Medical management of Crohn's disease

Adrian Thuraisingam, Keith Leiper

Current evidence strongly suggests that Crohn's disease is caused by an abnormal response to enteric flora. This review examines the current evidence for medical management of Crohn's disease, particularly focusing on alternative therapies to corticosteroids in managing disease relapses and preventing long-term complications.

This is an exciting time for physicians involved in the management of patients with Crohn's disease (CD). An expanding array of possible treatments is available; consequently clinicians are now able to explore more individualized management for their patients. This review will outline current management in induction and maintenance of remission of CD for non-inflammatory bowel disease (IBD) specialists and discuss potential new therapies.

CD can affect any part of the gastrointestinal tract and is characterized by patchy, transmural inflammation. The commonest patterns of disease are ileocolonic, ileal, colonic or upper gastrointestinal. The incidence of CD is 5–10 per 100 000 per year and is increasing. The peak incidence is between the ages of 10–14 years but it can present at any age. The pathogenesis of CD is complex and will not be explored in this review. However, evidence strongly suggests that CD is a partly genetically determined abnormal response to enteric flora resulting in a chronic inflammatory response. The symptoms of CD are heterogeneous and non-specific but usually include abdominal pain, weight loss and diarrhoea, often with systemic symptoms, e.g. fever and anorexia. Perianal involvement is common with perianal abscesses, fissures and fistulae. Diagnosis rests on a combination of clinical suspicion, radiology (*Figure 1*), endoscopy (*Figure 2*) and histology.

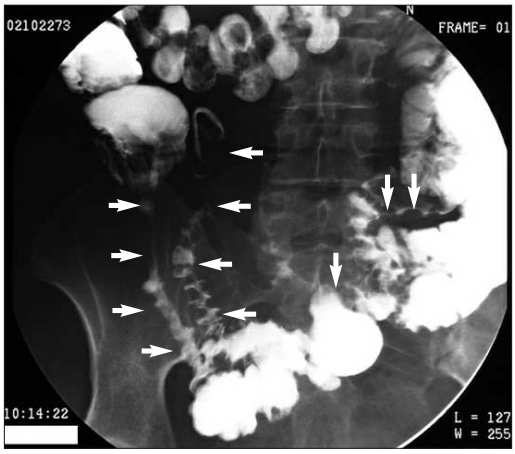
INDUCTION OF REMISSION

Corticosteroids

Corticosteroids have been the main treatment for inducing remission in CD. At a dose of prednisolone 40–60 mg/day remission is achieved in 60–80% of patients with CD compared to 33–38% with placebo (Summers et al, 1979; Malchow et al, 1984). Budesonide is more topically active and has less bioavailability because of its extensive first pass metabolism. Remission rates of 51% in active CD are achieved with budesonide 9 mg/day (Greenberg et al, 1994). Meta-analysis suggests that budesonide is marginally inferior to prednisolone but with a better side-effect profile (Papi et al, 2000).

There is an element of sophistry to the use of steroid treatment in CD. Arguably they merely achieve relatively good, short-term symptomatic control at the expense of both short- and long-term side effects while carrying the attendant risk of steroid dependency. Corticosteroids do

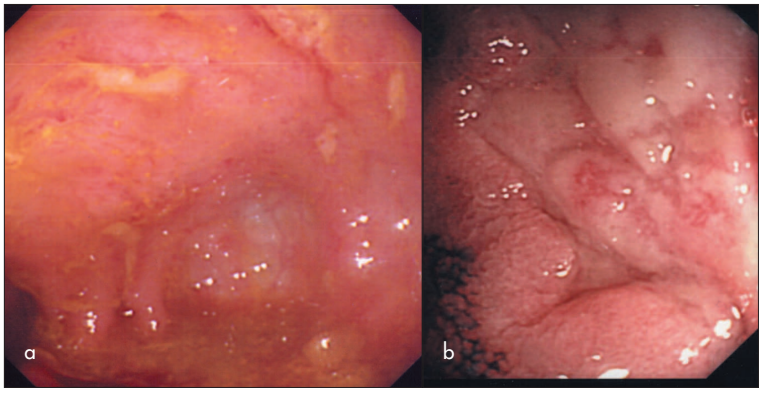
Figure 1. Small bowel X-ray showing extensive ileal stricturing in Crohn's disease.



Dr Adrian Thuraisingam is Specialist Registrar and **Dr Keith Leiper** is Consultant Gastroenterologist in the Department of Gastroenterology, Royal Liverpool and Broadgreen University Hospitals, Liverpool L7 8XP

Correspondence to: Dr K Leiper

Figure 2. Endoscopic appearance of (a) colonic and (b) ileal ulceration in Crohn's disease.



not heal ulceration in CD as seen in several studies showing either no healing or little correlation between endoscopic and clinical scores (Olaison et al, 1990). Relapse rates are high after a corticosteroid-induced remission with about 50% relapsing in the year following a steroid-induced remission and about 30% are unable to reduce and stop prednisolone because of relapse of disease on dose tapering (Modigliani et al, 1996). Furthermore corticosteroids are not effective in maintaining remission.

The short-term side-effect profile of steroids is well known: psychological effects including psychosis, infection risk, cushingoid features, diabetes, myopathy and aseptic necrosis of bones. Long-term effects include cataracts and osteoporosis, which occurs in about 30% of CD patients. Although steroids are one of the most commonly used treatments for CD, it is difficult to endorse a treatment with such an adverse side-effect profile, which has less than a 50% chance of maintaining remission and a 30% chance of inducing some dependency. A recent trial has also shown that corticosteroid use is the most important factor in postoperative complications in CD with an adjusted odds ratio (OR) of major infection of 5.54 (95% confidence interval (CI) = 1.12–27.26) compared to 1.20 (95% CI= 0.37–3.94) for azathioprine or mercaptopurine (Aberra et al, 2003). The authors' approach is to try and avoid steroid treatment in CD (see below), particularly in ileocolonic disease, as opposed to colonic CD that behaves more like ulcerative colitis (Present, 2000).

Nutritional therapy

The concept that nutritional therapy is effective in active CD is attractive for both patients and doctors. The efficacy of enteral feeding has been equivalent to oral corticosteroids in some trials with remission rates of up to 84% in compliant patients (Royall et al, 1994) and with evidence of endoscopic and histological remission. There is, however, considerable variation in responses to different enteral diets. Meta-analysis data show a pooled OR of 0.57 (95% CI = 0.35–0.94) by per protocol trials in favour of corticosteroids over liquid feeding (Griffiths et al, 1995). However, these meta-analysis data obscure some clear advantages of enteral feeding over corticosteroids. These include the lack of major side effects of nutritional therapy, improving nutritional status and increased growth in children.

Enteral feeding is an excellent preoperative treatment to gain short-term control of CD before surgery, improving nutritional status and eliminating the risk of steroid therapy. The mechanism of action of enteral nutrition is not clear but is likely to be multifactorial. Proposed mechanisms are a reduction of antigen load, modification of eicosanoid synthesis and immunomodulatory effects resulting in reduced cytokine production. The quantity and type of fat in a liquid feed may be an important determinant of therapeutic response. Questions still remain about the optimal liquid diet in CD, in particular about the amount and type of fat in the diet (Gassull et al, 2000; Leiper et al, 2000).

Antibiotics

A huge literature in animal IBD models and human data strongly support the pivotal role of bacteria in the pathogenesis of CD. Since the discovery of *Helicobacter pylori*, gastroenterologists are wary of dismissing specific bacteria as pathogens, but it is unlikely that a single microorganism is responsible for a substantial proportion of CD. Evidence points to some qualitative but mostly quantitative alteration in bacterial flora and an abnormal host response to normal bacterial flora. An intriguing possibility is that CD is also linked with the inability to adequately deal with intracellular bacteria (Rhodes, 1996).

With this in mind antibiotics are an obvious therapeutic option. Unfortunately most evidence for the use of antibiotics in CD is uncontrolled. Although anecdotal, there is strong evidence for use of metronidazole in perianal and fistulating disease (Bernstein et al, 1980). There are some data for the use of metronidazole as monotherapy but stronger evidence for the effect of either ciprofloxacin monotherapy or dual therapy with metronidazole (Prantera et al, 1996; Colombel et al, 1999). Uncontrolled data also suggest that clarithromycin (an antibiotic that has activity against intracellular bacteria) may be effective in CD (Leiper et al, 2000). Further studies are required on this and on other antibiotic combination regimens. However, antibiotics are a useful therapy in establishing remission in active CD.

Probiotics

Although it is an intellectually appealing therapeutic avenue, there is no large-scale controlled trial evidence on the use of probiotics as a primary or adjuvant therapy in active CD. At present, aside from anecdotal reports, there is no evidence to support probiotic use in active CD. Animal models show that different probiotics have positive and negative effects depending on the model. It remains to be seen whether different combinations of probiotics will be effective therapy in human CD; however, current data suggest that it is extremely difficult to permanently alter gut flora in adults. It may be that live

bacteria are not required and that immunostimulatory bacterial DNA is all that is required to ameliorate inflammation, as has been shown in a murine model (Rachmilewitz et al, 2002).

Immunomodulators

Thiopurines: In the last decade there has been increased use of the immunomodulators azathioprine (AZA) and 6-mercaptopurine (6-MP) in CD since they were first used in the 1960s. These drugs can be used almost interchangeably aside from dosage (AZA 2–2.5 mg/kg; 6-MP 1–1.5 mg/kg). 6-MP may be tried in patients intolerant of AZA or vice versa. The exact mechanism of action of thiopurines in IBD is unclear but is partly a result of the reduction of NK cells and cytotoxic T cells, together with an effect on purine synthesis and consequent effect on RNA and DNA synthesis.

Meta-analysis of eight trials show that both drugs are effective in inducing remission with an OR of 2.36 (95% CI = 1.57–3.53) compared to placebo, corresponding to a number needed to treat (NNT) of 5 (Sandborn et al, 2000). This improved after prolonged treatment (≥ 17 weeks) to NNT=4, suggesting a minimum duration of therapy before efficacy can be assessed. The main adverse effects are pancreatitis (3%), significant bone marrow depression (2–5%) and hepatitis (0.3%), with a further 10–15% of patients unable to tolerate therapy because of nausea or vomiting.

Approximately 0.3% of the population are deficient in thiopurine methyl transferase, an important enzyme in the metabolism of thiopurines, while about 10% have low activity. The former are at high risk of profound early myelosuppression with thiopurines while the latter are at a much lower risk. Thiopurine therapy should be monitored carefully with weekly full blood counts in the first month of therapy and thereafter every 3 months. Reassuringly there is no evidence of an increased risk of malignancy in patients with IBD treated with thiopurines (Fraser et al, 2002).

Methotrexate: Methotrexate is a folate analogue with an incompletely understood mechanism of action in CD. It may increase adenosine which has anti-inflammatory properties by decreasing neutrophil chemotaxis. There is only a single randomized trial of methotrexate in active CD showing induction of remission in 39% compared to 19% with placebo (NNT=5) using 25 mg once a week intramuscularly (Feagan et al, 1995). This, together with uncontrolled evidence, showed that methotrexate is well tolerated in the short term.

Cyclosporin: Cyclosporin is of no, or very limited value, in active CD with only one of four randomized trials showing a significant short-term effect with a high rate of side effects.

Anti-TNFα antibodies: Gordon and McDonald cover the mechanism of action of anti-tumour necrosis factor (TNF)-α antibodies in the accompanying article (p. 708). Like AZA and nutritional therapy, infliximab has been shown to heal endoscopic lesions.

5-aminosalicylates: Although widely used, there is no compelling evidence for a beneficial effect of 5-aminosalicylate (5-ASA) preparations in CD. Sulphasalazine at high dose has approximately 20% benefit over placebo but has a high rate of side effects. The newer 5-ASA preparations have no effect at low doses and mesalazine has a very modest effect at higher doses (4 g/day) (Singleton et al, 1993). They are an option in mild disease, but they can cause diarrhoea that can be misinterpreted as a worsening of CD.

New therapies

Thalidomide: Thalidomide has anti-TNFα activity, possibly acting by blocking TNFα RNA. Two open label trials have shown positive effects at a dose of 50–300 mg in patients with refractory CD with a response rate of up to 70% (Ehrenpreis et al, 1999; Vasiliauskas et al, 1999). It is interesting to note that some of the responders included patients who were previously infliximab non-responders. A randomized trial is needed, but blinding is very difficult because of the side effect of drowsiness with thalidomide.

Natalizumab: α4 integrins are involved in the migration of leukocytes across gut endothelium. Natalizumab is a monoclonal antibody against α4 integrins and theoretically should be effective in CD. However, in a recent randomized controlled trial, although some benefit was achieved, after one infusion there was no significant benefit over placebo for the primary end point of remission (Ghosh et al, 2003).

Tacrolimus: Although there is no compelling evidence to support cyclosporin in active CD, there are some data supporting another interleukin-2 inhibitor, tacrolimus, in CD. A recent randomized control trial of tacrolimus (0.2 mg/kg/day) in patients with fistulating disease showed that tacrolimus can improve fistulae but not lead to closure (Sandborn et al, 2003). This was at the expense of a significant increase in adverse events, particularly renal impairment and paraesthesia.

Granulocyte macrophage colony stimulating factor: As mentioned above, an intriguing hypothesis is that CD is in part caused by defects in the ability to eliminate phagocytosed bacteria. Although uncontrolled data, out of 15 patients with active CD 8 achieved remission and 12 achieved response with 8 weeks treatment with granulocyte macrophage colony stimulating factor (GM-CSF)

(Dieckgraefe and Korzenik, 2002). This approach is completely different in that it aims to enhance immune function as opposed to conventional therapy with corticosteroids that aims to suppress proinflammatory responses. Controlled trial data are awaited with considerable interest.

With the exception of anti-TNFα antibodies, none of the newer 'biological' therapies have been shown to be effective in active CD. Randomized controlled evidence shows no significant effect over placebo of interleukin-10, interleukin-11 or ICAM-1 antisense oligonucleotide.

MAINTENANCE OF REMISSION

Maintenance of medically-induced remission

Although there are several established therapies which are proven to induce remission there are fewer proven treatment modalities in maintenance of remission following either medically- or surgically-induced remission. The most important intervention is to try and stop cigarette smoking which is the most important factor in early relapse.

5-ASA: Sulphasalazine has no effect on the duration of remission. Likewise the newer 5-ASA drugs (mesalazine) confer a marginal advantage over placebo after medically-induced remission with an OR over placebo of -4.7% (95% CI = -9.6 to 2.8%). There are, however, possible advantages in pure colonic CD in the prevention of colonic cancer. Non-randomized evidence in ulcerative colitis suggests that 5-ASAs may reduce the risk of IBD-related colon cancer. The risk of cancer in colonic CD is similar to that of pan-ulcerative colitis and therefore the authors suggest that patients with pure colonic CD continue on long-term oral 5-ASA together with regular colonoscopic surveillance.

Corticosteroids: There are no data supporting an effect of either prednisolone or budesonide in maintaining remission in CD (Steinhart et al, 2001).

Immunomodulators: ***Thiopurines:*** Many of the original trials of AZA/6-MP were curiously trials of the effect of drug withdrawal on relapse rates. However, there are convincing data showing thiopurines are effective in maintaining remission. Meta-analysis shows a pooled OR of 2.16 (95% CI = 1.35–3.47) over placebo with a NNT of 7 and the beneficial effect is maintained for up to 4 years (Pearson et al, 2003). Current recommendations are to introduce AZA if there have been more than two relapses a year, features of high risk of relapse or patients relapsing when prednisolone reduced below 15 mg or within 6 weeks of corticosteroids being discontinued (McGovern and Travis, 2003).

Methotrexate: There are few data on methotrexate as maintenance therapy in CD. In the only randomized controlled trial, 76 patients who had achieved remission with methotrexate were randomized to intramuscular methotrexate 15 mg/week or placebo (Feagan et al, 2000). Remission rates at 40 weeks were 65% and 39% respectively and methotrexate was well tolerated. Uncontrolled evidence suggests oral administration may be effective, with an optimum dose for oral or parenteral use of 25 mg once a week (Fraser, 2003). Methotrexate is a second-line option for maintenance therapy for patients who are intolerant or unresponsive to AZA or 6-MP, particularly if infliximab is used to induce remission. Although not supported by randomized evidence the authors suggest folic acid supplementation to reduce side effects and use methotrexate as maintenance therapy for up to 4 years.

Infliximab: Three trials have examined the strategy of continuing regular infusions of infliximab following initial response. Rutgeerts et al (1999) studied 73 patients who responded to an initial infusion of infliximab and randomized them to 10 mg/kg or placebo every 8 weeks to week 36. At week 44, remission was maintained in 53% in the infliximab against 20% in the placebo group. However, after 44 weeks many of the infliximab patients relapsed suggesting, as expected, that the treatment effect is lost after 8 weeks.

In a much larger trial (Hanauer et al, 2002) 573 patients with active CD were given a single infusion of infliximab 5 mg/kg. The responders to the initial infusion at week 2 were then randomized into three groups to have repeated infusions: group 1 placebo infusions, group 2 two induction doses of 5 mg/kg then 5 mg/kg every 8 weeks to week 46, or group 3 two induction doses of 5 mg/kg then 10 mg/kg every 8 weeks to week 46. Remission at week 30 was achieved in 22% of placebo, 39% of group 2 and 46% of group 3 ($P<0.01$ for both doses). About 30% of patients had an infection during treatment and there were three deaths, one of which was likely to be related to infliximab.

In summary infliximab is effective in maintaining remission in about 40% of patients but the response is lost soon after stopping therapy. Long-term safety data are reassuring but there is a significant risk of infection and rarely life-threatening side effects. These trials are examining the effect of regular infusions on quality of life of patients with CD and not altering the natural history of disease.

Fish oils: The concept that fish oils may be beneficial in CD is based on the observation that there is a strong association with increasing incidence

of CD and diet high in animal fats, n-6 fatty acids and ratio of n-6 to n-3. n-3 fatty acids have anti-inflammatory actions, particularly in inhibiting pro-inflammatory prostaglandins IL-1β and TNFα. Trials of fish oil in CD are of very variable quality, particularly in placebo choice and compliance, thus the data are conflicting. In the best quality trial Belluzzi et al (1996) randomized patients in remission but with markers indicative of high chance of relapse to 2.7 g of n-3 fatty acids or placebo (capric and caprylic acid). At 1 year 28% relapsed in the fish oil group against 69% in placebo group ($P<0.001$). Although still largely an unproven therapy, fish oils are a safe option in trying to prevent recurrence.

Maintenance of surgically-induced remission

About 80% of patients with CD will have resection of bowel in the first 10 years after diagnosis and surgery is an effective therapy for the symptomatic relief from symptoms of CD. However, recurrence of CD after surgery is almost inevitable. In the first year after resection symptomatic recurrence occurs in 20–30%, thereafter there is an approximately 10% recurrence rate per year. Evidence of extensive (usually asymptomatic) endoscopic recurrence of CD a few months after surgery is a powerful predictor of symptomatic recurrence (Rutgeerts et al, 1990). The strongest environmental factor associated with recurrence of CD is current smoking which increases the risk by a factor of two. Although there are no data on the effect of intervention to encourage the cessation of smoking postoperatively, data show that patients who stop smoking for more than 1 year have a more benign disease course (Cosnes et al, 2001).

Several strategies have been tested to prevent postoperative recurrence of CD. The 5-ASA drugs, although widely used, have a very limited effect on recurrence rates with at most an 8% reduction in recurrence in a meta-analysis (Sutherland, 2000). There is no evidence that glucocorticoids (Hellers et al, 1999), interleukin-10 (Colombel et al, 2001) or the probiotic *Lactobacillus* GG (Prantera et al, 2002) reduces postoperative recurrence. Limited data are available on the effect of immunosuppressive drugs such as AZA and 6-MP in the prevention of postoperative recurrence. A 2-year study which included low dose 6-MP (50 mg/day) showed an endoscopic recurrence rate of 68% compared to 87% with placebo and clinical recurrence rates at 24 months of 50% for 6-MP compared with 69% for placebo (Korelitz et al, 1998).

One therapy that may be effective in the prevention of postoperative recurrence is metronidazole 20 mg/kg for 3 months after ileal resection. This significantly decreased the severity of endoscopic recurrent lesions (Rutgeerts et al, 1995). There was also a significant reduction in clinical recurrence at 1 year (4% *vs* 25%), although this effect was lost with further follow up.

CONCLUSIONS

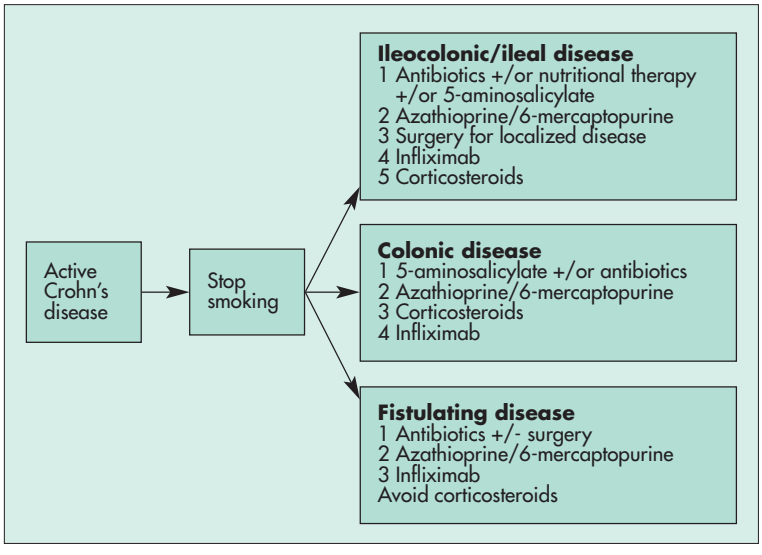
There is a wealth of possible treatments that can induce remission in active CD. It is one of the few conditions where the patient can genuinely choose from a number of fundamentally different therapies and treatment can be tailored to individual patient choice and response. The authors' approach is to try and avoid corticosteroids, particularly in ileocolonic disease, and induce remission with dietary therapy, 5-ASAs, antibiotics or surgery. Stopping smoking is pivotal in trying to prevent relapse, particularly after surgery. Early introduction of AZA or 6-MP is important to gain long-term control of frequently relapsing disease. A suggested plan of management for active CD is outlined in *Figure 3*. Although the prospect of new biological therapies is exciting, it must be remembered that there are many different ways to treat CD. In particular there is still considerable scope for development of nutritional therapy and therapeutic manoeuvres to manipulate enteric flora. HM

Conflict of interest: none.

Aberra FN, Lewis JD, Hass D et al (2003) Corticosteroids and immunomodulators: postoperative infectious complication risk in inflammatory bowel disease patients. *Gastroenterology* **125:** 320–7

Belluzzi A, Brignola C, Campieri M et al (1996) Effect of an enteric coated fish oil preparation on relapses in Crohn's disease. *N Engl J Med* **334:** 1557–60

Figure 3. Suggested treatment algorithm for active Crohn's disease.



Bernstein LH, Frank MS, Brandt LJ, Boley SJ (1980) Healing of perineal Crohn's disease with metronidazole. *Gastroenterology* **79:** 357–65
Colombel JF, Lemann M, Cassagnou M et al (1999) A controlled trial comparing ciprofloxacin with mesalazine for the treatment of active Crohn's disease. Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives (GETAID). *Am J Gastroenterol* **94:** 674–8
Colombel JF, Rutgeerts P, Malchow H et al (2001) Interleukin 10 (Tenovil) in the prevention of postoperative recurrence of Crohn's disease. *Gut* **49:** 42–6
Cosnes J, Beaugerie L, Carbonnel F et al (2001) Smoking cessation and the course of Crohn's disease: an intervention study. *Gastroenterology* **120:** 1093–9
Dieckgraefe BK, Korzenik JR (2002) Treatment of active Crohn's disease with recombinant human granulocyte-macrophage colony-stimulating factor. *Lancet* **360:** 1478–80
Ehrenpreis ED, Kane SV, Cohen LB et al (1999) Thalidomide therapy for patients with refractory Crohn's disease: an open-label trial. *Gastroenterology* **117:** 1271–7
Feagan BG, Rochon J, Fedorak RN et al (1995) Methotrexate for the treatment for Crohn's disease. *N Engl J Med* **332:** 292–7
Feagan BG, Fedorak RN, Irvine EJ et al (2000) A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. North American Crohn's Study Group Investigators. *N Engl J Med* **342:** 1627–32
Fraser AG (2003) Methotrexate: first-line or second- line immunomodulators? *Eur J Gastroenterol Hepatol* **15:** 225–31
Fraser AG, Orchard TR, Robinson EM (2002) Long-term risk of malignancy after treatment of inflammatory bowel disease with azathioprine. *Aliment Pharmacol Ther* **16:** 1225–32
Gassull MA, Fernandez-Banares F, Cabre E et al (2002) European Group on Enteral Nutrition in Crohn's Disease. Fat composition may be a clue to explain the primary therapeutic effect of enteral nutrition in Crohn's disease: results of a double blind randomised multicentre European trial. *Gut* **51:** 164–8
Ghosh S, Goldin E, Gordon FH et al (2003) Natalizumab for active Crohn's disease. *N Engl J Med* **348:** 24–32
Greenberg GR, Feagan BG, Martin F et al (1994) Oral budesonide for active Crohn's disease. Canadian Inflammatory Bowel Disease Study Group. *N Engl J Med* **331:** 836–41
Griffiths AM, Ohlsson A, Sherman PM et al (1995) Meta-analysis of enteral nutrition as a primary treatment of active Crohn's disease. *Gastroenterology* **108:** 1056–67
Hanauer SB, Feagan BG, Lichtenstein GR et al (2002) ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* **359:** 1541–9
Hellers G, Cortot A, Jewell DP et al (1999) Oral budesonide for prevention of recurrence following ileocaecal resection of Crohn's disease: a one-year placebo-controlled study. *Gastroenterology* **116:** 294–300
Korelitz B, Hanauer S, Rutgeerts P et al (1998) Postoperative prophylaxis with 6MP, 5-ASA or placebo in Crohn's disease: a 2 year multicenter trial. *Gastroenterology* **114:** A688

KEY POINTS

- The incidence of Crohn's disease is increasing.
- There are several established therapies which induce remission but few which maintain remission in Crohn's disease.
- Active Crohn's disease can be effective treated without the use of corticosteroids.
- Manipulation of the enteric flora is a logical approach to Crohn's disease but as yet there is not conclusive data supporting the use of probiotic or prebiotics.
- Surgery is a good option in Crohn's disease but disease nearly always recurs at some time after surgery and further work is required to find therapy that reduces postoperative recurrence rates.

Leiper K, Morris AI, Rhodes JM (2000) Open label trial of oral clarithromycin in active Crohn's disease. *Aliment Pharmacol Ther* **14:** 801–6
Leiper K, Woolner J, Mullan MM et al (2001) A randomised controlled trial of high versus low long chain triglyceride whole protein feed in active Crohn's disease. *Gut* **49:** 790–4
Malchow H, Ewe K, Brandes JW et al (1984) European Cooperative Crohn's Disease Study (ECCDS): results of drug treatment. *Gastroenterology* **86:** 249–66
McGovern DPB, Travis SPL (2003) Thiopurine therapy when to start and when to stop. *Eur J Gastroenterol Hepatol* **15:** 219–22
Modigliani R, Colombel JF, Dupas JL et al (1996) Mesalamine in Crohn's disease with steroid-induced remission: effect on steroid withdrawal and remission maintenance, Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives. *Gastroenterology* **110:** 688–93
Olaison G, Sjodahl R, Tagesson C (1990) Glucocorticoid treatment in ileal Crohn's disease: relief of symptoms but not of endoscopically viewed inflammation. *Gut* **31:** 325–8
Papi C, Luchetti R, Gili L et al (2000) Budesonide in the treatment of Crohn's disease: a meta-analysis. *Aliment Pharmacol Ther* **14:** 1419–28
Pearson DC, May GR, Fick G et al (2003) Azathioprine for maintenance of remission in Crohn's disease. In The Cochrane Library, Issue 4. John Wiley & Sons, Chichester
Prantera C, Zannoni F, Scribano ML et al (1996) An antibiotic regimen for the treatment of active Crohn's disease: a randomized, controlled clinical trial of metronidazole plus ciprofloxacin. *Am J Gastroenterol* **91:** 328–32
Prantera C, Scribano ML, Falasco G et al (2002) Lactobacillus or identical placebo for one year. Ineffectiveness of probiotics in preventing recurrence after curative resection for Crohn's disease: a randomised controlled trial with Lactobacillus GG. *Gut* **51:** 405–9
Present DH (2000) How to do without steroids in inflammatory bowel disease. *Inflamm Bowel Dis* **1:** 48–57
Rachmilewitz D, Karmeli F, Takabayashi K et al (2002) Immunostimulatory DNA ameliorates experimental and spontaneous murine colitis. *Gastroenterology* **122:** 1428–41
Rhodes JM (1996) Unifying hypothesis for inflammatory bowel disease and associated colon cancer: sticking the pieces together with sugar. *Lancet* **347:** 40–4
Royall D, Jeejeebhoy KN, Baker JP et al (1994) Comparison of amino acid v peptide based enteral diets in active Crohn's disease: clinical and nutritional outcome. *Gut* **35:** 783–7
Rutgeerts P, Geboes K, Vantrappen G et al (1990) Predictability of the postoperative course of Crohn's disease. *Gastroenterology* **99:** 956–63
Rutgeerts P, Hiele M, Geboes K et al (1995) Controlled trial of metronidazole treatment for prevention of Crohn's recurrence after ileal resection. *Gastroenterology* **108:** 1617–21
Rutgeerts P, D'Haens G, Targan S et al (1999) Efficacy and safety of retreatment with anti-tumor necrosis factor antibody (infliximab) to maintain remission in Crohn's disease. *Gastroenterology* **117:** 761–9
Sandborn W, Sutherland L, Pearson D et al (2000) Azathioprine or 6-mercaptopurine for inducing remission of Crohn's disease. Cochrane Database Syst Rev (2): CD000545
Sandborn WJ, Present DH, Isaacs KL et al (2003) Tacrolimus for the treatment of fistulas in patients with Crohn's disease: a randomized, placebo-controlled trial. *Gastroenterology* **125:** 380–8
Singleton JW, Hanauer SB, Gitnik GL et al (1993) Mesalamine capsules for the treatment of active Crohn's disease: results of a 16-week trial. Pentasa Crohn's Disease Study Group. *Gastroenterology* **104:** 1293–301
Steinhart AH, Ewe K, Griffiths AM et al (2001) Corticosteroids for maintaining remission of Crohn's disease. *Cochrane Database Syst Rev* (3): CD000301
Summers RW, Switz DM, Sessions JT et al (1979) National Cooperative Crohn's Disease Study: results of drug treatment. *Gastroenterology* **77:** 847–69
Sutherland LR (2000) Mesalamine for the prevention of post-operative recurrence: is nearly there the same as being there? *Gastroenterology* **118:** 436–8
Vasiliauskas EA, Kam LY, Abreu-Martin MT et al (1999) An open-label pilot study of low-dose thalidomide in chronically active, steroid-dependent Crohn's disease. *Gastroenterology* **117:** 1278–87