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 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 later al decubitus abdominal film.

Radiolabelled leucocyte scans  The intensity and extent of colonic uptake one hour after injection of autologous 99Tc-HMPAO or 111Indium-labelled leukocytes provides information about disease
activity and particularly extent, respectively, where doubt exists in patients with UC. Colonic uptake of leukocytes 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 | ENDOSCOPIC | NUTRITIONAL | MEDICAL |
|-----------------|-----------|-------------|---------|
| Explanation, psychosocial support | - balloon dilatation | - liquid formula diet | - corticosteroids i.v. (hydrocortisone or methylprednisolone) then p.o. (prednisolone) or when infection suspected |
| Specialist multidisciplinary care | - stool microscopy, culture, C. difficile toxin | - stool microscopy, culture, C. difficile toxin | - antibiotics for very sick febrile patients, or when infection suspected |
| ESTABLISHING THE DIAGNOSIS, EXTENT/SITE AND SEVERITY | - limited sigmoidoscopy and biopsy | - limited sigmoidoscopy and biopsy | - consider cyclosporin i.v. then p.o.) for steroid non-responders at 4-7 days |
| MONITORING PROGRESS | - daily clinical assessment | - daily clinical assessment | - continue high dose mesalazine (Pentasa or Asacol) |
| SUPPORTIVE TREATMENT | - stool chart | - stool chart | - continue high dose mesalazine (Pentasa or Asacol) |
| | - 4-hrly temperature, pulse | - 4-hrly temperature, pulse | - continue 5-ASA p.o. in patients already taking it; otherwise start when improvement begins |
| | - daily FBC, ESR, C-reactive protein, urea and electrolytes, albumin | - daily FBC, ESR, C-reactive protein, urea and electrolytes, albumin | - continue high dose mesalazine (Pentasa or Asacol) |
| SPECIFIC TREATMENT | Medical | Medical | Medical |
| | - corticosteroids i.v. (hydrocortisone or methylprednisolone) then p.o. (prednisolone) or when infection suspected | - corticosteroids i.v. (hydrocortisone or methylprednisolone) then p.o. (prednisolone or budesonide CR) | - corticosteroids i.v. (hydrocortisone or methylprednisolone) then p.o. (prednisolone or budesonide CR) |
| | -continue high dose mesalazine (Pentasa or Asacol) in patients already taking it; otherwise start when improvement begins | -continue high dose mesalazine (Pentasa or Asacol) in patients already taking it; otherwise start when improvement begins | -continue high dose mesalazine (Pentasa or Asacol) in patients already taking it; otherwise start when improvement begins |
| | - consider cyclosporin i.v. then p.o.) for steroid non-responders at 4-7 days | - consider cyclosporin i.v. then p.o.) for steroid non-responders at 4-7 days | - 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 | Surgical for non-responders at 5-7 days, toxic megacolon, perforation, massive haemorrhage | Surgical for non-responders at 5-7 days, toxic megacolon, perforation, massive haemorrhage |
| | - paraproctectomy with ileorectal anastomosis | - paraproctectomy with ileorectal anastomosis | - paraproctectomy with ileorectal anastomosis |
| | - subtotal colectomy with ileorectal anastomosis (rarely) | - subtotal colectomy with ileorectal anastomosis (rarely) | - subtotal colectomy with ileorectal anastomosis (rarely) |

Table 2 Management of active ileocecal Crohn’s disease.

General measures, monitoring progress and supportive treatment are essentially as for ulcerative colitis

| ESTABLISHING THE DIAGNOSIS, EXTENT/SITE AND SEVERITY | SPECIFIC TREATMENT | NUTRITIONAL | ENDOSCOPIC | SURGICAL |
|-------------------------------------------------------|-------------------|-------------|-----------|---------|
| - clinical evaluation | Medical |
| - FBC, ESR, C-reactive protein, ferritin, folate, B12, albumin, LFTs, Ca, Mg, Zn | - corticosteroids i.v. (hydrocortisone or methylprednisolone) then p.o. (prednisolone) or when infection suspected | - liquid formula diet | - balloon dilatation |
| - stool microscopy, culture, C. difficile toxin | - continue high dose mesalazine (Pentasa or Asacol) in patients already taking it; otherwise start when improvement begins | - liquid formula diet | - balloon dilatation |
| - plain abdominal X-ray | - consider cyclosporin i.v. then p.o.) for steroid non-responders |
| - consider colonoscopy and biopsy, small bowel barium radiology, ultrasound, CT, MRI, leucocyte scan | - rolling manoeuvre (if colon dilating) |
| - abdominal X-ray | - paraproctectomy with ileorectal anastomosis |

**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 surgery during their admission (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, 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.

**Drugs to avoid** Anti diarrhoeal drugs (loperamide, codeine phosphate, diphenoxylate), opioid, antispasmodics and anticholinergic drugs should not be prescribed in active UC since they may provoke acute colonic dilatation. Mesalazine and aminosalicylates are contraindicated in active UC due to the risk of exacerbation.

**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.

**Specific medical treatment**

The cornerstone of specific medical treatment of active severe UC remains corticosteroids. Aminosalicylates and antibiotics have minor roles. Cyclosporin has become a useful option, but oral
azathioprine and 6-mercaptopurine 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/L⁻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 carinii pneumonia, on account of which co-administration of prophylactic trimethoprim/sulphamethoxazole may be advisable; renal impairment, including a small reduction in glomerular filtration rate in 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 barrier by a vehicle, cromophor, 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 patients with steroid-refractory or dependent IBD. Unfortunately, however, they take up to 4 months to exert their effect and are thus inappropriate for acute severe UC.

Possible new treatments The possible roles of anti-TNF-alpha antibody [17], antibodies and antisense oligonucleotides to leucocyte/endothelialcellularadhesion molecules [18], and intravenous heparin [19] 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 (panproctocolectomy 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. 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. The working definitions of the American College of Gastroenterology 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, treatment (Table 2), obstruction, abscess and fistula require different therapeutic approaches, and need to be distinguished by appropriate investigation before specific treatment is begun.

**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.

**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 steatorrhea, 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 proximaly.

**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 small 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**

99Tc-HMPAO or 111InIndium- leucocyte scanning can be helpful to identify, non-invasively, 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 dilatation. 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 stricturing 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^, methylprednisolone 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 controlled ileal release formulation of budesonide (Entocort CR, Budenofalk) (9 mg·d^-1^). This steroid approaches prednisolone in efficacy, but because of first-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 immunomodulatory agent.

**Aminosalicylates**

Patients with only moderately active ileocaecal disease, most of whom can be treated as outpatients, can be tried on high 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 treatment, 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 discontinuation. 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 (2.25 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. 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. 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. 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, 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. Allopurinol, 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. In view of the potential toxicity of the long-term use of these drugs, their withdrawal should be considered in patients still in remission after four years treatment. Methotrexate Methotrexate, given weekly as a 25 mg intramuscular injection, improves symptoms and reduces steroid requirements in chronically active steroid-dependent CD, 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, 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 and double-blind controlled trials are needed to confirm these results. Cyclosporin Has not been confirmed as useful in active ileocaecal CD. 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; this drug was launched in the USA in 1998 and in Europe in 1999. In patients with CD refractory to steroids and/or conve ntitonal 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. Relapse tends to recur in the ensuing months: repeated infusions every 4 wk-8 wk may produce more lasting remissions. Infliximab is administered as a single or, to obtain a more prolonged response, multiple intravenous infusions 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 include 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 given infliximab. Rapid healing and fibrosis may precipitate bowel obstruction in patients with small intestinal strictures. Lastly, there are several reports of lymphoma in rheumatoid and Crohn’s patients given infliximab, although whether 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 with the effects
of methotrexate in infliximab-treated patients with rheumatoid arthritis, conventional immunosuppressant-resistive drugs may have a synergistic effect and reduce the incidence of the development of autoantibodies and other adverse effects. It is conceivable, however, that immunosuppressive agents could increase the risk of lymphoma in patients on infliximab. In the future, selection of patients to be treated with anti-TNF antibody may depend not only on the disease phenotype (e.g., 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. 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, 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 uncontrolled disease; 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 further 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 abdominal X-ray, the principal difficulty lies in deciding whether strictureing is due to active inflammation, fibrosis with scarring or even adhesions. Sometimes 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 corticosteroids 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 ileum or colon, enteroscopic or colonoscopic balloon dilatation can be undertaken; 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** Ultrasound, 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 surgically. Subsequent treatment is usually of the underlying pathological process, for example, ileocaecal inflammation.

**Intestinal fistula** The relevant anatomical connections are clarified using contrast radiology, CT, endoluminal ultrasound 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 may respond to oral metronidazole and/or 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 ileum or colon, enteroscopic or colonoscopic balloon dilatation can be undertaken; 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.

**Perianal disease** Non-suppurative perianal CD may respond to oral metronidazole and/or ciprofloxacin given for up to three months, and to azathioprine or 6-mercaptopurine in the long term. 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 this 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) sutures inserted to facilitate the continued drainage of chronic fistulae. Defunctioning 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[45]. 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 active 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, intraesophageal 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 fistulization.

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 IBDD 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 IBDD 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 IBDD, 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 must be looked upon as a person rather than a case. As treatment becomes more complex, and the options more varied, it is essential that the patient remains at the centre of the decision-making process, and the individual with IBDD must be the final arbiter of the type of treatment he or she is to be given.

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