Clinical Review

Treatment of Inflammatory Bowel Disease in Childhood: Best Available Evidence

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Summary: The physician treating children with inflammatory bowel disease is confronted with a number of specific problems, one of them being the lack of randomized, controlled drug trials in children. In this review, the role of nutritional therapy is discussed with a focus on primary treatment, especially for children with Crohn’s disease. Then, the available medical therapies are highlighted, reviewing the evidence of effectiveness and side effects in children, as compared with what is known in adults. Nutritional therapy has proven to be effective in inducing and maintaining remission in Crohn’s disease while promoting linear growth. Conventional treatment consists of aminosalicylates and corticosteroids, whereas the early introduction of immunosuppressives (such as azathioprine or 6-mercaptopurine) is advocated as maintenance treatment. If these drugs are not tolerated or are ineffective, methotrexate may serve as an alternative in Crohn’s disease. Cyclosporine is an effective rescue therapy in severe ulcerative colitis, but only will postpone surgery. A novel strategy to treat Crohn’s disease is offered by infliximab, a monoclonal antibody to the proinflammatory cytokine tumor necrosis factor (TNF)-α. Based on the best-available evidence, suggested usage is provided for separate drugs with respect to dosage and monitoring of side effects in children. Key Words: Review—Therapy—Children—Inflammatory bowel disease—Enteral nutrition.

INTRODUCTION

Therapy for inflammatory bowel disease (IBD, ulcerative colitis, and Crohn’s disease) is designed for induction of remission of disease activity, maintenance of remission, and prevention of relapse. In children, normal growth and pubertal development are additional indicators of successful treatment or sustained remission.

No matter what therapeutic strategy is studied, measures are needed to define endpoints objectively. Although inflammatory disease may be in remission clinically, there may not be endoscopic or mucosal healing. In children with IBD, clinical and endoscopic remission do not correlate very well (1). In this study, 20 children with active ulcerative colitis were assessed before and after 8 weeks of medical therapy with 5-aminosalicylic acid (5-ASA) derivatives and oral prednisolone (1–2 mg/kg/day, maximum 40 mg). Eighteen of the children showed clinical improvement on therapy, and 17 (85%) showed complete remission by 8 weeks. Reassessment of the colon after treatment showed an improved endo-
In adults with Crohn’s disease, reliable indices of the patients’ overall response to interventions that reflect the physician’s global assessment are the Crohn’s Disease Activity Index (CDAI), the Harvey-Bradshaw Index, and the van Hees Index (2). The CDAI is used most commonly and includes both subjective reporting of complaints and abnormalities in laboratory or physical examination (3). In children, the Pediatric Crohn’s Disease Activity Index (PCDAI), which also includes evaluation of longitudinal growth, is valuable for drug trials (4) along with CDAI for comparison. Both CDAI and PCDAI reflect disease activity in pediatric Crohn’s disease, but the PCDAI has been shown to discriminate better between levels of disease severity (5). In ulcerative colitis, no pediatric activity index exists, and various colitis activity indices are used to reflect clinical disease severity (6–13). When response to a certain therapy is studied, disease activity scores are useful, but, in general, the scores do not help the clinician determine the appropriate intervention.

The physician treating children with IBD is confronted with a number of specific problems. First, delay in longitudinal growth or pubertal development should be evaluated at the time of initial presentation and during the course of treatment, because impairment of longitudinal growth is a sensitive marker of persistent inflammatory activity. In children, the goal of treatment is not only remission of disease activity, but also the promotion of growth and development. Second, not only severity, but nature, localization, and extent of disease must be carefully assessed to establish an appropriate treatment plan that may consist of a combination of nutritional treatment (or supplementation), drug therapy, and possibly surgery. At diagnosis, children with ulcerative colitis are reported to have more extensive disease than adults (pancolitis in 29% versus 16%) (14). Because choice of treatment (nutritional, medical, or surgical) and treatment delivery (systemic or local) may depend on disease type and location, it is very important to assess type, site, and extent of disease at diagnosis. Third, in pediatric patients, who may face lifelong chronic disease, long-term effects of treatments are of particular concern. Fourth, noncompliance is an important problem, especially in adolescents.

Unfortunately, only a few randomized, controlled, drug trials in children with IBD have been published. To our knowledge, only one placebo-controlled trial has been performed in children with IBD (15). This is regrettable because a variable but considerable placebo response is reported in adults depending on the study, partly reflecting spontaneous healing. Clinical practice is often guided by extrapolation from studies of adult patients; pediatric gastroenterology awaits more evidence produced from pharmacokinetic studies and clinical trials in children.

There is reason for optimism because some of the major impediments (e.g., financial, legal) for pediatric studies are now being eliminated. The 1997 Food and Drug Administration Modernization Act (FDAMA) has a “pediatric exclusivity provision” that provides 6 months exclusivity (or patent protection) to manufacturers in return for conducting pediatric studies. Additionally, the 1999 Food and Drug Administration (FDA) Pediatric Rule mandates pharmaceutical companies to perform a pediatric assessment of every new drug (except when a waiver is granted), and of marketed drugs that are used in a substantial number of pediatric patients. This assessment should consist of “adequate studies to characterize the safety and effectiveness of a drug or biological product for the claimed indications in all relevant subpopulations” (16).

In this review, we discuss first the role of nutritional therapy with a focus on primary treatment, especially for children with Crohn’s disease. We then highlight the available medical therapies, reviewing the literature for evidence of effectiveness and side effects in children, as compared with what is known in adults.

Based on the “best available” evidence, suggested usage is provided for separate drugs with respect to dosage and monitoring of side effects in children.

**PARENTERAL NUTRITION**

In adults and children, parenteral nutrition is generally reserved for patients with serious illness or preoperative situations. Pediatric patients who are unable to tolerate sufficient quantities of enteral supplementation because of active inflammatory disease and diarrhea have been shown to benefit considerably from total parenteral alimentation (TPN) (17). Prolonged parenteral support may be required in children with intractable Crohn’s disease to induce remission (18). In addition, TPN with or without oral feedings is of value in improving the nutritional status of children or adolescents with IBD as demonstrated by weight gain or reversal of growth arrest (19–23). These beneficial effects occurred irrespective of whether there was an amelioration of clinical symptoms. The greatest successes of TPN in Crohn’s disease have been reported in children (21,24,25) who had no rectal bleeding and who were administered the treatment at home (HPN).
**ENTERAL NUTRITION**

Elemental diets, originally developed as part of the United States space program to minimize bowel actions in orbit, were initially thought to be best for all forms of enteral feeding (26). While there are theoretical advantages to elemental formulas (27–30), a meta-analysis could not show a distinct value of these compared with polymeric preparations (31). Proposed mechanisms of action are improvement of general condition, decreased gut motility, reduction of antigenic load, and changes in bowel flora, as reviewed elsewhere (32). In addition, the liquid nature of the diet (and its ease of transport through diseased or narrowed small bowel) may in itself be responsible for the effect (33). Lastly, in severely painful perianal disease, elemental feeding can minimalize fecal output while maintaining a good nutritional status.

Protein-energy malnutrition is reported in up to 85% of adult patients hospitalized with exacerbations of IBD (34), and in 23% of outpatients with Crohn’s disease (35). In children with IBD, chronic malnutrition (mainly caused by reduced nutritional intake) and persistent inflammation are responsible for growth failure. A decrease in height velocity is reported even before the onset of intestinal symptoms in almost half of pediatric Crohn’s disease patients (36). Weight loss is documented in approximately 85% of children with CD, and in 65% with UC at time of diagnosis (37). When enteral nutrition was first used, it either was seen as treatment of malnutrition in children with Crohn’s disease (30,38) or as nutritional rehabilitation in adult patients in preparation for intestinal surgery (27). Currently, there is intense debate among pediatric gastroenterologists regarding the primary role of enteral nutrition in the treatment of IBD in children. In contrast, there is strong indication for the adjunctive or supplementary use of enteral support considering the common growth retardation observed in children with IBD and the relatively short period of time available to treat linear growth failure before epiphyseal plates are closed.

**Evidence in Children**

Growth failure represents a common, serious complication unique to the pediatric age group of IBD patients. Nutritional deficiencies, caused by inadequate dietary intake in relation to overall nutrient requirements, seem to be a major factor related to growth failure in children and adolescents with Crohn’s disease (17).

Nutritional supplementation has been demonstrated to restore altered body composition and reverse linear growth arrest (39–41), confirming earlier studies showing that resumption of growth in children with Crohn’s disease and severe growth failure can be achieved by a 6-week course of continuous elemental enteral alimentation (38) or by intensive dietary consultation and oral supplementation (42). In a controlled trial of exclusive elemental diet versus high-dose steroids in 17 children with active Crohn’s disease of the small intestine, linear growth (assessed from height velocity over 6 months) was significantly greater in the children receiving an elemental diet (43). Also, in children with quiescent Crohn’s ileitis or ileocolitis, the nocturnal administration of an elemental formula (50–80 kcal/kg/night) monthly every 4 months over a 1-year period resulted in significantly higher height increments (7.0 ± 0.8 cm, representing 126% of ideal height change, predicted for the 50% percentile according to bone age) in the diet group compared with a control group, treated by conventional medical therapy (1.7 ± 0.8 cm, representing 29% of ideal height change) (30). Another study confirmed improved growth velocity after an elemental diet for 4 weeks, despite a greater increase in energy intake in a group of children receiving high-dose steroids (44).

In addition to its positive effect on growth, nutritional therapy has been advocated as primary therapy for disease activity in children with Crohn disease. The effect of nutritional treatment on Crohn’s disease activity in children has been assessed in numerous studies and is summarized in Table 1. Mean remission rates after enteral nutrition or steroids are similar, approximately 85%, as described in a recent meta-analysis of seven pediatric clinical trials (45) (five randomized (43,44,46–48), two unrandomized (49,50)). Controlled studies of elemental versus polymeric nutrition have not been performed in children with active Crohn’s disease, but a meta-analysis found no difference in efficacy (45). In children with active Crohn’s disease, remission rate after enteral nutrition was higher (86%) in children with new-onset disease as compared with those with recurrent-relapse disease (50%) (47).

Two pediatric studies have suggested that Crohn’s colitis is refractory to treatment with enteral nutrition (43,51), which has resulted in the deliberate exclusion of children with Crohn’s colitis from controlled trials. In patients with small bowel disease, remission was of longer duration if induced by an elemental diet (compared to steroids), whereas in patients with colonic disease, steroid-induced remission lasted longer than diet-induced remission (52). In contrast, available data from other pediatric (47,48) and from larger adult studies (53–55) suggest that large and small bowel disease respond equally well to nutritional therapy. For large and small bowel disease, none of the meta-analyses in children or...
<table>
<thead>
<tr>
<th>Study</th>
<th>Reference</th>
<th>Diet Description</th>
<th>Design</th>
<th>n^a</th>
<th>Disease Duration</th>
<th>Disease Location</th>
<th>Remission Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morin 1982</td>
<td>29</td>
<td>E, NG</td>
<td>U</td>
<td>10</td>
<td>new onset</td>
<td>all sites</td>
<td>100% at wk 3</td>
</tr>
<tr>
<td>Navarro 1982</td>
<td>56</td>
<td>E, NG</td>
<td>U</td>
<td>17</td>
<td>NS</td>
<td>all sites</td>
<td>NS (all cases improved clinically during first 2 mo)</td>
</tr>
<tr>
<td>O’Morain 1983</td>
<td>277</td>
<td>E, Oral (except 1, NG)</td>
<td>RC</td>
<td>15</td>
<td>NS</td>
<td>all SB, 5 SB/C</td>
<td>82% at wk 4</td>
</tr>
<tr>
<td>Seidman 1986a</td>
<td>278</td>
<td>E, NG</td>
<td>RC</td>
<td>9</td>
<td>new onset</td>
<td>all sites</td>
<td>77% at wk 3</td>
</tr>
<tr>
<td>Sanderson 1987</td>
<td>43</td>
<td>E, NG</td>
<td>RC</td>
<td>9</td>
<td>new onset</td>
<td>SB</td>
<td>88% at wk 6</td>
</tr>
<tr>
<td>Bell 1988</td>
<td>30</td>
<td>E, NG, nocturnal, intermittent (1 of 4 mo)</td>
<td>NC</td>
<td>8</td>
<td>NS</td>
<td>NS</td>
<td>NS; decrease in CDAI and daily prednisone intake</td>
</tr>
<tr>
<td>Seidman 1991a</td>
<td>46</td>
<td>E, NG</td>
<td>RC</td>
<td>10</td>
<td>new onset</td>
<td>all sites</td>
<td>80% at wk 3</td>
</tr>
<tr>
<td>Polk 1992</td>
<td>279</td>
<td>SE, NG, nocturnal, intermittent (1 of 4 mo)</td>
<td>U</td>
<td>6</td>
<td>relapsed</td>
<td>all sites</td>
<td>NS; decrease in CDAI and daily prednisone intake</td>
</tr>
<tr>
<td>Thomas 1993</td>
<td>44</td>
<td>E, oral (except 1, NG)</td>
<td>RC</td>
<td>12</td>
<td>new onset/relapsed</td>
<td>all sites</td>
<td>NS; increase in LSI in 100% at wk 4</td>
</tr>
<tr>
<td>Seidman 1993a</td>
<td>47</td>
<td>SE, NG</td>
<td>RC</td>
<td>34</td>
<td>new onset/relapsed</td>
<td>all sites</td>
<td>New onset: 86% at wk 4; Recurrent: 50% at wk 4</td>
</tr>
<tr>
<td>Beattie 1994</td>
<td>280</td>
<td>P (TGB-B rich), oral (except 2, NG)</td>
<td>U</td>
<td>7</td>
<td>new onset</td>
<td>mostly SB</td>
<td>NS; all improved LSI at wk 8; histological remission in 2/7</td>
</tr>
<tr>
<td>Breese 1994</td>
<td>49</td>
<td>E, P</td>
<td>U</td>
<td>9</td>
<td>NS</td>
<td>all sites</td>
<td>63%; histological remission in 5/9</td>
</tr>
<tr>
<td>Ruuska 1994</td>
<td>48</td>
<td>P, NG, daytime</td>
<td>RC</td>
<td>10</td>
<td>new onset/relapsed</td>
<td>all sites</td>
<td>90% at wk 8</td>
</tr>
<tr>
<td>Chafai 1995a</td>
<td>50</td>
<td>SE</td>
<td>NC</td>
<td>14</td>
<td>new onset</td>
<td>NS</td>
<td>100% at wk 12–15</td>
</tr>
<tr>
<td>Papadopoulou 1995</td>
<td>52</td>
<td>E, NG, oral</td>
<td>UR</td>
<td>19</td>
<td>NS</td>
<td>all sites</td>
<td>In 25/30 (83%) episodes within 6 wk</td>
</tr>
<tr>
<td>Khoshoosh 1996</td>
<td>281</td>
<td>E, NG, high-fat vs. low-fat</td>
<td>RC</td>
<td>14</td>
<td>relapsed</td>
<td>all sites</td>
<td>NS</td>
</tr>
<tr>
<td>Wilschanski 1996</td>
<td>51</td>
<td>E, SE, NG, nocturnal</td>
<td>UR</td>
<td>65</td>
<td>9 new onset, 56 relapsed</td>
<td>all sites</td>
<td>74% at 0.5–2.5 mo</td>
</tr>
<tr>
<td>Fell 2000</td>
<td>282</td>
<td>P (TGB-B rich), oral</td>
<td>U</td>
<td>29</td>
<td>new onset/relapsed</td>
<td>all sites</td>
<td>79% at wk 8</td>
</tr>
<tr>
<td>Akobeng 2000</td>
<td>283</td>
<td>P (rich vs. low glutamine), oral (except 5)</td>
<td>RC</td>
<td>18</td>
<td>new onset/relapsed</td>
<td>all sites</td>
<td>55.5% vs. 44.4% at wk 4</td>
</tr>
<tr>
<td>Phylactos 2001</td>
<td>284</td>
<td>P (TGB-B rich), oral</td>
<td>U</td>
<td>14</td>
<td>new onset/relapsed</td>
<td>all sites</td>
<td>93% at wk 8</td>
</tr>
</tbody>
</table>

^a Number of patients treated with (or randomized to receive) enteral nutrition.
a, abstract; E, elemental; NG, nasogastric tube; U, uncontrolled; NS, not stated; RC, randomized controlled; SB, small bowel; SB/C, small bowel and colon; NC, nonrandomized controlled; CDAI, Crohn’s Disease Activity Index; SE, semielemental; P, polymeric; LSI, Lloyd-Still activity index (reference 285); UR, uncontrolled retrospective.
adults have been able to detect differences in speed of remission induction or time to first relapse.

Long-term remission has been reported in pediatric Crohn’s patients who used an exclusive oligopeptide diet for up to 7 months (56); however, apart from the fact that long-term exclusive enteral nutrition and avoidance of a normal diet is an unreasonable therapeutic option, relapse occurred once the diet was discontinued. In a retrospective study, 60% of patients with an enteral nutrition-induced remission relapsed 12 months after cessation of enteral nutrition, and the patients who continued nocturnal supplementary feeding remained in remission longer (51). A randomized, controlled trial of cyclical diet therapy (exclusive semi-elemental diet for 4 weeks during each 16-week period) versus low-dose alternate-day prednisone (0.33 mg/kg every other day) as maintenance therapy of Crohn’s disease for 80 weeks revealed that the children receiving diet therapy had significantly fewer relapses and markedly increased growth velocity (57).

Evidence in Adults

The largest controlled trial of enteral nutrition versus drug treatment in active Crohn’s disease is the European Cooperative Crohn’s Disease Study IV (54), which showed clinical remission rates of 53% and 85% in patients on enteral nutrition or corticosteroids and sulfasalazine, respectively. These results contradicted earlier reports from smaller trials (58–61) that failed to detect a difference in response rate. Sufficient studies of the efficacy of enteral nutrition have been performed in adults to permit meta-analysis, and three have been published (31,62,63). In all three meta-analyses, corticosteroid therapy was found to be superior to elemental diet in achieving initial remission, even when drop-outs (because of unpalatability of elemental diet) were excluded. The studies show remission rates ranging from 53–80% after nutritional treatment, while placebo-response rates extracted from adult controlled clinical trials range from 18–42% (53,64–66). Enteral nutrition as maintenance treatment in Crohn’s disease has not been very successful (67).

Side Effects

When compared with corticosteroid therapy, enteral nutrition has an obvious lack of side effects. Nutrition can be administered orally, by nasogastric infusion, or by a gastrostomy tube, depending on the type and quantity of formula and the patient’s tolerance. Adverse treatment-related symptoms including loose stools, nausea, and night-time awakening (during nocturnal feeding) are common. Reversible diarrhea secondary to too rapid administration of the formula is the most common complication associated with intragastric feeding (17). In one of the meta-analyses, intolerance to liquid diets averaged 21% overall (ranging from 0–41%), but was greatest in trials in which oral administration was attempted (31). Nevertheless, in one pediatric study, more than half of the children who had experienced both corticosteroids and enteral nutrition stated a preference for liquid diet therapy, 24% considered them equally tolerable or intolerable, and 22% preferred prednisone (51).

Summary

In adults, enteral feeding is not as effective as corticosteroids as primary treatment of Crohn’s disease; however, there is mounting evidence supporting the use of enteral feeding in children, especially in those with new-onset Crohn’s disease. With enteral feeding, nutrition is improved, and growth and pubertal development can be promoted, while avoiding the systemic toxicity of corticosteroid therapy. There is insufficient evidence to prefer elemental nutrition over polymeric feeding, or to withhold nutritional treatment from children with Crohn’s colitis. Enteral nutrition may promote maintenance of remission in children with Crohn’s disease.

Based on the current evidence from the many studies in children, the summary in Table 2 seems a reasonable approach to the use of enteral nutrition in pediatric patients with Crohn’s disease.

AMINOSALICYLATES

The aminosalicylates, sulfasalazine (SASP) and 5-aminosalicylic acid (5-ASA, mesalamine or mesalazine), are first-line drugs that have modest anti-inflammatory effects. Mesalazine seems to be effective locally within the mucosa rather than through systemic absorption, and various delivery systems have been designed to optimize this characteristic (68). Aminosalicylates have been shown to alter a number of cellular functions relevant to inflammation (69). The dominant effect seems to be the inhibition of the lipoxygenase pathway of arachidonic acid metabolism, in particular production of leukotriene B4, which is a potent chemotactic factor. Other potential mechanisms of action have been reviewed elsewhere (70).

Experience in Children

Data regarding the pharmacokinetics in children are limited to three studies. Goldstein et al. measured plasma levels of sulfapyridine in 15 children with IBD, treated...
TABLE 2. Enteral nutrition as primary treatment of Crohn’s disease in children

<table>
<thead>
<tr>
<th>INDICATIONS</th>
<th>17,29,30,43,44,46–48,50–52,56,277–280,282</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth failure</td>
<td>30,38–41,43,44</td>
</tr>
<tr>
<td>Maintenance of remission</td>
<td>(51,56,57)</td>
</tr>
</tbody>
</table>

**REGIMEN FOR INDUCTION OF REMISSION**
- Exclusive polymeric feeding. 
- Calories and protein: 140%–150% RDA for height and age. 

**REGIMEN FOR MAINTENANCE OF REMISSION**
- When maintenance treatment: nasogastric tube or consider PEG (286–288).
- Nocturnal feeding (5/7 nights/wk) or intermittent daytime exclusive (1 mo of 4).

**CHECK DURING TREATMENT**
- If possible, assess REE
- Anthropometrics (height, weight, skin folds, pubertal stage)
- After instruction in hospital, child can continue nutritional therapy at home.
- Instruct patients to insert tube at night and remove in morning.
- PEG: Before placement, endoscopic examination and biopsy of stomach are necessary to assure that there is no evidence of gastric Crohn’s disease. (17)

References are given in parentheses.

RDA, required daily amount; PEG, percutaneous endoscopic gastrosynezy; REE, resting energy expenditure.

with sulfasalazine, and concluded that a dose of 1.5 to 2.0 g/m² of sulfasalazine can be safely administered (71). Two other studies focused on the pharmacokinetics of mesalazine (72,73). The study by Tolia et al. evaluated plasma levels and urinary excretion of mesalazine in four children with IBD (72); however, neither showed a significant difference compared with data obtained in adults.

Children seem to tolerate mesalazine better than sulfasalazine; symptoms of nausea and vomiting occurred more frequently during treatment with sulfasalazine compared with mesalazine (74). In 153 children treated with 5-ASA for a mean of 14.5 months, there were no severe adverse reactions (75). In a study of 26 children with Crohn’s ileocolitis, renal function was not different in children receiving sulfasalazine, compared with controls (76). Case reports have documented rare side effects of mesalazine in pediatric patients: pancreatitis (77,78), hepatotoxicity (79,80), interstitial nephritis (81) and pericarditis (82). In sulfasalazine hypersensitivity (with symptoms like rash, fever, hives, arthralgia, or hepatitis), desensitization has shown to be successful in approximately 56% of children (83).

In contrast to the abundant literature regarding efficacy of mesalazine in adult IBD patients, only two pediatric trials have been reported. A double-blind, placebo-controlled cross-over trial in children (n = 14) demonstrated a clinical and dose-related benefit of oral mesalazine (Pentasa, Shire Pharmaceuticals Group, PLC, Florence, KY, U.S.A.) in children with active small bowel Crohn’s disease (15), but this slight benefit was seen only in the six patients who completed the 20-week study. High drop-out and low recruitment rates required the study to be terminated before the accrual of the proposed 24 patients.

In children with mild to moderate ulcerative colitis, a multicenter, randomized, double-blind study compared the safety and efficacy of olsalazine (30 mg/kg/day) to sulfasalazine (60 mg/kg/day) (84). The estimated number of patients needed to show a significant difference in side effects was 90 in each group, but because of slow enrollment, recruitment of patients had to be stopped at 59 patients. Clinical remission was achieved in about 80% of the sulfasalazine-treated patients at 1, 2, and 3 months, whereas the response was around 45% in the olsalazine group at the same time points. According to the authors, the poorer efficacy of olsalazine may have been because of the low dose of olsalazine given. Side effects (such as headache, nausea, vomiting, rash, pruritis, increased diarrhea, and fever) occurred in about 40% of patients in both groups. There have been no controlled trials of efficacy of mesalazine maintenance treatment in children with IBD. Results from the earlier mentioned study by Barden et al. (74) suggest equivalent efficacy of mesalazine and sulfasalazine in maintaining remission in either ulcerative or Crohn’s colitis. Though hardly supported by evidence from controlled trials, the overall trend is to use high-dose mesalamine (up to 50–100 mg/kg/day) in children (15,75). This trend most likely is related to reports demonstrating the benefits of higher doses of 5-ASA in the treatment of IBD in adults, unaccompanied by an increase in side effects (65,85).

**Evidence of Efficacy in Adults**

Adult studies clearly demonstrate the efficacy of sulfasalazine and mesalazine in the induction and maintenance of remission in ulcerative colitis (86–88). In ileocolonic or colonic Crohn’s disease, sulfasalazine is still a very useful initial therapy in adults (64). In active Crohn’s disease, the majority of trials in adults have failed to show a clear beneficial effect of mesalazine (89–91). Mesalazine has no role in the maintenance of remission in adult CD (92–94), except in ileitis or after surgically induced remission of isolated small bowel disease, when 5-ASA maintenance treatment may give a slight reduction of relapse risk (92,95,96).

**Side Effects**

Sulfasalazine therapy is accompanied by a relatively high incidence of side effects, ranging from 10–45% of
patients. The most common side effects are related to intolerance (mostly attributed to the sulfapyridine moiety) and include nausea, dyspepsia, myalgias or arthralgias, and headache. Hypersensitivity (i.e., rash, fever) can occur as a reaction to the sulfapyridine component (common) or the mesalamine component (rare) (68,97). Reversible sperm abnormalities are common in males. A primary advantage of the newer 5-ASA formulations over sulfasalazine is improved tolerance (98). Of the sulfasalazine-intolerant patients, 80% are able to tolerate mesalazine (99). The 5-ASA drugs are more costly, however, and have been shown to cause dose-unrelated adverse effects in 14–24% of patients (100).

Summary

The aminosalicylates, so effective in ulcerative colitis, have shown minimal efficacy at best in maintaining remission in Crohn’s disease.

In the treatment of pediatric IBD, fear of side effects and successful marketing has caused mesalazine to be more popular than sulfasalazine. Sulfasalazine, however, is cheaper than mesalazine and can be administered more easily to children as a suspension rather than a large tablet.

CORTICOSTEROIDS

Along with sulfasalazine and the 5-ASA preparations, corticosteroids are extensively used as a primary treatment of both Crohn’s disease and ulcerative colitis. Corticosteroids were the first medications to be systematically studied in patients with inflammatory bowel disease and have been the mainstay of therapy of inflammatory bowel disease for many years. Although steroid therapy causes obvious symptomatic relief, there is no concomitant endoscopic improvement in most patients. In the Group d’Etude Therapeutique des Affections Inflammatoires Digestives study (GETAID), of all patients in clinical remission (after treatment with prednisolone 1 mg/kg/day for 3–7 weeks), only 29% actually achieved true endoscopic remission (101). Corticosteroids have a variety of effects on immune function that are likely to contribute to their therapeutic efficacy. Their mechanism of action has been reviewed elsewhere (69, 102,103). The toxicity of corticosteroids is a major drawback to their use; about 20–36% of patients with Crohn’s disease become steroid-dependent and 20% are steroid-resistant (104).

New steroid formulations such as budesonide aim at maximizing the mucosal effects while minimizing systemic exposure. In short-term use, they are associated with fewer side effects than corticosteroids. Prolonged administration of similar inhaled compounds in children with asthma has shown to effect growth rate (105). The reduction in growth velocity was shown to be transient (106), and adult height was unaffected (107).

Evidence in Children

In an open trial of oral prednisolone (1 mg/kg/day, 40 mg maximum) combined with mesalazine in 20 children with active ulcerative colitis, clinical remission was achieved in 85% of the patients (1). Colonoscopy was performed at 8 weeks, showing endoscopic remission in eight patients (40%) and full histologic remission in only three patients (15%). No controlled trials of steroids versus placebo have been performed in children. The efficacy of steroids compared with enteral nutrition in children with Crohn’s disease, however, has been studied in several trials (43,44,46–48), as was discussed in the section on enteral nutrition. In these trials, 84% of children receiving steroids achieved clinical remission, but the incidence of steroid-associated complications was not reported. Very recently, two multicenter, randomized, controlled trials of budesonide versus prednisolone in children with active Crohn’s disease (localized to ileocecal region or ascending colon) have been completed (108,109). Both trials have not been able to show a statistically significant difference in efficacy of budesonide (remission rate 47–55%) compared with prednisolone (remission rate 50–71%), but glucocorticosteroid-associated side effects and adrenal suppression were clearly fewer in the group of children receiving budesonide. Severe hypokalemia (110) and benign intracranial hypertension (108) have been described in children on oral budesonide treatment. Preliminary results from a trial of budesonide enemas in children with ulcerative colitis are encouraging (111).

In children, the long-term side effects of glucocorticosteroid treatment such as bone demineralization and growth retardation are a particular drawback to its use. At least 15% of children with inflammatory bowel disease have decreased bone mineral density (112), and cumulative corticosteroid dose is a significant predictor of reduced bone mass in these patients (36,112). Administration of calcium and vitamin D has been demonstrated to improve bone mineral density in children with rheumatic disease receiving corticosteroid therapy (113). Growth retardation can be a side effect of steroid treatment and undertreatment of inflammation (114,115). Linear growth is usually normal with use of the alternate-day regimen if the disease is quiescent and dietary intake is adequate (116–120); however, randomized, controlled
studies have not been performed and alternate-day corticosteroid therapy probably is not recommended long-term. In a small retrospective study, subnormal height velocity was observed in six prepubertal children receiving budesonide maintenance treatment (121). The implications of these initial observations are unclear because height velocity was already impaired before treatment in all but one child, and calculation of PCDAI demonstrated ongoing mild disease activity in two patients.

Evidence of Efficacy in Adults

The majority of patients with moderate to severe ulcerative colitis benefit from the administration of oral or parenteral corticosteroids (122,123). A dose-ranging trial proved 40–60 mg/day of oral prednisone to be more effective than 20 mg/day, though 60 mg/day was associated with increased toxicity without significant clinical improvement (124).

In Crohn’s disease, the clinical effectiveness to induce remission has been demonstrated clearly (53,64,125–127). Comparison of a short (7 weeks) versus a long (15 weeks) course of steroids showed similar remission rates of approximately 85% (128). Remission rates during treatment with the newer corticosteroid budesonide were 50–53%, numerically less but not significantly different compared with prednisolone; cortisol depression and side effects were higher with prednisolone (129,130).

Both the early studies and the results of controlled trials offer little support for long-term treatment with low doses of corticosteroids to prevent relapses of either ulcerative colitis or Crohn’s disease. Toxicity is the major drawback, accounting for high morbidity. Of the new steroid formulations, oral budesonide (for active ileocecal Crohn’s disease) has less incidence of side effects in children receiving short-term therapy.

Side Effects

The toxic effects of corticosteroids are well known and reviewed elsewhere (97,137,138). Common findings include fluid retention, weight gain, abdominal striae, fat redistribution, hypertension, hyperglycaemia, subcapsular cataracts, osteopenia, osteonecrosis, myopathy, and emotional disturbances. Most side effects seem to be related to the dose and duration of therapy; some patients may develop pseudoarthritis as steroids are tapered. Bone loss is an important complication that occurs particularly rapidly, within a few weeks to months after administration (139). Alternate-day treatment does not prevent bone loss, as was demonstrated in patients with rheumatoid arthritis (140) or bronchial asthma (141). Guidelines on prevention of glucocorticoid-induced osteoporosis have been developed by the American College of Rheumatology (142). The guideline recommends initiating preventive therapies as soon as steroids are prescribed, because bone loss is greatest in the first few weeks to months of therapy, and because the highest doses are used initially. Evidence of the effectiveness of calcium supplementation (143), vitamin D, or calcitriol (144) on the primary prevention of bone loss, and of bisphosphonates (145) on the prevention of bone loss in established osteoporosis, has been established in adult patients with various chronic inflammatory diseases.

Summary

Corticosteroids are very effective in controlling active Crohn’s disease and ulcerative colitis, accounting for clinical remission rates of 60–91%. There is, however, no benefit from steroid maintenance therapy in either disease. Toxicity is the major drawback, accounting for high morbidity. Of the new steroid formulations, oral budesonide (for active ileocecal Crohn’s disease) has less incidence of side effects in children receiving short-term therapy.

ANTIBIOTICS

Considering the central role postulated for bacterial flora in IBD, there is a paucity of data regarding the role of antibiotics in IBD therapy. The most closely examined antimicrobial agent for treatment of CD has been metronidazole.

Antibiotics can decrease chronic intestinal inflammation, which is a consequence of an overly aggressive cellular immune response to a subset of normal resident bacteria. The effect of antibiotics is presumed to be through alteration of the bacterial flora, such as by decreasing overall concentrations of luminal bacteria or by eliminating certain enteric bacterial subsets (146).

Evidence in Children

Though controlled trials have not been performed in children, metronidazole seems to be safe and relatively effective in perianal Crohn’s disease in children (147). An open-label trial of metronidazole in 20 children with CD showed that more than half of the patients improved clinically during 6 months of treatment; however, of the nine patients who discontinued the drug, five had a re-
Evidence of Efficacy in Adults

In the setting of severe colitis (fulminant colitis or toxic megacolon), intravenous antibiotics are used empirically as a component of an intensive regimen (151,152). Pouchitis usually responds to treatment with metronidazole or ciprofloxacin (153). Studies in Crohn’s disease showed metronidazole to have effects similar to sulfasalazine (154), and remission rates of 25–35% at 4 weeks, similar to placebo (155). Remission rates in mild active CD after ciprofloxacin versus mesalazine showed no differences (56% versus 55%) (156). In perianal Crohn’s disease, metronidazole induced healing or improvement of fistulae in 86% of patients, within 2 months (157); however, in a follow-up study, attempts to gradually reduce the dose or to discontinue treatment resulted in relapse in 83% of the patients (158). Ciprofloxacin is reported to be beneficial in the treatment of perianal or fistulous CD (159).

Side Effects

Common side effects of metronidazole include nausea and a metallic taste in the mouth. Approximately 5–10% of patients experience severe nausea and vomiting. Headache, dry mouth, furry tongue, glossitis, stomatitis, urticaria, vaginal and urethral burning, vaginal yeast infection, or upper abdominal pain occur in up to 90% (160). A disulfiram-like side effect can occur after alcohol ingestion. With prolonged administration, peripheral neuropathy characterized by paresthesias in the extreme-
colitis and pouchitis are encouraging, their efficacy in treatment or maintenance of remission of Crohn’s disease remains to be clarified. Because of strain-specific variability and clinical and therapeutic heterogeneity within Crohn’s disease and ulcerative colitis, it cannot be assumed that any single probiotic is equally suitable for all individuals (162).

In conclusion, it is still too soon to recommend routine use of probiotics in general practice; however, they may be useful as adjunctive therapy, particularly in maintenance of disease remission.

**AZATHIOPRINE OR 6-MERCAPTOPURINE**

The thiopurine agents azathioprine (AZA) and its metabolite 6-mercaptopurine (6-MP) have been used in both Crohn’s disease and ulcerative colitis primarily for those patients who are resistant to or dependent on corticosteroids. If treatment is successful, steroid sparing is accomplished while remission is maintained. Whether these agents should be a part of early therapy of IBD is currently under debate (170). These drugs are the main immunomodulators used in inflammatory bowel disease, they have similar side effects and efficacy, and they are used interchangeably. Azathioprine is 55% of 6-MP by molecular weight; once it is absorbed into the plasma, 88% is converted to 6-mercaptopurine. So, to achieve therapeutic efficacy, a conversion factor of 1.5–2.0 is needed when converting 6-MP to an equivalent dose of azathioprine (171). For unknown reasons, it seems that azathioprine is more popular in Europe and 6-mercaptopurine mostly in the United States and North America. Azathioprine is rapidly absorbed and converted to 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) shunts the metabolism of 6-MP away from the production of 6-thioguanine by producing 6-methylmercaptopurine. Pharmacogenetic differences in the activity of TPMT may explain why certain patients are predisposed to AZA/6-MP-induced cytotoxicity, whereas in others, disease is refractory to therapy (172). Measurement of TPMT activity is recommended before instituting therapy. The mechanism of action of these agents has been reviewed elsewhere (160,173).

**Experience in Children**

In children, the safety and efficacy of azathioprine and 6-mercaptopurine in CD and UC have been studied only in retrospective reviews until recently. Verhave et al. showed that 75% of pediatric IBD patients (nine had UC, 12 had CD) had either complete or partial clinical (and laboratory) improvement, with a median response time of 3 months in UC and 4 months in CD (174). More importantly, most of the patients were able to discontinue corticosteroid therapy within 6 months of starting azathioprine. Another pediatric study showed a clinical response in about 70% of children with CD; more than half were able to discontinue prednisone completely during the first 6 months of 6-MP use (175). Recurrence of disease after surgery may be prevented with 6-MP, as was shown in a small, uncontrolled study by Kader et al. (176).

In an uncontrolled trial by Ramakrishna et al., azathioprine or 6-mercaptopurine was started at the time of conversion of intravenous cyclosporine to oral administration in eight children with steroid-resistant IBD (177). Three (of eight) children taking azathioprine or 6-MP after a cyclosporine-induced remission achieved long-term remission (2–5 years) after tapering of cyclosporine, and did not require surgery. In a study of 20 children with severe UC, 70% benefited from the use of 6-MP or AZA, enabling complete steroid withdrawal in 75% with a median response time of 9 months (178). Low-dose intravenous azathioprine treatment has been used in severe fulminant colitis complicating both UC and CD. Three pediatric patients received intravenous azathioprine (3 mg/kg/day) for a period of 5–7 days, followed by a similar oral dose as maintenance treatment. The patients improved significantly within 7 days, and remission was sustained, suggesting a more rapid onset of clinical efficacy (179). This therapy is not currently recommended and should never be instituted without previous measurement of TPMT activity (172).

A randomized, multicenter, placebo-controlled trial of 6-mercaptopurine in newly diagnosed CD has been performed by Markowitz et al. (170). Fifty-five children were randomized to treatment with 6-MP (1.5 mg/kg/day) or placebo within 8 weeks of initial diagnosis. Both groups also received prednisone (starting dose, 40 mg/day). In this 18-month trial, remission was induced in 89% of both groups, but relapse was much more common in the control group (47%) than in the group receiving 6-MP (9%). Long-term remission rate (at 18 months) was 89% (6-MP) versus 39% (placebo). In addition, none of the children receiving 6-MP became steroid-dependent, though this was the case for 50% of the control group.

In a retrospective analysis of resective operations in children with Crohn’s disease, multivariate analysis identified factors influencing postoperative recurrence of disease (180). The investigators found that patients who require preoperative use of 6-MP are likely to suffer...
from more aggressive disease and would benefit from postoperative 6-MP prophylaxis. In adults, 6-MP effectively prevents recurrences after surgery.

In perianal disease, treatment with 6-MP or AZA has been shown to be effective in children, as was shown by a small retrospective study (181); among 15 patients who were treated for at least 6 months, 67% had an improvement in drainage, 73% in tenderness, 60% in induration, and 40% in fistula closure. Preliminary studies in adolescent patients with Crohn’s disease have correlated erythrocyte 6-thioguanine levels with clinical responsiveness to therapy (182).

Safety in children was reviewed in 95 patients by Kirschner, demonstrating side effects in 28%. In 18%, discontinuation of AZA or 6-MP was required because of hypersensitivity or infection (183). Pancreatitis was seen in 4%, gastrointestinal intolerance in 5%, and infectious complications in 8%. The most common abnormal serological finding was aminotransferase elevation (more than twice normal), which was found in almost 15% of patients. Leukopenia was seen in 10%, and it resolved either spontaneously or after dose reduction. Another retrospective pediatric study (184), in 45 children with IBD (38 had Crohn’s disease, 7 ulcerative colitis), showed minor side effects such as elevation of liver function tests and leukopenia in about 40% of patients.

Whether AZA and 6-MP will be associated with an increase in malignancy in pediatric patients who undergo long-term therapy is unknown, but is not suggested by the current literature (185–187).

Evidence of Efficacy in Adults

In UC, azathioprine facilitated steroid withdrawal (and complete discontinuation) without clinical worsening of colitis (188–192). Maintenance treatment resulted in a lower relapse rate than in placebo treatment (36% versus 59%) (193).

In CD, overall response rate in active disease is 54% (173), with best response in subjects with extensive colonic involvement. Reduction of steroid consumption was achieved in 65% of the patients after azathioprine or 6-MP treatment, and in 36% of the placebo-treated patients. The mean time to response for oral azathioprine or 6-mercaptopurine in active CD is 3.1 months (19% of the patients took more than 4 months to respond) (194). After intravenous loading of azathioprine (40 mg/kg) (195), remission was obtained within 8 weeks. Azathioprine/6-MP is effective in maintaining remission (rate 67% versus placebo 52%, with highest efficacy during 2.5 mg/kg/day of azathioprine) (196). Treatment may have a preventive effect on recurrent ileitis (197). Withdrawal from treatment is followed by a high rate of relapse in CD, ranging from 41–81% after 1 year (198–200). Relapse rate correlated with the duration of clinical remission on AZA or 6-MP, and was similar whether treatment was maintained or stopped after 4 years (201).

Side Effects

Nausea is common during the first month of treatment, and should be distinguished from pancreatitis, which may be present in 3–15% of patients (202).

Bone marrow suppression (particularly leukopenia), an important and potentially lethal complication, is dose-related and may develop at any time (range 2 weeks to 11 years after starting the drug) during treatment (203). Re-introduction of a lower dose is successful in about 50% of the patients. Monitoring blood levels of 6-thioguanine (6-TG) may obviate this complication.

The most common concern among both patients and physicians in deciding whether to use these medications in the treatment of IBD is fear of inducing a malignancy. To date, this fear is not supported by the data. It has been demonstrated that patients with Crohn’s disease already have an increased risk of non-Hodgkin’s lymphoma (NHL) (204). Three relatively large studies, including more than 1,300 patients treated with AZA or 6-MP for inflammatory bowel disease, reported 2 cases of lymphoma, one of which was fatal (185,201,203). The risk of neoplasia after azathioprine in 755 patients treated for inflammatory bowel disease was studied by Connell et al. (187). The patients received 2 mg/kg daily for a median of 12.5 months (range 2 days to 15 years) between 1962 and 1991; median follow-up was 9 years (range 2 weeks to 29 years). Overall, there was no significant excess of cancer as compared with the general population. In a recent study conducted by Lewis et al., decision analysis was used to determine the impact of azathioprine therapy in Crohn’s disease on survival and quality-adjusted life expectancy (205). This study showed that the benefits of treatment exceed the calculated increased risk of lymphoma, especially in young patients who have the lowest baseline risk of NHL and the greatest life expectancy.

Summary

In patients with chronically active Crohn’s disease or ulcerative colitis with frequent exacerbations, maintenance treatment with azathioprine or 6-MP is safe and efficacious.

A steroid-sparing effect has been demonstrated in 70–75% of (adult and pediatric) patients with Crohn’s dis-
ease or ulcerative colitis. In children with newly diagnosed Crohn’s disease, 6-MP is effective, steroid-sparing, and improves maintenance of remission. Based on these data, 6-MP (and its prodrug azathioprine) may be considered as part of the initial treatment of Crohn’s disease in children.

The slow onset of action (3–4 months) makes therapeutic use for acute active inflammation problematic, and, awaiting a response, treatment needs to be combined with steroids or nutritional therapy for at least 3 months.

Duration of treatment in both Crohn’s disease and ulcerative colitis should be over years, because discontinuation of AZA/6-MP leads to a high relapse rate within the first year.

Bone marrow depression may occur in 2–5% of patients at any time between 2 weeks to 11 years. Concerns about malignancy after long-term treatment are not supported by evidence from the available literature. Based on the available evidence in adults and children, Table 3 summarizes the approach in children.

**CYCLOSPORINE**

Cyclosporine is an immunosuppressive agent that was originally developed to prevent organ rejection following transplantation. Patients with inflammatory bowel disease (particularly ulcerative colitis) who are refractory to first-line treatment (sulfasalazine, mesalazine, and corticosteroids) or who have failed therapy with azathioprine or 6-mercaptopurine are appropriate candidates for cyclosporine treatment. Cyclosporine is a rapid-acting alternative or adjunct to AZA/6-MP therapy for refractory UC. It can be used intravenously (to induce disease remission) or orally for brief periods after remission is established. During treatment, cyclosporine levels in whole blood have to be monitored. The therapeutic window is narrow and difficult to define with certainty because doses vary in different studies (206–214). The mechanism of action has been reviewed elsewhere (215,216).

**Experience in Children**

Several noncontrolled trials have assessed the efficacy of cyclosporine in children with severe acute unresponsive ulcerative colitis (177,217–221). In most protocols, cyclosporine was added to high-dose steroids when the disease was refractory to steroids and parenteral nutrition. In up to 80% of the children, cyclosporine was effective in achieving clinical remission, but most responders needed colectomy within 1 year (218).

**TABLE 3. Use of azathioprine or 6-mercaptopurine in children with inflammatory bowel disease**

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>DOSAGE</th>
<th>CHECK BEFORE/DURING TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial treatment of CD (174) (with steroids) (170,175)</td>
<td>AZA: 2–2.5 mg/kg/d; 6-MP: 1.5 mg/kg/d</td>
<td>Before starting, check TPMT levels (low or absent levels indicate susceptibility to myelosuppression) (289)</td>
</tr>
<tr>
<td>Maintenance treatment of CD (178) and UC (176) if steroids cannot be tapered or more than 1–2 relapses occur</td>
<td>Both: stop if unsuccessful after 1 y. If successful, continue treatment for ≥4 y, adjusting dosage with weight gain</td>
<td></td>
</tr>
<tr>
<td>Prophylaxis after surgery, in CD (180)</td>
<td></td>
<td>During treatment, check levels of 6-TGN (to help predict cytotoxicity) and 6-MMP (to help predict hepatotoxicity) (290)</td>
</tr>
<tr>
<td>Perianal CD (181)</td>
<td></td>
<td>CBC: Weekly in 1st mo, fortnightly in 2nd and 3rd mo, every 2–3 mo thereafter for duration of treatment and in any case of unexplained fever or malaise</td>
</tr>
</tbody>
</table>

ALT and amylase: Monthly until end of 3rd mo, then once every 3 mo. In case of moderate or severe leukopenia (L < 3 × 10^9/l) or thrombocytopenia (platelets < 100 × 10^9/l), stop treatment and resume at lower, individualized dosage after normalization of blood count

References for pediatric studies are given in parentheses. If no reference, data were extrapolated from adult studies. CD, Crohn’s disease; UC, ulcerative colitis; AZA, azathioprine, 6-MP, 6-mercaptopurine; TPMT, thiopurine methyl transferase (the enzyme that metabolizes 6-MP to 6-methylmercaptopurine [6-MMP]); 6-TGN, 6-thioguanine nucleotides (cytotoxic metabolites of 6-MP); CBC, complete blood count.
In children with newly diagnosed or relapsed Crohn’s disease, initial treatment with oral cyclosporine was not significantly better (clinically, endoscopically, and histologically) than conventional treatment with steroids or enteral nutrition, as was shown in a controlled trial in 24 children (222).

When surgery becomes necessary in severe refractory ulcerative colitis, cyclosporine therapy may provide the time needed for education of families and their acceptance of this form of treatment (223).

**Evidence of Efficacy in Adults**

In the only placebo-controlled trial of cyclosporine in severe steroid-refractory UC, nine of 11 patients (82%) receiving continuous intravenous cyclosporine (4 mg/kg/day) had improved within 7 days as compared with none of nine (0%) of the patients receiving placebo (210). After improvement, patients were switched to oral cyclosporin A (CsA, 8 mg/kg/day) for 6 months. During this follow-up period, four of the nine patients underwent colectomy. Thus, the overall success rate at 6 months was 45%. A literature review of the use of intravenous cyclosporine in severe ulcerative colitis determined an overall response rate of 68% (125 out of 185 patients) and a sustained response after discontinuation of 42% (78 out of 185 patients) (215). In a relatively large series from a community experience, cyclosporine usage was demonstrated to be of only moderate efficacy; acute colectomy was avoided in 57% of patients, but the total colectomy rate within a 6-months follow-up period was 73% (224).

In steroid-refractory or steroid-dependent CD, three large, controlled studies have failed to document a significant impact of low-dose (≤5 mg/kg/day) cyclosporine in Crohn’s disease of varying severity (212–214). There may be a correlation between whole-blood concentrations and clinical response, because high-dose (oral ≥5 mg/kg/day or intravenous treatment) trials tend to show more favorable results than the low-dose trials (215).

In fistulous Crohn’s disease, initial closure is seen in 78% of patients, with a time to closure ranging from 0.5 to 4 weeks, and sustained closure in 55% (215).

**Side Effects**

In high-dose cyclosporine treatment, side effects are very common, mostly dose related, and reversible (215). The two most frequent complaints in the high-dose trials were paresthesias (in at least 20% of patients) and hypertrichosis (in up to 50%) (215). Paresthesias will resolve quickly when the dose is reduced, and overgrowth of hair will gradually resolve over weeks to months after discontinuation of cyclosporine therapy. The most damaging effect of cyclosporine is seen in the kidneys. A potential for permanent renal damage prevents the long-term use of cyclosporin at doses higher than 5 mg/kg/day. Almost all patients have a 20% reduction in the glomerular filtration rate (225,226), which is not always noted as a rise in serum creatinine.

Cyclosporine is a potent vasoconstrictor and loss of renal function usually results from vasoconstriction of afferent arterioles. Although renal function generally returns to normal within 2 weeks of stopping cyclosporine, histologic evidence of (irreversible) nephrotoxicity was demonstrated in 21% of 192 patients treated with oral cyclosporine (227). Hepatotoxicity occurs in up to 30% of patients (228,229), is mostly because of cholestasis, and generally resolves when the dose is reduced or cyclosporine is withdrawn. Infectious complications are infrequent in patients receiving low-dose treatment, but they are a risk in patients treated with intravenous cyclosporine or those patients who are already being treated with high-dose steroids or other immunosuppressive medications (97,230). Finally, cyclosporine treatment has been found to cause a slight increase in the incidence (to 0.3%) of malignant lymphoma in patients with autoimmune disease (231).

**Summary**

Cyclosporine may be useful in patients with severe refractory ulcerative colitis to avoid emergency colectomy. The time to response is significantly shorter than for azathioprine, but, in most cases, colectomy is only postponed. It seems that although the initial response to cyclosporine in acute refractory IBD is high and fast (within 2–3 weeks), withdrawal of the drug often leads to a recurrence of symptoms. Relapse may be prevented with azathioprine or 6-MP (177).

For closure of refractory fistulas in patients with Crohn’s disease, intravenous cyclosporine is effective, but maintenance of this success after tapering is a problem. Side effects (such as hypertrichosis and paresthesias) are frequent, especially in high-dose oral and intravenous treatment. The risk of (in some cases permanent) renal damage limits its use as a long-term drug. Based on the current evidence from the many studies in children, the summary in Table 4 seems a reasonable approach to the use of cyclosporine in pediatric patients.
METHOTREXATE

Methotrexate (MTX) is an anti-inflammatory drug that has been used widely in the treatment of psoriasis and rheumatoid arthritis since the early 1950s.

Much later, after an initial report by Kozarek et al. of its usefulness in inflammatory bowel disease (232), methotrexate was studied in adults with chronically active steroid-dependent Crohn’s disease. In contrast to rheumatoid arthritis, parenteral administration (intramuscular [IM] or subcutaneous [SC]) seems to be important in Crohn’s disease, particularly among patients with small bowel disease in whom drug absorption may be impaired. Methotrexate is a folate-inhibitor, and what is understood about its anti-inflammatory action has been described elsewhere (202).

TABLE 4. Use of cyclosporine in children with ulcerative colitis

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rescue treatment of severe UC (177,217–221)</td>
<td>Temporarily stop using AZA or 6-MP, if using them</td>
</tr>
<tr>
<td>Only in a center with experience, where cyclosporine levels can be determined readily</td>
<td>Start with 2–4 mg/kg/d as continuous intravenous infusion (in addition to high-dose steroids); continue at least 7–10 d, increasing dose to desired blood level</td>
</tr>
<tr>
<td>If no clinical improvement or worsening during intravenous treatment, refer for surgery</td>
<td>Before switching to oral dose, (re)start AZA or 6-MP</td>
</tr>
<tr>
<td></td>
<td>After 7–10 d intravenous, switch to oral cyclosporin, 8 mg/kg/d in 2 doses, continue 1–3 mo while tapering dose; take with milk or fruit juice not in a plastic cup (suspension sticks to plastic surface)</td>
</tr>
<tr>
<td></td>
<td>Use prophylaxis: trimethoprim/sulfamethoxazole for Pneumocystis carinii and Mycostatin (Apothecon, Princeton, NJ, U.S.A.) for candida</td>
</tr>
</tbody>
</table>

CHECK BEFORE/DURING TREATMENT

Before start: blood pressure, stool cultures including Clostridium difficile toxins A and B, serum creatinine, electrolytes, BUN, glucose, liver function tests, amylase, lipase, 24-hour creatinine clearance," serum cholesterol," serum magnesium,‘ CBC (including platelets, ESR, or CRP to monitor colitis activity) During first h of infusion: Monitor every 15 min for signs of allergy or anaphylaxis; discontinue infusion if any such signs develop and treat as necessary

During in-hospital intravenous treatment:
- Daily blood pressure
- Cyclosporine blood levels every 2 d (daily if abnormal) with aim of whole blood levels of 400–500 ng/ml
- Serum measurements every 2 d (daily if abnormal)
- Reduce cyclosporine dose by ≥25% if drug level is >500 ng/ml for 2 consecutive d

During outpatient oral treatment:
- Visit weekly for 4 wk, then fortnightly for 1 mo, then monthly
- Serum measurements as above at each visit
- Cyclosporine trough blood level (with aim of trough level of 150–300 ng/ml) every visit or within 1 wk after change in dosage
- Reduce cyclosporine dosage by ≥25% if drug level is ≥300 ng/ml for 2 consecutive d or serum creatinine increases by 30% over baseline or serum transaminases double or systolic blood pressure >150 mm Hg despite antihypertensive treatment

References for pediatric studies are given in parentheses. If no reference is provided, data extrapolated from adult studies.

a In cases in which serum creatinine is borderline
b Hypocholesterolemia (<120 mg/dl) should be corrected first by diet or parenteral intralipids, as it increases the risk for seizures in patients treated with cyclosporine (291)
c Hypomagnesemia (<1.5 mg/dl) should be corrected first by parenteral magnesium, as it increases the risk for seizures in patients treated with cyclosporine (291)

UC, ulcerative colitis; AZA, azathioprine, 6-MP, 6-mercaptopurine; BUN, blood urea nitrogen; CBC, complete blood count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

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Experience in Children

There is considerable experience with the use of low-dose oral methotrexate in pediatric patients with juvenile rheumatoid arthritis (JRA) (233), and this population is valuable for comparison with pediatric IBD patients, particularly in regard to safety. Side effects during treatment of 6 months were seen in 4% of patients, and none of them were severe.

In a retrospective review of 62 patients with polyarticular juvenile rheumatoid arthritis (234) treated from 84–296 weeks with oral MTX weekly, no stomatitis or rashes were observed and no serious adverse events were recorded. Transient liver function abnormalities developed in nine patients during treatment. In the 12 pa-
tients who underwent liver biopsy, none had fibrosis or cirrhosis.

A more recent study by Kugathasan et al. (235) described liver biopsy findings in nine children with JRA who received methotrexate for more than 3 years. All biopsies were interpreted as normal.

In pediatric patients with IBD, only one open label study has been published (236), apart from encouraging results from two abstracts (237,238). In the published trial (236), 14 patients with active steroid-dependent Crohn’s disease who failed or were unable to tolerate 6-MP treatment were given methotrexate 15 mg/m² subcutaneously on a weekly basis. All children received daily folic acid to minimize side effects. Improvement (measured as decreases in Pediatric Crohn’s Disease Activity Index, erythrocyte sedimentation rate [ESR], and prednisolone dose) was noted in 64% of the children at 4 weeks. Two patients discontinued treatment because of nausea and headache. One patient died unexpectedly, presumably from suppression of the adrenal cortex from daily corticosteroids, followed by lack of response to an acute illness.

**Evidence of Efficacy in Adults**

In UC, methotrexate was found to be no better than placebo in the induction or maintenance of remission (239).

In active CD, methotrexate (IM or SC 25 mg weekly) was twice as likely to allow steroid tapering and maintenance of remission as placebo (39% versus 19%), and improvement in symptoms was seen by 6 weeks (240). Lower-dose oral MTX (12.5 mg weekly) showed no significant benefit over placebo or 6-MP in overall steroid reduction or induction of remission (241). Similarly, low-dose oral MTX did not have a relapse-preventing effect on Crohn’s disease exacerbations (242), while parenteral MTX was effective in remaining remission (243).

The probability of relapse increased per treatment year in CD patients (29%, 41%, and 48% at 1, 2, and 3 yr, respectively) (244).

**Side Effects**

The most common side effect of low-dose MTX is gastrointestinal toxicity, including nausea (in 42%), anorexia, stomatitis, and diarrhea (7%). Headaches (17%), dizziness, fatigue (16%), and mood alterations may also occur (240). Many of these adverse reactions can be reduced by supplemental folic acid therapy. Hematologic toxicity (leukopenia, thrombocytopenia, and pancytopenia) is uncommon with low-dose MTX. Methotrexate is teratogenic, and was used as an abortifacient several decades ago. Pulmonary toxicity, primarily interstitial pneumonitis, may occur at any time during treatment and at any dose. The risk factors for this complication and its frequency are unknown (245). In a recent placebo-controlled study of MTX maintenance treatment in 76 adults with Crohn’s disease, none of the patients experienced pulmonary problems (243). Opportunistic infections are rare but may include localized or disseminated herpes zoster, fungal, and Pneumocystis carinii infections. No carcinogenic effect of low-dose MTX has been demonstrated to date in patients treated for either psoriasis or rheumatoid arthritis. In inflammatory bowel disease, continued surveillance is essential.

Hepatotoxicity has been a principal concern when patients receive MTX, particularly for psoriasis, but among patients with rheumatoid arthritis who receive low-dose MTX, the risk of serious liver disease has been projected to be less than 1 per 1000 cases after 5 years of treatment (246). This relatively low risk of hepatotoxicity may be attributable to the fact that lower doses of MTX have been used in rheumatoid arthritis (7.5–20 mg per week) than in psoriasis (20–50 mg per week), and that there was greater restriction of alcohol consumption in the rheumatoid patients (245). In a long-term follow-up study of 49 Crohn’s disease patients maintained on methotrexate for a median of 18 months (range, 7–59 months), a liver biopsy was performed in 11 patients; a mild steatosis was found in five, a slight dilatation of the sinusoids in one, granulomatous hepatitis with mild portal fibrosis in one, and slight periportal fibrosis in one patient (244).

**Summary**

Methotrexate is beneficial and steroid sparing in CD, but not in UC. One advantage of methotrexate over azathioprine/6-MP is its relative rapid onset in inducing disease remission. Hepatotoxicity is of concern and continued surveillance is essential.

In children with CD, experience with methotrexate is limited but encouraging. Until the long-term risks and benefits of subcutaneous MTX are fully known, methotrexate should only be considered in children and adolescents with CD who fail to respond to conventional drug (i.e., corticosteroids and azathioprine/6-MP) treatment or who are having significant complications from their other therapies.

Based on the available evidence in adults and children, our approach to the use of methotrexate in children is summarized in Table 5.
Anti-Tumor Necrosis Factor-\(\alpha\) Antibody (Infliximab)

Tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)) is a pivotal pro-inflammatory cytokine that is known to play an important role in the pathogenesis of Crohn’s disease. Cells expressing TNF can be found in the gut mucosa and lamina propria of patients with Crohn’s disease (49).

A chimeric monoclonal anti-TNF antibody (infliximab) can inhibit TNF-\(\alpha\) activity, thus modifying disease activity. Its mechanism of action has been described elsewhere (247).

The first patient to receive anti-TNF antibody was a 13-year-old girl with severe refractory Crohn’s colitis (248). This patient had a dramatic clinical response that was accompanied by healing of intestinal ulceration.

Experience in Children

The first controlled multicenter trial in children, a joint American-European effort, was a dose-ranging study performed by Baldassano et al. in 1999 (249). Twenty-one children with severe refractory Crohn’s disease were randomized to receive a single infusion of infliximab 1 mg/kg, 5 mg/kg, or 10 mg/kg. At 4 weeks, 86% of the children receiving 5 mg/kg had clinical response (reduction of PCDAI by ≥10 points, or reduction of CDAI by ≥70 points), while 14% reached clinical remission (PCDAI ≤10 or CDAI ≤150). The children receiving 10 mg/kg had a clinical response at week 4 in 57%, and reached remission in 43%. At 12 weeks and at 20 weeks, remission was 14% and 50%, respectively, in the 5 mg/kg group, and 33% and 33%, respectively, in the 10 mg/kg group. These results, however, are positively influenced by concomitant glucocorticoid treatment in the remitting patients.

Several other small, uncontrolled trials (250–254) of infliximab have followed, all showing promising results in children with refractory Crohn’s disease. In a case report of a child with metastatic Crohn’s disease, infliximab was shown to be relatively successful (255).

Of particular interest is the study by Kugathasan et al.,
which showed that in children with refractory Crohn’s disease of short (less than 2 years) duration, the clinical response to one infusion of infliximab 5 mg/kg lasted longer than in patients with “late” Crohn’s disease (251). In spite of the lack of a proper randomized trial in children, 62% of North-American pediatric gastroenterologists have now used infliximab in their Crohn’s disease patients, and approximately 617 children have been treated, as was demonstrated by a survey among the North American Society of Pediatric Gastroenterology and Nutrition (NASPGAN) members (256). Whether infliximab treatment eliminates the need for steroids in pediatric Crohn’s disease is a matter of controversy (257–259).

In children with UC, a small, open-label study has demonstrated encouraging short-term results of infliximab treatment in moderate to severe disease (260). Decrease of clinical disease activity (measured as Lichtiger Colitis Activity Index (210) and Physicians’ Global Assessment) was seen in 7 out of 9 patients at 2 days and 2 weeks after infusion.

**Evidence of Efficacy in Adults**

Two preliminary trials of infliximab for UC have been reported (261,262), with encouraging results.

In patients with refractory CD, infliximab induced significantly more clinical responses and complete clinical remissions (81%) as compared with placebo (17%) (263). During the 44-week follow-up period, remission was maintained in nearly all patients by repeated administration of infliximab 10 mg/kg (given every 8 weeks) (264). In patients who were treated concomitantly with azathioprine, remission lasted longer (265).

In fistulous Crohn’s disease, drainage from the fistulas stopped in 68% of patients receiving infliximab (5 mg/kg at week 0, 2, and 6), compared with 26% of the placebo treated patients. Mean time to reach this treatment success was 14 days, which was significantly shorter than in the conventionally-treated group (40 days) (266).

Since 1998, infliximab has been approved for clinical use in active refractory or fistulizing Crohn’s disease in adults in the U.S.A. In Europe, approval was reached in September 1999. Currently, a randomized trial of infliximab as primary treatment versus a conventional step-up strategy (starting with mesalazine, and adding corticosteroids and immunosuppressives) in adults with active Crohn’s disease is being planned in the Netherlands and Belgium.

**Side Effects**

Infusion reactions occur in about 6% of patients and are usually not severe. In most patients, infusions can be continued at a slower rate or after administration of an antihistamine or a steroid bolus dose. As infliximab is a mouse-human chimaeric antibody, human-antichimaeric-antibodies (HACAs) can be induced after one or several infusions. Adult studies show that HACAs are present in 13% of the patients, and their presence is associated with a slightly higher rate of infusion reactions upon reinfusion. Whether HACAs interfere with therapeutic efficacy is as yet unknown. Simultaneous use of immunosuppressive drugs seems to lower the rate of HACA development (247).

There is now evidence of an increased frequency of active tuberculosis after initiation of infliximab treatment, but not of other opportunistic infections (267). Development of malignancies is a concern, and the relationship between treatment and the development of lymphoma is currently under debate. In 1999, seven patients treated with infliximab (of the total 913 patients in clinical trials) had developed lymphoproliferative disorders (268). Four of the patients had rheumatoid arthritis, one had human immunodeficiency virus (HIV) infection, and two had Crohn’s disease. At that time, as of July 1999, no other cases of lymphoma had been reported in the approximately 15,000 CD patients treated with single or multiple infusions of infliximab. The follow-up period of most treated patients is still very short, and post-treatment surveillance is warranted.

**Summary**

Infliximab, anti-TNFα antibody, is very effective in active and fistulizing Crohn’s disease. It induces a rapid clinical remission and mucosal healing in adult, steroid-refractory Crohn’s disease patients. Maintenance of remission can be achieved by repeated infusions every 8 weeks. In UC, pilot studies have yielded encouraging results in adults and children. Short-term side effects are infrequent and not severe. As active tuberculosis may develop after treatment, TB screening should be performed before treatment. Whether treated patients have an increased risk of lymphoproliferative disease is unknown. Cancer surveillance is indicated, however, because follow-up studies are still of short duration.

Further controlled, multicenter studies focused on dose and the role of infliximab as maintenance treatment should be performed in children with Crohn’s disease. Additionally, it would be interesting to study infliximab in children with newly diagnosed Crohn’s disease, thereby investigating the actual effect of this “disease-modifying” drug on the course of the disease; however, in view of the still-undefined potential for side effects, in particular the risk of lymphoma, this approach should be given careful consideration.
Infliximab is now used on a large-scale basis in children with CD, despite the small amount of evidence from pediatric studies. In our opinion, treatment ideally should be incorporated into a randomized controlled study protocol. Notwithstanding, Table 6 offers some recommendations on the use of infliximab in children, with careful documentation of effects, side effects, and long-term follow-up.

**NEW THERAPIES**

An extensive review of new therapies for IBD has been published elsewhere (103). Biologic treatment may be targeted at TNFα (infliximab, and humanized anti-TNFα antibody CDP571), at interferon (IFN)-γ, at IL-12, at transcription factor NFκB (antisense oligonucleotide to NFκB p65), or at intercellular adhesion molecules (antisense oligonucleotide to ICAM-1). Agents directed against integrins (anti-α4 integrin and anti-α4β7 integrin), inhibit leukocyte recruitment, and may prove to be successful in CD. In addition, the anti-inflammatory cytokines IL-10 and IL-11 have been tried as treatment of active disease. However, narrowly targeted these agents are, there is extreme variability of clinical response. This may suggest that the inflammatory bowel diseases are far more heterogeneous in humans than in their murine counterparts (103). None of the therapies (except infliximab) have been approved for clinical use in patients with IBD.

Several pioneer trials have been performed with thalidomide (269–272), tacrolimus (FK-506) (273–275), and growth hormone (276) in children with IBD; however, it seems that all clinical studies of biologic treatments (except infliximab) have enrolled adult patients refractory to treatment with conventional therapies. In the future, patients with new-onset disease (who do not have the irreversible damage of long-standing Crohn’s disease) may be the more appropriate group to study; in

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TABLE 6. Use of infliximab in children with Crohn’s disease

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>DOSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-resistant moderate to severely active CD in patients who receive immunomodulatory treatment (249,250,251,253,254)</td>
<td>Continue immunomodulatory treatment (AZA, 6-MP, or methotrexate)</td>
</tr>
<tr>
<td>Maintenance of remission induced by infliximab</td>
<td>Infliximab 5 mg/kg intravenous in 250 ml NaCl over at least 2 h</td>
</tr>
<tr>
<td>Fistulizing CD</td>
<td>Infusion solution in glass infusion bottle or polypropylene or polyolefin infusion bag; use low protein binding filter (1.2 µm pore size) and polyethylene-lined pump set</td>
</tr>
<tr>
<td>DOSAGE</td>
<td>Infusions every 8 wk or tailored to individual response</td>
</tr>
<tr>
<td>First 3 infusions: Calculate CDAI and PCDAI before and 2, 4, and 8 wk after infusion to assess individual response</td>
<td>CHECK BEFORE/DURING TREATMENT</td>
</tr>
<tr>
<td>Before treatment: Evaluation for latent tuberculosis (PPD*)</td>
<td>References for pediatric studies are given in parentheses. If no reference is provided, data extrapolated from adult studies.</td>
</tr>
<tr>
<td>If PPD was not done before infusion, PPD and chest x-ray</td>
<td>In patients receiving immunosuppressive or immunomodulatory treatment purified protein derivative (PPD) test (tuberculin) is positive if induration is ≥5 mm.</td>
</tr>
<tr>
<td>Before each infusion:</td>
<td>CD, Crohn’s disease; AZA, azathioprine; 6-MP, 6-mercaptopurine; CDAI, Crohn’s disease activity index; PCDAI, pediatric Crohn’s disease activity index; T, temperature; P, pulse; R, respiratory rate; BP, blood pressure; CBC, complete blood count; ESR, erythrocyte sedimentation rate; alb, albumin; BUN, blood urea nitrogen; GGT, γ-glutamyltransferase; ALT, alanine aminotransferase.</td>
</tr>
<tr>
<td>Vital signs (T, P, R, BP), height, weight</td>
<td><strong>INDICATION</strong></td>
</tr>
<tr>
<td>Record symptoms (for calculation of PCDAI and CDAI)</td>
<td><strong>DOSAGE</strong></td>
</tr>
<tr>
<td>Record possible adverse effects from prior infusion</td>
<td>Continue immunomodulatory treatment (AZA, 6-MP, or methotrexate)</td>
</tr>
<tr>
<td>Record dose of prednisone or prednisolone</td>
<td>Infliximab 5 mg/kg intravenous in 250 ml NaCl over at least 2 h</td>
</tr>
<tr>
<td>Obtain lab work with intravenous placement: CBC + differential, platelets, ESR, alb, BUN, creatinine, GGT, ALT</td>
<td>Infusion solution in glass infusion bottle or polypropylene or polyolefin infusion bag; use low protein binding filter (1.2 µm pore size) and polyethylene-lined pump set</td>
</tr>
<tr>
<td>Premedicate with intravenous diphenhydramine hydrochloride, oral acetaminophen, and (if prior hypersensitivity reaction) intravenous solumedrol</td>
<td>Infusions every 8 wk or tailored to individual response</td>
</tr>
<tr>
<td>At bedside prn anaphylaxis, intravenous diphenhydramine hydrochloride 1 mg/kg (maximum dose 50 mg), epinephrine 1:1000 (0.01 ml/kg/dose) (maximum dose 0.35 ml) s.c.</td>
<td>First 3 infusions: Calculate CDAI and PCDAI before and 2, 4, and 8 wk after infusion to assess individual response</td>
</tr>
<tr>
<td>During infusion:</td>
<td><strong>CHECK BEFORE/DURING TREATMENT</strong></td>
</tr>
<tr>
<td>Vital signs 15 min after start of infusion, every 30 min throughout, and 30 min after infusion</td>
<td>Before each infusion:</td>
</tr>
<tr>
<td>And after infusion:</td>
<td>1. Vital signs (T, P, R, BP), height, weight</td>
</tr>
<tr>
<td>Record adverse effects</td>
<td>2. Record symptoms (for calculation of PCDAI and CDAI)</td>
</tr>
<tr>
<td>References for pediatric studies are given in parentheses. If no reference is provided, data extrapolated from adult studies.</td>
<td>3. Record possible adverse effects from prior infusion</td>
</tr>
<tr>
<td>* In patients receiving immunosuppressive or immunomodulatory treatment purified protein derivative (PPD) test (tuberculin) is positive if induration is ≥5 mm.</td>
<td>4. Record dose of prednisone or prednisolone</td>
</tr>
<tr>
<td>CD, Crohn’s disease; AZA, azathioprine; 6-MP, 6-mercaptopurine; CDAI, Crohn’s disease activity index; PCDAI, pediatric Crohn’s disease activity index; T, temperature; P, pulse; R, respiratory rate; BP, blood pressure; CBC, complete blood count; ESR, erythrocyte sedimentation rate; alb, albumin; BUN, blood urea nitrogen; GGT, γ-glutamyltransferase; ALT, alanine aminotransferase.</td>
<td>5. Obtain lab work with intravenous placement: CBC + differential, platelets, ESR, alb, BUN, creatinine, GGT, ALT</td>
</tr>
<tr>
<td><strong>TREATMENT OF PEDIATRIC IBD</strong> 51</td>
<td>6. Premedicate with intravenous diphenhydramine hydrochloride, oral acetaminophen, and (if prior hypersensitivity reaction) intravenous solumedrol</td>
</tr>
<tr>
<td>Inflammatory Bowel Diseases®, Vol. 9, No. 1, January 2003</td>
<td>7. At bedside prn anaphylaxis, intravenous diphenhydramine hydrochloride 1 mg/kg (maximum dose 50 mg), epinephrine 1:1000 (0.01 ml/kg/dose) (maximum dose 0.35 ml) s.c.</td>
</tr>
</tbody>
</table>
these, treatment may influence the course and prognosis of the disease. Whether it is ethical to include children in this “ideal” patient group or unethical to exclude them is an interesting point of discussion. Under the FDA Pediatric Rule (16), drug companies are mandated to perform a pediatric assessment of every new drug. As a result, children with inflammatory bowel disease will be invited to participate in future trials, and to get the opportunity to profit from the newest developments in the medical treatment of IBD.

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