sandborn WJ, Hanauer S, Van Assche G, Panés J, Wilson S, Petersson J, et al. Treating beyond symptoms with a view to improving patient outcomes in inflammatory bowel diseases. *J Crohns Colitis* 2014;8:927-35.
43 Fraser AG. Methotrexate: first-line or second-line immunomodulator? *Eur J Gastroenterol Hepatol* 2003;15:225-31.
44 Pittet V, Froehlich F, Maillard MH, Mottet C, Gonvers J-J, Felley C, et al. When do we dare to stop biological or immunomodulatory therapy for Crohn's disease? Results of a multidisciplinary European expert panel. *J Crohns Colitis* 2013;7:820-6.
45 Bressler B, Siegel CA. Beware of the swinging pendulum: anti-tumor necrosis factor monotherapy vs combination therapy for inflammatory bowel disease. *Gastroenterology* 2014;146:884-7.
46 Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010;362:1383-95.
47 Osterman MT, Sandborn WJ, Colombel J-F, Robinson AM, Lau W, Huang B, et al. Increased risk of malignancy with adalimumab combination therapy, compared with monotherapy, for Crohn's disease. *Gastroenterology* 2014;146:941-9.
48 Louis E, Mary J-Y, Vernier-Massouille G, Grimaud J-C, Bouhnik Y, Laharie D, et al. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. *Gastroenterology* 2012;142:63-70.e5; quiz e31.
49 UK IBD Audit Steering Group. National audits of the Organisation of Adult and Paediatric IBD services in the UK. 2012. www.rcplondon.ac.uk/projects/ibdauditround3.
50 Tilney HS, Constantinides VA, Heriot AG, Nicolaou M, Athanasiou T, Ziprin P, et al. Comparison of laparoscopic and open ileocecal resection for Crohn's disease: a metaanalysis. *Surg Endosc* 2006;20:1036-44.
51 Kim NK, Senagore AJ, Luchtefeld MA, MacKeigan JM, Mazier WP, Belknap K, et al. Long-term outcome after ileocecal resection for Crohn's disease. *Am Surg* 1997;63:627-33.
52 Yamamoto T, Watanabe T. Surgery for luminal Crohn's disease. *World J Gastroenterol* 2014;20:78-90.
53 Cattan P, Bonhomme N, Panis Y, Lémann M, Coffin B, Bouhnik Y, et al. Fate of the rectum in patients undergoing total colectomy for Crohn's disease. *Br J Surg* 2002;89:454-9.

54 Rahier JF, Ben-Horin S, Chowers Y, Conlon C, De Munter P, D'Haens G, et al. European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2009;3:47-91.
55 Tavernier N, Fumery M, Peyrin-Biroulet L, Colombel J-F, Gower-Rousseau C. Systematic review: fertility in non-surgically treated inflammatory bowel disease. *Aliment Pharmacol Ther* 2013;38:847-53.
56 Vermeire S, Carbonnel F, Coulie PG, Geenen V, Hazes JMW, Masson PL, et al. Management of inflammatory bowel disease in pregnancy. *J Crohns Colitis* 2012;6:811-23.
57 Waljee A, Waljee J, Morris AM, Higgins PDR. Threefold increased risk of infertility: a meta-analysis of infertility after ileal pouch anal anastomosis in ulcerative colitis. *Gut* 2006;55:1575-80.
58 Nielsen OH, Andreasson B, Bondesen S, Jacobsen O, Jarnum S. Pregnancy in Crohn's disease. *Scand J Gastroenterol* 1984;19:724-32.
59 Mahadevan U, Sandborn WJ, Li D-K, Hakimian S, Kane S, Corley DA. Pregnancy outcomes in women with inflammatory bowel disease: a large community-based study from Northern California. *Gastroenterology* 2007;133:1106-12.
60 Khosla R, Willoughby CP, Jewell DP. Crohn's disease and pregnancy. Gut 1984;25:52-6.
61 Katz JA, Pore G. Inflammatory bowel disease and pregnancy. *Inflamm Bowel Dis* 2001;7:146-57.
62 Jess T, Loftus E V, Velayos FS, Harmsen WS, Zinsmeister AR, Smyrk TC, et al. Risk of intestinal cancer in inflammatory bowel disease: a population-based study from olmsted county, Minnesota. *Gastroenterology* 2006;130:1039-46.
63 Leighton JA, Shen B, Baron TH, Adler DG, Davila R, Egan J V, et al. ASGE guideline: endoscopy in the diagnosis and treatment of inflammatory bowel disease. *Gastrointest Endosc* 2006;63:558-65.
64 Peyrin-Biroulet L, Khosrotehrani K, Carrat F, Bouvier A-M, Chevaux J-B, Simon T, et al. Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. *Gastroenterology* 2011;141:1621-8.e1-5.
65 Beaugerie L, Brousse N, Bouvier AM, Colombel JF, Lémann M, Cosnes J, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet* 2009;374:1617-25.
66 Kotlyar DS, Osterman MT, Diamond RH, Porter D, Blonski WC, Wasik M, et al. A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2011;9:36-41.e1.
67 Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006;295:2275-85.
68 Gong J, Zhu L, Guo Z, Li Y, Zhu W, Li N, et al. Use of thiopurines and risk of colorectal neoplasia in patients with inflammatory bowel diseases: a meta-analysis. *PLoS One* 2013;8:e81487.
69 Scott EM, Gaywood I, Scott BB. Guidelines for osteoporosis in coeliac disease and inflammatory bowel disease. British Society of Gastroenterology. *Gut* 2000;46 Suppl 1:i1-8.
70 Zhang CK, Hewett J, Hemming J, Grant T, Zhao H, Abraham C, et al. The influence of depression on quality of life in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2013;19:1732-9.
71 Lix LM, Graff LA, Walker JR, Clara I, Rawsthorne P, Rogala L, et al. Longitudinal study of quality of life and psychological functioning for active, fluctuating, and inactive disease patterns in inflammatory bowel disease. *Inflamm Bowel Dis* 2008;14:1575-84.
72 Persoons P, Vermeire S, Demyttenaere K, Fischler B, Vandenberghe J, Van Oudenhove L, et al. The impact of major depressive disorder on the short- and long-term outcome of Crohn's disease treatment with infliximab. *Aliment Pharmacol Ther* 2005;22:101-10.
73 Walker JR, Ediger JP, Graff LA, Greenfeld JM, Clara I, Lix L, et al. The Manitoba IBD cohort study: a population-based study of the prevalence of lifetime and 12-month anxiety and mood disorders. *Am J Gastroenterol* 2008;103:1989-97.
74 Kemp K, Griffiths J, Lovell K. Understanding the health and social care needs of people living with IBD: a meta-synthesis of the evidence. *World J Gastroenterol* 2012;18:6240-9.

Cite this as: *BMJ* 2014;349:g6670

Tables

Table 1| Clinical presentation as per Montreal classification in Crohn's disease

Disease location	Montreal classification	Clinical manifestations
Ileal	L1	Malabsorption and nutritional deficiencies; abdominal pain and weight loss; diarrhoea may be absent; acute terminal ileum disease can mimic acute appendicitis
Colonic	L2	Bloody diarrhoea; can mimic acute severe ulcerative colitis; obstruction due to stricturing disease
Ileocolonic	L3	Right sided abdominal pain, diarrhoea, weight loss; obstructive or pseudo-obstructive symptoms due to stricturing disease
Upper gastrointestinal	L4	Can mimic peptic ulcer disease; can present as chronic gastric outlet obstruction
Perianal	P	Recurrent perianal abscesses; perianal fistulas; anal skin tags

Table 2| Drugs used for induction and maintenance of remission in Crohn's disease[11 12 22-28]

Treatment	Indications and contraindications	Pretest initiation and monitoring	Common side effects	Long term risk	Monitoring	Pregnancy	Numbers needed to treat
Induction of remission:							
Steroids	Induction of remission—luminal disease; contraindicated in glaucoma, fractures, infection	None	Easy bruising; cushingoid facies; weight gain; myopathy; cataracts	Osteoporosis; hypertension; adrenal insufficiency; steroid induced diabetes	Blood glucose where appropriate	Can be used under specialist supervision	2-3
Biologics (infliximab, adalimumab)	Induction of remission—luminal and perianal disease; contraindicated in cancers, active sepsis, tuberculosis, demyelinating disease, congestive heart failure	Live vaccinations before start of treatment*; up to date inactivated vaccines†	Anaphylaxis; myalgia; malaise; rash; infections; rarely neutropenia	Rare: lymphoproliferative disorders; malignancy; reactivation of tuberculosis; opportunistic infections	Full blood count, liver function tests, urea and electrolytes before every infusion	Available data suggest safe in pregnancy, but no long term data available	3-4
Exclusive nutritional therapy	Induction of remission, especially in children; no contraindications	Ensure any electrolyte abnormalities corrected to prevent refeeding syndrome	Poorly tolerated	Steatohepatitis	Urea and electrolytes, magnesium, bone profile testing during initiation of treatment (to monitor for refeeding syndrome)	No contraindications	Not known
Maintenance of remission:							
Thiopurines (azathioprine, mercaptopurine)	Maintains remission, principally in luminal disease; contraindicated in cancers, active sepsis, tuberculosis	Thiopurines-methyltransferase before initiation; live vaccinations before initiation*; up to date inactivated vaccines†; thiopurine metabolites to guide dosing	Nausea and vomiting; hair loss; myalgia; rash; pancreatitis; neutropenia; deranged liver function test results	Rare: non-melanoma skin cancer and lymphoma	Full blood count, liver function tests; every 2 weeks on initiation followed by every 2-3 months once dosing regimen is stable	Can be used under specialist supervision if benefits outweigh harms	4-6
Methotrexate	Maintains remission; contraindicated in pregnancy, liver disease, blood dyscrasias, active sepsis, tuberculosis	Full blood count, liver function tests, urea and electrolytes; chest radiography; live vaccines before initiation*; up to date inactivated vaccines†	Nausea and vomiting; diarrhoea; stomatitis; neutropenia; deranged liver function test results	Hepatotoxicity; pneumonitis	Full blood count, liver function tests; every 2 weeks on initiation followed by every 2-3 months once dosing regimen stable	Contraindicated in pregnancy; discontinue 3-6 months before conception	4-5

*Varicella zoster; BCG (tuberculosis); yellow fever; measles, mumps, and rubella; rotavirus; oral polio; and live attenuated influenza.

†Hepatitis B; pneumococcus; influenza (except intranasal), polio (inactivated poliovirus vaccine); tetanus+diphtheria (combined diphtheria, tetanus, and pertussis vaccine); rabies, and human papillomavirus.

Figures

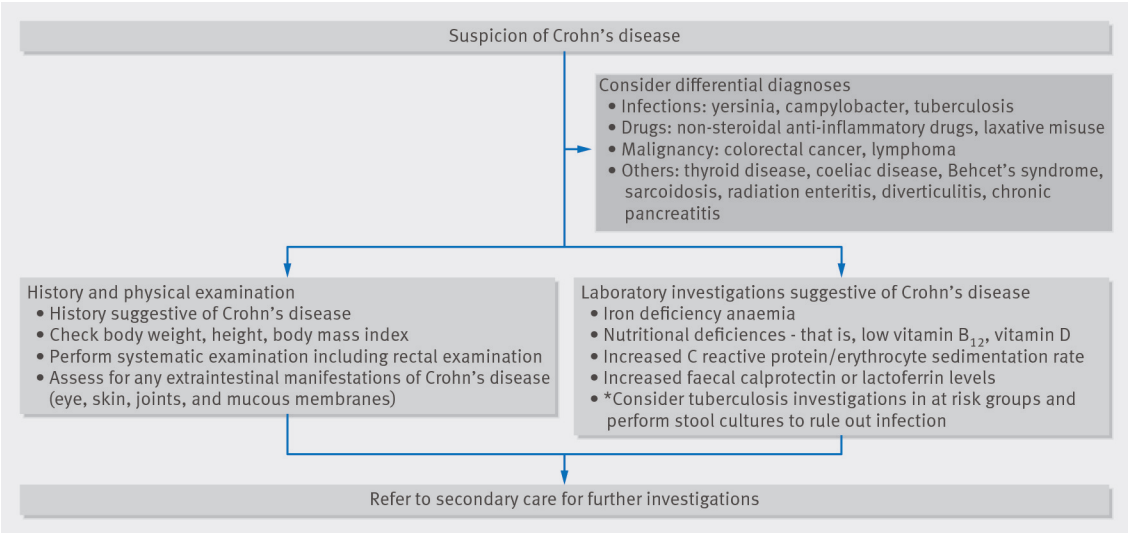

Fig 1 Key clinical features, laboratory investigations, risk factors, and differential diagnoses in patients with suspected Crohn's disease

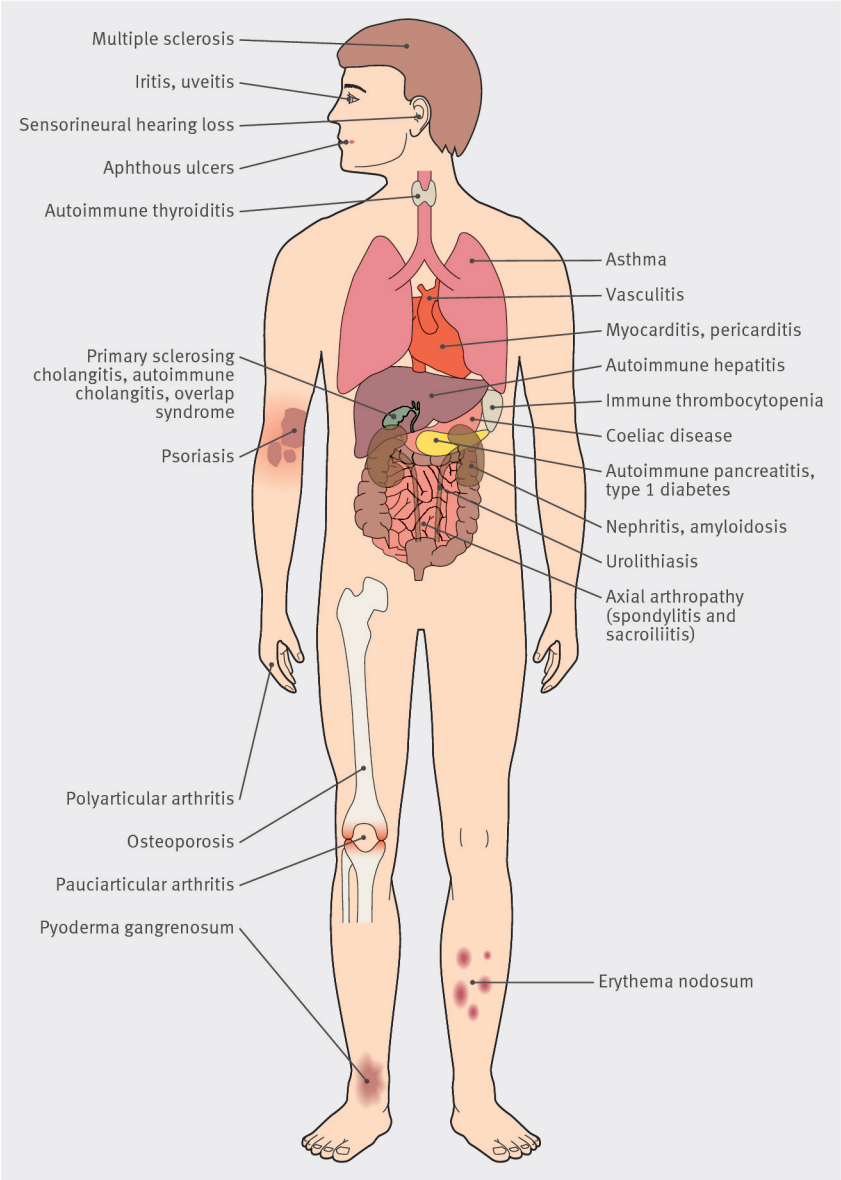

Fig 2 Extraintestinal manifestations and associated autoimmune disorders in patients with Crohn's disease. Adapted from Baumgart and Sandborn[7]

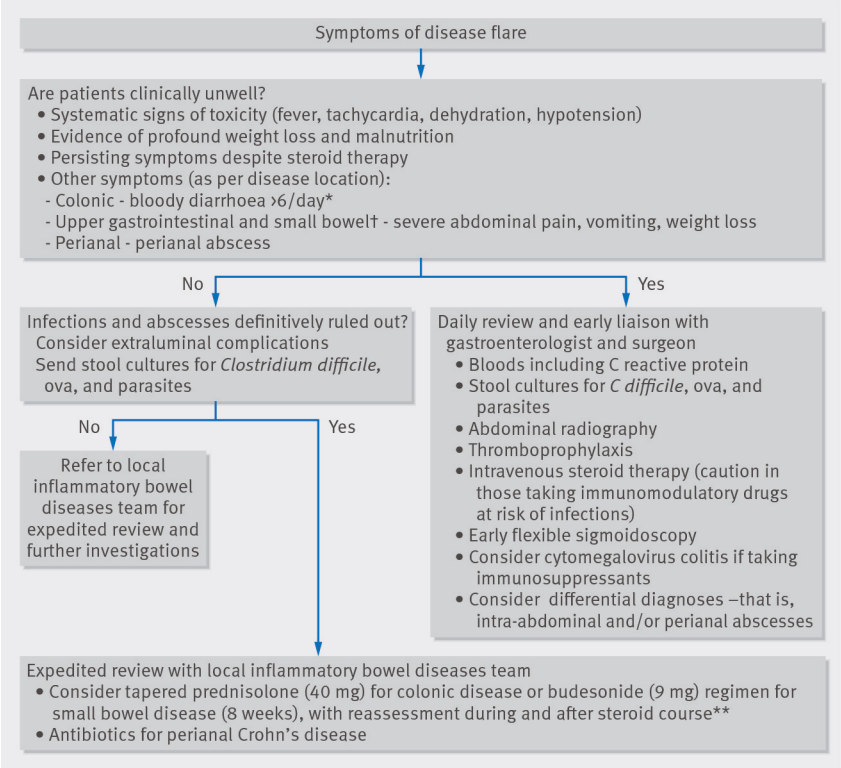

Fig 3 Management of disease flares in Crohn's disease. Although no defined criteria exist for hospital admission of patients, the figure shows the signs and symptoms that should prompt doctors to consider admission. Presentations can vary and often clinical judgment is necessary; particularly in immunosuppressed patients, who are at risk of opportunistic infections. *Colonic Crohn's disease can mimic presentations of acute severe colitis and although the Truelove Witt criteria are validated for ulcerative colitis,[26] These criteria can help guide general practitioners when assessing patients with acute Crohn's disease colitis. †Patients may present with obstructive or pseudo-obstructive symptoms and in some cases. **Steroids should be avoided in patients on dual immunosuppression or those on anti-tumour necrosis factor therapies and expedited specialist review should be sought. See the supplementary figure for a summary of the more pertinent aspects of Crohn's disease along with details on, for example, remission, screening tools, and colorectal cancer surveillance guidelines