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# Therapeutic aspects of inflammatory bowel disease in children

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**Inflammatory bowel disease (IBD), namely Crohn's disease (CD), ulcerative colitis and indeterminate colitis in children commonly presents between the ages of 9 and 15 years, but can present at a younger age. Various therapeutic options are available and choice of treatment depends on confirmation of the type of IBD, distribution of disease, and associated presenting features such as weight loss or short stature or complications such as bowel stricture. Choice of treatment needs to be tailored to the individual child, taking into account the potential morbidity and practicalities of administration of the various medications, and requires co-operation of both the child and the parents. Treatment of children differs from adults in that it is important to monitor and maintain optimal growth and meet the psychological needs of childhood. This paper discusses various available therapeutic options and indications for their use.**

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## Introduction

Treatment of inflammatory bowel disease (IBD) namely Crohn's disease (CD), ulcerative colitis (UC) and indeterminate colitis (IC), consists of bringing active disease into remission followed by maintenance of remission and consequently prevention of relapse. Choice of treatment is dependent on confirmation of the type of IBD, distribution of disease and associated presenting features such as weight loss or short stature. It is important to recognise that the condition of IBD is life long. It is essential to balance the possible effects of immediate treatment against the potential long term morbidity of treatment, whilst at the same time attempting to bring the disease into remission as quickly as possible to reduce the potential morbidity associated with on-going active disease. Growth failure and pubertal delay are common serious complications, unique to young children who present with IBD, particularly those with CD[1].

There is consensus among members of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) working group on IBD, that children with suspected IBD should undergo an upper gastro-intestinal (GI) endoscopy and colonoscopy with intubation of terminal ileum with multiple biopsies taken from all segments of the upper (oesophagus, stomach, duodenum) and lower intestinal tract (ileum, caecum, ascending colon, transverse colon, descending colon, sigmoid and rectum) and diagnosis should be based on tissue histology (ESPGHAN. Recommendations for diagnosis

of IBD in children; to be published, personal communication).

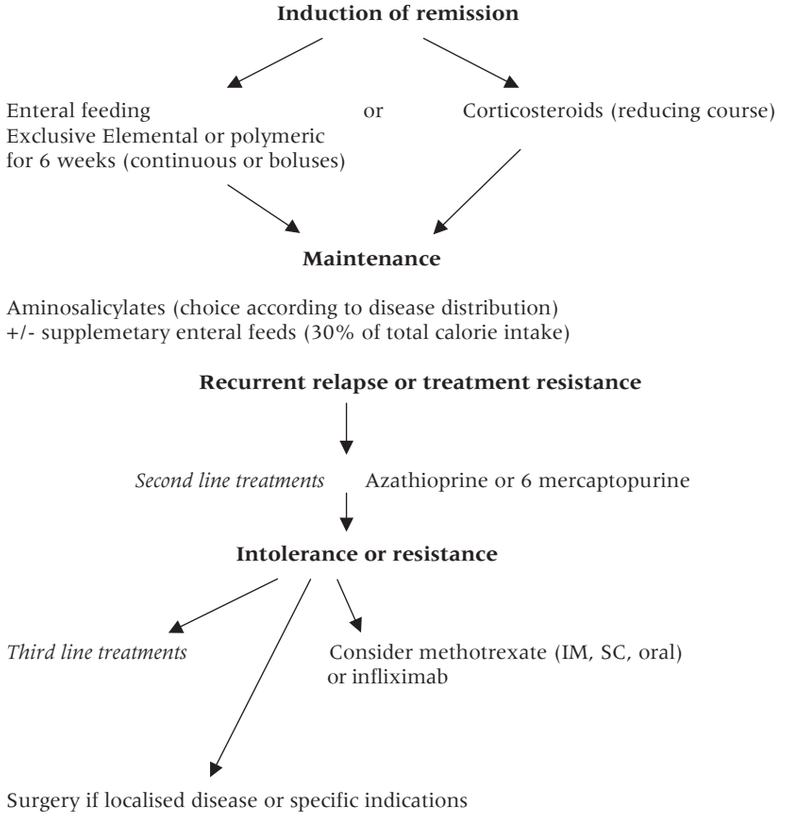
A barium meal and follow through should be performed in all children thought to have CD to evaluate the involvement of small bowel (Figure 1). Distribution of disease is important in aiding diagnosis particularly if pathognomic histological features are not present. Histological CD involving the upper GI tract can be present in up to 30% of cases even in the absence of upper GI symptoms and thus aid diagnosis[2]. Unlike adults, over 90% of children with UC have a pancolitis necessitating full colonoscopy for confirmation[3] (Figure 2). IC (approximately, 10% of cases of IBD) is the term used when histological evidence of inflammatory bowel disease localised to the colon is present but it is not possible to differentiate histologically between CD and UC and radiological evidence does not demonstrate involvement of small bowel. The majority of these cases behave like UC but a few later turn out to be CD. Once tissue diagnosis and disease distribution are documented, appropriate treatment can be chosen in a systematic way.

Ideally all children with suspected IBD should undergo investigation and management in a tertiary paediatric gastroenterology unit. The paediatrician in the local hospital should be involved as appropriate. Evaluation of treatment success depends on symptomatic clinical improvement, evidence of appropriate weight and height velocity, and biochemical remission, i.e. resolution of abnormal blood tests.

There are few randomised controlled drug trials in children for the treatment of IBD and evidence for efficacy of various medications and dosage, apart from enteral therapy, is based on adult literature only. Many of the medications are not licensed for children and do not come in a "child friendly" form, i.e. large tablets rather than liquid form. Application of medication is therefore dependent on the child's co-operation and the parents' willingness to administer the treatment. For instance, left sided colitis may be amenable to treatment with enemas but sometimes this may not be possible if the child does not co-operate.

An overall general approach to treatment is suggested in Figures 1 and 2 and the text below gives detailed information about each treatment.

**Figure 1** Crohn's disease treatment flow chart.



## Medication to induce remission

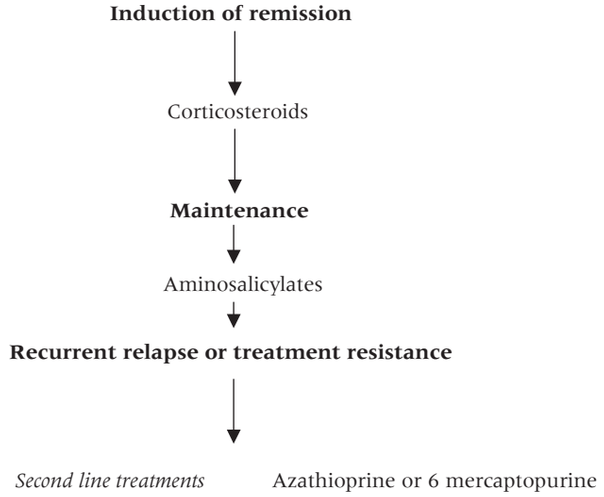
*Corticosteroids*

Corticosteroids are used extensively as primary treatment of active disease in both CD (Figure 1) and UC (Figure 2). Toxicity of corticosteroids is a significant consideration both in the short term (< 6 months) and the long term (> 6 months). Serious medical short term side effects include immunosuppression and potential increase in the risk of infection. In general, this risk does not seem to result in significant morbidity. However, young children in particular are at risk from varicella zoster (VZ, chickenpox) if not previously immune. Specific instructions need to be addressed in this instance and routine VZ serology should be taken at the time of diagnosis of IBD to confirm immune status. Courses of steroids may interfere with the immunisation schedule. Live vaccines should not be given at the time of or close to taking steroids and killed vaccines may not be taken up as efficiently whilst taking immunosuppressant medications.

Whilst there are a variety of other side effects to consider, the main one that usually bothers children, particularly adolescents, are those related to Cushingoid appearance such as weight gain, puffy cheeks, striae and acne. This can lead to non-compliance. Long term effects of steroid treatment are growth retardation, bone demineralisation and adrenal suppression. However, growth retardation can result from underlying uncontrolled IBD. It is not usually a major side effect of steroid treatment in the acute stage if the disease is brought into remission and the dose of steroids is reduced quickly. However, although steroid therapy leads to symptomatic relief and biochemical improvement there may be no concomitant endoscopic resolution in most patients[4]. Approximately, 20-36% patients with Crohns disease become steroid dependent and 20% are steroid resistant[5]. The toxicity of steroids restricts their use as maintenance therapy, although alternate day therapy if disease is in remission and dietary intake is adequate may not impair linear growth[6-9]. Children with CD seem more at risk from osteoporosis than those with UC[10]. Treatment with steroids at a young age may negatively influence future bone mass as an adult, because most of the bone loss occurs within the first 3 months of steroid use[11], although at this point some of the bone mass loss might be reversible with discontinuation of steroid treatment. However, cumulative steroid dose is

**Figure 2** Ulcerative colitis treatment flow chart.

Diagnosis of disease and disease distribution confirmed by histology following upper GI endoscopy and colonoscopy




**Specific Conditions**

| | |
|---|---|
| Acute toxic megacolon<br>Resistance to medical therapy | Surgery (consider cyclosporin) |
| Left sided/ distal colitis (UC) | Oral aminosalicylates +/-<br>Local treatment ie enemas (steroid or aminosalicylates) |

a significant predictor of reduced bone mass in children with IBD[12,13]. Those children with CD who used steroid treatment around the time of puberty have been shown to achieve lower adult height compared to those who did not[14]. At least 15% of children with IBD have decreased bone mineral density because of underlying active inflammation.

Remission is induced using prednisolone (2 mg/kg/day, maximum 60 mg/day). It is important that enough steroid therapy is used to suppress disease activity rapidly as ineffective lower doses may prolong the course of therapy and hence increase the risk of side effects. Remission rates following treatment with steroids are similar to those following treatment with enteral nutrition[15-18]. There is wide variation in how the dose of steroid treatment is reduced and the rate of reduction will depend on response of individual patients. Decrease in steroid dose is possible with continued clinical and biochemical remission.

If a prolonged course of prednisolone is necessary, alternate day therapy may be preferable as it is considered to have less long term side effects. However, there is no published evidence that alternate day prednisolone prevents relapse of disease, although in UC low dose steroid maintenance may maintain remission. With the addition of a second line agent it may be possible to reduce steroid therapy without alternate day tapering[19]. Initial intravenous administration of methylprednisolone may be necessary in those with severe CD or UC before changing to an oral preparation.

In view of the high morbidity related to the use of systemic steroids, new steroid formulations such as oral budesonide have been used. Budesonide is designed to be released in the terminal ileum and right colon and thus should only be used in CD where the disease activity is confined to these areas. Two multi-centre randomised controlled trials of budesonide vs oral prednisolone in children with active CD confined to ileo-caecal region or ascending colon have been performed[20,21]. Both trials confirmed that budesonide was as effective as oral prednisolone (remission rate 47–55% *vs* 50–75%). Side effects of steroids including adrenal suppression were fewer in the children receiving oral budesonide. There is no evidence for the use of budesonide in the treatment of UC.

*Enteral nutrition*

There are many benefits in considering enteral nutrition as first line treatment in children with acute CD. Children presenting with symptoms of CD for the first time or in relapse have invariably lost weight. Weight loss, delayed puberty and growth failure are common in children with CD[3,22,23]. This is usually because of chronic malnutrition (secondary to reduced intake) and persistent inflammation. Micronutrient deficiencies are also common which may favour disease perpetuation because of impairment of tissue repair mechanisms[24].

Nutritional supplementation has been demonstrated to restore altered body composition and reverse linear growth arrest[25-27]. Studies in children demonstrate that elemental feed not only restores weight loss and growth failure but induces biochemical and histological remission in CD[15]. Elemental diet was originally developed as part of the United States space programme to minimise bowel actions in orbit. Elemental diet consists of polypepetides (broken down proteins) and is generally formula derived, being sufficiently high in calories and balance with regards to daily mineral and vitamin requirements to sustain good weight gain when used exclusively with no solid food intake. It is not entirely clear how elemental feeds induce remission but proposed mechanisms are improvement of general condition, decreased gut motility, reduction of antigenic load and changes in bowel flora[28].

The other advantage of nutritional therapy compared to treatment with corticosteroids to induce remission is one of reduced morbidity or side effects of the corticosteroids such as osteopenia, short stature and Cushingoid features[29,30]. Randomised controlled trials have consistently shown that elemental diets achieve similar remission rates to corticosteroids[31,32]. Meta-analysis confirmed remission rates of approximately 80%, (range 50–92%) in both children and adults[33]. Initially, elemental diet (such as Elemental E028; Scientific Hospital Supplies, UK) was thought to be the best form of enteral feeding[34] but polymeric diet, such as Modulen IBD, when used exclusively also induces remission in active CD[35,36].

Controlled studies of elemental versus polymeric diets have not been performed but meta-analysis found no difference in efficacy. In five randomised clinical trials comprising of 147 children with CD, enteral therapy was as effective as corticosteroids at inducing remission RR = 0.95 (85% CI 0.67 – 1.34)[37]. Some paediatric studies have suggested that Crohn's colitis is refractory to treatment with elemental diet[15,38] and those that responded best had CD of the small bowel. Other studies have shown no difference in remission rates when using enteral feeding for either large or small bowel disease[16,17]. Meta-analysis found no significant difference.

Exclusive "feed" therapy is generally continued for a period of 6 weeks. Following this standard food can be re-started. Practices vary between hospitals from regrading, i.e. staged re-introduction of various food types such as dairy products, to no regrading but there is no substantive paediatric evidence for either practice. There is adult data showing that long chain triglycerides reduce the efficacy of enteral feeds in patients with active CD[39]. There may be a role for long term home maintenance treatment with supplemental overnight feeding. Patients receiving this appear to remain in remission for longer[40-42].

Exclusive enteral treatment is not used for the induction of remission of UC but has a general role in nutritional support in those children who are malnourished.

*Parenteral nutrition*

Parenteral nutrition in children is generally reserved for patients who are severely ill, e.g. suspicion of toxic megacolon, children unable to tolerate sufficient quantities of enteral supplementation or pre-operatively where enteral nutrition is not possible[1].

*Treatment of left sided / distal colitis*

Left sided/distal colitis is usually associated with UC, although it can occasionally be seen as part of the spectrum of CD. Unlike adults, left sided colitis is uncommon in children (<10% of UC cases)[3] and guidance for treatment is extrapolated from adult experience. In adults with distal UC or left sided colitis extending to the splenic flexure, topical aminosalicylates (e.g. Asacol foam enema®) in combination with oral aminosalicylates are considered first line treatment. Topical corticosteroids are thought to be less effective and are considered second line treatment for patients intolerant of topical aminosalicylates[43]. In children there is little evidence based medicine with regards to the treatment of left sided colitis but anecdotally predfoam enemas are generally more likely to be effective and easier to administer for the child and their parents than other forms of enemas. However, in many cases, a course of oral steroids is necessary to bring the disease into remission.

## Medication to maintain remission

*Aminosalicylates*

These have anti-inflammatory effects and are first line drugs in adults with IBD. However, as lone treatments, they are insufficient to induce remission in acute disease in the vast majority of children. They are used as regular daily medication to maintain remission. They have a direct effect locally on the mucosa rather than through systemic absorption. Sulphasalazine (Salzopyrin®) was the first aminosalicylate to be used in IBD. The active moiety is the 5-amino salicylate[44]. However, sulphasalazine is accompanied by a relatively high incidence of side effects (10–45%) in adults[45]. Nausea, dyspepsia, myalgia, arthralgia and headache are common, and usually attributed to the sulfapyridine moiety. Photosensitivity reaction and reversible sperm abnormalities can occur[46,47].

Hence, various new aminosalicylates based on the 5-amino moiety, known as "5-ASAs" or mesalazines were developed and designed to target different segments of the bowel via various controlled release formats such as pH[48]. Thus, when choosing an aminosalicylate it is important to consider the area of the bowel that needs to be targeted. It is one of the few times that the appropriate propriety named aminosalicylate is prescribed because of the different modes of action (Table 1). The format of the aminosalicylate is also a consideration in children. Sulphasalazine is the only product available as a liquid preparation, although not particularly palatable. Pentasa® tablets are large but dispersible in water, although not soluble.

It has been reported that children seem to tolerate mesalazines better than sulphasalazine[49,50]. Compared to literature available from adult studies there are only two paediatric trials reporting efficacy of mesalazine treatment, and both of these studies had small numbers[49,51]. Adult data supports the use of mesalazine in the induction and maintenance of remission in UC but has documented minimal effect in CD[52-55]. It is unusual to be able to induce remission in children with UC with mesalazine alone (50–100 mg/kg/day). This may be partly due to the fact that most children have a pancolitis but also because pharmacokinetic studies have not been performed in children and the appropriate dose may be higher. Mesalazine has been shown to perhaps have a role in maintaining remission in

**Table 1** Sites of delivery of different aminosalicylates

| Drug | Release mechanism | Site of delivery |
|---|---|---|
| Sulphasalzine/ Salazopyrin® | Bacterial cleavage | Colon |
| **Mesalazine** | | |
| Asacol® | pH > 7 | Colon +/- terminal ileum |
| Salofalk® | pH > 6 | Colon + ileum |
| Pentasa® | Time-dependent | Colon + ileum + jejunum |
| Olsalazine (Dipentum)® | Bacterial cleavage | Colon |
| Balsalazide (Colazide)® | Bacterial cleavage | Colon |

Crohn's ileitis or after surgically induced remission of isolated small bowel disease[56-58]. Appropriate doses in children are not known and one can only extrapolate from experience in adults. The overall trend is to use doses between 50 and 100 mg/kg/day in children[50,51].

## Second line immunosuppressive treatments

*Azathioprine or 6 mercaptopurine (thiopurines)*

Azathioprine and 6 mercaptopurine (MP) are interchangeable but the former is preferred in Europe, whereas 6 MP is more commonly used in North America. They are the most commonly used second line immunomodulators in IBD. Purine anti-metabolites inhibit ribonucleotide synthesis, but the mechanism of immunomodulation is by inducing T cell apoptosis by modulating cell signalling. Azathioprine is rapidly absorbed and converted into 6 MP which then undergoes rapid intracellular transformation into the active metabolite 6-thioguanine.

A second pathway mediated by the enzyme thiopurine methyl transferase (TPMT) influences the metabolism of 6 MP to produce 6-methylmercaptopurine rather than 6-thioguanine. Difference in activity of TPMT enzyme may explain why some patients are predisposed to azathiopurine/6 MP induced cytotoxicity whereas others are refractory to therapy. However, evidence that TPMT activity predicts side effects is limited and there is no agreement as to whether TPMT levels should be measured as routine prior to starting either medication[45,59].

Both agents have a slow onset of action (minimum 3–4 months) and need to be used in combination with other first line therapies such as corticosteroids or nutritional therapy to achieve acute control of active disease. The main indication for use is as a steroid sparing agent primarily in those who are resistant to or dependent on corticosteroids in both UC and CD. The dose of azathioprine is 2–3 mg/kg/day (single dose) and for 6 MP is 1–1.5 mg/kg/day (single dose).

Approximately 70% of children with CD were able to discontinue corticosteroids within 6 months of starting azathioprine[59,60]. In one randomised multicentre, placebo controlled trial with 6 MP conducted over 18 months, relapse in children receiving 6 MP was considerably less (6%) compared to controls on placebo (47%). The overall long term remission rate (at 18 months) was 89% (6 MP) *vs* 39% (placebo). In addition, none of the children receiving 6 MP became steroid dependent, compared with 50% of controls[61]. It also has a role in post-operative prophylaxis of complex (fistulating or extensive) CD[54] and perianal CD[62].

Duration of treatment in both CD and UC should be over years as relapse is common if treatment is stopped within the first year. In general, patients in remission are reassessed endoscopically and histologically for disease activity after 4 years, with a view to discontinuation of treatment.

Clearly, safety of these immunosupressant drugs in children is of great concern. The main concern is of bone marrow suppression. This occurs in 2–5% of patients and is often an idiosyncratic reaction (irrespective of TPMT levels)[63,64] occurring anywhere between 2 weeks and 11 years. Patients are advised to have a full blood count (FBC) checked weekly for the first 6 weeks and 2–3 monthly thereafter. It is important, however, to stress that if the patient feels unwell at any time a FBC should be checked. In addition, monitoring of FBC is helpful in adjusting the dose, as a degree of lymphopenia is desired.

Frequently, nausea and headache occur within the first month of treatment, which may necessitate dose reduction and gradual increase. In one study of 95 children, side effects were seen in 28% and azathioprine or 6 MP had to be discontinued in 18% of cases because of persisting intolerance. Pancreatitis (3–15%)[65] and hepatitis[15] can also occur and should be considered, particularly if symptoms of abdominal pain develop[66]. Concern with regards to development of malignancy in children on long term therapy is unknown but not supported by current literature[67-71] and the benefits of treatment are likely to outweigh the risks.

Some physicians have suggested that use of azathioprine/6 MP should be considered as part of the initial phase of treatment in CD because of its potential steroid sparing benefits but this remains controversial in view of the rare but significant side effects. Unfortunately, there appears to be no prognostic indicators that help identify which children would benefit. However, early use should be considered in those children where steroid tapering proves difficult or in those with recurrent early relapse, thus reducing the significant morbidity associated with prolonged steroid treatment.

*Methotrexate*

Experience with methotrexate (MTX) in children with IBD is limited, although it has been used for some time in the treatment of juvenile rheumatoid arthritis (JCA). Consideration of potential side effects including liver fibrosis in

particular, is of concern although this appears less of a problem than initially thought[72-76]. In comparison to treatment in JCA, intramuscular or subcutaneous administration of MTX rather than oral treatment is thought to be more beneficial in CD especially in those with small bowel CD, in whom absorption of MTX is variable.

The most common side effects are gastrointestinal such as nausea, stomatitis and diarrhoea (7%). Headaches, dizziness, fatigue (16%) and mood alterations may occur[77]. Many of these side effects can be reduced by supplemental folic acid therapy. Pulmonary toxicity, primarily interstitial pneumonitis may also occur irrespective of duration of treatment or dose of MTX.

MTX is indicated in adults for the treatment of active or relapsing CD refractory to or intolerant of azathioprine or 6 MP[72,78,79] and has been demonstrated to be effective in inducing remission in active CD. It has a steroid sparing role in CD but has no benefit in patients with UC. Treatment in children should be considered in similar circumstances, i.e. where conventional therapy has failed or in those children who are suffering significant morbidity from other therapies. There is increasing evidence documenting the efficacy and safety of weekly MTX in the induction of remission and maintenance of remission in children with CD[80,81]. Careful monitoring of FBC (myelotoxicity) and liver function tests is required. Surveillance liver biopsy is not indicated[73]. Unlike azathioprine, MTX is teratogenic.

*Cyclosporin*

Cyclosporin, an immunosuppressive agent initially developed as an anti-rejection medication following transplantation, is an inhibitor of calcineurin, preventing clonal expansion of T-cell subsets. In UC, high dose intravenous cyclosporin has been shown in a single randomised controlled trial to be effective for induction of remission in patients with severe colitis[82]. Several non-controlled trials in children with severe acute refractory UC have demonstrated clinical remission in up to 80% of cases when cyclosporin was added to high dose steroids[83-85]. However, when used in high doses concern exists with regard to toxicity of cyclosporin such as acute and chronic renal disease, neurotoxicity (convulsions) and opportunistic infections, particularly if used in combination with corticosteroids and azathioprine. Hypertrichosis and paraesthesia are minor side effects, which generally respond to dose reduction.

Because of the risk of developing the above side effects, continuation of cyclosporin beyond 6 months is not encouraged and it should be used as a bridge to azathioprine/6 MP therapy. In addition, it seems that although the initial response is high and fast (within 2–3 weeks), withdrawal of the drug frequently leads to relapse and thus only serves to delay colectomy in this group of severe UC patients[82,85]. However, this delay may be extremely useful and may avoid the need for emergency colectomy giving time for the child and family to come to terms psychologically with the illness and any future surgery[86]. A meta-analysis of trials in adults showed no benefit of cyclosporin in CD[87-89]. However, closure of refractory fistulas in patients with CD, may respond to intravenous or high dose (> 5 mg/kg/day) oral cyclosporin with sustained closure in 55% patients[90,91].

*Anti-tumour necrosis factor α antibody (infliximab)*

Infliximab is a chimeric anti-tumour necrosis factor (TNF) monoclonal antibody with potent anti-inflammatory effects. Numerous controlled trials in adults have demonstrated efficacy of infliximab in both active and fistulating CD[92-96]. Maintenance of remission can be achieved by regular infusions every 8 weeks[94]. Studies in children have been performed, (although none have been controlled trials and numbers are small) which confirm efficacy of infliximab in inducing remission in active CD and maintenance of remission[97-99]. A dose of 5 mg/kg was found to be the most effective[97]. One study showed that in children with refractory CD of short duration (< 2 years) the clinical response to one infusion of infliximab lasted longer than in children with "late" CD[100].

However, in view of limited information on possible long term effects of infliximab such as development of lymphoma, the routine use of infliximab cannot be justified. The National Institute of Clinical Excellence (NICE) (www.nice.org.uk) has produced guidelines for the use of infliximab in adults. Its recommended use is limited to patients with severe active CD refractory to or intolerance of steroids and other immunosuppression in whom surgical treatment is not appropriate. Sepsis is of major concern and active sepsis, for example an abscess, is an absolute contra-indication for use. In adults, the reactivation or development of tuberculosis has been reported and all patients should be screened for tuberculosis prior to treatment. Infliximab treatment in children must only be embarked upon under specialist guidance and supervision. Careful documentation of efficacy, side effects and long term follow up in children is essential.

There is increasing evidence that patients receiving recurrent infusions of infliximab are likely to

become refractory to treatment. All patients should receive an immunomodulator (azathioprine, 6 MP, methotrexate) if tolerated as these probably extend the interval between infusions and reduce the development of antibodies to infliximab[92]. Preliminary reports of infliximab use in adults and children with moderate to severe steroid refractory UC have been encouraging but have not led to routine recommendation for consideration of treatment in UC as in CD[101,102].

## Surgical treatment

*Ulcerative colitis*

In children, surgery is indicated for those who do not respond to medical treatment, either because of development of acute severe toxic megacolon, chronic steroid resistance or steroid dependent disease non-responsive to azathioprine or 6 MP. Total colectomy is curative. However, there is associated morbidity and mortality, especially in those who are acutely unwell and not in good nutritional status. The decision to operate should be made jointly by a paediatric gastroenterologist and a paediatric surgeon.

Surgery in children commonly involves formation of a temporary ileostomy with rectal mucosectomy followed by endorectal ileoanal pull-through and anastomosis performed as a two stage process. Children who undergo surgery adapt to having an ileostomy well, particularly as frequently they improve from a disease point of view. The second stage is performed as an elective procedure at least 3 months later. Post-operatively, it is not unusual for them to experience an increase in bowel movements as the small bowel takes time to adapt. In some, usually older children, a pouch is formed by creation of a distal ileal reservoir usually in a J shape. This is thought to help with post-operative continence, although inflammation of the pouch or "pouchitis" is a cumulative risk of up to 45% over a 10 year period[103]. The aetiology of pouchitis is unknown but various treatments such as metronidazole, mesalazine enemas, oral or topical corticosteroids, short chain fatty acid enemas or VSL#3 probiotic therapy may be helpful, although some cases can be quite resistant and difficult to treat.

Most studies have shown an increasing cancer incidence with time in patients with long standing, uncontrolled UC (approximately 10% greater incidence than the general population at 10 years)[104]. Thus, in adults, long standing disease or epithelial dysplasia of rectal and colonic mucosa is an indication for elective colectomy. Some children presenting with UC at a young age < 5years[3] will therefore only be in teenagers 10 years later. The role of colonoscopy surveillance for this group of people needs to be considered.

*Crohn's disease*

Unlike UC, in which disease activity is limited to the colon and surgery is curative, no definitive surgery exists for CD. Poor healing, post-operative complications and risk of recurrence of CD elsewhere mean that careful consideration for surgery is needed. Indication for surgery is reserved for acute and chronic complications of CD refractory to medical or nutritional therapy. Specific indications for surgery include intestinal obstruction, fistula, abscess, uncontrolled severe haemorrhage, toxic megacolon and perforation.

In children growth failure due to medically refractory, active localised disease of the terminal ileum or colon may be an indication for surgery[105,106]. Resection should be conservative and limited to macroscopic disease. CD will almost inevitably recur post surgery if patients are followed for long enough, just as with medical relapses. Approximately 50% of patients may require further surgery at 10 years. Additional post-operative medical therapy with mesalazine may delay recurrence, although the effect is thought to be minimal and remains controversial[58,107]. Azathioprine may have a better effect but the risk of potential side effects needs to be balanced. Thus prophylaxis post surgery remains controversial and further studies are needed.

## Other treatments

*Antibiotics*

The effect of antibiotics in the treatment of IBD is thought to be by altering the bacterial flora in the intestine, which is considered to play a role in the pathogenesis of inflammation[108]. The most frequently used antibiotic is metronidazole in the treatment of CD[109,110], although no controlled trials have been performed in children. In an open labelled study in children with perianal CD, improvement in disease control was seen during the 6 months of treatment but approximately 50% relapsed within one month of stopping treatment[111]. Metronidazole has been shown to be helpful in induction and maintenance of remission in pouchitis in adults[112]. However, side effects, in particular severe nausea, are common. Peripheral neuropathy is associated with long term use of metronidazole (> 6 months) and may not be reversible despite discontinuation of medication[113]. Wide spectrum intravenous antibiotics form part of the treatment of patients with severe acute colitis (fulminant colitis or toxic megacolon).

*Probiotics*

Probiotics are live micro-organisms that confer a health benefit by altering the indigenous bacterial microflora. They may do this is a number of ways; by altering the actual gut microflora by competitive interaction with indigenous population of bacteria, production of antimicrobial metabolites, or modulation of the local immune response to enteric bacteria[114]. Many children and parents are very keen to pursue this line of treatment rather than more conventional therapy. However, their efficacy in treatment or maintenance of remission in IBD is uncertain, although few studies have suggested clinical improvement in children with mild CD[115,116]. Two recent studies showed probiotic VSL#3 therapy to be effective in the treatment and prevention of pouchitis[117,118]. In summary, research into the role of probiotics and the treatment of IBD is of increasing interest but as yet still ill defined, although they may be useful as adjunctive therapy in maintaining disease remission.

## Conclusions

IBD in children is a chronic condition with 739 new cases in the UK per year (incidence of 5.2/100,000) and variable morbidity. Prompt and accurate diagnosis together with appropriate treatment will help in minimising short and long term effects of both disease and treatments. Optimal management usually requires a combination of nutritional and psychological support, medical treatment and appropriate surgical management where necessary. In CD there is considerable evidence that enteral therapy (elemental or polymeric) should be considered over corticosteroids as first line treatment, following which maintenance therapy should be introduced. Early introduction of second line immunosuppressives such as azathiopurine or 6 MP should be added, in order to reduce morbidity associated with prolonged courses of corticosteroids. Ongoing treatment depends on clinical response to medications but alternative third line treatments or surgery may be indicated.

The mainstay of treatment in children with UC is corticosteroids. Remission is generally induced by steroid treatment followed by maintenance therapy with an aminosalicylate. As above early introduction of second line immunosuppressives should be considered. Surgery is curative in UC but because of significant morbidity and mortality should be reserved for children who present with acute, severe colitis resistant to medical treatment or those with medically resistant chronic disease at risk of significant morbidity of treatment.

The aim of treatment is to minimise morbidity of disease whilst controlling exacerbations of disease and supporting the child and family in achieving as normal a life as possible. In children, additional challenges are to achieve optimal growth and pubertal development whilst preventing long term side effects of treatment. The child with IBD has to come to terms with living with the effects of having a chronic disease. Amongst many, these include missing school because of recurrent illness or frequent hospital visits, embarrassing symptoms, altered physical appearance and dealing with unpleasant investigations and treatments. Hence, management and treatment options for each child are decided on an individual basis. The shortage of controlled clinical trials means that doses and drug regimes are based on extrapolation of knowledge from adult experience. Further studies including the development of new drugs to treat IBD in children need to be considered. Involvement of the child and family in decisions about treatment is important and likely to improve compliance. For these specific reasons, the child with IBD needs to be under the care of an experienced multidisciplinary paediatric gastroenterology team, which includes a paediatric dietician, paediatric IBD nurse specialist, psychologist, paediatric gastroenterologist and a paediatric surgeon with a special interest in GI surgery. It is important that shared care arrangements are established with the local paediatrician to ensure that the child and family receive optimal management with the least inconvenience.

## References


1. Motil KJ, Grand RJ. Inflammatory Bowel Disease. In: Walker WA, Watkins JB eds. Nutrition in Pediatrics. 2nd edn. Hamilton, Ontario: B.C Decker, 1997: pp. 516-533.
2. Lenaerts C, Roy CC, Vaillancourt M et al. High incidence of upper gastrointestinal tract involvement in children with Crohn's disease. Pediatrics 1989; 83: 777-781.
3. Sawczenko A, Sandhu BK. Presenting features of inflammatory bowel disease in Great Britain and Ireland. Arch Dis Child 2003; 88: 995-1000.
4. Beattie RM, Nicholls SW, Domizio P et al. Endoscopic assessment of the colonic response to corticosteroids in children with ulcerative colitis. J Pediatr Gastroenterol Nutr 1996; 22: 373-379.
5. Munkholm P, Langholz E, Davidsen M et al. Frequency of glucocorticoid resistance and dependency in Crohn's disease. Gut 1994; 35: 360-362.
6. Sadeghi-Nejad A, Senior B. The treatment of ulcerative colitis in children with alternate-day corticosteroids. Pediatrics 1969; 43: 840-845.
7. Whitington PF, Barns HV, Bayless TM. Medical management of Crohn's disease in adolescence. Gastroenterology 1977; 72: 1338-1344.
8. Wales JK, Milner RD. Variation in lower leg growth with alternate day steroid treatment. Arch Dis Child 1988; 63: 981-983.

9. Fernando del Rosario J, Orenstein SR, Neigut DA et al. Retrospective analysis of alternate-day prednisone maintenance therapy for Crohn's disease. Clin Pediatr 1998; 37: 413-419.
10. Schoon EJ, Wolffenbuttel BHR, Stockbrugger RW. Osteoporosis as a risk in inflammatory bowel disease. Drugs Today 1999; 35: 17-28.
11. Hodsman AB, Toogood JH, Jennings B et al. Differential effect of inhaled budesonide and oral prednisone in serum osteocalcin. J Clin Endocrinol Metab 1991; 72: 530-540.
12. Gokhale R, Favus MJ, Karrison T et al. Bone mineral density assessment in children with inflammatory bowel disease. Gastroenterology 1998; 114: 902-911.
13. Boot AM, Bouquet J, Krenning EP et al. Bone mineral density and nutritional status in children with chronic inflammatory bowel disease. Gut 1998; 42: 188-194.
14. Alemzadeh N, Rekers-Mombarg LT, Mearin ML et al. Adult height in patients with early onset of Crohn's disease. Gut 2002; 51: 26-29.
15. Sanderson IR, Udeen S, Davies PS et al. Remission induced by an elemental diet in small bowel Crohn's disease. Arch Dis Child 1987; 62: 123-127.
16. Seidman EG, Griffiths AM, Jones A et al. Semi elemental diet versus prednisone in the treatment of active Crohn's disease in children and adolescents (abstract). Gastroenterology 1993; 104: 778.
17. Ruuska T, Savilahti E, Maki M et al. Exclusive whole protein enteral diet versus prednisolone in treatment of acute Crohn's disease in children. J Pediatr Gastroenterol Nutr 1994; 19: 175-180.
18. Thomas AG, Taylor F, Miller V. Dietary intake and nutritional treatment in childhood Crohn's disease. J Pediatr Gastroenterol Nutr 1993; 17: 75-81.
19. Leichtner AM, Jackson DW, Grand RJ. Crohn's disease. In Walker WA, Durie PJ, Hamilton JR, Walker-Smith JA, Watkins JB eds. Pediatric Gastrointestinal Disease. 2nd ed. Mosby-year book inc. 1996: 692-708.
20. Levine A, Weizman Z, Broide E et al. A comparison of budesonide and prednisone for the treatment of active pediatric Crohn's disease in children. J Pediatr Gastroenterol Nutrition 2003; 36: 248-252.
21. Escher JC, European Collaborative research group on Budesonide in Paediatric IBD. Budesonide versus prednisolone for the treatment of active Crohn's disease in children: a randomized, double-blind, controlled multicenter trial. Eur J Gastroenterol Hepatol 2004; 16: 47-54.
22. Spray C, Debelle GD, Murphy MS. Current diagnosis, management and morbidity in paediatric inflammatory bowel disease. Acta Paediatr 2001; 90: 400-405.
23. Ballinger AB, Savage MO, Sanderson IR. Delayed puberty associated with inflammatory bowel disease. Pediatr Res 2003; 53: 205-210.
24. Miralles-Barrachina O, Savoye G, Belmonte-Zalar L et al. Low levels of glutathione in endoscopic biopsies of patients with Crohn's colitis: the role of malnutrition. Clin Nutr 1999; 18: 313-317.
25. Motil KJ, Grand RJ, Maletskos CJ et al. The effects of disease, drug and diet on whole body protein metabolism in adolescents with Crohn's disease and growth failure. J Pediatr 1982; 101: 345-351.
26. Motil KJ, Grand RJ, Matthews DE et al. Whole body leucine metabolism in adolescents with Crohn's disease and growth failure during nutritional supplementation. Gastroenterology 1982; 82: 1359-1368.
27. Motil KJ, Altchuler SI, Grand RJ. Mineral balance during nutritional supplementation in adolescents with Crohn's disease and growth failure. J Pediatr 1985; 107: 473-479.
28. Klein S, Alpers DH, Grand RJ et al. Advances in nutrition and gastroenterology: summary of the 1997 A.S.P.E.N. Research Workshop. JPEN J Parenter Enteral Nutr 1998; 22: 3-13.
29. Griffiths AM, Nguyen P, Smith C, MacMillan H, Sherman PM. Growth and clinical course of children with Crohn's disease. Gut 1993; 34: 939-943.
30. Canalis E. Mechanisms of glucocorticoid action in bone: implications to glucocorticoid-induced osteoporosis. J Clin Endocrinol Metab 1996; 81: 3441-3447.
31. Griffiths AM, Ohlsson A, Sherman PM et al. Meta-analysis of enteral nutrition as a primary treatment of active Crohn's disease. Gastroenterology 1995;108:1056-1067.
32. O'Morain C, Segal AW, Levi AJ. Elemental diet as primary treatment of acute Crohn's disease: a controlled study. BMJ 1984; 228: 1859-1862.
33. Fernandez-Banares F, Cabre E, Esteve-Comas M, Gassull MA. How effective is enteral nutrition in inducing remission inactive Crohn's disease? A meta-analysis of the randomised clinical trials. JPEN J Parenter Enteral Nutr 1995; 19: 356-364.
34. Russell RI. Elemental diets. Gut 1975;16: 68-79.
35. Giaffer MH, North G, Holdsworth CD. Controlled trial of polymeric versus elemental diet in the treatment of active Crohn's disease. Lancet 1990; 335: 816-819.
36. Rigaud D, Cosnes J, Le Quintrec Y et al. Controlled trial comparing two types of enteral nutrition in treatment of active Crohn's disease: elemental vs polymeric diet. Gut 1991; 32: 1492-1497.
37. Heuschkel RB, Menache CC, Megerian JT et al. Enteral nutrition and corticosteroids in the treatment of acute Crohn's disease in children. J Pediatr Gastroenterol Nutr 2000; 31: 8-15.
38. Wilschanski M, Sherman P, Pencharz P et al. Supplementary enteral nutrition maintains remission in paediatric Crohn's disease. Gut 1996; 38: 543-548.
39. Middleton SJ, Rucker JT, Kirby GA, Riordan AM, Hunter JO. Long-chain triglycerides reduce the efficacy of enteral feeds in patients with active Crohn's disease. Clin Nutr 1995; 13: 229-236.
40 Knight CJ, El-Matary W, Spray C, Sandhu BK. Long-term outcome of enteral nutrition as primary therapy for Crohn's disease. Clin Nutr (in press)
41 Wilchanski M, Sherman P, Pencharz P et al. Supplementary enteral nutrition maintains remission in paediatric Crohn's disease. Gut 1996; 38: 543-548.
42 Seidman E, Jones A, Issenman R et al. Relapse prevention/growth enhancement in paediatric Crohn's disease: a multicenter randomised controlled trial of intermittent enteral nutrition versus alternate day prednisone (abstract). J Pediatr Gastroenterol Nutr 1996; 23: 344.
43. Carter MJ, Lobo AJ, Travis SPL. Guidelines for the management of inflammatory bowel disease. Gut 2004; 53: V7-V8.
44. Azad Khan AK, Piris J, Truelove SC. An experiment to determine the active therapeutic moiety of sulphasalazine. Lancet 1977; 2: 892-895.
45. Escher JC, Taminiau JAJM, Nieuwenhuis EES, Buller HA, Grand RJ. Treatment of inflammatory bowel disease in childhood: Best available evidence. Inflamm Bowel Dis 2003; 9: 34-58.

46. Hanauer SB. Medical therapy for ulcerative colitis. In: Kirsner JB, ed Inflammatory Bowel Disease. 5th edn. Philadelphia: WB Saunders Company, 2000: 529-556.
47. Zimmerman MJ, Jewell DP. Cytokines and mechanisms of action of glucocorticoids and aminosalicylates in the treatment of ulcerative colitis and Crohn's disease. Aliment Pharmacol Ther 1996; 10: 93-98.
48. Steinhart AH. Is mesalazine useful for treating Crohn's disease? In: Jewell DP, Warren BF, Mortensen NJ, eds. Inflammatory Bowel Disease. Oxford: Blackwell Science Ltd, 2001: pp. 99-109.
49. Barden L, Lipson A, Pert P et al. Mesalazine in childhood inflammatory bowel disease. Aliment Pharmacol Ther 1989; 3: 597-603.
50. D'Agata ID, Vanounou T, Seidman E. Mesalamine in paediatric inflammatory bowel disease: a 10-year experience. Inflamm Bowel Dis 1996; 2: 229-235.
51. Griffiths A, Koletzko S, Sylvester F et al. Slow-release 5-aminosalicylic acid therapy in children with small intestinal Crohn's disease. J Pediatr Gastroenterol Nutr 1993; 17: 186-192.
52. Sutherland L, Roth D, Beck P et al. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev 2000; 2: CD000543
53. Sutherland L, Roth D, Beck P et al. Oral 5-aminosalicylic acid for maintaining remission in ulcerative colitis. Cochrane Database Syst Rev 2000; 2: CD000544
54. Singleton J. Second trial of mesalamine therapy in the treatment of active Crohn's disease. Gastroenterology 1994; 107: 632-633.
55. Mahida YR, Jewell DP. Slow-release 5 aminosalicylic acid (Pentasa) for the treatment of active Crohn's disease. Digestion 1990; 45: 88-92.
56. Sutherland L, Martin F, Bailey RJ et al. A randomised, placebo-controlled, double blind trial of mesalamine in the maintenance of remission of Crohn's disease. Gastroenterology 1997; 112: 1069-1077.
57. International Mesalazine Study Group. Coated oral 5-aminosalicylic acid versus placebo in maintaining remission of inactive Crohn's disease. Aliment Pharmacol Ther 1990; 4: 55-64.
58. Camma C, Guinta M, Rosselli M et al. Mesalamine in the maintenance treatment of Crohn's disease: a meta-analysis adjusted for confounding variables. Gastroenterology 1997; 113: 1465-1473.
59. Verhave M, Winter HS, Grand RJ. Azathioprine in the treatment of children with inflammatory bowel disease. J Pediatr 1990; 117: 809-814.
60. Markowitz J, Rosa J, Grancher K et al. Long-term 6 mercaptopurine in Crohn's disease. Gastroenterology 1990; 99: 1347-1351.
63. Markowitz J, Grancher K, Kohn N et al. A multicenter trial of 6-mercaptopruine and prednisone in children with newly diagnosed Crohn's disease. Gastroenterology 2000; 119: 895-902.
62. Jeshion WC, Larsen KL, Jawad AF et al. Azathioprine and 6-mercaptopurine for the treatment of perianal Crohn's disease in children. J Clin Gastroenterol 2000; 30: 294-298.
63. Colombel JF, Ferrari N, Debuysere H et al. Genotypic analysis of thiopurine S-methyltransferase in patients with Crohn's disease and severe myelosuppression during azathioprine therapy. Gastroenterology 2000; 118: 1025-1030.
64. Lennard L, Gibson BE, Nicole T et al. Congenital thiopurine methyltransferase deficiency and 6-mercaptopurine toxicity during treatment for acute lymphoblastic leukaemia. Arch Dis Child 1993; 69: 577-579.
65. Hanauer SB, Kane SV. The pharmacology of anti-inflammatory drugs in inflammatory bowel disease. In: Bayless TM, Hanauer SB, eds. Advanced therapy of inflammatory bowel disease. Lewiston NY: B.C Decker 2001: pp. 510-528.
66. Kirschner BS. Safety of azathioprine and 6-mercaptopurine in pediatric patients with inflammatory bowel disease. Gastroenterology 1998; 115: 813-821.
67. Present DH, Meltzer SJ, Krumholz MP et al. 6-mercaptopurine in the management of inflammatory bowel disease: short and long term toxicity. Ann Intern Med 1989; 111: 641-649.
68. Larvol L, Soule JC, Le Tourneau A. Reversible lymphoma in the setting of azathioprine therapy for Crohn's disease. N Engl J Med 1994; 331: 883-884.
69. Connell WR, Kamm MA, Dickson M et al. Long-term neoplasia risk after azathioprine treatment in inflammatory bowel disease. Lancet 1994; 343: 1249-1252.
70. Lewis JD, Schwartz JS, Lichtenstein GR. Azathioprine for maintenance of remission in Crohn's disease: benefits outweigh the risk of lymphoma. Gastroenterology 2000; 118: 1018-1024.
71. Carter MJ, Lobo AJ, Travis SP, IBD Section, British Society of Gastroenterology. Guidelines for the management of inflammatory bowel disease. Gut 2004; 53: V1-V16.
72. Alfdhli AA, McDonald JW, Feagan BG. Methotrexate for induction of remission in refractory Crohn's disease (Cochrane Review). Cochrane Database Syst Rev 2003; 1: CD003459.
73. Te HS, Schiano TD, Kuan SF et al. Hepatic effects of long-term methotrexate use in the treatment of inflammatory bowel disease. Am J Gastroenterol 2000; 95: 3150-3156.
74. Lenmann M, Zenjari T, Bouhnik Y et al. Methotrexate in Crohn's disease: long-term efficacy and toxicity. Am J Gastroenterol 2000; 95: 1730-1734.
75. Weinblatt ME. Methotrexate for chronic diseases in adults. N Engl J Med 1995; 332: 330-331.
76. Aker AM, Funch D, Dreyer NA et al. Determinants of serious liver disease among patients receiving low-dose methotrexate for rheumatoid arthritis. Arthritis Rhem 1993; 36: 329-335.
77. Feagan BG, Rochan J, Fedorak RN et al. Methotrexate for the treatment of Crohn's disease. The North American Crohn's Study for Group Investigators. N Engl J Med 1995; 332: 292-297.
78. Feagan BG, Fedorak RN, Irvine EJ et al. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. The North American Crohn's Study for Group Investigators. N Engl J Med 2000; 342: 1627-1632.
79. Fraser AG. Methotrexate: first or second line immunomodulator? Eur J Gastroenterol Hepatol 2003; 15: 225-231.
80. Wilson D, Pieterse L, Rogers P et al. Induction of remission by methotrexate in azathioprine – resistant Crohn's disease (abstract). J Pediatr Gastroenterol Nutr 2003.
81. Rawat D, Furman M, Fagbemi A et al. Use of methotrexate in childhood Crohn's disease (abstract). J Pediatr Gastroenterol Nutr 2003.
82. Lichtiger S, Present DH, Kornbluth A et al. Cyclosporin in severe ulcerative colitis refractory to steroid therapy. N Engl J Med 1994; 330: 1841-1845.
83. Ramakrishna L, Langhans N, Calenda K et al. Combined use of cyclosporin and azathioprine or 6-mercaptopurine in pediatric inflammatory bowel disease. J Pediatr Gastroentrol Nutr 1995; 28: 54-58.

84. Benkov KJ, Rosh JR, Schwersenz AH et al. Cyclosporin as an alternative to surgery in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 1994; 19: 290-294.
85. Teem WR,Cohen J, Davis PM et al. Cyclosporine for the treatment of fulminant ulcerative colitis in children. Immediate response, long-term results and impact on surgery. Dis Colon Rectum 1995; 38: 474-479.
86. Nicholls SW, Domizio P, Williams CB et al. Cyclosporin as initial treatment of Crohns disease. Arch Dis Child 1994; 71: 243-247.
87. Feagan BG. Cyclosporin has no proven role as a therapy for Crohn's disease. Inflamm Bowel Dis 1995; 1: 335-339.
88. Stange EF, Modigliana R, Pena AS et al. European trial of cyclosporine in chronic active Crohn's disease: a 12 month study. The European Study Group. Gastroenterology 1995; 109: 774-782.
89. Jewell DP, Lennard-Jones JE, the Cyclosporin Study Group of Great Britain and Ireland. Oral cyclosporine for chronic active Crohn's disease: a multicenter controlled trial. Eur J Gastroenterol Hepatol 1994; 6: 499-505.
90. Hanauer SB, Smith MB. Rapid closure of Crohn's disease fistulas with continuous intravenous cyclosporin A. Am J Gastroenterol 1993; 88: 646-649.
91. Present DH, Lichtiger S. Efficacy of cyclosporin in treatment of fistula of Crohn's disease. Dig Dis Sci 1994; 39: 374-380.
92. Rutgeerts P, Van Assche G, Vermieire S. Optimising anti-TNF treatment in inflammatory bowel disease. Gastroenterology 2004; 126: 1593-1610.
93. Targan SR, Hanauer SB, van Deventer SJ et al. A short term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. N Engl J Med 1997; 337: 1029-1035.
94. Hanauer SB, Feagan BG, Lichtenstein GR et al. Maintenance for infliximab for Crohn's disease; the ACCENT 1 randomised trial. Lancet 2002; 359: 1541-1549.
95. Present DH, Rutgeerts P, Targan S et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999; 340: 1398-1405.
96. Sands BE, Anderson FH, Bernstein CN et al. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med 2004; 350: 876-885.
97. Baldassano R, Vasiliauskas E, Braegger CP et al. A multicenter study of infliximab (anti-TNF alpha antibody) in the treatment of children with active Crohn's disease (abstract). Gastroenterology 1999; 116: A665.
98. Hyams JS, Markowitz J, Wyllie R. Use of infliximab in the treatment of Crohn's disease in children and adolescents. J Pediatr 2000; 137: 192-196.
99. Serrano MS, Schmidt-Sommerfeld E, Kilaugh TJ et al. Use of infliximab in pediatric patients with inflammatory bowel disease. Ann Pharmacol Ther 2001; 35: 823-828.
100. Kugathasan S, Werlin SL, Martinez A et al. Prolonged duration of response to infliximab in early but not late pediatric Crohn's disease. Am J Gastroenterol 2000; 95: 3189-3194.
101. Sands BE, Tremaine WJ, Sandborn WJ et al. Infliximab in the treatment of severe, steroid-refractory ulcerative colitis: a pilot study. Inflamm Bowel Dis 2001; 7: 83-88.
102. Chey W, Hussain A, Ryan C et al. Infliximab is an effective therapeutic agent for ulcerative colitis (abstract). Gastroenterology 2000; 95: A230
103. Penna C, Dozois R, Tremaine W et al. Pouchitis after ileal pouch-anal anastomosisfor ulcerative colitis occurs with increased frequency in patients with associated primary sclerosing cholangitis. Gut 1996; 38: 234-239.
104. Lennard-Jones JE, Morson BC, Ritchie JK et al. Cancer surveillance in ulcerative colitis: experience over 15 years. Lancet 1983; 2: 149-152.
105. Sentongo TA, Stettler N, Christian A et al. Growth after intestinal resection for Crohn's disease in children, adolescents and young adults. Inflamm Bowel Dis 2000; 6: 265-269.
106. Shand WS. Surgical therapy of chronic inflammatory bowel disease in children. Baillieres Clin Gastroenterol 1994; 8: 149-180.
107. Lochs H, Mayer M, Fleig WE et al. Prophylaxis of postoperative relapse in Crohns disease with mesalamine. European Cooperative Crohn's Disease Study VI. Gastroenterol 2000; 118: 264-273.
108. Sartor RB. Antibiotics as therapeutic agents in Crohn's disease. In: Bayless TM, Hanauer SB eds. Advanced Therapy of Inflammatory Bowel Disease. Lewiston, NY: BC Decker, 2001: 359-362.
109. Hildebrand H, Berg NO, Hoevels J, Ursing B. Treatment of Crohn's disease with metronidazole in childhood and adolescence. Evaluation of a six months trial. Gastorenterol Clin Biol 1980; 4: 19-25.
110. Grand RJ, Ramakrishna, Calenda KA. Therapeutic strategies for paediatric Crohn's disease. Clin Invest Med 1996; 19: 373-380.
111. Bernstein LH, Frank MS, Brandt LJ et al. Healing of perianal Crohn's disease with metronidazole. Gastroenterology 1980; 70: 599.
112. Sandborn WJ, McLeod R, Jewell DP. Medical therapy for induction and maintenance of remission in pouchitis: a systematic review. Inflamm Bowel Dis 1999; 5: 33-39.
113. Duffy LF, Daum F, Fisher SE et al. Peripheral neuropathy in Crohn's disease patients treated with metronidazole. Gastroenterology 1985; 88: 681-684.
114. Shanahan F. Probiotics and inflammatory bowel disease: is there a scientific rationale? Inflamm Bowel Dis 2000; 6: 107-115.
115. Kruis W, Schutz E, Fric P et al. Double-blind comparison of an oral Escherichia coli preparation and mesalazine in maintaining remission of ulcerative colitis. Aliment Pharmacol Ther 1997; 11: 853-858.
116. Rembacken BJ, Snelling AM, Hawkey PM et al. Non-pathogenic Escherichia coli versus mesalazine for the treatment of ulcerative colitis: a randomised trial. Lancet 1999; 354: 635-638.
117. Gionchetti P, Rizello F, Venturi A et al. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind placebo-controlled trial. Gastroenterology 2000; 119: 305-309.
118. Gionchetti P, Rizello F, Helwig U et al. Prophylaxis of pouchitis onset with probiotic therapy: a double blind, placebo-controlled trial. Gastroenterology 2003; 124: 1202-1209.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# *Paediatric and Perinatal Drug Therapy*

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