Management of difficult inflammatory bowel disease: where are we now?

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INTRODUCTION

Medical care of patients with inflammatory bowel disease (IBD) comprises general measures and specific pharmacological, nutritional, endoscopic and surgical therapies (Table 1)[1-3]. In this paper, current management options for patients with two commonly difficult presentations of IBD, acute severe ulcerative colitis (UC) and steroid-refractory or dependent ileocaecal Crohn's disease (CD), are discussed. Practical considerations and newer developments are emphasized.

MANAGEMENT OF ACUTE SEVERE ULCERATIVE COLITIS

These patients should be admitted immediately to a gastroenterology ward for close joint medical, surgical and nursing care. The nutrition team and a stoma therapist in patients likely to need surgery should be involved promptly. Patients undergoing an acute attack of UC need to be made aware from the outset that they have a one in four chance of failing to respond to the primary treatment (intravenous steroids), and thus need either cyclosporin or colectomy during their admission (Table 1).

Establishing the diagnosis, extent and severity of disease

A carefully targeted history and appropriate investigations can help establish the diagnosis (Table 2) in patients presenting for the first time and, in those with established UC, to exclude infection and to assess disease extent (if not already known) and severity.

Blood and stool tests Stool should be sent to look for

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pathogens, and serology checked for amoebiasis, strongyloidiasis and schistosomiasis. Blood tests are better for establishing the activity of UC than making the diagnosis or identifying its extent. However, a raised platelet count is more common in UC than in infective colitis. The best measures of disease activity are haemoglobin, platelet count, ESR, C-reactive protein[4] and serum albumin.

Sigmoidoscopy and rectal biopsy Cautious rigid or flexible sigmoidoscopy in the unprepared patient, and without excessive air insufflation, provides immediate confirmation of active colitis. Sigmoidoscopy also allows biopsy for histology: to minimise the risks of bleeding and perforation a small superficial biopsy should be taken from the posterior rectal wall less than 10 cm from the anal margin using small-cupped forceps. Anecdotally, colonoscopy may cause colonic perforation and dilatation in acute severe UC, and although some authorities have reported that it is both safe and useful for decision-making [5], most patients can be managed satisfactorily without it. In patients with established UC, rectal biopsy is not routinely necessary. However, in those presenting for the first time, infective colitis may be suggested by an acute, focal and superficial inflammatory infiltrate with minimal goblet cell depletion and preservation of crypt architecture[6]. Although colitis due to Clostridium difficile, cytomegalovirus, amoebiasis and *Crohn's* disease often has characteristic macroscopic appearances, histology may confirm these diagnoses.

Plain abdominal X-ray A plain film at presentation can be used to assess disease extent, since faecal residual visible on X-ray usually indicates sites of uninflamed colonic mucosa. Plain abdominal X-ray is also used to assess disease severity and in particular to exclude colonic dilatation (diameter > 5.5 cm) in sick patients, however, the gas pattern on a plain film may be misleading if there has been excessive air insufflation during a sigmoidoscopy or colonoscopy done shortly beforehand. In patients with suspected colonic perforation, the diagnosis can be confirmed by erect chest X-ray or a lateral decubitus abdominal film.

Radiolabelled leucocyte scans The intensity and extent of colonic uptake one hour after injection of autologous ^{99}Tc-HMPAO or ^{111}Indium-labelled leukocytes provides information about disease

activity and particularly extent, respectively, where doubt exists in patients with UC. Colonic uptake of leucocytes is not of course specific for UC and positive results are obtained in other inflammatory colonic diseases.

Table 1 Principles of management of acute severe ulcerative colitis

GENERAL MEASURES
  Explanation, psychosocial support
          - patient support groups
  Specialist multidisciplinary care
          - physicians, surgeons, nutrition team, nurses, stoma therapist,counsellor
ESTABLISHING THE DIAGNOSIS, EXTENT/SITE AND SEVERITY
          - clinical evaluation
          - FBC, ESR, C-reactive protein, albumin, LFTs, amoebic serology
          - stool microscopy, culture, C. difficile toxin
          - limited sigmoidoscopy and biopsy
          - plain abdominal X-ray
          - consider radiolabelled leucocyte scan
MONITORING PROGRESS
          - daily clinical assessment
          - stool chart
          - 4-hrly temperature, pulse
          - daily FBC, ESR, C-reactive protein, urea and electrolytes, albumin
          - daily plain abdominal X-ray
SUPPORTIVE TREATMENT
          - i.v. fluids, electrolytes (Na, K), blood transfusion
          - nutritional supplementation
          - heparin s.c.
          - haematinics (folate)
          -avoid antidiarrhoeals (codeine, loperamide, diphenoxylate),opiates, NSAIDs
          - rolling manoeuvre (if colon dilating)
SPECIFIC TREATMENT
Medical   -corticosteroids i.v. (hydrocortisone or methylprednisolone) then p.o. (prednisolone)
          -continue 5-ASA p.o. in patients already taking it; otherwise start when improvement begins
          -antibiotics for very sick febrile patients, or when infection suspected
          -consider cyclosporin i.v. then p.o.) for steroid non-responders at 4-7 days
Surgical (for non-responders at 5-7 days, toxic megacolon, perforation, massive haemorrhage)
          - panproctocolectomy with ileoanal pouch or permanent ileostomy
          - subtotal colectomy with ileorectal anastomosis (rarely)

Table 2 Management of active ileocaecal Crohn's disease. General measures, monitoring progress and supportive treatment are essentially as for ulcerative colitis

ESTABLISHING THE DIAGNOSIS, EXTENT/SITE AND SEVERITY
          - clinical evaluation
          - FBC, ESR, C-reactive protein, ferritin, folate, B12, albumin, LFTs, Ca, Mg, Zn
          - stool microscopy, culture, C difficile toxin
          - plain abdominal X-ray
          - consider colonoscopy and biopsy, small bowel barium radiology,ultrasound, CT, MRI, leucocyte scan
SPECIFIC TREATMENT(separately or in combination)
Medical   - corticosteroids i.v. (hydrocortisone or methyl prednisolone) then p.o. (prednisolone or budesonide CR)
          - continue high dose mesalazine (Pentasa or Asacol) in patients already taking it; otherwise start when improvement begins
          - consider metronidazole, ciprofloxacin; also broad spectrum antibiotics for very sick febrile patients, or when infection/collection suspected
          -consider azathioprine/6-mercaptopurine (slow response) or anti TNF antibodies (infliximab) for steroid non-responders
Nutritional - liquid formula diet
Endoscopic - balloon dilatation
Surgical   - resection or stricturoplasty

Monitoring progress

Progress is monitored by twice daily clinical assessment, stool chart and 4-hourly measurement of temperature and pulse. Blood count, ESR, C-reactive protein, routine biochemistry and plain abdominal X-ray should be done daily in sick patients. The two most useful variables in predicting the outcome of the acute attack are stool frequency and C-reactive protein at three days: patients with values above 8 stools/day or 45 mg/L, respectively, have an 85% chance of failing to respond to intravenous steroids and needing cyclosporin or surger y during their admission[4] (Table 1).

Supportive treatment

Intravenous fluids and blood Most patients require intravenous fluids and electrolytes, particularly potassium, to replace diarrhoeal losses. Serum potassium concentration should be maintained at or above 4 mmol/L, since hypokalaemia may predispose to colonic dilatation. Blood transfusion is recommended if the haemoglobin falls below 100g/L.

Nutritional support Patients can usually eat normally, with liquid protein and calorie supplements if necessary. Very sick patients may need total parenteral nutrition.

Anticoagulation Because active UC is associated with a high risk of venous and arterial thrombo-embolism[7], patients should be given prophylactic subcutaneous heparin (e.g. low molecular mass heparin 3000-5000 U daily). Heparin does not appear to increase rectal blood loss even when given intravenously[8].

Drugs to avoid Antidiarrhoeal drugs (loperamide, codeine phosphate, diphenoxylate), opioid analgesics, antispasmodics and anticholinergic drugs should not be prescribed in active UC since they may provoke acute colonic dilatation[9]. Patients should also avoid NSAIDs in view of their adverse effects on the clinical course of IBD[10]. If relief of mild pain is needed, oral paracetamol appears to be safe, while severe pain suggests colonic dilatation or perforation needing urgent intervention.

Rolling manoeuvre In very sick patients, particularly those with clinical and/or radiological evidence of incipient colonic dilatation, rolling into the prone or knee-elbow position for 15 minutes every two hours may aid in the evacuation of gas per rectum, particularly from the transverse colon[11].

Specific medical treatment
The cornerstone of specific medical treatment of acute severe UC remains corticosteroids[1,12]. Aminosalicylates and antibiotics have minor roles . Cyclosporin has become a useful option, but oral

azathioprine and 6-mercapto purine are too slow to work in patients with acute steroid-refractory attacks (Table 1).

Corticosteroids Hydrocortisone (300 mg/d-400 mg/d) or methyl prednisolone (40 mg/d-60 mg/d) are given intravenously. There is no advantage in giving higher doses, although continuous infusion may be more effective than once or twice daily boluses[12]. On this treatment, about 70% patients improve substantially in 5 d-7 d. They are then switched to oral prednisolone (40 mg/d-60 mg/d), the dose being tapered to zero over 2-3 months. Conventionally, failure to respond to intravenous steroids after 7 d indicates urgent colectomy, but introduction of intravenous cyclosporin can now be considered as an alternative.

Aminosalicylates Aminosalicylates in full dose are continued in patients already taking them at the time of admission, and well enough to take oral medication, but do not have a primary therapeutic in acute severe UC. In case patients given aminosalicylates for the first time prove to be allergic to, or intolerant of them, initiation of these drugs is best delayed until the patient shows sufficient improvement on intravenous steroids to switch to oral treatment.

Antibiotics Although one study has suggested a role for adjunctive oral tobramycin[13], the use of antibiotics is usually restricted now to very sick febrile patients, or to those in whom an infective component to their colitis is strongly suspected. Under such circumstances, a combination of antibiotics, for example ciprofloxacin or a cephalosporin with metronidazole, is often given.

Cyclosporin The only current evidence-based indication for cyclosporin in IBD is steroid-refractory acute severe UC. In a single small controlled trial[14], the results of which have been largely confirmed by subsequent experience[15,16], intravenous (4 mg·kg^{-1}·d^{-1}) for about 5 d) followed by oral (5 mg·kg^{-1}·d^{-1}-8 mg·kg^{-1}·d^{-1}) cyclosporin, given with continued corticosteroids, averted colectomy in the acute phase in 80% of patients failing to respond to 5 d-7 d of intravenous steroids alone. Enthusiasm for this approach has to be tempered by the frequency of relapse necessitating colectomy (up to 50%) that follows withdrawal of cyclosporin, and by its serious adverse effects which in turn demand frequent monitoring of cyclosporin blood levels and serum biochemistry in treated patients. The therapeutic range for monoclonal radioimmunoassay is 250 μg/$^{-1}$-400 μg/L^{-1} during intravenous treatment, and 150 μg/L^{-1}-300 μg/L^{-1} as the trough level on oral treatment. Biochemical disturbances induced by cyclosporin include hyperkalaemia, hypomagnesaemia and *hyperuricaemia*, as well as renal dysfunction. The most serious side effects of cyclosporin are opportunistic infections (20% patients) including pneumocystis car inii pneumonia, on account of which co-administration of prophylactic trimethop rim/sulphamethoxazole may be advisable; renal impairment, including a small reduction in glomerular filtration ratein most patients and, sometimes, an interstitial nephritis which is not always reversible on stopping cyclosporin; hypertension (30% patients); hepatotoxicity (up to 20%); and epileptic fits (3%), due to penetration of the blood-brain barr ier by a vehicle, cremophor, in cyclosporin and essentially confined to patients with low serum cholesterol and/or magnesium concentration. Less serious side-effects include nausea, headache, paraesthesiae and hypertrichosis.

Further studies are needed to determine optimal usage of cyclosporin in UC. For example, precisely when should patients be given the drug, will a lower dose (2 mg·kg^{-1}·d^{-1} iv) be as effective but safer, should trimethoprim/sulphamethoxazole be coprescribed as prophylaxis against pneumocystis carinii infection, and should oral cyclosporin or azathioprine be prescribed after the intravenous treatment? It is clear, however, that intravenous cyclosporin can be invaluable in patients with steroid-refractory acute severe UC, not least for buying time for improving their nutrition prior to, and/or preparing them psychologically for surgery.

Azathioprine and 6-mercaptopurine Oral azathioprine and 6-mercaptopurine are very effective in inducing and maintaining remission in pat ients with steroid-refractory or dependent IBD. Unfortunately, however, they take up to 4 months to exert their effect and are thus inappropriate for acute s evere UC.

Possible new treatments The possible roles of anti-TNF-alpha antibody[17], antibodies and antisense oligonucleotides to leucocyte/endothelial cellular adhesion molecules[18], and intravenou s heparin[8] require further evaluation in controlled clinical trials.

Surgery
A colorectal surgeon should be involved in the care of patients with acute severe UC throughout their admission. Indications for urgent colectomy, which is required in about 25% of patients with acute severe colitis, include toxic colonic dilatation which does not respond within 24 h to intensification of medical treatment with rolling[11,12], antibiotics and nasogastric suction, and deterioration or failure to improve on medical therapy in 5 d-7 d. Emergency surgery, after immediate resuscitation, is required in the rare patients, who develop colonic perforation or massive colonic haemorrhage.

Details of the surgical options available (pan-proctocolectomy with ileoanal pouch or permanent ileostomy, or, rarely, sub-total colectomy with ileorectal anastomosis) and their elective indications, are beyond the scope of this review.

MANAGEMENT OF ACTIVE CROHN'S DISEASE

Treatment of CD depends not only on disease activity and site, as in UC, but also needs to be tailored according to the patient's clinical presentation[2,3]. Inflammation (Table 2), obstruction, abscess and fistula require different therapeutic approaches, and need to be distinguished by appropriate investigation before specific treatment is begun.

Assessment of disease activity

Its heterogeneous presentation makes assessment of disease activity in CD more complicated than in UC. For clinical trials, a large number of multifactorial clinical and/or laboratory-based scoring systems, such as the Crohn's Disease Activity Index (CDAI), has been devised, but none is suitable for ordinary clinical use[2]. The working definitions of the American College of Gastroenterology[2] are more practicable. Many patients with active CD can be looked after as outpatients, but those with moderate-severe and severe-fulminant disease need prompt, and in the latter instance immediate, hospital admissi on.

General measures

As for UC, patients with active CD should be looked after by a multi-disciplinary team with special expertise in IBD in a gastroenterology clinic or ward. Options for treatment (medical, nutritional, surgical) are wider than in UC, and it is essential that the patient is kept fully informed about his/her illness, and takes a place at the centre of the therapeutic decision-making process[2,3].

Establishing the diagnosis and clinicopathological problem

In many patients, the diagnosis of CD and identification of its principal site will have been made before the current relapse. Investigations, therefore, are directed primarily to clarifying the dominant clinicopathological process so as to optimise subsequent treatment. In those individuals presenting acutely for the first time, the diagnosis needs to be established (Table 2).

Clinical evaluation Terminal ileal and ileocaecal CD usually present with pain, diarrhoea and/or a tender mass in the right iliac fossa. Inflammation and abscess tend to cause constant pain, often with fever; in patients with small bowel obstruction, the pain is more generalised, intermittent, colicky and associated with borborygmi, abdominal distension and vomiting. Where the diagnosis of CD has not yet been made, an appendix mass, caecal carcinoma, lymphoma and, in some ethnic groups, ileocaecal tuberculosis require careful consideration.

Blood tests As in UC, the main value of blood tests is in assessing and monitoring disease activity, which is related directly to the platelet count, ESR and C-reactive protein and inversely to serum haemoglobin and albumin. However, in very sick patients, particularly with extensive small bowel disease and steatorrhoea, there may be laboratory evidence of malnutrition and malabsorption (anaemia, low serum iron, folate, Vit.B12, albumin, calcium, magnesium, zinc, essential fatty acids).

Endoscopy and biopsy In patients with right iliac fossa pain where the diagnosis of CD is in doubt, colonoscopy to the terminal ileum, with biopsies, is helpful. It can also be used to balloon-dilate short strictures. In established Crohn's colitis, colonoscopy during acute relapse is not routinely necessary and may be unsafe. In previously undiagnosed patients, digital rectal examination and sigmoidoscopy may show rectal induration or ulceration, or the presence of perianal disease. Furthermore, biopsy of macroscopically normal rectal mucosa may reveal epithelioid granulomata in a minority of patients with overt CD more proximally.

Plain abdominal X-ray A plain film is essential if intestinal obstruction is suspected. It may also hint at a mass in the right iliac fossa, and is often helpful, as in UC, in estimating extent or severity of Crohn's colitis.

Barium radiology Because it may exacerbate obstructive symptoms and pre-existing perforation, conventional barium follow through and sm all bowel enema should be avoided in severely ill patients with small bowel disease. In many centres, colonoscopy, because it allows biopsy and when necessary balloon dilatation of strictures, is used in preference to barium enema in patients with suspected large bowel and terminal ileal disease. Contrast fistulography is useful for the clarification of anatomical connections in patients with abdominal sinuses or fistulae.

Radiolabelled leucocyte scans ^{99}Tc-HMPAO or [111]Indium- leucocyte scanning can be helpful to identify, non-inv asively, not only sites of large bowel inflammation, as in UC, but also in the small intestine. Delayed scanning can also be helpful in identifying intra-abdominal abscesses.

Ultrasound, CT scan and magnetic resonance imaging (MRI) Abdominal ultrasound and CT scan can be very useful in active CD, allowing not only the evaluation but also the percutaneous drainage of localised collections. CT also plays a central role in

defining abdominal fistulous tracks and sinuses, while endoluminal ultra sound and MRI are particularly useful for the anatomical delineation of perianal abscesses and fistulae.

Supportive treatment
Patients with active CD, like those with acute severe UC, need meticulous supportive treatment, including, as necessary, intravenous fluids and electrolytes, blood transfusion and prophylactic subcutaneous heparin[7](Table 2).

Dietary advice and nutritional support All patients should be carefully assessed in relation to their nutritional intake and status, the latter clinically by measurement of body mass index [mass (kg)/height (m)^2; (normal >20)]. Patients with stricturing small bowel CD should avoid high residue foods (e.g. citrus fruit segments, nuts, sweetcorn, uncooked vegetables) which might cause bolus obstruction. Special dietary and nutritional modifications are needed for patients with extensive small bowel CD or short bowel syndrome. Sick inpatients may need enteral or parenteral nutrition to restore nutritional deficits, while liquid formula diets offer effective primary therapy for some patients with active small bowel CD.

Smoking Patients with CD who smoke should be strongly advised to stop, since this habit has a major adverse effect on the long-term natural history of the disease, particularly in women[19].

Drugs Codeine phosphate and loperamide are useful for the control of diarrhoea in patients with small bowel CD or resection; they should, as in UC, be avoided in active Crohn's colitis in case they provoke colonic dilat ation. Cholestyramine sachets (4 g one to three times daily) reduce watery diarrhoea due to bile salt malabsorption induced by extensive terminal ileal disease or resection. Haematinics (Fe, folate, Vit.B12), calcium, magnesium, zinc and fat soluble Vit. (A,D,E,K) may be needed for the replacement of particular deficiencies, as may appropriate drugs for incipient or established osteoporosis.

Drugs to avoid NSAIDs may precipitate relapse of CD, as of UC[10], and should be avoided. Likewise, in patients with small bowel st ricturing due to CD, delayed release drugs should not be prescribed in case they cause bolus obstruction.

SPECIFIC TREATMENT OF ACTIVE ILEOCAECAL CROHN′S DISEASE
Therapeutic options include drugs, liquid formula diet and surgery, as separate alternatives or in combination, depending on the individual patient's age, presentation and personal preference (Table 2)[2,3].

Drug therapy
Corticosteroids In active disease, oral steroids provide the quickest and most reliable response, 60%-80% patients improving in 3 wk-4 wk. Conventionally, prednisolone (40 mg·d^{-1}-60 mg·d^{-1}) is used, the dose being tapered by 5 mg every 7 d-10 d once improvement has begun. Very sick patients, or those needing to be fasted because of intestinal obstruction, need intravenous corticosteroids at least initially (e.g. hydrocortisone 300 mg·d^{-1}-400 mg·d^{-1}, methyl prednisolone 40 mg·d^{-1}-60 mg·d^{-1}). In patients able to take oral treatment in whom systemic steroid side effects are a major problem, a useful recent advance is the introduction of an oral con trolled ileal release formulation of budesonide (Entocort CR, Budenofalk) (9 mg·d^{-1}). This steroid approaches prednisolone in efficacy, but because oirst-pass metabolism, has fewer systemic side-effects and causes much less a drenocortical suppression, albeit at greater financial cost[20]. Up to 20% of patients with CD may be difficult to wean off steroids after relapse. Of these, many will be able partially or totally to discontinue steroid therapy on introduction of an aminosalicylate or *immunomod*-ulatory agent.

Aminosalicylates Patients with only moderately active ileocaecal disease, most of whom can be treated as out-patients, can be tried on h igh dose oral mesalazine (e.g. Pentasa 2 g b.d., Asacol 1.2 g t.d.s.)[21,22]: about 40% will go into remission in 2-3 months on such tre atment, which may be preferred by individuals reluctant to use prednisolone.

Metronidazole and other antibiotics Metronidazole alone[23]or in combination with ciprofloxacin[24]is moderately effective in mild moderately active CD, but is insufficiently potent for use as sole therapy in patients ill enough to need hospital admission. Treatment needs to be given for up to 3 months, but may be confounded by nausea, vomiting, an unpleasant taste and/or patients' unwillingness to abstain from alcohol during this time. More seriously, metronidazole taken long-term may cause a peripheral neuropathy not always reversible on its discon tinuation. The place of other antibiotics such as clarithromycin, clofazimine and rifabutin has not yet been adequately established in controlled trials. Conventional antituberculous therapy was not beneficial in a controlled trial in CD[25]. Antibiotics such as amoxycillin, trimethoprim, ciprofloxacin and metronidazole are sometimes useful for the treatment of diarrhoea or steatorrhoea due to bacterial overgrowth in patients with small bowel CD.

Azathioprine and 6-mercaptopurine Patients not

responding to or dependent on corticosteroids who, because of extensive disease or previous resection, need to avoid operative treatment, can be treated with adjunctive oral azathioprine (2-2.5 mg·kg^{-1}·d^{-1}) or 6-mercaptopurine (1-1.5 mg·kg^{-1}·d^{-1}); the dose of steroids is reduced as improvement occurs[26-28]. Such patients must be well enough to wait for up to four months for this to become apparent. Hopes that intravenous azathioprine could be used to accelerate response in active Crohn's have not been confirmed in a controlled trial[29]. Up to 20% of patients cannot tolerate azathioprine because of nausea, rash, fever, arthralgia, upper abdominal pain and headache; in a minority of these patients, a switch to 6MP may avert these problems. More seriously, both drugs may cause acute pancreatitis in about 3% of patients, particularly in the first few weeks of treatment. Their other potentially serious side effects, bone marrow depression (which occurs in 2% patients) and cholestatic hepatitis, necessitate blood tests every two weeks for the first two months of therapy: thereafter, white cell count, platelet count and liver function tests should be monitored every 2 months [30]. Opportunistic infections and a serious form of glandular fever have been reported in patients on azathioprine or 6MP. Although existing data in IBD is reassuring[31], very long-term use, as in transplant patients, may yet prove to increase the risk of malignancy. Indeed, the risk of skin cancer makes it advisable to recommend to white patients on azathioprine or 6MP that they avoid excessive exposure to sunlight. Homozygous deficiency of 6-thiopurine methyl transferase (6TPMT), the enzyme responsible for the safe metabolic breakdown of azathioprine and 6-MP, occurs in about 0.2% of the population and may contribute to the occasionally serious side-effects of both drugs and its routine assay is not yet available. Allopur inol, by inhibiting xanthine oxidase, reduces metabolism of azathioprine. Patients on this drug should not be given either thiopurine. Usage of azathioprine and 6-mercaptopurine in CD is long term. However, in patients maintained in remission on azathioprine or 6MP, the risk of relapse after four years of treatment appears to be similar whether the drug is continued or stopped[32]. In view of the potential toxicity of the long-term use of these- drugs, their withdrawal should be considered in patients still in re mission after four years treatment.

Methotrexate Methotrexate, given weekly as a 25 mg intramu scular injection, improves symptoms and reduces steroid requirements in chronically active steroid-dependent CD[33], but its potential side effects (bone marrow depression, hepatic fibrosis, pneumonitis, opportunistic infections) restrict its use to the very small number of patients with difficult CD refractory to safer treatments. Although a lower dose (12.5 mg weekly), given orally, may also prove beneficial in CD[34], all patients given methotrexate need careful blood monitoring.

Mycophenolate mofetil In an unblinded trial in complicated CD, this newer immunomodulatory drug appeared to act quicker and produce fewer side-effects than azathioprine[35] and double-blind controlled trials a re needed to confirm these results.

Cyclosporin Has not been confirmed as useful in active ileocaecal CD[38-40].

Anti-TNF-alpha antibody The first specific cytokine-related therapy to reach the bedside in CD is infliximab, a mouse-human chimeric (cA2) antibody to-TNF-alpha[36-38]; this drug was launched in the USA in 1998 and in Europe in 1999. In patients with CD refractory to steroids and/or conve ntional immunosuppressive drugs, a single infusion of infliximab produced, at 4 weeks, some improvement in 64% patients, compared with 17% after placebo; remission occurred in 33% patients treated with infliximab but only 4% of those given placebo[39]. Relapse tends to recur in the ensuing months: repeated infusions every 4 wk-8 wk may produce more lasting remissions[40]. Infliximab is administered as a single[40] or, to obtain a more prolonged response, multiple intravenous infusions[40,41] at 4 wk-8 wk intervals, each given over 2 hours. The dose is 5 mg·kg^{-1} per infusion, and the cost about £ 1000 (US $1600) per infusion. Common minor side-effects inc lude headache, nausea and upper respiratory tract infections. Serious, but not opportunistic, infections including salmonella enterocolitis, pneumonia and cellulitis have been reported. Infusion reactions occur in up to 20% patients, are usually mild and respond to antihistamines: however, adrenaline and corticosteroids should also be available when infusions are given. The development of human antichimeric antibodies (HACA) in up to 15% patients may cause a serum sickness reaction and diminished clinical response to repeated infusions. A lupus syndrome has been associated with anti-double-stranded DNA antibodies and cardiolipin antibodies in rheumatoid patients g iven infliximab. Rapid healing and fibrosis may precipitate bowel obstruction i n patients with small intestinal strictures. Lastly, there are several reports of lymphoma in rheumatoid and Crohn's patients given infliximab, although wheth er these are due to the drug or the underlying disease is not yet clear.The benefits, or otherwise, of coprescription of azathioprine or 6-mercaptopurine in patients given anti-TNF antibody are not yet established. By analogy wit h the effects

of methotrexate in infliximab-treated patients with rheumatoid arthritis, conventional *immunosupp*-ressive drugs may have a synergistic eff ect and reduce the incidence of the development of autoantibodies and other adverse effe cts. It is conceivable, however, that immunosuppressive agents could increase the risk of lymphoma in patients on infliximab[42]. In the future, select ion of patients to be treated with anti-TNF antibody may depend not only on the ir disease phenotype (eg fistulating disease), but also their genotype. Preliminary evidence suggests that CD patients who are pANCA positive, and have particular TNF microsatellite haplotypes, for instance, show a poor response to infliximab.

Dietary therapy
In patients with a poor response to, or preference for avoiding corticosteroids, in those with extensive small bowel disease, and in children, an alternative primary therapy is a liquid formula diet. This can be either elemental (aminoacid-based), protein hydrolysate (peptide-containing) or polymeric (containing whole protein and not therefore hypoallergenic), and is given for 4-6 weeks as the sole nutritional source[43]. This approach is probably as effective as corticosteroid therapy in the short term, about 60% patients achieving remission. Unfortunately, after the resumption of a normal diet, many patients relapse (50% at six months). Whether this can be prevented by selective and gradual reintroduction of particular foods to which individual patients are not intolerant[44], or by the intermittent use of further enteral feeding for short periods, remains to be proven. The success of enteral nutrition as a primary therapy for CD is also limited by its cost, the unpleasant taste of some of the available preparations and the need often to give the feed by nasogastric tube or percutaneous gastrostomy. Such therapy does, nevertheless, offer a valuable alternative in the compliant minority of adults for whom it is appropriate.

Surgery
In patients whose ileocaecal disease fails to respond to drug or dietary therapy, particularly if they have short segment (less than 20 cm) rather than extensive disease, surgery is indicated. Indeed, some patients prefer surgery at presentation to the prospect of pharmacological or nutritional treatment of unce rtain duration; there is no controlled data to confirm which approach is best. After surgery, there is a 50% chance of recurrent symptoms at 5 years and of f urther surgery at 10 years.

SPECIFIC TREATMENT OF OTHER PRESENTATIONS OF ACTIVE CROHN'S DISEASE
Obstructive small bowel Crohn's disease In patients presenting with obstructive symptoms and signs, with appropriate abnormalities on plain ab dominal X-ray, the principal difficulty lies in deciding whether stricturing is due to active inflammation, fibrosis with scarring or even adhesions. Sometime s laboratory markers (e.g. raised platelet count, ESR, C-reactive protein) and/or radiolabelled leucocyte scan can help to identify individuals with active inflammatory Crohn's, but in most instances a short trial of intravenous corticoste roids is given in addition to intravenous fluids and, if necessary, nasogastric suction. Parenteral nutrition is required if resumption of an oral diet is not likely in 5 d-7 d. If the stricture is in the upper jejunum, terminal ile um or colon, enteroscopic or colonoscopic balloon dilatation can be undertaken[45]; the value of concomitant local injection of triamcinolone around the stricture is as yet unclear. In patients not settling after 48 h-72 h of conservative treatment, surgery is needed, options being local resection or, for short and/or multiple strictures, stricturoplasty. Patients responding to conservative therapy should be advised to take a low residue diet to reduce the chance of recurrent symptoms.

Intra-abdominal abscess Ultra sound, CT scan and/ or radiolabelled leucocyte scan are usually used to confirm suspected intra- abdominal abscess in patients with Crohn's. Broad spectrum antibiotics are given and the abscess drained percutaneously under radiological control, and/or surgica lly. Subsequent treatment is usually of the underlying pathological process, fo r example, ileocaecal inflammation.

Intestinal fistula The relevant anatomical connections are clarified using contrast radiology, CT, endoluminal ultra sound and/or MRI. Restitution of nutritional well being is required using enteral or parenteral nutrition. Where there is no obstruction distal to the site of intestinal fistulae, medical therapy with oral, rectal or intravenous metronidazole and/or oral azathioprine or 6-mercaptopurine[26] cause some fistulae to heal. Uncontrol led reports suggest that intravenous cyclosporin may heal fistulous Crohn's, wh ile a controlled trial shows anti-TNF-alpha antibody (infliximab) infusions to be a promising option[41]. Most patients with enterocutane ous, *vesical or* vaginal fistulae, however, require surgical resection of the fistula and local resection of involved intestine and/or other viscera.

Perianal disease Non-suppurative perianal CD may respond to oral metronidazole[46] and/or ciprofloxacin given for up to three m onths, and to azathioprine or 6-mercaptopurine in the long term [26]. Successful healing of >50% perianal (and other) fistulae was reported in 62% patients treated with three intravenous infusions of anti-TNF-alpha

antibody (infliximab) compared with 26% of those given placebo[41]. Although in t his study it is not clear whether the fistulous tracks, rather than simply their openings on to the skin, healed, and reopening of fistulae was common in the 6 months after treatment was stopped, infliximab may prove a useful advance in therapy. Patients with suppurating perianal CD need surgery, minimised as far as possible and abscesses should be drained and loose (seton) s utures inserted to facilitate the continued drainage of chronic fistulae. Defunc tioning ileostomy or colostomy is of uncertain benefit.

Crohn's colitis The treatment of active Crohn's colitis closely resembles that of active UC (Table 1). In contrast to UC, oral metronidazole (400 mg b.d. for up to three months), if tolerated, can be used in patients with only moderately active disease who wish to avoid corticosteroids or aminosalicylates: the response rate is up to 50%[23]. There is no data to support the use of cyclosporin.. Meta-analysis data suggest that Crohn's colitis, like ileocaecal disease, responds to a liquid formula diet[43]. In patients who require total colectomy, permanent ileostomy is usually preferred to an ileoanal pouch because of the high incidence of pouch breakdown and sepsis in CD. Ileorectal anastomosis is an option in patients with rectal sparing, though recurrence requiring further surgery is far more common than after ileostomy. In rare individuals with refractory segmental colitis, local resections of short diseased segments can be performed. Toxic megacolon is even more rare in acute severe Crohn's than it has become in UC.

Oral and upper gastrointestinal Crohn's disease
Treatment of oral and upper gastrointestinal CD follows the usual principles outlined above. Patients with oral Crohn' s are best managed in close conjunction with specialists in oral medicine: controlled trial data are lacking, but options include topical, intral esional and oral steroids as well as oral thiopurines and liquid formula diet. Duodenal Crohn's may respond to omeprazole[47]; endoscopic balloon dilatation of strictures can be helpful, but surgery other than stricturoplasty may be technically demanding and complicated by fistulation.

MEDICAL TREATMENT OF IBD—THE FUTURE
Improvements in future medical treatments are likely to take several directions. First, conventional therapies, such as steroids and aminosalicylates, are likely to be made available in formulations which focus delivery more accurately on the site of disease and thereby further reduce systemic side effects. More excitingly, the increase in our knowledge of the aetiology and pathogenesis of IBD will inevitably lead to the development of more selectively targeted pharmacological agents, of

which the first to reach clinical application has been anti-TNF-alpha antibody. Gene therapy, for example applied topically to involved gut mucosa, may prove an important step forward in UC and Crohn's as in other chronic inflammatory diseases outside the gut. The choice of treatment in individual patients with IBD will depend not only on the phenotypic expression of their disease, but also on their genotype.

Whatever therapeutic advances are made in the coming years, the management of patients with IBD, whether apparently straightforward or difficult, will continue to depend on close collaboration between physicians, surgeons, specialist nurses, dieticians, radiologists, pathologists and counsellor, and a clinical geneticist may need to join this team. Most importantly, the patient with IBD m ust be looked upon as a person rather than a case. As treatment becomes more com plex, and the options more varied, it is essential that the patient remains at t he centre of the decision-making process, and the individual with IBD must be t he final arbiter of the type of treatment he or she is to be given.

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