Crohn's disease for the general physician: management

Crohn's disease presents to general physicians in a variety of ways. The previous article outlined clinical features and initial investigations, and this article covers management of Crohn's disease, including monitoring and drug toxicity.

Treatment of Crohn's disease has advanced rapidly in the last two decades. The advent of anti-tumour necrosis factor (anti-TNF) therapy has revolutionized medical management, and therapeutic monitoring has enabled better use of both anti-TNF drugs and conventional immunosuppressive agents such as azathioprine. Assessment of infection risk and vaccination strategy is an important part of patient assessment for therapy. Newer biologics are now available, including vedolizumab and ustekinumab. Treatment options are thus opening up and fewer patients are having surgery or remaining on long-term corticosteroids, but monitoring and avoiding side effects of immunosuppressive therapies is increasingly important. Better assessment of disease activity including use of faecal calprotectin, magnetic resonance imaging and capsule endoscopy makes it easier to assess response to therapy and make therapeutic decisions. Surgical treatment remains necessary, however, for non-responders to medical therapy, or for those with complications of their disease including bowel obstruction, perforation, fistulae, abscesses or malignancy.

Treatment strategies

Planning treatment for Crohn's disease requires an initial assessment to determine disease extent, and complications including stricturing or fistulae, as well as nutritional status and specific vitamin or micronutrient deficiencies. A bone density scan is indicated if there are risk factors for osteoporosis (smoking, significant weight loss, immobility). While a course of prednisolone is a fast-acting and effective short-term treatment, it is important to plan more definitive maintenance therapy to avoid corticosteroid dependency with all its side effects (weight gain, moon face, osteoporosis, myopathy, diabetes, cataracts, osteonecrosis). Smoking cessation improves disease course and referral for counselling is vital for any patient who is having trouble stopping.

The natural history of Crohn's disease is variable, with some patients having prolonged remission after an initial attack, while others have rapidly progressive disease with early relapse and rapid extension of disease sites. Predictors of those with an aggressive phenotype remain crude (young age at onset, extensive disease, smoking, perianal fistulae), but there is great interest in more accurate predictors (such as gene expression profiling of T cell subsets; Lee et al, 2011). For those with risk factors, early and more aggressive immunosuppressive therapy is needed. Despite the medical advances, at least half of patients will need surgery at some stage for their Crohn's disease.

Ileocolonic disease

Inflammation affecting the colon and terminal ileum is usually treated at initial presentation with corticosteroids. Outpatients with severe disease (significant diarrhoea including nocturnal sleep disturbance, weight loss, abdominal pain, extraintestinal manifestations or other signs of systemic disturbance such as fever, anaemia or low albumin) should take oral prednisolone 40 mg daily, reducing by 5 mg each week. For localized ileocaecal disease with mild or moderate symptoms, budesonide in ileal-release formulation, with topical action, high first-pass metabolism and few systemic side effects, can be used in a starting dose of 9 mg daily. (For localized ileocaecal stricturing disease see surgical section below.) Sulphasalazine and mesalazine are not effective in ileocaecal disease, and at best are modestly beneficial in mild colonic disease, but budesonide is a preferable treatment (Gomollón et al, 2016).

Some patients with mild or localized disease may achieve remission with a single course of corticosteroids, and may remain well on no maintenance therapy or a slow tailing dose of budesonide (e.g. 9 mg reducing by 3 mg every 2 months). Those with more extensive or severe disease, those whose symptoms worsen as corticosteroids are withdrawn, or those requiring two or more courses of prednisolone in a year, will require maintenance therapy with immunomodulators. For this reason, once diagnosis is established, bloods should be taken for thiopurine methyltransferase levels (needed for correct dosing of the immunosuppressant medications azathioprine and 6-methylmercaptopurine) and an infection screen (*Table 1*).

Dr JJ Barlow, Gastroenterology Specialist Trainee, Department of Gastroenterology, University Hospital of Wales, Cardiff

Dr AB Hawthorne, Consultant Physician and Gastroenterologist, Department of Gastroenterology, University Hospital of Wales, Cardiff CF14 4XW

Correspondence to: Dr AB Hawthorne (barney.hawthorne@wales.nhs.uk)

Table 1. Screening tests after diagnosis of Crohn's disease

Thiopurine methyltransferase
Hepatitis B, C and HIV serology
Varicella serology (unless clear history of chickenpox)
Screen for tuberculosis (history of risk factors, chest radiograph, tuberculin skin test or interferon gamma release assay according to local policy)

From Rahier et al (2009)

Table 2. Azathioprine use and side effects

Adverse event	Frequency	Management
Nausea and vomiting	5–10%	Mild nausea sometimes resolves after few days. If persistent, switch* or stop
Hypersensitivity: headache, rash, joint pains, malaise	5–10%	Reduce dose, switch*
Leucopaenia	3–5%	Reduce dose if total white cell count <3.5x10^9/litre, stop if <3x10^9/litre
Liver abnormality	15% mild rise in liver function tests. 5% hepatotoxicity	Stop if >x2 upper limit of normal. Switch*, or use low-dose azathioprine (0.5 mg/kg daily) with allopurinol 200 mg and monitor thiopurine metabolites
Pancreatitis	4–5%	Stop
Infection (particularly viral)	1–3%	Treat and consider stopping if alternative treatment available
Non-melanoma skin cancer	0.07–0.5% per year (age dependent)	Remove and consider stopping if alternative treatment available
Lymphoma	Rare (age dependent)	Stop

** Switch to 6-mercaptopurine (dose 1–1.5 mg/kg). A proportion of patients with toxicity from azathioprine will tolerate 6-mercaptopurine. From Fraser et al (2002), Gisbert et al (2007), Beaugerie et al (2009), Peyrin–Biroulet et al (2011)*

Immunosuppressive therapy

Azathioprine is the standard second-line therapy and is often started with a course of prednisolone as onset of action takes at least 2 months. Mercaptopurine is the metabolite of azathioprine and has the same action but is less often used first line in the UK. Information should be given to the patient including risks (*Table 2*). Thiopurine methyltransferase levels and infection screen should be checked before treatment. Azathioprine dose is 2–2.5 mg/kg for those with normal thiopurine methyltransferase levels. For those with intermediate thiopurine methyltransferase levels (heterozygote) the dose is 1 mg/kg. For homozygous low thiopurine methyltransferase, azathioprine should be avoided. Check full blood count and liver enzymes 2 weeks after all dose increases, and every 3 months. Patients should be advised about vaccination (influenza, pneumococcus). Avoid live vaccination. Avoid excessive sun exposure.

Metabolite measurement (6-thioguanine and 6-methylmercaptopurine) is now more widely available and can aid dose optimization in patients not responding after 3 months, and in managing toxicity. If 6-thioguanine is absent then non-adherence should be suspected. If 6-thioguanine is low then the dose is increased. If there is a high 6-methylmercaptopurine:6-thioguanine ratio, then preferential methylation is occurring (often associated with high thiopurine methyltransferase levels) and non-response or toxicity is common. In this situation use allopurinol 200 mg in conjunction with a reduced (0.5 mg/kg) azathioprine dose to improve response and reverse toxicity (*Table 2*), preferably with ongoing metabolite monitoring.

Patients who are well controlled with azathioprine can discontinue the drug after prolonged (2–3 years) remission, as lifelong treatment may have slightly more risk than benefit. Patients should be warned that relapse may occur, but after a gap of 3–6 months. A short course of prednisolone while the drug is restarted usually restores remission.

Methotrexate is an alternative to azathioprine, and has similar potency. It is given initially as a subcutaneous injection of 25 mg once a week, with oral folic acid 5 mg 2 days later. Again it is slow in onset of action, and in responders the dose can be reduced after 3 months to 15 mg (subcutaneous or oral) once a week. The most important side effect is teratogenicity and it should be avoided in young women if there is any risk of pregnancy during treatment and for 6 months after stopping. Data are less clear on risks for males fathering children. Other side effects include hepatotoxicity, rash and nausea. Other immunosuppressive drugs include ciclosporin, tacrolimus, mycophenolate mofetil and thalidomide (unlicensed) but these drugs have significant toxicity and anti-TNF therapy is used in preference currently.

Anti-TNF therapy is used in those failing to respond to azathioprine or methotrexate. Infliximab is given by intravenous injection (5 mg/kg with loading doses at 0, 2 and 6 weeks and then 8-weekly). Adalimumab is given subcutaneously with a loading dose of 160 mg at week 0, 80 mg at week 2 and then 40 mg alternate weekly. Infliximab biosimilars (Inflectra or Remsima) are significantly cheaper than the originator molecule (Remicade) and a biosimilar adalimumab will soon be available. Infliximab is more effective given as combination therapy with azathioprine or methotrexate, but evidence is less clear on the benefits of combination therapy of these drugs with adalimumab. The benefits of combination therapy include greater efficacy and less chance of developing anti-drug antibodies, but benefits should be weighed against the higher incidence of side effects (Gomollón et al, 2016).

Patients in remission should probably switch to monotherapy with anti-TNF drug after 1–2 years, and at some stage should stop the anti-TNF therapy. Assessment with ileocolonoscopy to confirm mucosal healing (or measurement of faecal calprotectin as a surrogate measure) helps to assess who should stop or reduce therapy. Complications of anti-TNF drugs are shown in *Table 3*.

The different agents have rapid onset of action (1–3 weeks) and similar efficacy. Choice of drug depends on risk of non-adherence (choose intravenous drug), patient choice and price. Other anti-TNF agents are used much less (golimumab is only licensed for ulcerative colitis, etanercept is much less effective in Crohn's disease than rheumatoid arthritis, and certolizumab pegol is not licensed in the UK).

Measurement of infliximab or adalimumab drug levels and anti-drug antibody levels is now available. The best evidence is for assessment of those who respond initially and then lose response (secondary loss of response) as shown in *Figure 1*.

Vedolizumab is a new class of monoclonal antibody therapy that binds to the α4β7 integrin present on the surface of gut-homing lymphocytes. This prevents these cells from binding to the MADCAM-1 receptors in the gut vascular endothelial cells. This specific blockade prevents lymphocytes entering the gut, and provides a gut-specific immunosuppression. It is given intravenously with a loading dose of 100 mg at weeks 0, 2 and 6, followed by 8-weekly maintenance treatment (Sandborn et al, 2013). Onset of action is slow, and some patients with Crohn's disease need an extra dose at week 10. It is more effective in ulcerative colitis (Feagan et al, 2013), and should only be used in Crohn's disease patients failing anti-TNF therapy. Ustekinumab is a selective inhibitor of IL-12 and IL-23 used in treating psoriasis, but is effective in Crohn's disease (Feagan et al, 2016). It is likely to be licensed in the UK shortly.

Perianal fistulae

These usually present with a perianal abscess and the priority is incision and drainage of pus under anaesthetic. After the abscess has healed, a pelvic magnetic resonance scan will map fistula(e) anatomy, followed by examination under anaesthetic to identify and probe any fistulae in order to pass stitches (setons) (*Figure 2*) to prevent blockage of the fistula track, which can precipitate further abscess formation. There may be multiple branching fistulae, which are extremely difficult to locate at examination under anaesthetic. Superficial fistulae can be laid open to allow healing, but if they cross the anal sphincters, this can cause incontinence. Treatment with azathioprine or methotrexate, and early addition of TNF inhibitor therapy gives the best chance of healing (Sands et al, 2004). Corticosteroids are not an appropriate treatment for fistulizing disease.

With a good clinical response (dry opening with no pus expressed on palpation, and complete resolution of pain) the setons can be removed to give the fistula track a chance to close. Unfortunately, even with aggressive medical therapy, over 40% of patients will have fistula recurrence within 1 year (Makowiec et al, 1995). Non-responsive disabling fistulizing disease requires a defunctioning operation,

Table 3. Complications of anti-tumour necrosis factor therapy

Complication	Detail	Per cent requiring cessation
Infusion reaction	Infection site reaction, non-immunoglobulin E anaphylactoid reaction (true anaphylaxis rare)	2.7%
	Delayed infusion reaction	6.1%
Serious infection	Bacterial viral and fungal, including herpes zoster, tuberculosis and other opportunistic infections	0.9%
Neurological	Demyelination	0.5%
Skin	Eczema or psoriasis overlap	3%
Joints	Lupus-like syndrome with arthropathy (mild in 8.9%)	1.1%
Malignancy	New or recurrence of previous cancer. Level of risk unclear	Rare
Miscellaneous	Neutropaenia, heart failure*, autoimmunity	Rare

*From Schnitzler et al (2009), Beigel et al (2011), Cleynen et al (2016). *Infliximab tends to worsen heart failure in patients with existing heart disease.*

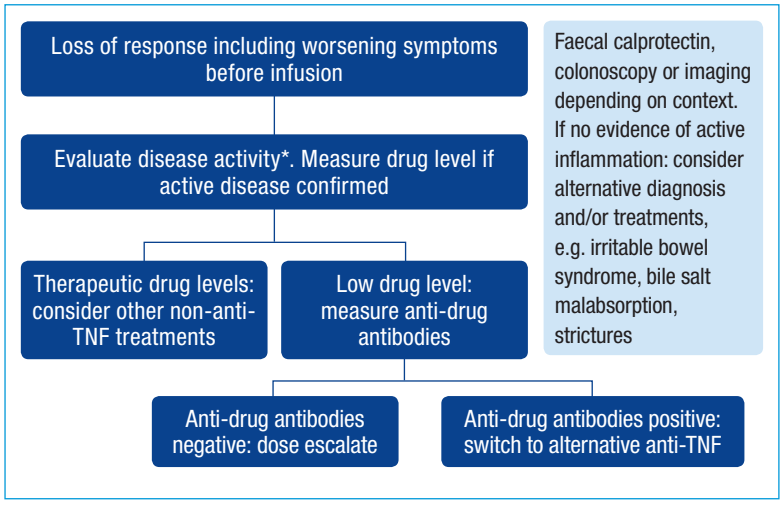

Figure 1. Anti-tumour necrosis factor (TNF) drug and antibody levels in management of loss of response.

Figure 2. Perianal fistula and abscess anatomy and seton in situ.

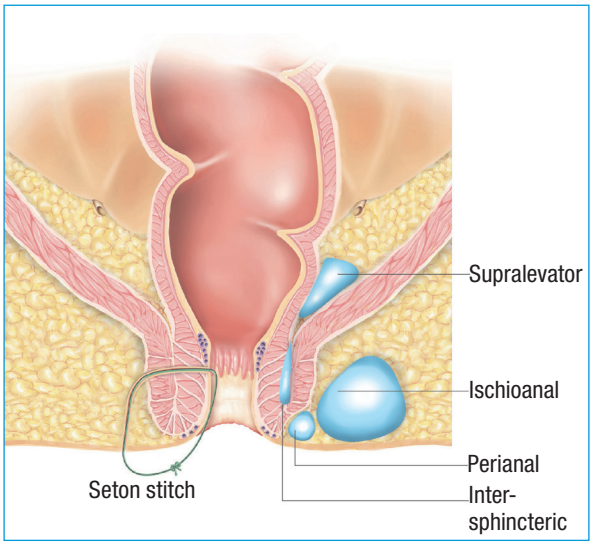

Table 4. Specific complications of Crohn's surgery

Operation	Symptom	Mechanism
Ileocaecal resection	Diarrhoea	Bile salt malabsorption, loss of ileocaecal valve
Terminal ileal resection	Anaemia	Vitamin B_{12} deficiency
Extensive small bowel resection with intact colon	Renal colic	Renal oxalate stone formation as a result of fat malabsorption
Extensive small bowel resection with high ileostomy or jejunostomy	Diarrhoea and weight loss	Short gut
	Renal failure	Dehydration causing pre-renal failure and/or renal stone formation
General	Enterocutaneous fistula	Aggressive fistulizing disease
General	Peristomal ulceration	Pyoderma gangrenosum (*Figure 3*)

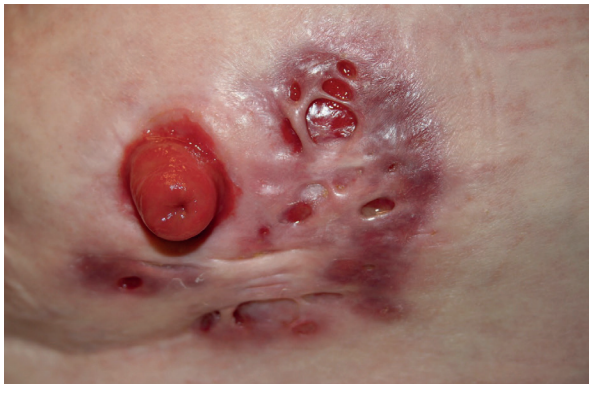

Figure 3. Peristomal pyoderma gangrenosum.

which may result in the disease process remitting, but many require continuing medical therapy as well. Restoration of bowel continuity later generally results in recurrence of active perianal disease and proctectomy is usually necessary ultimately.

Multidisciplinary inflammatory bowel disease team

Fistulising perianal disease is a good example of Crohn's disease requiring multidisciplinary team involvement with colorectal surgeon, gastroenterologist, inflammatory bowel disease nurse to monitor biological therapy, and often stoma nurses. An inflammatory bowel disease service is best managed with regular inflammatory bowel disease multidisciplinary team meetings to discuss joint medical and surgical management of complex cases, with advice from specialist radiologists. Advice from a gastrointestinal pathologist is needed where diagnosis is unclear. Other input from clinical psychology may be needed to support the mental wellbeing of patients, while gastrointestinal pharmacists can coordinate and monitor complex drug regimens. Inflammatory bowel disease nurses can support self-directed management for stable patients, with easy access to clinics through telephone advice lines. Adolescent inflammatory bowel disease transition clinics with paediatric and adult gastroenterologists are vital to support teenagers with Crohn's disease.

Surgery for Crohn's disease

At diagnosis patients with obstructive symptoms from ileocaecal disease (pain and distension on eating, weight loss, vomiting) may well benefit from primary surgical therapy, particularly if investigation suggests significant structuring (tight structuring with prestenotic dilatation). Ileocaecal resection can often result in prolonged remission without medical therapy, but those with a more aggressive phenotype will experience recurrence. Ileocolonoscopy at 6 months postoperatively to look for ulceration upstream of the anastomosis can trigger early immunosuppressive therapy, but repeat ileocaecal resection may be needed in the future. For patients with more extensive colonic or ileocolonic disease, surgery would only be indicated for failed medical therapy, and for complications (e.g. abscesses caused by localized perforation, or bowel obstruction as a result of strictures). Surgery would generally require a permanent ileostomy unless there is well-documented rectal sparing in which case an ileorectal anastomosis is possible. Surgical complications are shown in *Table 4*.

Patients with long-standing Crohn's colitis have an increased risk of developing colorectal cancer, as in ulcerative colitis. Risk is related to uncontrolled inflammation, and better disease control is likely to reduce the risk. Regular colonoscopic surveillance is indicated after 8–10 years.

Dietary therapy

Patients with active Crohn's disease can be treated with an exclusive polymeric liquid feed (stopping all other food intake), either taken orally or via nasogastric tube. This has an anti-inflammatory effect as well as improving nutrition and can induce mucosal healing, but the mechanism is unclear. It is widely used to induce remission in children, where it is of similar efficacy to corticosteroids, but has no adverse effect on growth (Ruemmele et al, 2014). It can be followed by partial enteral nutrition but most patients will require ongoing maintenance immunosuppressive therapy. Because of the impact this has on lifestyle and consequent adherence issues, the treatment is used much less in adults.

Emergency presentations of Crohn's disease

As well as presentations of undiagnosed Crohn's disease, established Crohn's disease can also present as a complication of both disease and its treatment, and common and serious issues are illustrated in *Table 5*. Patients with severe abdominal pain, shock or sepsis, requiring intravenous therapy, or needing surgical assessment for an acute abdomen require admission. If there is uncertainty then a senior gastroenterology opinion should be sought. Where there is a clear diagnosis and management with oral drugs is appropriate, then patients can be discharged with plans for early gastroenterology clinic review.

Conclusions

Crohn's disease management has changed rapidly with increasing availability of novel immunomodulatory drugs, to supplement traditional therapies with corticosteroids and thiopurines. Despite recent advances, a significant number of patients fail to respond to these drugs, and surgery remains a key part of management for disease complications and failed medical therapy. Management of complex disease is best coordinated through a multidisciplinary team approach. **BJHM**

Conflict of interest: none.

Beaugerie L, Brousse N, Bouvier AM et al; CESAME Study Group (2009) Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet* **374**(9701): 1617–1625. https://doi.org/10.1016/S0140-6736(09)61302-7

Beigel F, Schnitzler F, Paul Laubender R et al (2011) Formation of antinuclear and double-strand DNA antibodies and frequency of lupus-like syndrome in anti-TNF-α antibody-treated patients with inflammatory bowel disease. *Inflamm Bowel Dis* **17**(1): 91–98. https://doi.org/10.1002/ibd.21362

Cleynen I, Van Moerkercke W, Billiet T et al (2016) Characteristics of skin lesions associated with anti–tumor necrosis factor therapy in patients with inflammatory bowel disease. *Ann Intern Med* **164**(1): 10–22. https://doi.org/10.7326/M15-0729

Feagan BG, Rutgeerts P, Sands BE et al; GEMINI 1 Study Group (2013) Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* **369**(8): 699–710. https://doi.org/10.1056/NEJMoa1215734

Feagan BG, Sandborn WJ, Gasink C et al; UNITI–IM-UNITI Study Group (2016) Ustekinumab as induction and maintenance therapy for Crohns disease. *N Engl J Med* **375**(20): 1946–1960. https://doi.org/10.1056/NEJMoa1602773

Fraser AG, Orchard TR, Jewell DP (2002) The efficacy of azathioprine for the treatment of inflammatory bowel disease: a 30 year review. *Gut* **50**(4): 485–489. https://doi.org/10.1136/gut.50.4.485

Gisbert JP, Luna M, González-Lama Y, Pousa ID, Velasco M, Moreno-Otero R, Maté J (2007) Liver injury in inflammatory bowel disease: long-term follow-up study of 786 patients. *Inflamm Bowel Dis* **13**(9): 1106–1114. https://doi.org/10.1002/ibd.20160

Gomollón F, Dignass A, Annese V et al (2016) 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohns Disease 2016: Part 1: Diagnosis and Medical Management. *J Crohns Colitis* **11**(1): 3–25. https://doi.org/10.1093/ecco-jcc/jjw168

Lee JC, Lyons PA, McKinney EF et al (2011) Gene expression profiling of CD8+ T cells predicts prognosis in patients with Crohn disease and ulcerative colitis. *J Clin Invest* **121**(10): 4170–4179. https://doi.org/10.1172/JCI59255

Makowiec F, Jehle EC, Starlinger M (1995) Clinical course of perianal fistulas in Crohns disease. *Gut* **37**(5): 696–701. https://doi.org/10.1136/gut.37.5.696

Peyrin–Biroulet L, Khosrotehrani K, Carrat F et al (2011) Increased risk for nonmelanoma skin cancers in patients who receive thiopurines for inflammatory bowel disease. *Gastroenterology* **141**(5): 1621–1628. e5. https://doi.org/10.1053/j.gastro.2011.06.050

Rahier JF, Ben-Horin S, Chowers Y et al; European Crohns and Colitis Organisation (ECCO) (2009) European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* **3**(2): 47–91. https://doi.org/10.1016/j.crohns.2009.02.010

Ruemmele FM, Veres G, Kolho KL et al; European Crohns and Colitis Organisation; European Society of Pediatric Gastroenterology, Hepatology and Nutrition (2014) Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohns disease. *J Crohns Colitis* **8**(10): 1179–1207. https://doi.org/10.1016/j.crohns.2014.04.005

Sandborn WJ, Feagan BG, Rutgeerts P et al; GEMINI 2 Study Group (2013) Vedolizumab as induction and maintenance therapy for Crohns disease. *N Engl J Med* **369**(8): 711–721. https://doi.org/10.1056/NEJMoa1215739

KEY POINTS

- Thiopurines (azathioprine and mercaptopurine) remain the standard immunosuppressive maintenance therapy and management has been made easier by measurement of metabolites.
- Anti-tumour necrosis factor therapy and newer biological agents are greatly increasing treatment options for control of Crohn's disease. Measurement of drug levels and antibodies to drug facilitate management of loss of response.
- Faecal calprotectin is useful to measure response to treatment or to confirm relapse to plan further therapy.
- Surgical treatment remains necessary in at least half of patients with Crohn's disease during the course of their disease.
- Multidisciplinary team management is important for a complex disease with increasingly complex therapy choices.

Table 5. Common pitfalls in Crohn's disease presenting in the emergency room

Presentation	Comments
Diarrhoea ?gastroenteritis	Infective gastroenteritis (including *Clostridium difficile*) can complicate established Crohn's disease and stool cultures must be taken. If there is doubt corticosteroid treatment of Crohn's disease should not be delayed while gastroenteritis is excluded. In general empiric antibiotics should not be given pending culture results
Acute severe epigastric pain	Beware patients who started azathioprine or mercaptopurine in the last 4 weeks. Pancreatitis occurs in 4%, and is more common in those on concurrent prednisolone
Severe abdominal pain	Pericolic perforation with localized abscess
Small or large bowel obstruction	Stricturing Crohn's segment or colorectal cancer complicating chronic uncontrolled inflammation (small bowel cancer can also complicate chronic small bowel disease)
Sepsis	Leucopaenia as a result of azathioprine, mercaptopurine or methotrexate
Disseminated pneumonia	*Pneumocystis jirovecii* as a result of multiple immunosuppression (corticosteroids, azathioprine, anti-tumour necrosis factor therapy). Miliary tuberculosis (anti-tumour necrosis factor therapy)
Cholecystitis or cholangitis	Gallstones are a common complication of Crohn's disease
Fever, lymphadenopathy, hepatosplenomegaly	Lymphoma as a result of long-term azathioprine
Venous thromboembolism	Venous thromboembolic disease is more common in patients with active Crohn's disease. Consider pulmonary embolism in patients presenting with unexplained breathlessness. All inpatients with active Crohn's disease should receive prophylactic low molecular weight heparin

Sands BE, Anderson FH, Bernstein CN et al (2004) Infliximab maintenance therapy for fistulizing Crohns disease. *N Engl J Med* **350**(9): 876–885. https://doi.org/10.1056/NEJMoa030815

Schnitzler F, Fidder H, Ferrante M et al (2009) Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-centre cohort. *Gut* **58**(4): 492–500. https://doi.org/gut.2008.155812