Diagnosis and treatment of inflammatory bowel disease in children

Escher, J.C.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Part 3
Medical treatment of childhood IBD
Budesonide versus prednisolone for the treatment of active Crohn’s disease in children

Johanna C. Escher
and the European Collaborative Research Group on Budesonide in Paediatric IBD

Department of Paediatric Gastroenterology and Nutrition
Emma Children’s Hospital-AMC, Amsterdam, The Netherlands
Members of the group listed in Appendix

Submitted for publication
Abstract

Background and Aim
Budesonide is a corticosteroid with low systemic bioavailability because of its high first-pass metabolism in the liver. In this first pediatric, randomised, double blind, double dummy, controlled, multicenter trial, the efficacy and safety of budesonide versus prednisolone were evaluated in children with active Crohn's disease (CD).

Patients and Methods
Forty-eight children, aged 6-16 yrs, with active CD (CDAI > 200) in ileum and/or ascending colon were randomised to receive budesonide (9 mg/day for 8 wks, 6 mg/day for 4 wks) or prednisolone (1 mg/kg/day for 4 wks, tapering 8 wks).

Results
The groups were comparable for age, sex, pubertal stage, disease activity and disease duration. Remission (CDAI ≤ 150) was seen at 8 weeks in 12/22 (55%) patients treated with budesonide and in 17/24 (71%) patients receiving prednisolone (difference -16%; 95% CI -45, 13; p=0.25). Mean morning plasma cortisol concentration was significantly higher in the budesonide group (200 nmol/L) than in the prednisolone group (98 nmol/L) after 8 weeks, reflecting less adrenal suppression by budesonide (difference -102 nmol/L; 95% CI -226, -52; p = 0.0028). Glucocorticosteroid side effects such as moon face and acne occurred significantly less frequently in the budesonide group.

Conclusions
Remission rates were not significantly different in the two groups. However, there was a trend for prednisolone to be more effective for inducing remission. Conversely, significantly fewer side effects and less adrenal suppression were observed in the children receiving budesonide.
Budesonide versus prednisolone

Background

Corticosteroids were among the first medications to be systematically studied in patients with inflammatory bowel disease (IBD)\(^1\)\(^{-2}\) and have been the mainstay in therapy of inflammatory bowel disease for many years. Toxicity however is a major drawback to their use. In children, the side effects of systemic glucocorticosteroid treatment such as bone demineralization and growth retardation are of particular concern\(^3\). In addition, acute disfiguring side effects such as acne, moon face, and striae have made corticosteroids unpopular especially among adolescents, and this may lead to non-compliance.

Budesonide is a potent corticosteroid due to its high affinity for the corticosteroid receptor\(^4\). In addition, its bioavailability is low as a result of an extensive first-pass metabolism in the liver. Thus, systemic exposure has been shown to be minimal (10% to 15%), while the mucosal effects are maximal\(^5\).

In inflammatory bowel disease, safety and efficacy of oral budesonide was first assessed in adults with Crohn's disease involving the ileum and/or ascending colon\(^6\)\(^{-7}\). These first trials, and many subsequent studies in adults, have shown that budesonide is efficacious\(^8\), that its ability to induce clinical remission is superior to mesalamine\(^9\) and not significantly different from prednisolone or methylprednisolone\(^10\)\(^{-12}\), while causing less suppression of the hypothalamic-pituitary-adrenal axis. In Europe, oral budesonide was approved for the treatment of adults with Crohn's disease in 1998. Since then, the experience and comfort with this new treatment modality in the adult population has grown. At the same time, it has made both physicians and industry realize the unmet medical need of the small, but severely affected, pediatric Crohn's disease population. As a result, this trial is the first to assess efficacy and safety of oral budesonide versus prednisolone in children with active Crohn's disease involving the ileum and/or ascending colon.
Materials and Methods

Selection of patients
The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committees and Institutional Review Boards at all 36 European centers. All parents gave written informed consent, and children (if older than 12 years) signed a statement of assent. The goal was to enroll 120 patients, ages 6-16 years, with active Crohn’s disease, as defined by a score of 200 or higher on the Crohn’s Disease Activity Index (CDAI). Patients were included only if the disease was confined to the ileum and/or ascending colon. Crohn’s disease was diagnosed after small bowel follow-through (or enteroclysis) and colonoscopy plus histology. Patients were not eligible if they had active Crohn’s disease in more distal parts of the colon, as verified by sigmoidoscopy within 8 weeks prior to study start; had an ileostomy, pouch or colostomy, or small bowel resection exceeding 50 cm; had signs of septic complications, abscess, mechanical obstruction, perforation, or an active fistula. Patients who were considered to be candidates for surgery due to fibrous strictures, were also excluded. Patients who had received any corticosteroid within 30 days before randomization were excluded, as well as children who had received azathioprine, 6-mercaptopurine, cyclosporine, or any other immunosuppressive drug within 90 days prior to randomization. Salicylates or antibiotics were allowed, as long as the dose had been kept constant more than 30 days before study start and during study treatment. Dependency on enteral or parenteral nutrition during the study was not allowed.

Study drugs
The budesonide capsules used in the study (Entocort®, AstraZeneca, Sweden) contained 3 mg of budesonide distributed in approximately 100 pellets that had an outer coating of Eudragit L100-55 (which dissolves above pH 5.5) and a rate-limiting mixture of ethylcellulose and budesonide as an inner layer. This formulation has been designed to release budesonide during passage through the distal part of the ileum and throughout the colon. Placebo drugs for
Budesonide versus prednisolone

Budesonide capsules were identical in appearance to the active drug. Prednisolone tablets of 2.5 mg, 5 mg, and 10 mg were manufactured by AstraZeneca, as were the placebo tablets for prednisolone that were identical in appearance.

**Trial design**

This randomised, double blind, double dummy, controlled clinical trial involved 36 pediatric centers in 8 European countries (Appendix 1). The primary outcome measure in the study was the proportion of patients in clinical remission after 8 weeks of treatment, defined by a CDAI of 150 or less. A secondary outcome variable was the frequency of glucocorticosteroid (GCS)-associated side effects and adrenal function, measured as morning plasma cortisol levels and ACTH tests. Stratification was done according to pubertal stage so that 50% of the patients in each treatment group was prepubertal (as defined by Tanner stage ≤ II\(^{13}\)). Using this method, a truly pediatric population was selected. Separate randomization in blocks, for each country and each stratum, was performed centrally by computer. A double dummy technique was used to ensure complete masking of the study treatment: subjects took either prednisolone tablets and placebo capsules or budesonide capsules and placebo tablets. Study drugs were taken once daily, in the morning, before breakfast. Treatment duration was 12 weeks. Patients treated with prednisolone had a dosing scheme that was determined by body weight: 1 mg/kg daily for 4 weeks, followed by 8 weeks of tapering to a dose of 2.5 mg/day (Appendix 2). Patients treated with budesonide received 9 mg (3 capsules of 3 mg) daily for 8 weeks, followed by 6 mg for 4 weeks, irrespective of age or weight of the patient. Concomitant placebo capsules (in the group taking prednisolone tablets) or placebo tablets (in the patients taking budesonide capsules) were administered in a dosing regimen identical to the active drugs.
Efficacy

Disease activity was assessed before treatment and after 2, 4, 8, and 12 weeks by CDAI\textsuperscript{14} and Paediatric CDAI (PCDAI)\textsuperscript{15}. For the purpose of this study, CDAI was minimally modified for use in pediatric patients: hematocrit cut-off value was set at 41%, and standard weight was replaced by ideal (50\textsuperscript{th} percentile) weight for actual height, as determined from growth diagrams for children in the Netherlands\textsuperscript{16}.

Safety

Safety assessment at each visit consisted of the recording of any adverse events; clinical chemical and hematological measurements; physical examination; vital signs; and active questioning for possible glucocorticosteroid (GCS)-associated side effects. Blood samples for morning plasma cortisol levels were drawn at 2, 4 and 12 weeks between 8 and 10 a.m. In addition, a short adrenocorticotropic hormone (ACTH) stimulation test, measuring plasma cortisol before, 30 and 60 minutes after intravenous injection of 0.25 mg of ACTH, was performed before study start and after 8 weeks of treatment. Test results were considered normal if basal cortisol was 150 nmol per liter (5.4 $\mu$g per deciliter) or more, and either peak cortisol was at least 400 nmol/L (14.5 $\mu$g per deciliter) or increase was at least 200 nmol/L (7.25 $\mu$g per deciliter), or both. Cortisol samples from all participating centers were analyzed by modified high-performance liquid chromatography\textsuperscript{17}.

Statistical analysis

The sample size of 120 patients was chosen in order to detect a 20% difference in remission rate between the treatment groups at week 8, with a power of 80% and a significance level of 5%. According to an intention-to-treat approach, all patients who underwent randomization were included in the analysis. All outcome measures were analyzed with use of the last available value after the baseline measurement, whenever data were missing. To compare remission rates in the 2 groups, chi-square tests were used. Analysis of variance was used for comparison of all other data, with the pre-treatment
value as covariate and country and treatment as factors. All tests were two-tailed. P-values of 0.05 or below were considered to indicate statistical significance. For comparison of GCS side effects in both groups, an analysis of treatment emergent GCS side effects was performed. A GCS side effect was considered treatment emergent if it was not present at baseline but present at some time during the treatment, or if it had higher intensity during treatment than at baseline. No interim statistical analyses were carried out.

Results

Patients were included from April 1998 to December 2000. At this time, 56 patients had been enrolled at 22 (of the 36 participating) centers and the study was terminated prematurely due to low enrolment numbers. Patient flow is shown in Figure 1.

![Patient flow diagram](https://example.com/patient_flow.png)

**Figure 1.**
In both treatment groups, a considerable number of patients had to discontinue treatment because of worsening of Crohn’s disease. Mean time to discontinuation was 35 days in the budesonide group, and 43 days in the prednisolone group. The patients were well matched for age, sex, pubertal stage, disease activity, and time since diagnosis (Table 1).

**Table 1.** Baseline characteristics of patients with active CD treated with budesonide or prednisolone (means ±SD)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Budesonide group</th>
<th>Prednisolone group</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>22</td>
<td>26</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>15/7</td>
<td>18/8</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>13 ± 2.2</td>
<td>13 ± 2.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>40 ± 10.4</td>
<td>40 ± 10.4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>155 ± 15.0</td>
<td>156 ± 15.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>16 ± 3.0</td>
<td>16 ± 2.3</td>
</tr>
<tr>
<td>Tanner stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>&gt;2</td>
<td>10</td>
<td>13</td>
</tr>
<tr>
<td>Disease location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ileum</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Ileum and colon</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Colon</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>CDAI</td>
<td>239 ± 32</td>
<td>268 ± 61</td>
</tr>
<tr>
<td>PCDAI</td>
<td>39 ± 10.7</td>
<td>45 ± 10.7</td>
</tr>
<tr>
<td>Time since diagnosis (yr)</td>
<td>0.6 ± 1.1</td>
<td>0.8 ± 1.5</td>
</tr>
</tbody>
</table>

The differences between the groups were not significant.
Clinical Efficacy

At baseline, patients in both treatment groups had mild to moderate disease as indicated by CDAI and PCDAI. In the prednisolone group, mean CDAI and PCDAI were slightly higher than in the budesonide group. In addition, there were more patients with ileocolonic disease in the prednisolone group, compared to the budesonide group that consisted of patients with predominantly ileal disease. These differences were not statistically significant. In both the budesonide group and the prednisolone group, about 50% of the patients were in clinical remission within 2 weeks of treatment. At the primary endpoint of 8 weeks, 12/22 patients in the budesonide group (55%) and 17/24 patients in the prednisolone group (71%) were in clinical remission (difference -16%; 95% CI -45, 13; p = 0.25) (Figure 2)

Figure 2.

Mean (+SE) proportion of patients with Crohn’s disease in remission after 2, 4, 8, and 12 weeks of treatment with budesonide or prednisolone. Remission was defined as a score of 150 or lower in the Crohn’s Disease Activity Index (CDAI). At none of the timepoints, a significant difference was reached.
Mean CDAI values in the budesonide group stayed higher at all timepoints during treatment, compared to the prednisolone group. Both treatment groups reached the maximal clinical effect at week 8: mean CDAI was 149 with budesonide, and 97 with prednisolone ($p = 0.047$) (Figure 3).

![Graph showing CDAI scores](image)

**Figure 3.**

Mean ($\pm$SE) scores on the Crohn's Disease Activity Index (CDAI) at baseline and during treatment with budesonide or prednisolone. At week 8, there was statistical significance (*$p = 0.047$) for the difference between the treatment groups in mean CDAI.
Mean PCDAI values showed a similar trend, with a significant difference at week 4 (Figure 4). Correlation between PCDAI and CDAI scores recorded on a total of 176 occasions was good (Pearson’s correlation coefficient, $r = 0.822$, $p<0.001$).

![Figure 4.](image)

Mean (±SE) scores on the Pediatric Crohn’s Disease Activity Index (PCDAI) at baseline and during treatment with budesonide or prednisolone. At week 4, there was statistical significance (*$p = 0.034$) for the difference between the treatment groups in mean PCDAI.

**Laboratory variables**

Mean erythrocyte sedimentation rate (ESR) decreased in both groups during treatment: the mean change (±SD) from baseline was −5 (±13) mm/hr in the budesonide group and −13 (±15) mm/hr in the prednisolone group ($p<0.05$). There was a slight increase in mean hematocrit levels (0.7% and 3.1%) and mean hemoglobin values (5 g/l and 17 g/l) during treatment in both the
budesonide and the prednisolone groups, respectively. All other results of chemistry and hematology tests did not show any clinically relevant changes during treatment in either group.

**Adverse events**

Adverse events were common in both groups: 91% of patients in the budesonide group and 96% of patients receiving prednisolone experienced at least 1 adverse event. The adverse events (Table 2) were mostly gastrointestinal disorders, and did not show significant differences between the treatment groups. Headache of mild to moderate intensity was relatively common in both groups. Fatigue was present in 3 budesonide-treated patients, but in none of the patients receiving prednisolone.

**Table 2. Most commonly reported Adverse Events**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th><strong>Budesonide Group</strong></th>
<th><strong>Prednisolone Group</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=22</td>
<td>n=26</td>
</tr>
<tr>
<td></td>
<td>number of patients</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Anorexia</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Fever</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>ESR increased</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Anemia hypochromic</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Most common adverse events: reported in more than 2 patients, during any treatment. None of the differences were statistically significant.

Eight patients in the prednisolone group and 3 patients in the budesonide group experienced serious adverse events, the majority being hospitalizations due to worsening of Crohn’s disease. Seven of the prednisolone patients and 1 of the budesonide patients were withdrawn from the study in connection with a serious adverse event. A relationship between these serious adverse events...
and the study drug was judged to be unlikely by the investigators. Discontinuations due to non-serious adverse events (all aggravation of Crohn's disease) occurred in 1 prednisolone patient and 3 budesonide patients.

Glucocorticosteroid (GCS)-associated side effects

Possible GCS-associated side effects were reported from active questioning at each study visit, and are presented in Table 3. In 11/22 patients receiving budesonide and in 20/26 patients receiving prednisolone, at least one GCS-side effect (such as moon face, buffalo hump, acne, hirsutism, striae, bruising, swollen ankles, hair loss, mood swings, depression, and insomnia) occurred. Moon face and acne occurred significantly less in the patients taking budesonide. None of the patients experienced any changes in pulse rate, blood pressure, or physical findings that were considered clinically relevant.

Table 3. Treatment emergent (i.e., new or aggravated) possible glucocorticosteroid-associated side effects in patients treated with budesonide or prednisolone

<table>
<thead>
<tr>
<th></th>
<th>Budesonide n=22</th>
<th>Prednisolone n=26*</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moon face</td>
<td>5</td>
<td>15</td>
<td>0.01</td>
</tr>
<tr>
<td>Buffalo hump</td>
<td>0</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Acne</td>
<td>1</td>
<td>7</td>
<td>0.033</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>2</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>Skin striae</td>
<td>0</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Bruising easily</td>
<td>1</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Swollen ankles</td>
<td>0</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Hair loss</td>
<td>1</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>Mood swings</td>
<td>3</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Depression</td>
<td>2</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Any such sign**</td>
<td>11</td>
<td>20</td>
<td>0.030</td>
</tr>
</tbody>
</table>

* One of these had no on-treatment data regarding possible GCS side effects.
** Some patients had more than one sign.
NS = not statistically significant
Cortisol and ACTH tests

Plasma cortisol levels decreased during treatment in both groups as shown in Figure 5. Mean morning plasma cortisol levels were significantly higher in the budesonide group at all times except at week 12, reflecting less adrenal suppression during budesonide treatment. At week 8, plasma cortisol was 200 nmol/L, compared to 98 nmol/L in the prednisolone group (difference -102 nmol/L; 95% CI -226, -52; p = 0.0028). A morning plasma cortisol level of ≥150 nmol/l (5.4 μg/dl) was considered normal. In the budesonide group, 58% of the patients had a normal basal cortisol level at week 8, whereas in the prednisolone group, only 29% had a morning plasma cortisol level of ≥150 nmol/l (p=0.052, chi-square test).

Figure 5.

Mean (±SE) plasma cortisol concentrations in patients with active Crohn's disease at baseline and after 2, 4, 8, and 12 weeks of treatment with budesonide or prednisolone. Plasma cortisol was measured between 8 and 10 a.m. at each visit. A value of 150 nmol/l (5.4 μg/dl) or more was considered to be normal. To convert plasma cortisol values to μg/dl, divide by 27.6. At week 2, 4 and 8, the difference in cortisol levels between the treatment groups was statistically significant (*p < 0.0001, p = 0.0026, and p = 0.0028, respectively).
At baseline, ACTH test results were normal in all patients, except for 1 patient in the budesonide group. After 8 weeks of treatment, ACTH test results were normal in 6 patients (of 16 patients tested, 38%) in the budesonide group, and in 2 patients (of 18, 11%) in the prednisolone group (p=0.07, t-test).

Discussion

We present the first prospective trial of oral budesonide versus prednisolone in children with Crohn’s disease. The study is unique in being the first pediatric, randomised, controlled, double blind, multicenter drug trial in Crohn’s disease in Europe. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) undertook the study as a combined effort of investigators in 8 countries: Sweden, the Netherlands, Belgium, Germany, the United Kingdom, France, Spain, and Switzerland. The study shows that budesonide is a safe and effective drug for the treatment of children with active Crohn’s disease involving ileum and/or ascending colon. Although remission rates at 8 weeks were not significantly different for budesonide and prednisolone, there was a trend for prednisolone to be more effective. In adults, a recent meta-analysis of 4 studies comparing budesonide and conventional corticosteroids7, 10-12, including a total of 621 adult patients, did show that budesonide was slightly but significantly less effective than conventional corticosteroids for inducing remission in active Crohn’s disease (pooled risk difference −8.5%, p=0.02)18.

Small sample size is a limitation of our study. Several reasons for low enrolment of patients existed, such as the exclusion of patients presenting with colitis (instead of localized disease) and the tendency to treat primarily children with new-onset Crohn’s disease with enteral nutrition. It seems obvious to blame the small sample size for the non-significance of the observed 16% difference in remission rate. However, even with 120 patients, this difference would not have been significant (p = 0.063).
There was a non-significant imbalance between the two groups before treatment. We do not know whether the slightly higher clinical disease activity at entry and the predominance of ileocolonic disease in the prednisolone group has influenced remission rate negatively.

The proportion of patients who had worsening of disease activity during the 12-week treatment period was high: 6/22 patients in the budesonide group, and 8/26 in the prednisolone group. Worsening of clinical symptoms occurred both before and after tapering of the dose. The relative number of discontinuations in both groups was twice as high in children as compared to the similar study in adults with active ileocecal Crohn's disease. Although at entry the children in this study had similar disease activity as the adults, most children had new-onset disease. The "relapse rate" in our study population is consistent with the rate of steroid dependency of 36% that has been reported in a prospective study of first steroid treatment course in adults.

As for clinical side effects, moon face was almost 3 times as common in the prednisolone group, and acne was reported significantly more often. Most of the other Cushingoid features tended to occur more often as a result of prednisolone treatment, although not reaching statistical significance.

It appears that the frequency of moon face in children during prednisone treatment (in 15/26, 60%) is almost twice that reported in adults (25%-35%) receiving the same treatment. For budesonide, the difference was less striking: 5 of 22 patients (23%) developed moon face during treatment, compared to 7%, 14% and 17% of the adults. Striae were not reported in adults, while the incidence was 12% in pediatric patients. Could the higher incidence of certain GCS-associated side effects in children as compared to adults be attributed to a higher dose per kg body weight in the pediatric patients? In the adult dose-ranging study, cortisol suppression was clearly dose-related, but GCS-associated side effects were not. The budesonide dose that was chosen for all children in our study was 9 mg daily, identical to the dose shown to be effective and safe in adults. The prednisolone dose was determined by body weight (1 mg per kg), while in adults it was 40 mg for the first 2 weeks followed by a tapering scheme. Mean body weight in this pediatric study was 40 kg.
Budesonide versus prednisolone

(range 22-58 kg); in the adults it was approximately 60 kg. The range of body weights of the children in this study has made it possible to look for a relation between dose and effect or between dose and side effects. In reality, we have not been able to find any such correlation between the dose of budesonide per kg and side effects and we do not have a good explanation for the difference in clinical side effects in children and adults.

Likewise, there was no correlation of dose per kg and any of the efficacy variables: the mean daily dose of budesonide in children achieving remission was 0.246 mg/kg/day, while the dose was 0.224 mg/kg/day in non-remitters (p=0.32, t-test).

Long-term glucocorticosteroid associated side effects in children such as linear growth retardation and bone demineralization have not been studied here, and they need to be evaluated in long-term maintenance studies.

In summary, we could not detect a significant difference between remission rates with oral budesonide and prednisolone as treatment of children with active Crohn's disease involving the ileum and/or ascending colon. There was however a trend for prednisolone to be more effective. Regardless, the highly significant difference in glucocorticosteroid side effects and adrenal axis suppression outweighs the possibility that prednisolone may be slightly more effective than budesonide in pediatric patients. In children and adolescent patients in particular, cosmetic changes such as moon face and acne can severely reduce self-esteem and social functioning. If effective, budesonide is a good alternative for prednisolone in children with mild to moderate ileocecal Crohn's disease.
Appendix 1. European Collaborative Research Group on Budesonide in Pediatric IBD

Steering committee

Astrid Lindgren Children’s Hospital, Karolinska Hospital

Huddinge University Hospital

Sophia Children’s Hospital

Emma Children’s Hospital AMC

Institute of Child Health, Birmingham Children’s Hospital

Royal Free Hospital

Booth Hall Children’s Hospital

University Hospital for Children

Deutsche Klinik für Diagnostik

Hôpital Robert Debré

Hôpital Necker - Enfants Malades

Hôpital Jeanne de Flandre

Universitäts-Kinderspital

Stockholm, Sweden

Huddinge, Sweden

Rotterdam, The Netherlands

Amsterdam, The Netherlands

Birmingham, United Kingdom

London, United Kingdom

Manchester, United Kingdom

Bonn, Germany

Wiesbaden, Germany

Paris, France

Paris Cedex, France

Lille Cedex, France

Zürich, Switzerland

Hans Hildebrand

Bo Lindquist

Hans Büller

Johanna (Hankje) Escher

Jan Taminiau

Bert Derkx

Stephen Murphy

John A. Walker Smith

Victor Miller

Adrian Thomas

Michael Lentze

Klaus-Michael Keller

Jean Pierre Cezard

Jean Francois Mougenot

Olivier Goulet

Dominique Turck

Christian Braegger

Advisory committee

Children’s Hospital

Massachusetts General Hospital

Texas Children’s Hospital

Hospital for Sick Children

Boston, Massachusetts, USA

Boston, Massachusetts, USA

Houston, Texas, USA

Toronto, Ontario, Canada

Richard J Grand

Harland Winter

George D Ferry

Anne Griffiths

Investigators

Östra Sjukhuset

Medical and Dental School of Barts and the London Queen Mary

Booth Hall Children’s Hospital

Göteborg, Sweden

London, United Kingdom

Manchester, United Kingdom

Robert Saalman

Nick Croft

Ian Sanderson

Suzanne Davison
<table>
<thead>
<tr>
<th>Institution</th>
<th>City</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheffield Children’s Hospital</td>
<td>Sheffield</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>University Hospital for Children</td>
<td>Erlangen</td>
<td>Germany</td>
</tr>
<tr>
<td>JWG University</td>
<td>Frankfurt</td>
<td>Germany</td>
</tr>
<tr>
<td>Klinik für Kinderheilkunde und Jugendmedizin, Marienhospital, Munich</td>
<td>Munich</td>
<td>Germany</td>
</tr>
<tr>
<td>Kinderpoliklinik der Universität München</td>
<td>Munich</td>
<td>Germany</td>
</tr>
<tr>
<td>University Children’s Hospital Queen Fabiola</td>
<td>Brussels</td>
<td>Belgium</td>
</tr>
<tr>
<td>Brussels University Academic Hospital</td>
<td>Brussels</td>
<td>Belgium</td>
</tr>
<tr>
<td>University Clinic Saint Luc</td>
<td>Brussels</td>
<td>Belgium</td>
</tr>
<tr>
<td>University Hospital Gasthuisberg</td>
<td>Leuven</td>
<td>Belgium</td>
</tr>
<tr>
<td>Queen Paola Children’s Hospital</td>
<td>Antwerpen</td>
<td>Belgium</td>
</tr>
<tr>
<td>University Hospital Antwerp</td>
<td>Edegem</td>
<td>Belgium</td>
</tr>
<tr>
<td>Hospital St. Joseph Espérance</td>
<td>Montegnée</td>
<td>Belgium</td>
</tr>
<tr>
<td>University Hospital</td>
<td>Gent</td>
<td>Belgium</td>
</tr>
<tr>
<td>Hospital La Fe</td>
<td>València</td>
<td>Spain</td>
</tr>
<tr>
<td>Hospital San Joan de Deu</td>
<td>Barcelona</td>
<td>Spain</td>
</tr>
<tr>
<td>Hospital de La Paz</td>
<td>Madrid</td>
<td>Spain</td>
</tr>
<tr>
<td>Hospital Niño Jesús</td>
<td>Madrid</td>
<td>Spain</td>
</tr>
<tr>
<td>Hospital 12 de Octubre, Hospital Materno Infantil</td>
<td>Madrid</td>
<td>Spain</td>
</tr>
<tr>
<td>Ostschweizer Kinderspital</td>
<td>St Gallen</td>
<td>Switzerland</td>
</tr>
</tbody>
</table>

**Investigators, continued**

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>C J Taylor</td>
<td>Sheffield Children’s Hospital</td>
</tr>
<tr>
<td>Rolf Behrens</td>
<td>University Hospital for Children</td>
</tr>
<tr>
<td>Hans-Georg Posselt</td>
<td>JWG University</td>
</tr>
<tr>
<td>Burkhard Rodeck</td>
<td>Klinik für Kinderheilkunde und Jugendmedizin, Marienhospital, Munich</td>
</tr>
<tr>
<td>Sibylle Koletzko</td>
<td>Kinderpoliklinik der Universität München</td>
</tr>
<tr>
<td>Samy Cadranel</td>
<td>University Children’s Hospital Queen Fabiola</td>
</tr>
<tr>
<td>Yvan Vandenplas</td>
<td>Brussels University Academic Hospital</td>
</tr>
<tr>
<td>Jean-Paul Buts</td>
<td>University Clinic Saint Luc</td>
</tr>
<tr>
<td>Geneviève Veereman</td>
<td>University Hospital Gasthuisberg</td>
</tr>
<tr>
<td>Micheline Bertrand-van Caillie</td>
<td>Queen Paola Children’s Hospital</td>
</tr>
<tr>
<td>André Deprettere</td>
<td>University Hospital Antwerp</td>
</tr>
<tr>
<td>Francoise Bury</td>
<td>Hospital St. Joseph Espérance</td>
</tr>
<tr>
<td>Myrian Vanwinckel</td>
<td>University Hospital</td>
</tr>
<tr>
<td>Carmen Ribes</td>
<td>Hospital La Fe</td>
</tr>
<tr>
<td>Vicente Varea</td>
<td>Hospital San Joan de Deu</td>
</tr>
<tr>
<td>Gerardo Prieto</td>
<td>Hospital de La Paz</td>
</tr>
<tr>
<td>Dolores García Novo</td>
<td>Hospital Niño Jesús</td>
</tr>
<tr>
<td>Javier Manzanares</td>
<td>Hospital 12 de Octubre, Hospital Materno Infantil</td>
</tr>
<tr>
<td>Denise Herzog</td>
<td>Ostschweizer Kinderspital</td>
</tr>
</tbody>
</table>

**Sponsor**

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>AstraZeneca</td>
<td>Lund, Sweden</td>
</tr>
<tr>
<td>Eva Lyckegaard</td>
<td>Tore Persson</td>
</tr>
</tbody>
</table>
Appendix 2. Prednisolone dosing and tapering scheme

<table>
<thead>
<tr>
<th>Week</th>
<th>1-4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 25 kg</td>
<td>20</td>
<td>17.5</td>
<td>15</td>
<td>12.5</td>
<td>10</td>
<td>7.5</td>
<td>5</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>&gt;25-≤ 30 kg</td>
<td>25</td>
<td>20</td>
<td>15</td>
<td>12.5</td>
<td>10</td>
<td>7.5</td>
<td>5</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>&gt;30-≤ 35 kg</td>
<td>30</td>
<td>25</td>
<td>20</td>
<td>15</td>
<td>12.5</td>
<td>10</td>
<td>7.5</td>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td>&gt;35-≤ 40 kg</td>
<td>35</td>
<td>30</td>
<td>25</td>
<td>20</td>
<td>15</td>
<td>10</td>
<td>7.5</td>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td>&gt;40 kg</td>
<td>40</td>
<td>35</td>
<td>30</td>
<td>25</td>
<td>20</td>
<td>15</td>
<td>10</td>
<td>5</td>
<td>2.5</td>
</tr>
</tbody>
</table>
References


Successful treatment of metastatic Crohn’s disease with infliximab

Johanna C Escher\textsuperscript{1,2}
Tom J Stoof\textsuperscript{3}
Sander JH van Deventer\textsuperscript{4}
A Marcelien van Furth\textsuperscript{5}

Department of Pediatric Gastroenterology and Nutrition
Emma Children’s Hospital AMC, Amsterdam, The Netherlands\textsuperscript{1}
Center for Inflammatory Bowel Disease
Division of Gastroenterology and Nutrition
The Children’s Hospital, Boston, USA\textsuperscript{2}
Department of Dermatology
Free University Hospital, Amsterdam, The Netherlands\textsuperscript{3}
Department of Experimental Internal Medicine
AMC, Amsterdam, The Netherlands\textsuperscript{4}
Department of Paediatric Infectious Diseases
Free University Hospital, Amsterdam, The Netherlands\textsuperscript{5}

**Introduction**

Extra-intestinal manifestations of Crohn's disease are not uncommon and may precede the emergence of gastrointestinal symptoms. Dermatological manifestations, reported in 1-10% of children with Crohn's disease\(^1\), can occur without specific histopathological abnormalities (i.e. erythema nododum, pyoderma gangrenosum) or may be referred to as metastatic Crohn's disease, with characteristic granulomatous skin lesions affecting the groins, the male and female genitalia, or submammary regions. Isolated symptoms of the skin of penis and scrotum have been described before in several case reports of children\(^2-5\). Medical treatment of this rare condition has been of limited value. We report a boy with cutaneous, metastatic Crohn's disease of the penile and scrotal skin, who was the first to be treated with anti-tumor necrosis factor \(\alpha\) antibody (infliximab).

**Case report**

An otherwise healthy boy presented at the age of 10 years with a 6-week history of a swollen penis and scrotum, causing only minor discomfort during tennis playing but major embarrassment at shower sessions after school gymnastics. Over the past 2.5 years, he had episodes of minimal rectal bleeding associated with firm stools in the presence of a small anal fissure. There was no history of malaise, anorexia, weight loss, fever, profuse sweating, diarrhea, dysuria or hematuria.

On examination, the boy was in excellent condition with a normal height and weight for his age. A diffuse non painful soft swelling of the prepubertal penis and scrotum was seen, and the scrotal skin was slightly red. The perianal region showed one indolent perianal tag, a small anal fissure but no fistula. All hematological laboratory values were normal, thus demonstrating no signs of an acute infection or inflammatory disease. His urine contained no bacteria, nor white or red blood cells.
Local genital symptoms increased after a biopsy from the penile skin, which showed granulomas in the dermis and lymphatic spaces (Figure 1). A biopsy from the perianal skin showed similar abnormalities.

**Figure 1.** Histopathology of scrotal skin biopsy; granulomatous infiltrate

Appropriate tests ruled out local anatomic or vascular abnormalities, infectious causes such as tuberculosis or atypical mycobacterial infection, syphilis, chlamydia, fungal infection or leishmaniasis or presence of immune-mediated disease such as histiocytosis or sarcoidosis.

Expecting to establish a diagnosis of inflammatory bowel disease, a thorough gastrointestinal work-up was performed. However, ultrasound, enteroclysis, upper endoscopy and ileocolonoscopy with multiple biopsies failed to show any evidence of intestinal inflammation. Magnetic Resonance Imaging scan of the sacral region demonstrated a slight thickening of the rectal mucosa. Ileocolonoscopy and histology, repeated 1½ years after initial presentation was still normal. On the basis of the above, Crohn’s disease with metastatic genital granulomatous lymphangitis was diagnosed.
In our patient, treatment with oral prednisolone alone or in combination with azathioprine or courses of intravenous cyclosporine only transiently reduced his genital lymphedema (Figure 2A). Based on previous experience with therapy-resistant perineal metastatic Crohn's disease, it was decided to start treatment with a monoclonal anti-tumor necrosis factor antibody (anti-TNF-α, infliximab, 5 mg/kg infusions at week 0, 4 and 12) in combination with oral azathioprine, 1 year and 10 months after onset of the symptoms. Within one week after a single infusion, swelling and variable redness decreased (Figure 2B). With two repeat infusions (at week 4 and 12), treatment success was maintained (Figure 2C). The boy had experienced moderate fatigue, the first two days after the second and third infusion, but no other side effects were demonstrated. Maintenance treatment with azathioprine (2.5 mg/kg/day) was continued.

Relapse of genital swelling occurred, 14 months after cessation of infliximab infusions, and the treatment was re-installed on a 8-weekly-basis. Again, remission of symptoms was observed within 2 weeks, and still no signs of gastrointestinal Crohn's disease were present. At present, the boy receives infliximab maintenance treatment (infusion every 6-8 weeks for the past 12
months), and there is some remaining indurated swelling of scrotum and penis. For cosmetic reasons, surgery is currently being planned. Now more than 4 years after first presentation of the genital manifestations, no bowel symptoms are present.

**Discussion**

The symptom of isolated genital edema in a boy has a differential diagnosis, listed in Table 1, that would normally not include metastatic Crohn’s disease.

**Table 1. Differential diagnosis of genital edema**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Clinical features and appropriate test(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute epididymitis</td>
<td>Acute onset, painful</td>
</tr>
<tr>
<td>Orchitis</td>
<td>Acute onset, painful</td>
</tr>
<tr>
<td>Testicular trauma</td>
<td>Hematoma, history of trauma</td>
</tr>
<tr>
<td>Henoch-Schönlein purpura (with isolated oedema of scrotal skin, or vasculitis affecting the testis)</td>
<td>Characteristic purpuric skin lesions, acute onset, accompanied by abdominal pain, joint disease, or renal disease; skin biopsy: vasculitis</td>
</tr>
<tr>
<td>Idiopathic scrotal (or penile) oedema</td>
<td>Rapid onset, accompanied by erythema, extending to abdominal wall; ultrasound: edema of scrotal wall</td>
</tr>
<tr>
<td>Testicular torsion</td>
<td>Painful, unilateral, discoloration; immediate surgery on suspicion</td>
</tr>
<tr>
<td>Primary lymphedema of scrotum and penis</td>
<td>Concurrent oedema of legs; ultrasound, lymphangiogram</td>
</tr>
<tr>
<td>Scrotal hernia</td>
<td>Characteristic palpation; ultrasound</td>
</tr>
<tr>
<td>Large pelvic tumor (compressing pelvic and inguinal lymphatic and venous systems)</td>
<td>Abdominal mass; ultrasound</td>
</tr>
<tr>
<td>Posterior urethral valves (resulting in bladder distention accompanied by venous and lymphatic obstruction)</td>
<td>Abdominal mass; ultrasound, cystogram</td>
</tr>
</tbody>
</table>

In this case, other conditions were certainly considered, but all were ruled out on the basis of either laboratory results or clinical condition. After the skin biopsy, the differential diagnosis could be narrowed down to that of a
granulomatous skin infiltration, as listed in Table 2. Positive signs of Crohn's disease in this case were the characteristic granulomatous infiltrate of the scrotal skin, and the presence of subtle perianal lesions, such as a tag and a minor fissure.

Table 2. Differential diagnosis of granulomatous skin lesions in genital region

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Clinical features and appropriate test(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarcoïdosis</td>
<td>Fever of unknown origin, lung problems, fatigue, skin rash, lymphadenopathy; chest X-ray, biopsy of &gt; 1 organ showing non-caseating granuloma on histology</td>
</tr>
<tr>
<td>Tuberculosis of skin and/or lymph nodes or atypical Mycobacterial infection</td>
<td>Lymph nodes firm on palpation, low grade fever; PPD and tuberculin skin test (often negative), PCR and culture of biopsy</td>
</tr>
<tr>
<td>Foreign body reactions</td>
<td>History of trauma; ultrasound</td>
</tr>
<tr>
<td>Fungal infections (i.e. histoplasmosis, sporotrichosis)</td>
<td>Histoplasmosis: fever, weight loss, lymphadenopathy, skin lesions; culture from skin lesions; Lymphocutaneous sporotrichosis: erythematous papule, then nodule, sometimes lymphatic spread, formation of s.c. nodules that ulcerate; culture from skin and/or lymph node: Sporothrix schenckii</td>
</tr>
<tr>
<td>Lymphogranuloma venereum (chlamydia)</td>
<td>Skin ulcers on genitals, swollen inguinal lymph nodes, oedematous and red skin, systemic signs; syphilis test often falsely positive, biopsy of skin and/or lymph node, culture</td>
</tr>
<tr>
<td>Filariasis</td>
<td>Lymphatic filariasis: history of travel, lymphoedema of extremities and/or genital area (elefantiasis); direct exam of blood smear, antigen detection, PCR: nematode species (i.e. W. Bancrofti, Onchocerca Volvulus)</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>History of exposure to sandflies or travel, systemic symptoms, skin lesions (ulcers, macules or papules); Montenegro skin test, skin and/or lymph node biopsy, culture</td>
</tr>
<tr>
<td>Connective tissue disorders</td>
<td>Systemic signs and other &quot;specific&quot; symptoms; various serological tests, none of them specific</td>
</tr>
<tr>
<td>Paraneoplastic syndromes</td>
<td>Depending on primary neoplasm</td>
</tr>
<tr>
<td>Wegener's granulomatosis</td>
<td>Starting with upper respiratory problems, i.e. chronic sinusitis, but initial symptoms may also be granulomatous skin reaction; biopsy of nasal mucosa, of skin and/or lung, serology: C-ANCA</td>
</tr>
<tr>
<td>Langerhans' cell histiocytosis</td>
<td>Failure to thrive, seborrheic dermatitis of scalp, generalized rash, sometimes bone pain; bone X-ray, skin biopsy (Langerhans' cells)</td>
</tr>
<tr>
<td>Metastatic Crohn's disease</td>
<td>Perianal signs (tags, fissure, abscess, fistula), gastrointestinal complaints, systemic signs; ileocolonoscopy with biopsies</td>
</tr>
</tbody>
</table>
Four cases very similar to this have been described$^{2-5,7}$, but all patients had bowel symptoms (and gastrointestinal inflammation) occurring either before$^2$, simultaneously$^{3,7}$, or years after the onset of genital symptoms$^{4,5}$. In an excellent review and additional case reports by Ploysangam et al., 80 cases of cutaneous Crohn’s disease are described, 14 of whom are children; two thirds of the children had genital involvement, and in 11 of the children, cutaneous Crohn’s disease preceded intestinal Crohn’s disease by weeks to 6 years$^7$. Metastatic Crohn’s disease in the skin of male genitals seems to present in a different way in children$^{2-5}$, as compared to the disease in adults$^{8-10}$. Children present with genital oedema, whereas adult men have ulceration of the penile and/or scrotal skin, often in conjunction with perianal disease, such as extensive fistulae. Recently, however, two young adult cases were described to present with genital swelling as well$^{11}$. Apart from this location, cases of metastatic Crohn’s disease have been described in the face$^{12}$, retro-auricular area$^{13}$, upper or lower extremities$^{14-20}$, perineal area$^6$, vulva$^{7,21-24}$, and lungs$^{25}$. Treatment of metastatic Crohn’s disease with different chemotherapeutic agents including oral steroids$^{2-5,7,10,18}$, topical steroids$^{7,8}$, azathioprine$^{3,4,10,13}$, sulfasalazine$^3$, metronidazole$^{3,4,12}$, or tetracyclines$^{21}$ has demonstrated to have variable success. In general, treatment seems to be less effective when metastatic Crohn’s disease has been of long duration. Two adults with therapy-resistant metastatic Crohn’s disease in the perineum have succesfully been treated with anti-tumor necrosis factor antibody$^6$, and this experience lead us to decide to use similar treatment in our patient. Table 3 shows the various treatment options for metastatic Crohn’s disease in the skin of penis and scrotum. This unusual manifestation of metastatic Crohn’s disease in a child is the first case to demonstrate a beneficial effect of immunomodulatory treatment with infliximab and azathioprine on genital lymphedema in a boy, even if treatment begins almost two years after onset. Whether this child will have further intestinal inflammation in the coming years is of course unknown.
### Table 3. Treatment options for metastatic Crohn's disease in penis and scrotum

<table>
<thead>
<tr>
<th>Reference</th>
<th>Pediatric/adult</th>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherton 1978&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Pediatric (boy, 6 y)</td>
<td>Bed rest, scrotal support, penicillin, oral prednisolone (30 mg daily)</td>
<td>Some reduction normal genitalia after 3 weeks</td>
</tr>
<tr>
<td>Cockburn 1980&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Adult (36 y)</td>
<td>Oral prednisone, diuretics, topical steroid, excision</td>
<td>No response</td>
</tr>
<tr>
<td>Slaney 1986&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Adult (25 y and 27 y)</td>
<td>Case 1: azathioprine (2 mg/kg/d)</td>
<td>General improvement, fistula healing, but persistent ulcer at base of penis</td>
</tr>
<tr>
<td>Case 2: cotrimoxazole and steroids</td>
<td></td>
<td></td>
<td>After 6 weeks, almost complete healing; one year follow-up: no relapse</td>
</tr>
<tr>
<td>Ninan 1992&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Pediatric (boy, 10 y)</td>
<td>Scrotal support, metronidazole (200 mg t.i.d.), 2 weeks, oral prednisolone (40 mg/d), 2 weeks, rapid tapering; maintenance treatment: salazopyrine</td>
<td>Slow reduction of genital oedema, persistent induration of scrotal and penile skin; relapse after 5 years</td>
</tr>
<tr>
<td>Relapse treatment: repeat of above, then azathioprine</td>
<td></td>
<td></td>
<td>No response, some resolution</td>
</tr>
<tr>
<td>Ploysangam 1997&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Pediatric (boy, 10 y)</td>
<td>Metronidazole (250 mg t.i.d.), 1 month</td>
<td>Decreased erythema and induration of scrotum</td>
</tr>
<tr>
<td>Chiba 1997&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Adult (22 y)</td>
<td>Topical steroid</td>
<td>Good response, healing of ulcer</td>
</tr>
<tr>
<td>Lehnhbecher 1999&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Pediatric (boy, 9 y)</td>
<td>Metronidazole (20 mg/kg/d), 2 weeks and oral prednisone (2 mg/kg/d, tapered to 1 mg/kg/d, continued as maintenance treatment for 1-2 years)</td>
<td>Marked improvement, fistula healing;</td>
</tr>
<tr>
<td>Relapse treatment: metronidazole (20 mg/kg/d); maintenance on prednisone (0.3 mg/kg/d, eventually alternate day) and azathioprine (1.5 mg/kg/d) metronidazole (5 mg/kg/d)</td>
<td></td>
<td></td>
<td>Relapse after 2 years</td>
</tr>
<tr>
<td>Relapse after 2 years</td>
<td>Fast response; sustained remission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case report NEJM 2000&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Pediatric (boy, 13 y)</td>
<td>Antibiotics and topical steroids, mesalamine, metronidazole, prednisolone</td>
<td>No response, less gastrointestinal complaints, but no improvement in lymphedema</td>
</tr>
</tbody>
</table>
References


Treatment of inflammatory bowel disease in childhood: best available evidence

Johanna C Escher¹²
Jan Taminiau¹
Edward ES Nieuwenhuis³
Hans A Büller⁴
Richard J Grand²

Department of Pediatric Gastroenterology and Nutrition
Emma Children’s Hospital AMC, Amsterdam, The Netherlands¹
Center for Inflammatory Bowel Disease
Division of Gastroenterology and Nutrition
The Children’s Hospital, Boston, USA²
Gastroenterology Division, Brigham and Women’s Hospital
Harvard Medical School, Boston, USA³
Department of Pediatrics, Sophia Children’s Hospital
Erasmus University of Rotterdam, The Netherlands⁴

Condensed version accepted for publication in Inflammatory Bowel Diseases
Abstract

The physician treating children with inflammatory bowel disease (IBD, ulcerative colitis and Crohn’s disease) is confronted with a number of specific problems, one of them being the lack of randomized, controlled drug trials in children. 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 this review, the role of nutritional therapy is discussed first with a focus on primary treatment, especially for children with Crohn’s disease. Then, the available medical therapies are highlighted, reviewing the mechanism of action, experience in children and evidence of effectiveness and side effects 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, while the early introduction of immunosuppressives (such as azathioprine or 6-mercaptopurine) is advocated as maintenance treatment, or even as initial therapy with corticosteroids in Crohn’s disease. If these drugs are not tolerated or are ineffective, methotrexate may serve as an alternative. Cyclosporine is an effective “rescue therapy” in severe ulcerative colitis, but will only postpone surgery. A novel strategy to treat Crohn’s disease is offered by infliximab, a monoclonal antibody to the pro-inflammatory cytokine tumor necrosis factor (TNF)-α. This biologic agent has now been evaluated in several open-label studies of children and adolescents with severe, treatment resistant Crohn’s disease. Based on the “best available” evidence, suggested usage is provided for separate drugs with respect to dosage and monitoring of side effects in children. The review concludes by proposing three treatment algorithms that will guide the pediatrician or pediatric gastroenterologist in the complex medical care of a child with Crohn’s disease or ulcerative colitis.
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. While 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. In this study, twenty 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%) complete remission by 8 weeks. Reassessment of the colon after treatment showed an improved endoscopic appearance in 15 (75%) and complete remission in eight (40%). Histological improvement was seen in 13 (65%), with full remission in only three (15%).

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. The CDAI is used most commonly and includes both subjective reporting of complaints and abnormalities in laboratory or physical examination. In children, the Pediatric Crohn's Disease Activity Index (PCDAI), which also includes evaluation of longitudinal growth, is valuable for drug trials 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. In ulcerative colitis, no pediatric activity index exists, and various colitis activity indices are used to reflect clinical disease severity. 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 in order 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. As 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, longterm effects of treatments are of particular concern. Fourth, non-compliance 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 IBD15. This is to be regretted, as 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, as some of the major impediments (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 six months exclusivity (or patent protection) to manufacturers in return for conducting pediatric studies. Additionally, the 1999 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"\textsuperscript{16}. In this review, we shall discuss first the role of nutritional therapy with a focus on primary treatment, especially for children with Crohn's disease. We will then highlight the available medical therapies, discussing their mechanism of action, and reviewing the literature for evidence of effectiveness and side effects in children, as compared to 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. Although the various medications are discussed separately here, a combination of two or more drugs, as well as continuous nutritional support is common practice in the treatment of children with IBD. For example, medication for treatment of disease activity (i.e. corticosteroids) and maintenance treatment (i.e. immunosuppressives such as azathioprine or 6-mercaptopurine) are frequently used simultaneously. This review concludes by proposing three treatment algorithms that will guide the pediatrician or pediatric gastroenterologist in the complex medical care of a child with Crohn's disease, fistulous Crohn's disease or ulcerative colitis. Currently, these algorithms are designed in a "step-up" fashion, starting with medications that have little or no side effects, and stepping up to drugs that are more potent and toxic. It may well be that in the near future, a different attitude will be adopted, namely the concept of "stepping down", where initial treatment with potent biologicals is aimed at extremely rapid control of disease activity, effectively influencing the course and prognosis of disease. Future pediatric study designs will hopefully address this new concept which is particularly challenging in children with Crohn's disease.
Parenteral nutrition

In both adults and children, parenteral nutrition is generally reserved for patients with serious illness or pre-operative 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\(^{19-22;23}\). These beneficial effects occurred whether or not 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 administered the treatment at home.

Enteral nutrition

Protein-energy malnutrition is reported in up to 85% of adult patients hospitalized with exacerbations of IBD\(^{26}\), and in 23% of outpatients with Crohn's disease\(^{27}\). 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\(^{28}\). Weight loss can be documented in approximately 85% of children with CD, and 65% with UC at time of diagnosis\(^{29}\). When enteral nutrition was first used, it was either seen as treatment for malnutrition in children with Crohn's disease\(^{30;31}\) or as nutritional rehabilitation in adult patients in preparation for intestinal surgery\(^{32}\). Currently, there is intense debate among pediatric gastroenterologists regarding the primary role of enteral nutrition in the treatment of IBD in children. In contrast, strong indication for the adjunctive or
supplementary use of enteral support exists in view of the common growth retardation observed in children with IBD and the relatively short period of time available to treat linear growth failure prior to closure of epiphyseal plates.

**Mechanism of action**

Elemental diets, originally developed as part of the United States space program in order to minimize bowel actions in orbit, were initially thought to be best for all forms of enteral feeding\(^33\). The first type of enteral nutrition used in Crohn's disease was a diet based on amino acids\(^31;32;34;35\), as this elemental feeding was assumed to bypass the diseased gut, particularly the terminal ileum, because it was absorbed in the proximal small intestine. Thus, a beneficial “bowel rest” was supposed to be provided to the inflamed mucosa by reducing gut motility and excretion. However, Greenberg et al. have demonstrated that bowel rest may not be so essential in achieving remission of disease activity\(^36\), as will be discussed in more detail in the paragraph on efficacy in adults with Crohn’s disease. Furthermore, as the colon is dependent upon luminal nutrients (especially complex carbohydrates converted to short chain fatty acids by the flora\(^37\)), it is not clear that “bowel rest” is actually beneficial. This needs further study. Meanwhile, a meta-analysis could not show a distinct value of elemental feeding compared to polymeric preparations\(^38\).

The mechanism of efficacy of enteral nutrition in IBD is still poorly understood. Apart from the fact that the liquid nature of the diet (and its ease of transport through diseased and/or narrowed small bowel) may in itself be responsible for the effect\(^39\), several hypotheses exist. A reduction of cytokine production by lamina propria lymphocytes has been shown following polymeric enteral nutrition to an extent equivalent to steroids and cyclosporine\(^40\). Postulated modes of action of enteral nutrition are improvement of general nutrition, bowel rest, alteration of gut flora, reduction of antigenic load, presence of glutamine, and improved intestinal permeability. However, most of the hypotheses are based on animal data only. For example, the concept of gut flora modification is supported by a rat model, showing interaction between fecal flora and dietary
composition that changed mucosal architecture and mucus composition\textsuperscript{41}. In humans however, effects of an elemental diet on fecal flora have not been demonstrated\textsuperscript{42,43}. Also, clinical studies fail to show a relation between the overall nutritional and therapeutic effects of an enteral diet\textsuperscript{44}, while bowel rest has been shown not to be the mechanism responsible for diet-induced clinical remission in adult Crohn's disease patients\textsuperscript{36}. The equal efficacy of elemental and polymeric (whole protein) diets\textsuperscript{38} indicates that reduction of immune stimuli as a result of the removal of dietary whole protein is not a probable mechanism either. The aminoacid glutamine (a constituent of elemental diets) is reported to modulate enteric immune function in rats\textsuperscript{45}, and to prevent deterioration of gut permeability in postoperative patients when added to parenteral nutrition\textsuperscript{46}. The nutritional benefits of glutamine in humans with inflammatory bowel disease, however, remain to be proven\textsuperscript{47}.

Fatty acid chain length has been proposed to influence enteral diet response in adult patients with Crohn's disease\textsuperscript{48}. In this randomized trial, remission rates were negatively correlated with the amount of energy derived from long-chain triglycerides. Polyunsaturated fatty acids such as eicosapentenoic acid (EPA) that affect eicosanoid metabolism resulting in a decrease of leukotriene B4 production have been shown to be beneficial in both Crohn's disease\textsuperscript{49,50} and ulcerative colitis\textsuperscript{49,51,52}. Lastly, in severely painful perianal disease, elemental feeding can minimize fecal output while a good nutritional status is maintained. Future research in the interactions between specific nutrients and the immune system will likely increase our understanding of the causes of IBD, as well as enhance the development of novel nutritional therapies.

**Evidence in children**

Growth failure represents a common, serious complication unique to the paediatric age group of IBD patients. Nutritional deficiencies, caused by inadequate dietary intake in relation to overall nutrient requirements, appear to be a major factor related to growth failure in children and adolescents with Crohn's disease\textsuperscript{17}. Nutritional supplementation has been demonstrated to
restore altered body composition and reverse linear growth arrest\textsuperscript{53-55}, 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\textsuperscript{30} or by intensive dietary consultation and oral supplementation\textsuperscript{56}. In the first published controlled trial of an 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 six months) was significantly greater in the children receiving an elemental diet\textsuperscript{57}. Also in children with quiescent Crohn's ileitis or ileocolitis, the nocturnal administration of an elemental formula (50-80 kcal/kg/night) monthly every four 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 to a control group, treated by conventional medical therapy (1.7 ± 0.8 cm, representing 29\% of ideal height change)\textsuperscript{31}. 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\textsuperscript{58}. In addition to its positive effect on growth, nutritional therapy has been advocated as primary therapy for disease activity in children with inflammatory bowel disease. The effect of nutritional treatment on Crohn's disease activity in children has been assessed in numerous studies, summarized in Table 1.
Medical treatment 3.3

Table 1. Studies on enteral nutrition as primary treatment in pediatric CD

<table>
<thead>
<tr>
<th>Study</th>
<th>Diet</th>
<th>Design</th>
<th>n</th>
<th>Disease duration</th>
<th>Disease location</th>
<th>Remission rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morin 1982</td>
<td>E, ng</td>
<td>U</td>
<td>10</td>
<td>N</td>
<td>All sites</td>
<td>100% at wk 3</td>
</tr>
<tr>
<td>Navarro 1982</td>
<td>E, ng</td>
<td>U</td>
<td>17</td>
<td>NS</td>
<td>All sites</td>
<td>NS, all improved</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>clinically during</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>first 2 mths</td>
</tr>
<tr>
<td>O'Morain 1983</td>
<td>E, oral</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 1986</td>
<td>E, ng</td>
<td>RC</td>
<td>9</td>
<td>N</td>
<td>SB</td>
<td>77% at wk 3</td>
</tr>
<tr>
<td>Sanderson 1987</td>
<td>E, ng</td>
<td>RC</td>
<td>9</td>
<td>N</td>
<td></td>
<td>88% at wk 6</td>
</tr>
<tr>
<td>Belli 1988</td>
<td>E, ng, nocturnal, intermittent</td>
<td>NC</td>
<td>8</td>
<td>NS</td>
<td></td>
<td>NS; decrease in</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CDAI in all; relapse</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>in 2/8 during 1 year</td>
</tr>
<tr>
<td>Seidman 1991</td>
<td>E, ng</td>
<td>RC</td>
<td>10</td>
<td>N</td>
<td>All sites</td>
<td>80% at wk 3</td>
</tr>
<tr>
<td>Polk 1992</td>
<td>SE, ng, nocturnal, intermittent</td>
<td>U</td>
<td>6</td>
<td>R</td>
<td>All sites</td>
<td>NS; decrease in</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CDAI and daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>prednisone intake</td>
</tr>
<tr>
<td>Thomas 1993</td>
<td>E, oral</td>
<td>RC</td>
<td>12</td>
<td>N and R</td>
<td>All sites</td>
<td>NS; increase in</td>
</tr>
<tr>
<td></td>
<td>(except 1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LSI in 100% at wk 4</td>
</tr>
<tr>
<td>Seidman 1993</td>
<td>SE, ng</td>
<td>RC</td>
<td>34</td>
<td>N and R</td>
<td>All sites</td>
<td>At wk 4: N: 86%, R:50%</td>
</tr>
<tr>
<td>Beattie 1994</td>
<td>P (TGF-β rich), oral</td>
<td>U</td>
<td>7</td>
<td>N</td>
<td>Mostly SB</td>
<td>NS; improved LSI at</td>
</tr>
<tr>
<td></td>
<td>(except 2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>wk 8 in 7; histo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>remission in 2</td>
</tr>
<tr>
<td>Breese 1994</td>
<td>E and P</td>
<td>U</td>
<td>9</td>
<td>NS</td>
<td>All sites</td>
<td>63%; histo remission</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>in 5</td>
</tr>
<tr>
<td>Ruuska 1994</td>
<td>P, ng, daytime</td>
<td>RC</td>
<td>10</td>
<td>N and R</td>
<td>All sites</td>
<td>90% at wk 8</td>
</tr>
<tr>
<td>Chafai 1995</td>
<td>SE</td>
<td>NC</td>
<td>14</td>
<td>N</td>
<td>NS</td>
<td>100% at wk 12-15</td>
</tr>
<tr>
<td>Papadopoulou 1995</td>
<td>E, ng and oral</td>
<td>UR</td>
<td>19</td>
<td>NS</td>
<td>All sites</td>
<td>In 25/30 episodes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(83%) within 6 wks</td>
</tr>
<tr>
<td>Khosho 1996</td>
<td>E, ng high/low fat</td>
<td>RC</td>
<td>14</td>
<td>R</td>
<td>All sites</td>
<td>NS</td>
</tr>
<tr>
<td>Wischanski 1996</td>
<td>E and SE, ng nocturnal</td>
<td>UR</td>
<td>65</td>
<td>9 N, 56 R</td>
<td>All sites</td>
<td>74% at 0.5-2.5 mths</td>
</tr>
<tr>
<td>Fell 2000</td>
<td>P, TGF-β, oral</td>
<td>U</td>
<td>29</td>
<td>N and R</td>
<td>All sites</td>
<td>79% at wk 8</td>
</tr>
<tr>
<td>Akobeng 2000</td>
<td>P (rich/lower glutamine) oral except 5</td>
<td>RC</td>
<td>18</td>
<td>N and R</td>
<td>All sites</td>
<td>55.5% vs 44.4% at</td>
</tr>
<tr>
<td>Phylactos 2001</td>
<td>P (TGF-β rich), oral</td>
<td>U</td>
<td>14</td>
<td>N and R</td>
<td>All sites</td>
<td>93% at wk 8</td>
</tr>
</tbody>
</table>

a Abstract; *n* = number of patients treated with (or randomized to receive) enteral nutrition; E, elemental; SE, semi-elemental; P, polymeric; ng, nasogastric tube; NS, not stated; U, uncontrolled; UR, uncontrolled, retrospective; RC, randomized controlled; N, new-onset; R, relapsed; NC, nonrandomized controlled; LSI, Lloyd-Still activity index; SB, small bowel; SB/C, small bowel and colon.
Mean remission rates after enteral nutrition or steroids are similar, approximately 85%, as described in a recent meta-analysis of 7 pediatric clinical trials$^{59}$ (5 randomized$^{57;58;60-62}$, 2 unrandomized$^{63;64}$). 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$^{59}$. In children with active Crohn’s disease, remission rate after enteral nutrition was higher (86%) in children with new-onset disease as compared to those with recurrent-relapse disease (50%)$^{61}$. Two pediatric studies have suggested that Crohn’s colitis is refractory to treatment with enteral nutrition$^{57;65}$. This has resulted in the deliberate exclusion of children with Crohn’s colitis from controlled trials. In addition, in patients with small bowel disease, remission was of longer duration if induced by an elemental diet (compared to steroids), while in patients with colonic disease, steroid-induced remission lasted longer than diet-induced remission$^{66}$. In contrast, available data from other pediatric$^{61;62}$ as well as from larger adult studies$^{67-69}$ suggest that large and small bowel disease respond equally well to nutritional therapy. None of the meta-analyses in children or 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$^{70}$. 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 twelve months after cessation of enteral nutrition, while the patients who continued nocturnal supplementary feeding remained in remission longer$^{65}$. 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$^{71}$. 
Evidence of efficacy in adults

Ulcerative colitis: induction of remission
Studies of the effect of enteral nutrition as a primary therapy for ulcerative colitis are scarce; only one (uncontrolled) study has been performed in adults. This study showed that elemental diet was unsuccessful in four patients with active ulcerative colitis. In controlled studies comparing enteral and parenteral nutrition as adjunctive therapy to steroids in patients with severe ulcerative colitis, enteral nutrition was as effective as total parenteral nutrition, and was associated with fewer side effects. An uncontrolled study of supportive enteral nutrition (with a polymeric formula) in severe UC demonstrated that it was well tolerated and had an anabolic effect, but no effect on outcome. In this context, certain fatty acids may have an important role in the treatment of UC. The fish oil n-3-omega-fatty acids, inhibitors of leukotriene synthesis, were found to be therapeutically useful in one open trial and two placebo-controlled cross-over studies in adults with mild to moderate ulcerative colitis. The study by Aslan et al showed that in 11 patients, mean disease activity index declined by 56% for patients receiving fish oil and 4% for patients on placebo (p<0.05), while a reduction or elimination of anti-inflammatory therapy was achieved in eight patients receiving fish oil.

Another therapeutic approach which has been tried in distal UC is the rectal administration of short chain fatty acids. Butyrate enemas may help to reduce mucosal inflammation in distal colitis, although their effect was not very impressive.

A conclusion as to whether nutritional therapy is effective as primary treatment in ulcerative colitis can not be made on the basis of the available evidence.

Ulcerative colitis: maintenance of remission
Studies have not been performed.
**Crohn's disease: induction of remission**

Controlled studies of enteral nutrition versus oral food ("placebo") intake are scarce; in only one study, the effects of an elemental diet administered through a nasogastric tube, total parenteral nutrition and nil by mouth, or partial parenteral nutrition and oral food were compared in adults with active Crohn's disease. In this study, remission rates after 3 weeks were not significantly different (58%, 71% and 60%, respectively). The largest controlled trial of enteral nutrition versus drug treatment in active Crohn's disease is the European Cooperative Crohn's Disease Study IV, which showed clinical remission rates of 53% and 85% in patients on enteral nutrition or corticosteroids and sulfasalazine, respectively. Sufficient studies of the efficacy of enteral nutrition have been performed in adults to permit meta-analysis, and three have been published. These three studies have reviewed a total of 18 trials, six trials being analysed in all three and another six being analysed in two of the meta-analyses. All included randomized trials of liquid diet therapy versus corticosteroids, and two also compared elemental with non-elemental formulas. 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. In both the Canadian and the Spanish meta-analysis, the question of superiority of elemental feeding over a polymeric formulation remained unanswered as data were either insufficient or inconclusive.

The general conclusion from these analyses is that enteral nutrition can be a primary treatment Crohn's disease, but in adults is not preferable to prednisone. 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%. Thus, it is clear that nutritional treatment alone has a significant therapeutic effect in adults.

Four other remarks about the meta-analyses should be made at this point. First, 4 of the total combined 18 trials included were pediatric studies. In children with Crohn's disease, a recent meta-analysis (of all available
pediatric studies) revealed that enteral nutrition is as effective as steroids\textsuperscript{59}, as will be discussed below. Second, most patients in the trials had disease located in both ileum and colon, while data on small bowel disease alone are not available. Third, the meta-analyses have combined studies in which a variety of elemental and of polymeric diets have been used; and last, data on the duration of Crohn’s disease (new-onset or longstanding) has been documented in only 6 of the 18 studies analyzed, while new-onset disease may well be more responsive to dietary treatment. Until we understand the mechanism by which enteral nutrition is effective, and the quality and duration of remission achieved, a definite conclusion on the use of nutrition as primary treatment can probably not be made.

\textit{Crohn’s disease: maintenance of remission}

Few studies have reported follow-up data allowing for the ascertainment of the number of patients maintaining remission at 1 year after successful nutritional treatment. Overall, 2/3 of patients who entered remission as a result of either enteral nutrition or steroid treatment had relapsed by 1 year\textsuperscript{36,80,82}. After initial remission, the use of a diet which excludes specific foods to which a patient is intolerant or the introduction of foods as an elimination diet may\textsuperscript{95}, or may not\textsuperscript{96,97} increase long-term remission rates.

In a Japanese study, total enteral feeding at home after induction of remission was continued in 61 CD patients on a long-term basis resulting in 1-year remission rates higher (94\%) than remission rates on maintenance drugs (63\%) or remission rate with no maintenance treatment (50\%\textsuperscript{98}).

\textbf{Other indications for enteral nutrition in patients with IBD}

Enteral feeding has been used as therapy for a number of other indications in patients with Crohn’s disease, including\textsuperscript{99}: incomplete small bowel obstruction, in order to relieve symptoms in patients awaiting surgery; severe painful perianal disease, in order to maintain good nutritional status and to minimize fecal output; borderline intestinal failure, after surgical complications or while
weaning off TPN; failure of corticosteroids in active disease; to buy time before a diagnosis is established, when investigations are difficult, steroids are contraindicated, or in the differential diagnosis between infection and IBD; in children with delayed longitudinal growth and puberty, as will be discussed below.

**Side effects**
When compared to corticosteroid therapy, there is an obvious lack of side effects when using enteral nutrition. Nutrition can be administered orally, by nasogastric infusion or via a gastrostomy tube, depending on the type and quantity of formula and tolerance by the patient. Adverse treatment-related symptoms including loose stools, nausea, and nighttime awakening (during nocturnal feeding) are common. Reversible diarrhoea 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 where oral administration was attempted\(^38\). 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\(^65\).
Summary

While in adults, enteral feeding is not as effective as corticosteroids as primary treatment of Crohn's disease, 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 to 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.

Table 2. Enteral nutrition as primary treatment of Crohn's disease in children

<table>
<thead>
<tr>
<th>Indications</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induce remission</td>
<td>Exclusive polymeric feeding, 6 weeks or more; oral, if possible</td>
</tr>
<tr>
<td></td>
<td>If not: nasogastric tube, continuous or intermittent (nocturnal)</td>
</tr>
<tr>
<td>Growth failure</td>
<td>Nil by mouth except clear liquids</td>
</tr>
<tr>
<td></td>
<td>Calories and Protein: 140 to 150% RDA for height and age</td>
</tr>
<tr>
<td></td>
<td>When maintenance treatment: nasogastric tube, or consider PEG</td>
</tr>
<tr>
<td></td>
<td>Nocturnal feeding (5/7 nights a week), or intermittent daytime exclusive</td>
</tr>
<tr>
<td></td>
<td>Check during treatment</td>
</tr>
<tr>
<td></td>
<td>If possible, assess REE</td>
</tr>
<tr>
<td></td>
<td>Anthropometrics (height, weight, skinfolds, pubertal stage)</td>
</tr>
<tr>
<td></td>
<td>After instruction in the hospital, the child can continue nutritional</td>
</tr>
<tr>
<td></td>
<td>therapy at home</td>
</tr>
<tr>
<td></td>
<td>Instruct patients to insert tube at night and to remove it again in the</td>
</tr>
<tr>
<td></td>
<td>morning</td>
</tr>
<tr>
<td></td>
<td>PEG: Prior to placement endoscopic examination and biopsy of the stomach</td>
</tr>
<tr>
<td></td>
<td>are necessary to assure that there is no evidence of gastric Crohn's</td>
</tr>
<tr>
<td></td>
<td>disease</td>
</tr>
</tbody>
</table>

RDA, required daily amount; REE, resting energy expenditure
Aminosalicylates

The aminosalicylates, sulfasalazine (SASP) and 5-aminosalicylic acid (5-ASA, mesalamine or mesalazine) are first-line drugs, that have modest anti-inflammatory effects. In current practice, if monotherapy with an aminosalicylate is ineffective, a course of corticosteroids or enteral nutrition may be added to this regimen. Efficacy and side effects of 5-ASA compounds depend on the site and extent of absorption, but it is the non-absorbed fraction (70-80%) that has an important luminal effect in the colon. 5-ASA appears to be effective locally within the mucosa rather than via systemic absorption, and various delivery systems have been designed in order to optimize this system. Systemic absorption is minimized in the various oral aminosalicylate preparations. In addition, both 5-ASA suppositories and enemas are available for local treatment of distal colitis.

Sulfasalazine is composed of 5-ASA linked to sulfapyridine via a diazo bond; a minority (3-12%) is absorbed, while the rest is cleaved by bacterial azoreductases in the colon to yield the two components\textsuperscript{100}. Of these, 5-ASA has been found to be the therapeutically active component, while sulfapyridine is assumed to function as a carrier molecule, ensuring that 5-ASA is delivered to the colon\textsuperscript{101-103}. Sulfapyridine is responsible for most of the side effects of SASP, but it may have a potentiating effect on 5-ASA as well\textsuperscript{104}.

Unbound or uncoated 5-ASA is absorbed in the upper jejunum and is unable to reach the colon in therapeutic concentrations. When conjugated to another 5-ASA molecule (yielding olsalazine), to an inert carrier (balsalazide), or formulated with a time-, or pH dependent coating (mesalamine or mesalazine), the release of oral 5-ASA is maximized at distal sites of inflammation.

The various oral formulations of 5-ASA are listed in Table 3.
### Table 3. Properties of currently available aminosalicylate preparations

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Formulation</th>
<th>Release mechanism</th>
<th>Site of delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfasalazine</td>
<td>Sulfapyridine carrier, azo bond: sulfapyridine and 5-ASA</td>
<td>Bacterial azoreduction</td>
<td>Colon</td>
</tr>
<tr>
<td>Salazopyrine®</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olsalazine</td>
<td>5-ASA carrier, azo bond: 5-ASA and 5-ASA</td>
<td>Bacterial azoreduction</td>
<td>Colon</td>
</tr>
<tr>
<td>Dipentum®</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesalazine</td>
<td>Eudragit-S coating</td>
<td>pH &gt; 7</td>
<td>Distal ileum-colon</td>
</tr>
<tr>
<td>Asaco®</td>
<td>Eudragit-L coating</td>
<td>pH &gt; 6</td>
<td>Ileum-colon</td>
</tr>
<tr>
<td>Claversa®</td>
<td>Eudragit-L coating</td>
<td>pH &gt; 6</td>
<td>Ileum-colon</td>
</tr>
<tr>
<td>MesasaK©</td>
<td>Eudragit-L coating</td>
<td>pH &gt; 6</td>
<td>Ileum-colon</td>
</tr>
<tr>
<td>Salofalk®</td>
<td>Ethylcellulose microgranules</td>
<td>Time and pH-dependent release</td>
<td>Duodenum-colon</td>
</tr>
<tr>
<td>Pentasa®</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baizalazide disodium</td>
<td>Inert carrier (4-aminobenzoyl-β-alanine): azo bond to 5-ASA; acid resistant granules</td>
<td>Bacterial azoreduction</td>
<td>Colon</td>
</tr>
<tr>
<td>Colazal®</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Mechanism of action

Aminosalicylates have been shown to alter a number of cellular functions relevant to inflammation\(^{105}\). The dominant effect seems to be the inhibition of the lipoxygenase pathway of arachidonic acid metabolism, in particular production of leukotriene B\(_4\), which is a potent chemotactic factor. Other potential mechanisms of action include inhibition of production of platelet activating factor\(^ {106}\), impairment of cytokine-induced lymphocyte proliferation and function, inhibition of interleukin-1 production by macrophages\(^ {107}\) and immunoglobulin (IgA) production by mononuclear intestinal cells\(^ {104,108}\). In addition, sulfasalazine inhibits the upregulation of leukocyte adhesion molecules normally induced by TNFα\(^ {109}\). Both sulfasalazine and 5-ASA inhibit the production of reactive oxygen species and scavenge reactive oxygen metabolites\(^ {110,111}\). Recently, it has been shown that sulfasalazine (and not 5-ASA) is a potent and specific inhibitor of transcription factor NF-kappaB, which may explain some of the known immunosuppressive properties of this drug\(^ {112}\).
Hence, much of the inflammatory cascade activated in IBD is in some manner influenced by the aminosalicylates. It is therefore somewhat surprising that 5-ASA and SASP are clinically not more effective.

**Evidence 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 with sulfasalazine, and concluded that a dose of 1.5 to 2.0 g/m2 of sulfasalazine can be safely administered\(^\text{113}\). Two other studies focused on the pharmacokinetics of mesalazine\(^\text{114,115}\). However, neither showed a significant difference compared to 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 to mesalazine\(^\text{116}\). In 153 children treated with 5-ASA for a mean of 14.5 months, there were no severe adverse reactions\(^\text{117}\). In a study of 26 children with Crohn's ileocolitis, renal function was not different in children receiving sulfasalazine, compared to controls\(^\text{118}\). Case reports have documented rare side effects of mesalazine in pediatric patients: pancreatitis\(^\text{119,120}\), hepatotoxicity\(^\text{121,122}\), interstitial nephritis\(^\text{123}\) and pericarditis\(^\text{124}\). In sulfasalazine hypersensitivity (with symptoms like rash, fever, hives, arthralgia, or hepatitis), desensitization has shown to be successful in approximately 56% of children\(^\text{125}\). 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®) in children with active small bowel Crohn's disease\(^\text{15}\), but this slight benefit was only seen in the 6 patients who completed the 20 week study. High dropout and low recruitment rates required the study to be terminated prior to accrual of the proposed 24 patients.
In children with mild to moderate ulcerative colitis, a multicenter, randomised, double-blind study compared the safety and efficacy of olsalazine (30 mg/kg/day) to sulfasalazine (60 mg/kg/day)\textsuperscript{126}. The estimated number of patients needed to show a significant difference in side effects was 90 in each group, but due to slow enrolment, 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, while 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 due to the low dose of olsalazine given. Side effects (such as headache, nausea, vomiting, rash, pruritis, increased diarrhoea and/or 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.\textsuperscript{116} 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\textsuperscript{15,117}. This trend is most likely 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\textsuperscript{93,127}.

**Evidence of efficacy in adults**

**Ulcerative colitis: induction of remission**

In adults, ulcerative colitis is often limited to the rectum and/or distal colon, while pancolitis is less common. In a large Danish cohort study, incidence of proctosigmoiditis, left-sided colitis and pancolitis in 515 adult patients was 44%, 36%, and 18%, respectively\textsuperscript{128}. Another study demonstrated that in teenage children, this situation is very different: proctitis, left-sided colitis or pancolitis is seen at diagnosis in 19%, 38%, and 40%, respectively\textsuperscript{14}. In distal colitis, topical treatment in the form of suppositories or enemas is recommended,
sometimes in combination with oral sulfasalazine or 5-ASA. For pancolitis, oral therapy can be used alone or in combination with topical therapy.

Since the 1940s, placebo controlled studies have confirmed the efficacy of oral sulfasalazine for treatment of moderately active ulcerative colitis\(^{129,130}\). In the first placebo-controlled study by Baron et al\(^{129}\), 89% of the patients receiving sulfasalazine achieved complete clinical remission or partial clinical improvement, compared to 35% of patients in the placebo group. The same results were demonstrated by Dick et al.\(^{130}\), showing improvement in 78% (sulfasalazine group) and 43% (placebo group). In patients with distal colitis, sulfasalazine enemas were shown to be effective in 74% of patients, as compared to 21% receiving placebo\(^{131}\). The evidence for efficacy of rectal 5-ASA for inducing remission or symptomatic improvement in active ulcerative colitis was clearly demonstrated in a meta-analysis that showed a pooled odds ratio of 7.36 (5-ASA versus placebo)\(^{132}\). In a placebo controlled trial, published after the meta-analysis, rectal administration of topical 5-ASA enemas resulted in clinical response (physician’s global assessment) in 65-75% of patients, which was clearly more effective than placebo\(^{133}\).

After the introduction of newer oral 5-ASA preparations, intended to avoid the adverse effects of sulfasalazine, multiple controlled trials have been conducted comparing oral 5-ASA versus placebo or oral 5-ASA versus sulfasalazine.

When comparing different trials in ulcerative colitis, one of the problems is the absence of uniform definitions of remission or improvement. For example, both treatment with oral 5-ASA and SASP for 8 weeks was demonstrated to result in clinical remission in about 75%, while adverse effects were 14% and 24% respectively\(^ {10}\). In the same study, endoscopic remission was seen in about 50% of patients treated with 5-ASA or sulfasalazine. In one of the placebo-controlled trials of oral mesalazine (4.8 g/day), a complete (clinical and endoscopic) response at 6 weeks was seen in 24% of the medication group, and in 5% of the placebo group\(^{134}\).

A recent meta-analysis of 19 clinical trials, involving 2032 patients with mild to moderate ulcerative colitis, showed that the oral 5-ASA preparations have a
slight statistical benefit over sulfasalazine. The authors state however that a clinical benefit seems unlikely\textsuperscript{135}.

**Ulcerative colitis: maintenance of remission**

Also for prevention of relapse of ulcerative colitis, oral sulfasalazine has long been shown to be effective\textsuperscript{136}. With oral 5-ASA (at doses of 1.5-4 g/day, with a slightly increased efficacy at the 4 g dosage), maintenance of remission at 12 months was seen in 54-80\% of patients\textsuperscript{137-139}. In a randomized, double-blind comparison of balsalazide 3 g daily (1.04 g 5-ASA) and mesalazine 1.2 g daily, relapse rate at 3 months was 10\% vs. 28\%, while remission at 12 months was 58\% for both drugs\textsuperscript{140}. Maintenance of remission at 48 weeks of treatment with either mesalazine or sulfasalazine was shown to maintain remission rates of about 40\% in both treatment groups\textsuperscript{141}. More favorably, a meta-analysis by Sutherland et al. showed that approximately 75\% of UC patients remained in remission when taking 2 to 4 g/day of sulfasalazine, efficacy being increased slightly at the highest dose\textsuperscript{142}. This meta-analysis also showed that sulfasalazine had a modest, but statistically significant benefit over 5-ASA in the trials of six months duration.

For distal colitis, studies on topical 5-ASA maintenance treatment show a clear benefit of rectal 5-ASA over placebo: in a meta-analysis by Marshall et al., five placebo-controlled trials assessed remission of maintenance with rectal 5-ASA, and when compared to placebo gave a pooled odds ratio of 16.22\textsuperscript{132}.

**Crohn’s disease: induction of remission**

While the efficacy of sulfasalazine in Crohn’s colitis has been convincingly shown, efficacy in small bowel CD is less clear\textsuperscript{92}. The National Cooperative Crohn’s disease Study (NCCDS) results showed that treatment with sulfasalazine at a dose of 3 g/day was beneficial in 58\% of patients with active Crohn’s disease, but in a subgroup analysis, treatment was found to be effective only with the disease confined to the large bowel.

The efficacy of mesalazine in active mild to moderate Crohn’s disease has been shown in only one trial, where 43\% of the patients with small bowel or
ileocolonic Crohn's disease achieved clinical remission using 4 g/day, compared to a placebo response rate of 18%\textsuperscript{93}. Importantly, the investigators conducted a second identical trial but were not able to confirm the earlier results, as published only as a letter\textsuperscript{143}. All other trials in patients with small bowel and/or colonic disease using a lower dose of 1.5 g/day failed to demonstrate superiority of mesalazine over placebo\textsuperscript{144,145}. Placebo response rate (partial or complete remission) in 12 placebo-controlled trials was 9-50%\textsuperscript{146,147}. Thus, there is little evidence that 5-ASA has an important role in the treatment of active CD in adults.

**Crohn's disease: maintenance of remission**

In maintenance of remission of CD, sulfasalazine has no advantage over placebo\textsuperscript{148}. It is not clear however if this lack of effect can be attributed to the low doses (3 g/day or less) used in these trials.

For mesalazine, the efficacy data on maintenance treatment for CD are controversial as well. The largest randomised trial was conducted by the International Mesalazine Study Group, reporting a relapse rate after one year of 22.4\% versus 36.2\% in the treatment versus placebo group. When analysed by site of disease, the positive effects were only significant for ileitis\textsuperscript{149}. In concordance with this, a recent study failed to show a statistically significant benefit of maintenance treatment over placebo, except for a subgroup of patients with ileocolonic disease who had fewer relapses (21\%) compared to placebo treated patients (41\%)\textsuperscript{150}. A meta-analysis that was adjusted for confounding variables showed a statistically significant but not clinically impressive effect of 5-ASA maintenance treatment, mainly seen in patients with surgically induced remission, ileitis, and prolonged disease duration\textsuperscript{151}. Finally, a recent placebo controlled study failed to show any relapse-preventing effect of mesalazine 4 g/day for 18 months during the postoperative course, except for a small effect in patients with isolated small bowel disease\textsuperscript{152}. Including this study by Lochs et al\textsuperscript{152}, a new meta-analysis was performed very recently\textsuperscript{153}. According to this study, postoperative reduction of relapse risk was
only 10% with mesalazine, corresponding to a number needed to treat of 10. It is therefore difficult to recommend 5-ASA in the postoperative setting\(^{154}\).

**Side effects**
Sulfasalazine therapy is accompanied by a relatively high incidence of side effects, ranging from 10 to 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 (rash, fever) can occur as a reaction to the sulfapyridine component (common) or the mesalamine component (rare)\(^{155,156}\). Reversible sperm abnormalities are common in males. Many patients with intolerance to sulfasalazine -even those with minor allergic reactions characterized by rash and fever- can be safely and successfully treated through the process of desensitization. To accomplish this, the drug is started at one-eighth of a tablet daily, and doubled every 3 days until a therapeutic dose is reached\(^{157-159}\). Sulfasalazine interferes with the absorption of folic acid and may cause megaloblastic anemia if a folate supplement is not administered\(^{160}\). A primary advantage of the newer 5-ASA formulations over sulfasalazine is improved tolerance\(^{161}\). Of the sulfasalazine-intolerant patients, 80% are able to tolerate mesalazine\(^{162}\). The 5-ASA drugs are more costly, however, and have been shown to cause dose-unrelated adverse effects in 14-24% of patients\(^{163}\). Adverse effects are listed in Table 4.
Table 4. Side effects of the aminosalicylates

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Side effect</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfasalazine</td>
<td>Headache, malaise, nausea, vomiting, anorexia, heartburn, epigastric distress, diarrhea, hemolysis</td>
<td>Dose-related: 15-30%</td>
</tr>
<tr>
<td></td>
<td>Reversible sperm abnormalities (number and motility)</td>
<td>Not dose-related: 80%422</td>
</tr>
<tr>
<td></td>
<td>Skin eruptions, fever, cholestasis, hepatitis, pancreatitis, pneumonia, hemolysis, bone marrow toxicity, generalized allergic reactions, exacerbation of colitis</td>
<td>Hypersensitivity: rare</td>
</tr>
<tr>
<td></td>
<td>Megaloblastic anemia</td>
<td>Not when folic acid is supplemented</td>
</tr>
<tr>
<td></td>
<td>Interstitial nephritis</td>
<td>Dose-related (5-10 times less than with sulfasalazine)</td>
</tr>
<tr>
<td>5-ASA (mesalazine)</td>
<td>Nausea, vomiting, dizziness, headache, abdominal pain, diarrhea, rash, hair loss</td>
<td>10-15%</td>
</tr>
<tr>
<td></td>
<td>Pancreatitis, hepatitis, pneumonitis, pericarditis, aplastic anemia, nephritis</td>
<td>Hypersensitivity: rare</td>
</tr>
<tr>
<td></td>
<td>Interstitial nephritis</td>
<td>Dose-related</td>
</tr>
<tr>
<td>Olsalazine</td>
<td>As mesalazine, and secretory diarrhea</td>
<td>5-25%</td>
</tr>
</tbody>
</table>

**Summary**

The aminosalicylates, so effective in ulcerative colitis, have shown, at best, minimal efficacy 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. Based on the current evidence from the adult literature, and the scarce studies in children, the summary in Table 5 seems a reasonable approach to the use of 5-ASA preparations in pediatric patients.
**Table 5.** Use of sulfasalazine (SASP) and mesalazine (5-ASA) in children

<table>
<thead>
<tr>
<th>Indication</th>
<th>SASP</th>
<th>5-ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction of remission in UC&lt;sup&gt;126&lt;/sup&gt; and CD colitis; Maintenance treatment in UC&lt;sup&gt;116&lt;/sup&gt;</td>
<td></td>
<td>Induction of remission in UC&lt;sup&gt;126&lt;/sup&gt;, Maintenance treatment in UC&lt;sup&gt;116&lt;/sup&gt;, if intolerant to SASP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td>50-75 mg/kg/d p.o. divided in 3 doses, maximum dose 6 g/d, start low dose, build up dose in 2 weeks</td>
<td>50-60 mg/kg/d p.o. divided in 3 doses, total (oral plus rectal) maximum dose 4 g/d</td>
</tr>
<tr>
<td>Supplement folic acid</td>
<td></td>
<td>In proctitis: topical (rectal) mesalazine 1-4 g/day (individualize according to response and preference)</td>
</tr>
<tr>
<td>Sulfasalazine discours the urine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Check during treatment**<sup>423</sup> Both SASP and 5-ASA: Routine blood counts, liver function tests, Blood urea nitrogen, serum creatinine, urinalysis

<table>
<thead>
<tr>
<th></th>
<th>Month 1-3</th>
<th>Month 4-12</th>
<th>Year 1-4</th>
<th>Year 5-</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>at least every 4 wk.</td>
<td>every 3 months</td>
<td>every 6 months</td>
<td>each year</td>
</tr>
</tbody>
</table>

*References are given for pediatric studies. If no reference is provided, data were extrapolated from adult studies; p.o., per os*
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. Their toxicity however is a major drawback to their use; about 20-36% of patients with Crohn's disease become steroid-dependent, while 20% are steroid-resistant. While steroid therapy causes obvious symptomatic relief, there is no concomitant endoscopic improvement in most patients. In the GETAID study (Group d'Etude Therapeutique des Affections Inflammatoires Digestives), 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. Corticosteroids can be administered orally, parenterally or rectally. 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. The reduction in growth velocity was shown to be transient, and adult height was unaffected.

Mechanism of action

Corticosteroids have a variety of effects on immune function that are likely to contribute to their therapeutic efficacy. Such effects are the inhibition of both peripheral and intestinal B lymphocyte immunoglobulin secretion as well as inhibition of production of a host of proinflammatory cytokines, including IL-1 and IL-6, the chemokine IL-8, the Th1 cytokines IL-2 and IFN-γ, and the Th2 cytokines IL-4 and IL-5. Some of these immunoregulatory effects appear to be mediated by an inhibition of the activation of nuclear factor (NF) kappa B transcription by steroids. Activation of NFκB appears to be pivotal for the
sustained upregulation of inflammation molecule expression in many inflammatory diseases. It seems, therefore, most likely that the enormous therapeutic potency of steroids is not achieved by a single action of the drug.\textsuperscript{172,173} Corticosteroids also exert significant inhibitory effects on neutrophil activation and functions, such as chemotaxis, adhesion, transmigration, apoptosis, oxidative burst, and phagocytosis,\textsuperscript{174} and interfere with prostaglandin synthesis. Phospholipase A\textsubscript{2} and cyclooxygenases, the key enzymes of prostaglandin biosynthesis, are targets of glucocorticoid action; the molecular mechanisms, however, are not yet understood in detail.\textsuperscript{175} In addition to the various effects on immune function and immunoregulation, corticosteroids enhance rectal sodium and water absorption, resulting in a direct reduction of diarrhea\textsuperscript{176} and improve the sense of well-being.\textsuperscript{177} In an effort to reduce the systemic effects of standard corticosteroid agents, potent formulations (beclomethasone, tixocortol and budesonide) have been developed that have enhanced receptor-binding properties,\textsuperscript{178-181} and an increased first-pass hepatic metabolism, resulting in lower bioavailability (Table 6). In short term use, they are associated with fewer side effects than corticosteroids, but with prolonged administration of inhaled compounds similar complications emerge\textsuperscript{166-168,182,183} in children, as will be discussed below.

### Table 6.

Systemic and topical corticosteroids: relative binding capacity in relation to hydrocortisone and bioavailability\textsuperscript{178,180,181,424-426}

<table>
<thead>
<tr>
<th>GCR affinity</th>
<th>Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>1</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>13</td>
</tr>
<tr>
<td>Beclomethasone</td>
<td>80</td>
</tr>
<tr>
<td>BDP (inhaled)</td>
<td>43</td>
</tr>
<tr>
<td>Budesonide</td>
<td>195</td>
</tr>
</tbody>
</table>

GCR, glucocorticoid receptor; NR, not reported; BDP, beclomethasone dipropionate. 
* depending on delivery device and inhalation technique
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. Colonoscopy was performed at 8 weeks, showing endoscopic remission in 8 patients (40%) and full histologic remission in only 3 patients (15%). No controlled trials of steroids versus placebo have been performed in children. The efficacy of steroids compared to enteral nutrition in children with Crohn’s disease, however, has been studied in several trials, 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 randomised controlled trials of budesonide versus prednisolone in children with active Crohn’s disease (localised to ileocecal region and/or ascending colon) have been completed. Both trials have not been able to show a statistically significant difference in efficacy of budesonide (remission rate 47%-55%) compared to prednisolone (remission rate 50%-71%), while glucocorticosteroid-associated side effects and adrenal suppression was clearly less in the group of children receiving budesonide. Severe hypokalemia and benign intracranial hypertension have been described in children on oral budesonide treatment. Preliminary results from a trial of budesonide enemas in children with ulcerative colitis are encouraging.

In children, the long-term side effects of glucocorticosteroid treatment such as bone demineralisation and growth retardation are a particular drawback to its use. At least 15% of children with inflammatory bowel disease have decreased bone mineral density, and cumulative corticosteroid dose is a significant predictor of reduced bone mass in these patients. Administration of calcium and vitamin D has been demonstrated to improve bone mineral density in children with rheumatic disease receiving corticosteroid therapy. Growth retardation can be a side effect of steroid treatment as well as undertreatment of inflammation. Linear growth is usually normal with use of the alternate-day regimen if the disease is quiescent and dietary intake is adequate.
However, randomized controlled studies have not been performed and alternate-day corticosteroid therapy is probably not recommended long-term. In a small retrospective study, subnormal height velocity was observed in six prepubertal children receiving budesonide maintenance treatment\textsuperscript{197}. The implications of these initial observations are unclear, as 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**

*Ulcerative colitis: induction of remission*

Several early uncontrolled studies demonstrated the efficacy of steroids in UC\textsuperscript{198-200}. In the first placebo-controlled trial, Truelove and Witts showed that steroid-treated patients did better than placebo-treated patients. However, not surprisingly, the steroid-treated patients had more frequent pyogenic complications\textsuperscript{6}. The majority of patients with moderate to severe ulcerative colitis benefit from the administration of oral or parenteral corticosteroids\textsuperscript{201,202}. In a dose-ranging trial, 40 to 60 mg/day of oral prednisone proved more effective than 20 mg/day for patients with moderately active disease, though 60 mg/day was associated with increased toxicity without significant clinical improvement\textsuperscript{203}. Topically (rectally) administered steroids may be used to control moderately active distal colitis, the response ranging from 41-89\%\textsuperscript{204}. Topical steroids are also significantly absorbed from the rectum and can lead to adrenal suppression with prolonged administration. Several controlled studies in distal ulcerative colitis or proctitis demonstrate that budesonide enemas (2 mg/100 ml) seem to be effective and safe (no decrease in endogenous morning plasma cortisol levels)\textsuperscript{205-207}.

*Ulcerative colitis: maintenance of remission*

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\textsuperscript{6,202,208}. The new topical compounds such as budesonide enemas might appear to be especially valuable when there is a long-term requirement for corticosteroids\textsuperscript{209}, but controlled trials have not yet been performed, and long term use of budesonide by other routes led to increasing side effects over time\textsuperscript{167,168}.

\textit{Crohn's disease: induction of remission}

Both uncontrolled\textsuperscript{210-212} and controlled trials of the National Cooperative Crohn's Disease Study (NCCDS)\textsuperscript{92} and the European Cooperative Crohn's Disease Study (ECCDS)\textsuperscript{67} clearly demonstrate the clinical efficacy of steroids. In the NCCDS, 85 patients with active CD were treated with prednisone (0.25 mg/kg to 0.75 mg/kg) or placebo. After 17 weeks, 60\% of those treated with prednisone achieved remission, compared to only 30\% in the placebo group. In the ECCDS, 47 patients with active disease received 48 mg of methylprednisolone tapered to 12 mg over 6 weeks. Overall, there was significant benefit in the steroid-treated group for all disease locations.

In only one study\textsuperscript{213}, the effects of a short (7 weeks) versus a long (15 weeks) course of steroids were compared in active Crohn's disease. After induction of remission in the first 3 weeks of methylprednisolone therapy (40 mg/day i.m.), steroids were administered orally and tapered during either a 4 week or a 12 week period. At the end of the course of steroid treatment, remission in both groups was about 85\%.

The efficacy of controlled ileal-release budesonide in active ileocecal Crohn's disease has been compared to placebo and to prednisolone. Remission rates on budesonide (9 mg/day) of 50\%-53\% were not significantly different from those on prednisolone, but toxicity was two times higher with prednisolone\textsuperscript{214,215}. Whether steroids are more effective when given as divided oral doses or as intermittent or continuous intravenous infusions is not known\textsuperscript{216}. Interestingly, while steroid therapy causes obvious symptomatic relief, there is no concomitant endoscopic improvement in most patients. In the GETAID study (Group d'Etude Therapeutique des Affections Inflammatoires Digestives), 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\textsuperscript{165}.

\textit{Crohn's disease: maintenance of remission}

The results of controlled trials offer little support for long-term treatment with low doses of corticosteroids to prevent relapse of either ulcerative colitis or Crohn's disease\textsuperscript{208}. A recent Cochrane meta-analysis of the three double-blind placebo-controlled studies on maintenance of remission in Crohn’s disease\textsuperscript{67,92,217} demonstrated that corticosteroids do not reduce the relapse rate over a 6, 12 or 24 month follow-up period\textsuperscript{218}.

With controlled ileal-release budesonide, the median time to relapse was prolonged (about 9 months, compared to 3 months with placebo) though at one year, relapse rates were similar, about 65%\textsuperscript{219,220}. In patients that had undergone ileocecal resection, oral budesonide (6 mg/day) maintenance treatment was not more effective than placebo\textsuperscript{221}, if ileal/ileocecal fibrostenotic Crohn’s disease had been the indication for surgery. However, in patients who had surgery for refractory disease activity, the endoscopic recurrence rate at 12 months was lower (32%) in patients receiving budesonide (6 mg daily), compared to patients taking placebo (65%). Glucocorticosteroid-associated adverse events were comparable in the two groups, but there was significant adrenal suppression at 52 weeks of budesonide (6mg/day) treatment.

\textbf{Side effects}

The toxic effects of corticosteroids are well known and reviewed elsewhere\textsuperscript{155,222}. Common findings include fluid retention, weight gain, abdominal striae, fat redistribution, hypertension, hyperglycaemia, subcapsular cataracts, osteopenia, osteonecrosis, myopathy and emotional disturbances (Table 7).
Table 7. Corticosteroid side effects

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushingoid features</td>
<td></td>
</tr>
<tr>
<td>Moon face</td>
<td></td>
</tr>
<tr>
<td>Prednisone ≤ 12 mg, ≥ 60 days:</td>
<td>13%</td>
</tr>
<tr>
<td>Prednisone ≥ 5 yr.:</td>
<td>66%</td>
</tr>
<tr>
<td>Buffalo hump</td>
<td></td>
</tr>
<tr>
<td>Truncal obesity</td>
<td></td>
</tr>
<tr>
<td>Acne</td>
<td></td>
</tr>
<tr>
<td>Hirsutism</td>
<td></td>
</tr>
<tr>
<td>4 times greater than controls</td>
<td></td>
</tr>
<tr>
<td>Cutaneous effects</td>
<td></td>
</tr>
<tr>
<td>Bruising, acne 50-54%</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>4-5 times greater than controls;</td>
<td></td>
</tr>
<tr>
<td>0.9% (versus placebo 0.2%)</td>
<td></td>
</tr>
<tr>
<td>Glucose intolerance</td>
<td></td>
</tr>
<tr>
<td>4 times greater than controls;</td>
<td></td>
</tr>
<tr>
<td>Diabetes: 1.2% (versus placebo 0.3%)</td>
<td></td>
</tr>
<tr>
<td>Posterior subcapsular cataracts</td>
<td>9%</td>
</tr>
<tr>
<td>Osteopenia/osteoporosis</td>
<td>Bone density 2 SD below controls in 33%, correlation with steroid treatment</td>
</tr>
<tr>
<td>Osteonecrosis</td>
<td>1-2%</td>
</tr>
<tr>
<td>Cognitive disorders</td>
<td>up to 7%</td>
</tr>
<tr>
<td>Psychiatric effects, mood disorders, sleep disturbance</td>
<td>1.3-18.4%</td>
</tr>
<tr>
<td>Infectious complications</td>
<td>Bacterial sepsis 6.5% (versus placebo 4.8%)</td>
</tr>
<tr>
<td></td>
<td>Herpes Zoster</td>
</tr>
<tr>
<td>Growth retardation in children</td>
<td>Common in CD and UC; cumulative dose of steroids is predictor</td>
</tr>
<tr>
<td>Other: Oral, esophageal, vaginal candidiasis</td>
<td>Incidence unknown</td>
</tr>
<tr>
<td>Impaired responses to cutaneous antigens (PPD, allergens)</td>
<td></td>
</tr>
</tbody>
</table>

Most side effects (aside from osteonecrosis) seem to be related to the dose and duration of therapy. Additionally, some patients may develop pseudoarthritis as steroids are tapered. Bone loss is an important complication that occurs particularly rapidly, a few weeks to months after administration. Osteopenia is defined as a bone mineral content greater than 2 SD below the
age and sex matched normal mean value. Compstom et al have reported that 41% of the adult patients with Crohn's disease have osteopenia, in contrast to only 14% of patients with ulcerative colitis\textsuperscript{224}. Corticosteroid use is a statistically significant predictor of osteopenia\textsuperscript{224,225}. Bone loss may lead to serious complications such as vertebral collapse. Alternate-day treatment (40 mg of prednisone every other day over a period of 3 months) is associated with fewer side effects than daily dosing, and effectively prevents relapse in adult patients with ulcerative colitis\textsuperscript{226}. However, alternate day regimens do not prevent bone loss, as was demonstrated in patients with rheumatoid arthritis\textsuperscript{227} or bronchial asthma\textsuperscript{228}. In general, the effects of glucocorticoids appear to be both dose and duration dependent. Guidelines on prevention of glucocorticoid-induced osteoporosis have been developed by the American College of Rheumatology\textsuperscript{229}. The guideline recommends initiating preventive therapies as soon as steroids are prescribed, as 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\textsuperscript{230}, vitamin D or calcitriol\textsuperscript{231} on the primary prevention of bone loss, and of bisphosphonates\textsuperscript{232} on the prevention of bone loss in established osteoporosis, has been established in adult patients with various chronic inflammatory diseases. No statistically significant benefit has been shown of adding calcitonin to calcitriol (1,25-dihydroxyvitamin D) or cholecalciferol (vitamin D)\textsuperscript{231,233}. In patients with inflammatory bowel disease, osteoporosis may develop independent of corticosteroid use. The above mentioned recommendations (Table 8) for prevention and treatment of corticosteroid-induced osteoporosis have been adapted to the clinical setting of IBD\textsuperscript{223}. At present, prolonged use of steroids cannot be recommended as single drug therapy as potent adjunctive agents are available (see below under immunomodulatory treatment).
Table 8. Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment, then yearly:</td>
<td>BMD: DXA (lumbar spine and femoral neck)</td>
<td>BMD: DXA (lumbar spine and femoral neck)</td>
</tr>
<tr>
<td>Serum 25-hydroxyvitamin D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 weeks after treatment: 24-hr urinary calcium level or urinary N-telopeptide level</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medication</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary prevention:</td>
<td></td>
<td>Primary prevention:</td>
</tr>
<tr>
<td>Calcium intake 1500 mg/day</td>
<td>Calcium intake:</td>
<td></td>
</tr>
<tr>
<td>Vitamin D (800 IU/day or 50.000 IU/week)</td>
<td>1-5 years: 800 mg/day</td>
<td></td>
</tr>
<tr>
<td>If no decrease of 24-hr urinary calcium level or urinary N-telopeptide level, 4 wk. after start:</td>
<td>6-10 years: 1200 mg/day</td>
<td></td>
</tr>
<tr>
<td>add hydrochlorothiazide and dietary sodium restriction</td>
<td>11-24 years: 1500 mg/day</td>
<td></td>
</tr>
<tr>
<td>Established osteoporosis:</td>
<td>Vitamin D (400 IU/day)</td>
<td></td>
</tr>
<tr>
<td>postmenopausal women: HRT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>biphosphonates (e.g. etidronate 400 mg/day, intermittently)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or calcitonin (100 IU/1-2 days s.c. or 200 IU/day intranasally)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other measures</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical therapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; HRT, hormonal replacement therapy

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 ileocelecal Crohn's disease) and budesonide enemas (for active ulcerative colitis) have fewer side effects in
adults receiving short-term therapy. Based on the available evidence in adults and children, Table 9 summarizes the approach in children.

Table 9. Use of corticosteroids in children with IBD

<table>
<thead>
<tr>
<th>Prednisolone</th>
<th>Budesonide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td></td>
</tr>
<tr>
<td>Induction of remission in UC&lt;sup&gt;1&lt;/sup&gt; and CD&lt;sup&gt;7,36;60;62&lt;/sup&gt;,</td>
<td>Oral: Remission induction in ileocecal CD&lt;sup&gt;194,195;429;430&lt;/sup&gt;</td>
</tr>
<tr>
<td>but NOT for maintenance treatment</td>
<td></td>
</tr>
<tr>
<td>I.v. in severe disease</td>
<td>Rectal: Remission induction in distal ulcerative colitis</td>
</tr>
<tr>
<td>(when oral feeds cannot be tolerated)</td>
<td></td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td></td>
</tr>
<tr>
<td>Oral: 1-2 mg/kg/d, single morning dose, &quot;maximum&quot; 40-60 mg/d</td>
<td>Oral: 9 mg/day for 8 weeks, then taper to nil</td>
</tr>
<tr>
<td>Taper after 4-6 weeks, by 5 mg every week and/or decrease to alternate day</td>
<td>Rectal: 2 mg/100 ml enemas 1-2 daily</td>
</tr>
<tr>
<td>0.5 mg/kg/d</td>
<td></td>
</tr>
<tr>
<td>Maximal duration of treatment 12 weeks</td>
<td></td>
</tr>
<tr>
<td>I.v. methylprednisolone:</td>
<td></td>
</tr>
<tr>
<td>2 mg/kg/d or more, in 2-3 divided doses switch to oral prednisolone</td>
<td></td>
</tr>
<tr>
<td>as soon as feasible and follow plan as above</td>
<td></td>
</tr>
<tr>
<td><strong>Check before/during treatment</strong></td>
<td></td>
</tr>
<tr>
<td>Before treatment, then yearly: BMD: DXA (lumbar spine and femoral neck)</td>
<td></td>
</tr>
<tr>
<td>Before treatment: PPD, EBV and varicella status</td>
<td></td>
</tr>
<tr>
<td>Blood pressure, serum glucose and potassium, glucose in urine</td>
<td></td>
</tr>
<tr>
<td>Linear growth</td>
<td></td>
</tr>
<tr>
<td>Prevention/treatment of osteopenia: Vitamin D (400 IU/day) and Calcium</td>
<td></td>
</tr>
<tr>
<td>age 1-5 years: 800 mg/day</td>
<td></td>
</tr>
<tr>
<td>age 6-10 years: 1200 mg/day</td>
<td></td>
</tr>
<tr>
<td>age 11-24 years: 1500 mg/day</td>
<td></td>
</tr>
<tr>
<td>Cataract: ophthalmologic examination, every 12 months</td>
<td></td>
</tr>
<tr>
<td>Vertebral collapse: X-ray of spinal vertebral column</td>
<td></td>
</tr>
</tbody>
</table>

*References are given for pediatric studies. If no reference is provided, data were extrapolated from adult studies; BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; PPD, purified protein derivative test (tuberculin); EBV, Epstein Barr virus.
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. A long empiric tradition has supported their use in active Crohn's disease\textsuperscript{234,235} and in fistulous disease, but not in ulcerative colitis. The most closely examined antimicrobial agent for treatment of CD has been metronidazole.

Mechanism of action

Antibiotics have several potential actions that could decrease intestinal and systemic inflammation. The effect of antibiotics is presumed to be through alteration of the bacterial flora, for instance by decreasing overall concentrations of luminal bacteria, or by eliminating certain enteric bacterial subsets\textsuperscript{236}. Results from experimental models have complemented clinical observations in Crohn's disease, such as the correlation between fecal \textit{Bacteroides} concentration and clinical response to metronidazole\textsuperscript{237}. Another clinical example is the recurrence of disease after restoration of bowel continuity, suggesting that luminal components induce intestinal inflammation\textsuperscript{238}. These results support the concept that certain subsets of normal resident bacterial flora provide the stimulus for chronic, relapsing intestinal inflammation and provide a rationale for therapeutic approaches that broadly suppress luminal bacteria or selectively inhibit subsets responsible for disease induction\textsuperscript{236}. Besides their antibiotic action, metronidazole and quinolones may also possess immunomodulatory activity\textsuperscript{239,240}. Metronidazole is effective against anaerobes (such as \textit{Bacteroides} species), but also affects the phagocytic capacity of granulocytes, and inhibits delayed hypersensitivity in mice\textsuperscript{239}. Ciprofloxacin is effective against gram-negative aerobic bacteria, but quinolones also have an immunomodulatory action on cytokine production by peripheral blood mononuclear cells\textsuperscript{240}. In patients with active Crohn's disease treated with metronidazole, there is reduction in \textit{Bacteroides} strains\textsuperscript{237}. In addition, clarithromycin is a broad spectrum macrolide antibiotic with good
penetration into macrophages and may be effective in eradicating the organisms that are presumed to be at the centre of the granulomatous reaction in Crohn's disease.

**Evidence in children**

Though controlled trials have not been performed in children, metronidazole appears to be safe and relatively effective in perianal Crohn's disease in children. A trial of metronidazole in 20 children with CD was performed by Hildebrandt et al., showing that more than half of the patients improved clinically during six months of treatment; however, of the 9 patients who discontinued the drug, five had a relapse within one month. The occurrence of peripheral neuropathy was studied in 13 pediatric patients with Crohn's disease treated with metronidazole for 4-11 months. Eleven of 13 patients (85%) had a sensory peripheral neuropathy, determined by abnormal neurologic examinations or reduced nerve conduction velocities, or both. Only 6 of the 11 patients were symptomatic. After discontinuation, complete resolution of the peripheral neuropathy occurred in 5, improvement in 3, and no change in 1.

In juvenile animals, fluoroquinolone-induced cartilage damage has been demonstrated, but data from over 1700 children in the UK failed to disclose arthropathy while extensive paediatric use of norfloxacin in Japan and ciprofloxacin in developing countries has been free of articular effects. The efficacy of quinolones such as ciprofloxacin has not been studied in children with IBD; although the quinolones appear to be well tolerated, further investigations are needed to determine the risk of arthropathy in young children.
Evidence of efficacy in adults

**Ulcerative colitis**
No consistent benefit has been demonstrated for antibiotic treatment in active or quiescent ulcerative colitis, though one trial suggested benefit from ciprofloxacin in maintenance of remission. In the setting of severe colitis (fulminant colitis or toxic megacolon), intravenous antibiotics are used empirically as a component of an intensive intravenous regimen. Pouchitis, which may occur after colectomy and ileal pouch-anal anastomosis, usually responds to treatment with metronidazole or ciprofloxacin.

**Crohn’s disease: induction of remission**
Metronidazole has effects similar to sulfasalazine in Crohn’s disease, as was demonstrated in a randomized, double-blind, cross-over trial of metronidazole (800 mg/day) versus sulfasalazine (3g/day) for four months each. In a double-blind trial conducted by Sutherland et al., treatment with metronidazole (10 mg/kg or 20 mg/kg) for 16 weeks was compared to placebo in active Crohn’s disease. The CDAI improved significantly with both metronidazole dosages compared to placebo in Crohn’s colitis or ileocolitis, but not in isolated small bowel disease. Rates of remission at 4 weeks, however, were similar (25-35%) in the three groups. A 6-week trial of ciprofloxacin (1 g/day) versus mesalazine (4 g/day) in mild active CD showed no differences (56% versus 55%) in complete remission rates. An open trial of ciprofloxacin in combination with metronidazole for 10 weeks in patients with active Crohn’s disease of the ileum and/or colon showed that a clinical response was seen more often in patients with colonic disease compared to isolated ileal disease (84% versus 64%).
Fistulous Crohn’s disease
As it is important to treat not only the fistulizing disease but also the underlying intestinal disease activity, it is difficult to evaluate exactly how antibiotics work in fistulous Crohn’s disease, as they also reduce intestinal disease activity. Placebo-controlled studies have not been performed with antibiotics. In perianal Crohn’s disease, metronidazole treatment (20 mg/kg/day) resulted in healing or improvement of fistulae in 86% of patients\textsuperscript{256}, this effect was seen within two months in most. However, in a follow-up study, attempts to gradually reduce the dose or to discontinue treatment resulted in relapse in 83% of the patients\textsuperscript{257}.

Ciprofloxacin is also reported to be beneficial in the treatment of perianal or fistulous CD\textsuperscript{258}. The present experience supports the idea that if antibiotics are chosen in the treatment of fistulizing Crohn’s disease, the treatment must be continued for a very long time, provided the patients do not experience side effects.

Crohn’s disease: maintenance of remission
Metronidazole has not been studied for maintenance treatment, except in patients with surgical remission. In a placebo-controlled trial in patients after ileocecal resection, metronidazole during three months after surgery was shown to decrease clinical recurrence rate at 1 year (4% versus 25%), but not at 2 or 3 years\textsuperscript{259}. At 12 weeks, 21 of 28 patients (75%) in the placebo group had recurrent lesions in the neoterminal ileum as compared with 12 of 23 patients (52%) in the metronidazole group (P = 0.09). The incidence of severe endoscopic recurrence was significantly reduced by metronidazole (3 of 23; 13%) as compared with placebo (12 of 28; 43%; P = 0.02). In conclusion, only a short term prophylactic effect is to be expected from treatment with metronidazole after ileocecal resection. The clinical relevance of these data is uncertain.

Ciprofloxacin has shown promising results in a 6-month placebo-controlled study, only published in abstract\textsuperscript{260}; the medication group had a significantly lower CDAI than the placebo group after 6 months (122 versus 205). In an
uncontrolled trial by Gui et al\textsuperscript{261}, designed to test the hypothesis that treatment of \textit{Mycobacterium paratuberculosis} would cure Crohn's disease, patients were treated with azithromycin or clarithromycin plus rifabutin for a mean period of 18 months; 82.5\% of the patients achieved remission at some point of the trial, while in 69\% of those patients, remission was maintained at 24 months. However, a double-blind placebo-controlled trial with anti-tuberculous triple therapy (rifampicin, isoniazid and ethambutol) had already shown that treatment for up to 2 years did not result in a difference in corticosteroid use or CDAI\textsuperscript{262}.

\textbf{Side effects}
Common side effects of metronidazole include nausea and metallic taste in the mouth. About 5-10\% of patients experience severe nausea and vomiting. Side effects such as headache, dry mouth, furry tongue, glossitis, stomatitis, urticaria, vaginal and urethral burning, vaginal yeast infection, or upper abdominal pain occur in up to 90\%\textsuperscript{263}. A disulfiram-like side effect can occur after alcohol ingestion. With prolonged administration, peripheral neuropathy characterised by paresthesias in the extremities can occur in up to 50\% of patients\textsuperscript{257}. This particular effect appears to be dose-related and usually appears after an average of 6 to 7 months of treatment\textsuperscript{264}. Side effects are generally reversible with discontinuation of the drug, except for the neuropathy that occasionally persists despite cessation\textsuperscript{243}.

\textbf{Summary}
In adults, evidence of a role for antibiotic therapy (metronidazole and/or ciprofloxacin or clarithromycin) has been stronger in Crohn's disease and in fistuluous disease than in ulcerative colitis. Treatment can and should be continued on a long term basis. Side effects of some agents, though mostly minor, are frequent. In children, data on efficacy are lacking. The therapeutic
use of metronidazole, summarized in Table 10, is therefore mostly extrapolated from studies in adults.

**Table 10.** Use of antibiotics in children with Crohn’s disease

| Indication* | Perianal fistulas in CD
<table>
<thead>
<tr>
<th></th>
<th>Induction of remission in mild to moderate CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>Metronidazole: 20 mg/kg/d divided in 2-3 doses maximum 1 g/d; after response, continue treatment in lower dose: 10 mg/kg/d, for maximal 6 months</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin: 250-500 mg, 2 times daily, maximum 1 g/d</td>
</tr>
<tr>
<td>Check during treatment</td>
<td>Peripheral neuropathy: neurologic exam and/or nerve conduction velocity, every 3-6 months:</td>
</tr>
<tr>
<td></td>
<td>Potential for cartilage defects</td>
</tr>
</tbody>
</table>

*References are given for pediatric studies. If no reference is provided, data were extrapolated from adult studies.
Probiotics

In contrast to most conventional forms of drug therapy that suppress or modify the host immune response, probiotic therapy is aimed at one of the contributors to disease pathogenesis: the gut microflora. Probiotics are live microorganisms that confer a health benefit by altering the indigenous microflora. Lactobacilli, bifidobacteria, and other members of the resident gut flora with no apparent pathogenicity are commonly selected as probiotics. Probiotics may alter the gut microflora by competitive interactions with indigenous bacteria, production of antimicrobial metabolites, or modulation of the local immune response to enteric bacteria\textsuperscript{265}. The exact mechanism of action in inflammatory bowel disease remains to be defined. In children, two studies of probiotics have been published. In the first, oral bacteriotherapy with human Lactobacillus casei strain GG (given to 14 children with Crohn's disease) resulted in an increase in the gut IgA immune response\textsuperscript{266}. A recent open label pilot study of lactobacillus GG, given for 6 months to 4 children with mildly to moderately active CD showed clinical improvement and concomitant decrease in intestinal permeability\textsuperscript{267}.

In adults with IBD, a few randomized controlled trials (of probiotic therapy versus mesalazine treatment) have been published, showing a modest effect of the probiotic agent on relapse rate in UC\textsuperscript{268,269} and CD\textsuperscript{270,271}. All studies, except one\textsuperscript{271}, have used an oral preparation of a nonpathogenic \textit{E.coli} strain as maintenance treatment. In ulcerative colitis patients, relapse rates (at 12 weeks) were similar (about 15%) during treatment with mesalazine (1.5 g/day) or with the \textit{E. coli} strain\textsuperscript{268}. This equivalency was confirmed in another study\textsuperscript{269} that compared treatment with \textit{E.coli} or mesalazine in active ulcerative colitis. Remission was achieved in approximately 75% of patients in both groups, while relapse rates within 12 months were similar as well (73% in the mesalazine group, 67% of patients in the \textit{E. coli} group)\textsuperscript{269}. The results of this study are more difficult to interpret, as the group of patients was heterogeneous (mild to severe disease activity), and concomitant treatment consisted of various corticosteroid preparations. Two studies have promoted the benefits of a new
probiotic, VSL#3, containing 4 strains of *lactobacilli*, 3 strains of *bifidobacteria*, and one strain of *Streptococcus salivarius* as maintenance treatment of ulcerative colitis\(^{272}\) and chronic pouchitis\(^{273}\). In the first (and uncontrolled) study, 75% of the patients remained in clinical remission during a year of therapy\(^{272}\). The other study evaluated the efficacy of VSL#3 compared with placebo in the maintenance of remission of chronic pouchitis after ileal pouch-anal anastomosis for ulcerative colitis\(^{273}\). Relapse rate within the 9-month follow-up period was 15% in the VSL#3 group, and 100% in the placebo group. In the only study on maintenance treatment of Crohn’s disease\(^{271}\), *Saccharomyces boulardii*, a nonpathogenic yeast, was used. Thirty-two patients with Crohn’s disease in clinical remission (CDAI < 150) were randomly treated for six months with either mesalazine 1 g three times a day or mesalazine 1 g two times a day plus a preparation of *Saccharomyces boulardii* 1 g daily. Clinical relapses were observed in 37.5% of patients receiving mesalazine alone and in 6.25% of patients in the group treated with mesalazine plus the probiotic agent\(^{271}\). Long-term treatment data are needed for this preparation. A new therapeutic approach to the use of probiotics has been demonstrated in mice administered the murine enteric bacterium *Lactococcus lactis*, genetically engineered to produce the anti-inflammatory cytokine IL-10 within the gut. There was therapeutic efficacy in two mouse models of colitis\(^{274}\). The results of probiotics in UC and pouchitis are encouraging, but 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 CD and UC, it cannot be assumed that any single probiotic is equally suitable for all individuals\(^{265}\). 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 or not these agents should be a part of early therapy of IBD is currently under debate\textsuperscript{275}. These drugs are the main immunomodulators used in inflammatory bowel disease, have similar side effects and efficacy, and 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 is needed when converting 6-MP to an equivalent dose of azathioprine\textsuperscript{276}. 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 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 is needed when converting 6-MP to an equivalent dose of azathioprine\textsuperscript{276}. 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-methyl-mercaptopurine. 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\textsuperscript{277}. Measurement of TPMT activity is recommended prior to instituting therapy.
Mechanism of action
The mechanism of action of these agents has been extensively reviewed\textsuperscript{263,278}. The metabolites of azathioprine and 6-MP (the 6-thioguanine nucleotides) are thought to be lymphocytotoxic, and the beneficial effects of treatment were first seen in the prevention of organ rejection in transplant patients and in children with leukemia. The immunosuppressive properties of azathioprine and 6-MP are mediated through their interference with protein synthesis and nucleic acid metabolism. After intracellular transformation, the active 6-thioguanine is formed; it functions as an antimetabolite. After incorporation into DNA, breakage of DNA and interference with DNA replication follows, and thus inhibition of purine ribonucleotide synthesis and cell proliferation\textsuperscript{263,278}.

These agents also alter the immune response via inhibition of natural killer cell activity and suppression of cytotoxic T-cell function\textsuperscript{263}, which may explain the 3- to 6 month delay in the onset of clinical efficacy\textsuperscript{279}. The half-lives of AZA and 6-MP in plasma are very short, ranging from 1 to 2 hours\textsuperscript{280,281}. In contrast, the half-life of 6-thioguanine in red blood cells is prolonged (3-13 days). As early pharmacokinetic study showed that time to reach steady state could range from 4 days to 3 years\textsuperscript{282-284}, this was thought to be the cause for prolonged and variable time to clinical response\textsuperscript{285}. However, steady state for these active metabolites has now been shown to be only 2-3 weeks\textsuperscript{284,286}. Interestingly, an intravenous loading dose of azathioprine did not affect the time to response, which was only 4-8 weeks, both in oral treatment and after an intravenous dose of azathioprine\textsuperscript{287}.

Evidence in children
In children, the safety and efficacy of azathioprine and 6-mercaptopurine in CD and UC have until recently been studied only in retrospective reviews. Verhave et al. showed that 75% of pediatric IBD patients (9 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\textsuperscript{288}. 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. Recurrence of disease after surgery may be prevented with 6-MP, as was shown in a small uncontrolled study by Kader et al.

In an uncontrolled trial by Ramakrishna et al., azathioprine or 6-mercaptopurine was started at the time of conversion of i.v. cyclosporine to oral administration in eight children with steroid-resistant IBD. 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. 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. This therapy is not currently recommended and should never be instituted without previous measurement of TPMT activity.

A randomized, multicenter placebo-controlled trial of 6-mercaptopurine in newly diagnosed CD has been performed by Markowitz et al. 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, while 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 \(^{294}\). 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 (see below).

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 \(^{295}\); 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\(^{296}\).

Safety in children was reviewed in 95 patients by Kirschner et al., demonstrating side effects in 28%. In 18%, discontinuation of AZA or 6-MP was required because of hypersensitivity or infection\(^{297}\). 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 resolved either spontaneously or after dose reduction. Another retrospective pediatric study\(^{298}\), 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 longterm therapy is unknown, but is not suggested by the current literature\(^{299-301}\).
Evidence of efficacy in adults

**Ulcerative colitis: induction of remission**

The effects of AZA/6-MP on induction of remission are not very clear, as in all clinical trials of active ulcerative colitis, treatment with azathioprine (or 6-MP) is combined with prednisolone. All trials, however, demonstrate that azathioprine facilitates steroid withdrawal (and complete discontinuation) without clinical worsening of colitis.\(^{302-306}\)

**Ulcerative colitis: maintenance of remission**

In a placebo controlled, double blind trial of withdrawal or continuation of azathioprine in patients with ulcerative colitis, 67 patients in full remission were randomized. Patients maintained on azathioprine were less likely to have a relapse than those on placebo (36% versus 59%).\(^{307}\) Longer duration of remission was inversely related to relapse rate. The data further suggested that maintenance treatment seemed to be beneficial for a minimum of two years, and that in patients who were not in remission within 6 months after starting azathioprine, there was little value in continuing it.

**Crohn’s disease: induction of remission**

Azathioprine and 6-mercaptopurine are both used to treat patients with active, steroid-refractory and steroid-dependent Crohn’s disease. In a recent Cochrane meta-analysis, both response rate and the ability to reduce prednisone or prednisolone (while maintaining remission) of 6-MP and AZA were reviewed including all randomized controlled trials in adults.\(^{92,308-314}\) The overall response rate was 54% for treatment compared to 33% for placebo. In many of the above studies, subjects with extensive colonic involvement appeared to response best to the immunosuppressive therapy. 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. Thus, 6-MP and AZA have a significant steroid-sparing effect in patients with chronically active Crohn’s disease. The use of 6-MP and AZA in a subgroup of patients with
refractory fistulae showed a trend favouring healing which did not reach statistical significance\textsuperscript{92,311,312}. The mean time to response for azathioprine and 6-mercaptopurine in active Crohn's disease is 3.1 months (19\% of the patients take more than 4 months to respond\textsuperscript{311}). However, in a placebo controlled trial of an i.v. loading dose of azathioprine (40 mg/kg)\textsuperscript{287}, maximal remission rates (of 25\% and 24\%) were obtained within 8 weeks in both groups (oral treatment alone and oral treatment after i.v. dose). This trial failed to show a decrease in time to response in patients that had received the i.v. loading dose.

**Crohn's disease: maintenance of remission**

A recent Cochrane meta-analysis\textsuperscript{315} reviewed five randomized, double-blind and placebo-controlled trials of maintenance treatment with AZA or 6-MP\textsuperscript{92,308,313,316,317}. The overall remission rate was 67\% for treatment compared to 52\% for placebo. The number needed to treat to prevent one recurrence was 7. In addition, the meta-analysis reviewed the data for the effect of azathioprine dose (1 mg/kg/day, 2 mg/kg/day or 2.5 mg/kg/day); maintenance of remission was shown to increase with the dose administered. In a subgroup of patients who underwent ileocecal resection for Crohn's disease, azathioprine treatment may have had a preventive effect on recurrent ileitis\textsuperscript{318}. In the two studies reporting steroid consumption\textsuperscript{308,316}, 87\% of the azathioprine-treated patients were able to reduce steroids, compared to 53\% of those on placebo.

An important issue is the duration of maintenance treatment with AZA or 6-MP, as there is concern about the potential risk of long-term administration. In patients who have been successfully treated by either drug, withdrawal from treatment is followed by a high rate of relapse, ranging from 41-81\% after one year\textsuperscript{317,319,320}. In a study by Bouhnik, the relapse rate correlated with the duration of clinical remission on AZA or 6-MP\textsuperscript{321}. In patients who had been in remission while on the drugs for at least four years, the relapse rate was similar whether treatment was maintained or stopped. However, a subsequent placebo-controlled withdrawal trial could not confirm these results: relapse rate in patients continuing azathioprine was lower (8\%) than in patients receiving
placebo (21%) for 18 months after being in remission with azathioprine for at least 42 months\textsuperscript{322}.

**Side effects**

Adverse effects occur in 10-15% of the patients treated with azathioprine or 6-MP and can be categorized as being either of the allergic type (dose independent) or of the nonallergic type (dose and metabolism dependent)\textsuperscript{323}. Examples of the allergic type include fever, pancreatitis, rash, arthralgias, malaise, nausea and diarrhea. Nonallergic toxicities include severe leukopenia, thrombocytopenia, infection, hepatitis and possibly malignancy. Pancreatitis is seen in 3-15%\textsuperscript{263,299}, bone marrow depression in 2-5%\textsuperscript{299,324}, allergic reactions in 2-3%\textsuperscript{299,320}, and drug hepatitis in 0.3%\textsuperscript{299}. Infectious complications are seen in 7%. Pancreatitis typically presents within the first weeks of therapy and promptly resolves on drug withdrawal\textsuperscript{325}. Rechallenge with 6-MP has resulted in recurrence of pancreatitis in all patients and attempts of desensitization were unsuccessful. Bone marrow suppression (particularly leukopenia), an important and potentially lethal complication is dose-related and may develop at any time (range 2 weeks-11 years after starting the drug) during treatment\textsuperscript{324}. Severe leukopenia can occur abruptly or develop over more than two months, while recovery is seen within one month after cessation of treatment\textsuperscript{324}. Reintroduction of a lower dose is successful (without development of leukopenia or trombocytopenia) in about 50% of the patients\textsuperscript{324}. Monitoring blood levels of 6-TG (6-thioguanine) may obviate this complication.

The enzyme thiopurine methyltransferase (TPMT) is responsible for drug metabolism and has a key role in myelosuppression. In childhood leukaemia, a relation was seen between intracellular 6-mercaptopurine metabolites and leukopenia\textsuperscript{216}. Deficiency of this enzyme is present in 1 in 300 individuals, while 11% of the population has intermediate enzyme activity\textsuperscript{326}. Patients with a TPMT-deficient or TPMT-heterozygous phenotype have an increased risk for drug-induced toxicity\textsuperscript{327}. Alternatively, only 27% of Crohn's disease patients with myelosuppression during azathioprine therapy had mutant alleles of the
TPMT gene associated with enzyme deficiency. While some authors suggest that a certain amount of cytopenia, in particular neutropenia, may be needed to achieve a therapeutic effect, neutropenia is more likely simply to be a marker of higher blood levels of 6-TG.

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. However 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). Three relatively large studies, including more than 1300 patients treated with AZA or 6-MP for inflammatory bowel disease, reported 2 cases of lymphoma, one of which was fatal. These data are similar to those in adults with rheumatologic disease treated with azathioprine, in whom the incidence of malignancy was not greater than that in a control disease population not exposed to azathioprine. The risk of neoplasia after azathioprine in 755 patients treated for inflammatory bowel disease was studied by Connell et al. 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 to 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. 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 disease or ulcerative colitis. A recent study has convincingly shown that 6-MP is effective, steroid-
sparing, and improves maintenance of remission in children with newly diagnosed Crohn's disease. 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 for years, as discontinuation of AZA/6-MP leads to a high relapse rate within the first year (41-81% for CD, 59% for UC). In CD, recent evidence suggests that azathioprine/6-MP should be continued even after 4 years.

Side effects occur in 10-15% of both adults and children, the most worrisome being bone marrow depression (2-5%), which may occur at any time between 2 weeks to 11 years. However, adverse events are usually reversible after cessation of treatment or reduction of the dose. 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 11 summarizes the approach in children.
Table 11. Use of azathioprine or 6-mercaptopurine in children with IBD

<table>
<thead>
<tr>
<th>Indication*</th>
<th>Dose</th>
<th>Check before/during treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial treatment of Crohn's disease</td>
<td>Azathioprine: 2-2.5 mg/kg/d, 1 single dose</td>
<td>For both AZA and 6-MP:</td>
</tr>
<tr>
<td>Maintenance treatment of CD and UC, if steroids cannot be tapered or more than 1-2 relapses occur</td>
<td>6-Mercaptopurine: 1.5 mg/kg/d, 1 single dose</td>
<td>Before starting: TPMT levels (to identify patients with low or absent levels, susceptible to myelosuppression)</td>
</tr>
<tr>
<td>Prophylaxis in CD</td>
<td>Both: if unsuccessful after 1 year: stop</td>
<td>During treatment: 6TGN levels (to help predict cytotoxicity) and 6 MMP levels (to help predict hepatotoxicity)</td>
</tr>
<tr>
<td>Perianal CD</td>
<td>If successful, continue treatment for ≥4 years (adjust dose as weight increases)</td>
<td></td>
</tr>
</tbody>
</table>

Complete blood count (CBC):
- 1st mth: weekly
- 2nd and 3rd mth: every 2 wks
- after 3rd mth: every 2-3 mths, throughout the duration of treatment and in any case of unexplained fever or malaise

ALT and amylase:
- 1st, 2nd, 3rd mths: every mth
- after 3rd month: every 3 mths

In case of:
- moderate leukopenia (L 2-3 x 10⁹/l),
- severe leukopenia (L ≤ 2 x 10⁹/l)
- or thrombocytopenia (platelets ≤ 100 x 10⁹/l):

Stop treatment and resume at a lower, individualized dose after normalization of blood count

*References are given for pediatric studies. If no reference is provided, data were extrapolated from adult studies; TPMT, thiopurine methyl transferase, the enzyme which metabolizes 6-MP to 6-methylmercaptopurine (6-MMP); 6-TGN, 6-thioguanine nucleotides, which are cytotoxic metabolites of 6-MP.
Cyclosporine

Cyclosporine is an immunosuppressive agent that was originally developed to prevent organ rejection following transplantation. Patients with ulcerative colitis who are refractory to first-line treatment (sulfasalazine, mesalazine and corticosteroids) and/or have failed therapy with azathioprine or 6-mercaptopurine are appropriate candidates for cyclosporine treatment. As mentioned in the former section, azathioprine and 6-MP have a slow onset of action. Cyclosporine is a rapidly acting alternative or adjunct to AZA/6-MP therapy for refractory UC. It can be used intravenously (to induce disease remission) or by mouth for brief periods after remission is established. Oral bioavailability in Crohn’s disease patients is 25-30%, which is similar to the average value of 30% in transplant patients. The microemulsion formulation of cyclosporine (Neoral®) has a higher bioavailability and oral dosage may result in more stable drug levels than the traditional cyclosporine A formulation. During treatment, cyclosporine levels in whole blood have to be monitored. The therapeutic window is narrow and difficult to define with certainty, as doses vary in different studies.

Mechanism of action
Cyclosporine A (CsA) is a lipophilic cyclic peptide produced by the soil fungus Tolypocladium inflatum gams. It acts to interrupt the cellular immune response by inhibiting calcineurin, a cytoplasmic phosphatase enzyme, thereby blocking the production of interleukin-2 (IL-2) by T-helper lymphocytes. CsA may also indirectly inhibit the function of other cytoplasmatic enzymes like calmodulin and protein kinase C, within T-cells that appear to be involved in the immune response. In addition to its direct inhibition of T-cell proliferation, CsA also indirectly inhibits B-cell function by blocking the production of B-cell activating factors and interferon-γ by T-helper cells. The functions of other leukocytes, including granulocytes, monocytes and macrophages, are not altered by CsA.
Cyclosporine inhibits prednisolone clearance in patients treated with both drugs simultaneously\textsuperscript{350} and can therefore lead to an increased incidence of Cushingoid facies and glucose intolerance\textsuperscript{351}.

**Evidence in children**

Several non-controlled trials have assessed the efficacy of cyclosporine in children with severe acute un-responsive ulcerative colitis\textsuperscript{291,352-356}. 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 one year\textsuperscript{353}. 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\textsuperscript{357}. When surgery becomes necessary, cyclosporine therapy may provide the time needed for education of families and their acceptance of this form of treatment\textsuperscript{358}.

**Evidence of efficacy in adults**

*Ulcerative colitis: induction and maintenance of remission*

The use of intravenous cyclosporine as an alternative to surgery in cases refractory to intensive steroid treatment has been reported by several groups\textsuperscript{340,341,359}. Only one randomized placebo-controlled trial of intravenous and subsequent oral cyclosporine has been performed for the treatment of severe steroid-refractory ulcerative colitis. In this multicenter trial, conducted by Lichtiger et al., 9 of 11 patients (82\%) receiving continuous intravenous cyclosporine (4 mg/kg/day) had improved as compared to none of 9 (0\%) of the patients receiving placebo\textsuperscript{342}. The mean time to improvement was 7 days. After improvement, patients were switched to oral CsA (8 mg/kg/day) for 6 months.
During this follow-up period, 4 of the nine patients underwent colectomy. Thus, the overall success rate at 6 months was 45%. Similar results were reported in a later (uncontrolled) trial\textsuperscript{340}, but other (also uncontrolled) studies are less favourable, with short-term efficacy of 56-70\% and long-term efficacy of 40-44\%\textsuperscript{343,360}. In the trial by Hyde et al., almost one third (29\%) of the patients relapsed within a short time of discharge on oral cyclosporine (5 mg/kg/day) and required colectomy, the majority within 3 months\textsuperscript{343}. A literature review of the use of i.v. cyclosporin 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)\textsuperscript{361}. 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\%\textsuperscript{362}. Thus, the use of intravenous cyclosporine for induction of a rapid remission in severe refractory ulcerative colitis can be recommended for use in centers, experienced in the care of IBD. Use of oral cyclosporine alone for maintenance therapy cannot be considered part of routine management\textsuperscript{363}. Other adjunctive agents should be used (e.g. AZA/6-MP).

\textit{Crohn's disease: induction and maintenance of remission}

Cyclosporine has also been studied in steroid-refractory or steroid-dependent Crohn's disease. Three of four large controlled studies (all using oral low-dose \( \leq 5 \text{ mg/kg/day} \)) have failed to document a significant impact of low-dose cyclosporine in Crohn's disease of varying severity\textsuperscript{344-346}. In the first controlled 3-month trial (using an oral dose of 8 mg/kg/day), 59\% of the cyclosporine-treated patients improved, compared to 32\% of the placebo-treated patients\textsuperscript{339}. However, a final report of this study showed that at the end of a subsequent follow-up period of 6 months, 81\% of patients formerly treated with cyclosporine showed no improvement compared to their initial condition\textsuperscript{364}. There may be a correlation between whole blood concentrations and clinical response, as high-dose (oral \( \geq 5 \text{ mg/kg/day} \) or intravenous treatment) trials tend to show more favourable results than the low-dose trials\textsuperscript{361}. In fistulous Crohn's disease,
anecdotal and uncontrolled trials\textsuperscript{338,365-367} show a frequency of initial closure of fistulae of 78\% overall, with a time to closure ranging from 0.5 to 4 weeks\textsuperscript{361}, using initial infusion with 4 mg/kg and subsequent oral doses of 8-10 mg/kg/day. Overall frequency of sustained fistula closure in 7 trials reviewed by Sandborn was 55\%\textsuperscript{361}.

**Side effects**

In a review of multiple trials by Sandborn, the frequency of side effects in 343 IBD patients receiving high-dose cyclosporine (i.v or oral \(>5\) mg/kg/day) was high, 0.94 adverse events/patient\textsuperscript{361}: paresthesia (26\%), hypertrichosis (13\%), hypertension (11\%), tremor (7\%), nausea/ vomiting (6\%), increase in serum creatinine \(>30\%\) (6\%), headache (5\%), infection (3\%), hepatotoxicity (3\%), gingival hyperplasia (2\%), seizure (1\%), anaphylaxis after i.v. administration (0.3\%). In nearly all cases, adverse events were dose related and reversed when cyclosporine was discontinued or the dose was reduced. In a large controlled trial of low-dose (\(\leq 5\) mg/kg/day) oral cyclosporine for Crohn’s disease, the frequency of adverse events was relatively low; withdrawal due to adverse events was 14.6\% in the cyclosporine group, as compared to 3.2\% in the placebo group\textsuperscript{346}.

The two most frequent complaints in the high-dose trials were paresthesias (in at least 20\% of patients) and hypertrichosis (in up to 50\%)\textsuperscript{361}. 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 \(>5\) mg/kg/day. Almost all patients will have a 20\% reduction in the glomerular filtration rate\textsuperscript{366,369}, 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 two weeks of stopping cyclosporine, histologic evidence of (irreversible) nephrotoxicity was demonstrated in 21\% of
192 patients treated with oral cyclosporine (mean dose 7.1 mg/kg/day) for a mean duration of 13 months. Patients receiving high-dose intravenous (4 mg/kg/day) treatment are at greatest risk of developing nephropathy. Hepatotoxicity occurs in up to 30% of patients, is mostly due to cholestasis, and generally resolves when the dose is reduced or cyclosporine is withdrawn. Infectious complications are infrequent in patients receiving low-dose treatment, but is a risk in patients treated with intravenous cyclosporine or those patients who are already being treated with high-dose steroids or other immunosuppressive medications. 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.

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 (mean 63% for Crohn's disease, 80% for ulcerative colitis) and fast (within 2-3 weeks), withdrawal of the drug often leads to a recurrence of symptoms. Relapse may be prevented by concomitant treatment with azathioprine or 6-MP. For closure of refractory fistulas in patients with Crohn's disease, intravenous cyclosporine is effective in 78% of adults studied but, again, maintenance of this success after tapering is a problem; only in 55% of patients, fistula closure is sustained after discontinuation of cyclosporine. Side effects (such as hypertrichosis and paresthesias) are frequent, especially in high-dose oral and i.v. 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 12 seems a reasonable approach to the use of cyclosporine in pediatric patients.
Table 12. Use of cyclosporine in children with ulcerative colitis

**Indication**
Rescue treatment of severe UC\(^{591,202-206}\)
Only in a center with experience, in which cyclosporine levels can be determined readily
If no clinical improvement or worsening during i.v. treatment: referral for surgery

**Dose**
When using AZA or 6-MP, stop this temporarily
Start with 2-4 mg/kg/day, as continuous i.v. infusion (in addition to high-dose steroids); continue for at least 7-10 days, increasing the dose to the desired blood level
Before switching to oral dose, (re)start azathioprine or 6-MP
After 7-10 days of i.v., switch to oral cyclosporin (Neoral\(^{®}\)), 8 mg/kg/day in 2 doses, continue for 1-3 months while tapering the dose; take with milk or fruit juice, not in plastic cup (suspension sticks to the surface)
Use prophylaxis: Trimethoprim/Sulfamethoxazole (Pneumocystis carinii) and Mycostatin (Candida)

**Check before and during treatment**
- **Before start:**
  - blood pressure, stool cultures, including Clostr. difficile toxins A+B
  - serum creatinine, electrolytes, BUN, glucose, liver function tests, amylase, lipase, 24-hour creatinine clearance**, serum cholesterol***, serum magnesium****, complete blood count, including platelets, ESR or CRP (to monitor colitis activity)
- **During the first hour of infusion:**
  - Monitor every 15 minutes for signs of allergy or anaphylaxis
  - Discontinue infusion if any such signs develop and treat as necessary
- **During in-hospital i.v. treatment:**
  - Daily blood pressure
  - Cyclosporine blood levels every two days (daily, if abnormal), aim: whole blood levels of 400-500 ng/ml
  - Serum measurements every two days (daily, if abnormal)
  - Reduce cyclosporine dose (by \(\geq 25\%\)) if drug level is \(> 500\ ng/ml\) for 2 consecutive days
- **During out-patient oral treatment:**
  - Visits first 4 weeks: every week; then every two weeks for a month; then monthly
  - Serum measurements as above at each visit
  - Cyclosporine trough blood level (aim: trough level of 150-300 ng/ml), every visit or within 1 week after a change in dose
  - Reduce cyclosporine dose (by \(\geq 25\%\)) if: drug level is \(> 300\ ng/ml\) for 2 consecutive days or serum creatinine increases by 30% over baseline or serum transaminases double or systolic blood pressure > 150 mm Hg despite antihypertensive treatment

*References are given for pediatric studies. If no reference is provided, data were extrapolated from adult studies;
** in cases in which serum creatinine is borderline;
*** hypcholesterolemia (\(< 120\ mg/dl\)) should be corrected first by diet or parenteral intralipids, as it increases the risk for seizures in patients treated with cyclosporine\(^{432}\);
**** hypomagnesemia (\(< 1.5\ mg/dl\)) should be corrected first by parenteral magnesium, as it increases the risk for seizures in patients treated with cyclosporine\(^{432}\).
Methotrexate

Methotrexate (MTX) is an anti-inflammatory drug that has been used widely in the treatment of psoriasis and rheumatoid arthritis since the early '50s. Much later, after an initial report by Kozarek et al. of its usefulness in inflammatory bowel disease, methotrexate was studied in adults with chronically active steroid-dependent Crohn's disease. In contrast to rheumatoid arthritis, parenteral administration (i.m. or s.c.) seems to be important in Crohn's disease, particularly among patients with small bowel disease in whom drug absorption may be impaired. Presently, low-dose methotrexate (administered parenterally once a week) has been demonstrated to be efficacious as a steroid sparing agent in Crohn's disease. Whether it should be used instead of azathioprine/6-mercaptopurine in Crohn's disease is still uncertain. Hepatotoxicity is of concern.

Mechanism of action

Methotrexate is a folate-inhibitor, possessing immune-modulatory and anti-inflammatory properties. Although the mode of action is not completely understood, a variety of effects have been reported, including impaired DNA-synthesis through inhibition of dihydrofolate reductase, generation of adenosine, decreased expression of IL-1, and induction of apoptosis.

Evidence in children

There is considerable experience with the use of low-dose oral methotrexate in pediatric patients with juvenile rheumatoid arthritis (JRA), and this population is valuable for comparison with pediatric IBD patients, particularly in regard to safety. Side effects during treatment for 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, treated from 84 to 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 patients who underwent liver biopsy, none had fibrosis or cirrhosis. A more recent study by Kugathasan et al.\(^{379}\) 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\(^ {380}\), apart from encouraging results from two abstracts\(^ {381,382}\). In the published trial\(^ {380}\), 14 patients with active steroid-dependent Crohn's disease, who failed or were unable to tolerate 6-MP treatment, were given methotrexate 15 mg/m\(^2\) 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, 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**

**Ulcerative colitis: induction of remission or maintenance of remission**
In a randomized, double blind multicenter trial, methotrexate at a weekly oral dose of 12.5 mg was found to be no better than placebo in the induction or maintenance of remission in patients with chronic active ulcerative colitis\(^ {383}\).

**Crohn's disease: induction of remission**
A multicenter placebo-controlled trial enrolling 141 patients with active Crohn's disease demonstrated that parenteral methotrexate 25 mg i.m. or s.c. weekly over 16 weeks was twice as likely to allow steroid tapering and maintenance of remission as placebo (39% versus 19%)\(^ {384}\). Improvement in symptoms as assessed by the Crohn's Disease Activity Index and the Inflammatory Bowel Disease Questionnaire (on quality of life) was detectable by six weeks. Another
controlled trial of lower-dose oral MTX (12.5 mg weekly) showed no significant benefit in overall steroid reduction or induction of remission, compared to placebo and 6-mercaptopurine (50 mg daily)\textsuperscript{314}.

**Crohn's disease: maintenance of remission**

A small placebo-controlled trial in 33 steroid-dependent Crohn's disease patients by Arora et al. failed to demonstrate a significant relapse-preventing effect of oral MTX (12.5 mg weekly) on Crohn's disease exacerbations after 1 year, compared to placebo \textsuperscript{385}. However, a 40 week trial of parenteral MTX (15 mg i.m. weekly) in patients with MTX-induced remission showed that more patients were in remission (65\% versus 39\% in the placebo group), while fewer patients needed prednisone for relapse (28\% versus 58\% in the placebo group)\textsuperscript{386}. In a study of the long-term outcome of MTX treatment, 41 (of 49) patients achieved complete clinical remission and were maintained on methotrexate for a median of 18 months (range, 7-59 months). In these patients the probabilities of relapse increased per treatment year (29\%, 41\%, and 48\% at 1, 2, and 3 yr, respectively)\textsuperscript{387}.

**Side effects**

The most common side effect of low-dose MTX is gastrointestinal toxicity, including nausea, anorexia, stomatitis and diarrhea. Headaches, dizziness, fatigue, mood alterations may also occur. Many of these adverse reactions can be reduced by supplemental folic acid therapy. In the largest trial of MTX (using 25 mg weekly i.m. for 16 weeks), nausea and vomiting were seen in 42\%, headache in 17\%, fatigue in 16\%, diarrhea in 7\% and skin rash in 6\%\textsuperscript{384}. Hematologic toxicity (leukopenia, thrombocytopenia, and pancytopenia) is uncommon with low-dose MTX. Risk factors include unrecognized renal disease, untreated folate deficiency, a superimposed infection, or concomitant use of drugs such as trimethoprim-sulfamethoxazole. 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\(^{386}\). In a recent placebo-controlled study of MTX maintenance treatment in 76 adults with Crohn’s disease, none of the patients experienced pulmonary problems\(^{386}\). Opportunistic infections are rare but may include localized or disseminated herpes zoster, fungal and Pneumocystis carinii infections. In both the abovementioned trial\(^{386}\)(MTX treatment of 40 weeks) and another maintenance trial\(^{387}\)(mean MTX treatment of 18 months), no opportunistic infections have been observed. 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 five years of treatment\(^{389}\). 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 to 20 mg per week) than in psoriasis (20 to 50 mg per week), and that there was greater restriction of alcohol consumption in the rheumatoid patients\(^{388}\). Recommendations for the monitoring of patients with rheumatoid arthritis who are receiving methotrexate include regular (every 4-8 weeks) assessment of liver function tests, and adjustment of drug dose if necessary, but no routine liver biopsies of patients with normal test results\(^{390}\). It is not known whether these recommendations can be applied to patients with IBD. 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\(^{387}\).
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 13.
Table 13. Use of methotrexate in children with Crohn's disease

**Indication**
Treatment of steroid-dependent chronically active CD
when AZA/6-MP (>4 mths) fails or when intolerance of AZA/6-MP

**Dose**
Discontinue AZA/6-MP right before starting
15 mg/m² s.c., 1x/week; increase dose as follows,
- week 1: 50% of dose
- week 2: 75% of dose
- week 3: 100% of dose

Administered by general practitioner, parent, or visiting nurse
Start immediately with oral folic acid p.o. 1-2 mg/day
in order to minimize side effects

In case of disease remission, taper steroids
After cessation of steroids, when disease activity is stable (6-9 months),
- decrease dose by 20%; when disease still stable, decrease again by 20%,
  3-6 months later; hold at that dose

Caution with Trimethoprim-Sulfamethoxazole (risk of bone marrow depression)
No alcohol (increased risk of hepatotoxicity)
In young women, birth control should be instituted, if applicable (teratogenic effect)

**Check before and during treatment**
*Before start:*
Consider pregnancy test
Chest X-ray and PFTs, CBC+differential, ESR, LFTs, total protein, alb

*1st–2nd month: CBC+differential, ESR, LFTs, every 2 wks
after 3rd month: CBC+differential, every 6 wks;
LFTs, ESR, alb, every 8-12 wks

Annually: Chest X-ray and PFTs
If any side effects appear, dose adjustment as follows:
- Cut the dose by 50%, if leukocytes ≤ 4 x 10⁹/l or neutrophils ≤ 1.5 x 10⁹/l or platelets ≤ 120 x 10⁹/l or ALT ≥ twice baseline;
- Resume at a lower dose after normalisation, increasing dose according to clinical and laboratory findings
- Stop treatment,
  - if leukocytes ≤ 3 x 10⁹/l or neutrophils ≤ 1.0 x 10⁹/l or platelets ≤ 100 x 10⁹/l or ALT ≥ 3x baseline;
- Resume treatment very carefully after CBC is normal
  and/or ALT is ≤ baseline value
- In case of persistent increase in transaminases: consider liver biopsy

*References are given for pediatric studies. If no reference is provided, data were extrapolated from adult studies.*
Anti-Tumor Necrosis Factor-α antibody (infliximab)

Evidence that antigen-driven and poorly down-regulated activation of mucosal T-lymphocytes is a major mechanism in Crohn’s disease, has led to novel therapeutic strategies, with drugs described as disease-modifying drugs or biologicals. Tumor necrosis factor-α (TNF-α) is a pivotal pro-inflammatory cytokine which 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. A chimeric monoclonal anti-TNF antibody (infliximab) can inhibit TNF-α activity, thus modifying disease activity. In fact, the first patient to receive anti-TNF antibody was a 13-year old girl with severe refractory Crohn’s colitis. This patient had a dramatic clinical response, which was accompanied by healing of intestinal ulceration.

Mechanism of action

Infliximab is a chimaeric (75% human, 25% murine) monoclonal antibody to human TNF-α constructed by linking the variable regions of a mouse antihuman TNF monoclonal antibody to human IgG1. It neutralises soluble and membrane-bound TNF, resulting in a direct anti-inflammatory effect. It acts very rapidly, and the effects of a single infusion are sustained for 10-12 weeks in most patients, producing prolonged clinical effects. The potency of this clinical effect is probably caused by specific targeting of activated T-lymphocytes. Infliximab has been shown to induce T-lymphocyte apoptosis, which is one of the mechanisms that control T-lymphocyte activation and proliferation.
**Evidence 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\(^{393}\). 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 concomittant glucocorticoid treatment in the remitting patients. Several other small uncontrolled trials\(^{394-398}\) 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 \(^{399}\). 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\(^{395}\).

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 NASPGAN members\(^{400}\).

In children with UC, a small open label study has demonstrated encouraging short term results of infliximab treatment in moderate to severe disease\(^{401}\). Decrease of clinical disease activity (measured as Lichtiger Colitis Activity Index\(^{342}\) 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

Ulcerative colitis
Two preliminary trials of infliximab for ulcerative colitis have been reported\textsuperscript{402,403}. The first study enrolled 11 adult patients with severely active steroid-refractory ulcerative colitis that were treated with either infliximab or placebo. At two weeks, a clinical response was observed in most of the patients receiving infliximab, but in none of the placebo-treated patients. The second study, published as an abstract, also showed encouraging results\textsuperscript{403}. Further controlled studies in patients with UC are needed.

Crohn’s disease: induction of remission and maintenance of remission
After the initial dramatic response in a young girl to two infusions of infliximab 10 mg/kg\textsuperscript{391}, a small uncontrolled pilot study in 10 patients with refractory Crohn’s disease showed equal results: most patients had an excellent response after a single infusion of infliximab\textsuperscript{404}. The response was rapid (within a few days) and intestinal ulcerations healed.

The first controlled trial included 108 patients with refractory Crohn’s disease, who were randomised to receive infliximab (5 mg/kg or 10 mg/kg) or placebo\textsuperscript{405}. The results showed that infliximab induced significantly more clinical responses and complete clinical remissions (81%) as compared with placebo (17%). These responses could be maintained in nearly all patients by repeated administration of infliximab 10 mg/kg (given every 8 weeks) during the 44 week follow-up period\textsuperscript{406}. Another study showed that relapse occurred later in patients who were treated concomitantly with azathioprine\textsuperscript{407}.

In patients with fistulous Crohn’s disease, infliximab also induced remarkable healing, as was demonstrated in the first (and only) controlled trial in this patient group\textsuperscript{408}. In 68% of patients receiving infliximab 5 mg/kg at week 0, 2 and 6, drainage from the fistulas stopped, compared to 26% of the placebo treated patients. The mean time to reach this treatment success was 14 days, which was significantly shorter than in the conventionally-treated group (40 days).
Since 1998, infliximab has been approved for clinical use in active refractory or fistulizing Crohn's disease in adults in the USA. In Europe, approval was reached in September 1999. Currently, a randomised 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-anti-chimaeric-antibodies (HACA's) can be induced after one or several infusions. Adult studies show that HACA's are present in 13% of the patients, and their presence is associated with a slightly higher rate of infusion reactions upon reinfusion. Whether HACA's interfere with therapeutic efficacy is as yet unknown. Simultaneous use of immunosuppressive drugs seems to lower the rate of HACA development. There is now evidence of an increased frequency of active tuberculosis after initiation of infliximab treatment, but not of other opportunistic infections. Development of malignancies is a concern, and the relationship between treatment and the development of lymphoma is currently under debate. In 1999, 7 patients treated with infliximab (of the total 913 patients in clinical trials) had developed lymphoproliferative disorders. Four of the patients had rheumatoid arthritis, 1 had HIV infection, and 2 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 as well as mucosal healing in adult, steroid-refractory Crohn’s disease patients. Maintenance of remission can be achieved by repeated infusions every eight weeks. Side effects are infrequent and not severe. As active tuberculosis may develop after treatment, TB screening should be performed prior to treatment. Whether treated patients have an increased risk of lymphoproliferative disease is unknown. Cancer surveillance is however indicated, as 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. In addition, it would be extremely 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 should ideally incorporated into a randomized controlled study protocol. Notwithstanding, Table 14 offers some recommendations on the use of infliximab in children, with careful documentation of effects, side effects and longterm follow-up.
Table 14. Use of infliximab in children with Crohn’s disease

| **Indication** | Treatment resistant moderate to severely active CD, in patients who receive immunomodulatory treatment. Maintenance of remission (induced by infliximab) Fistulizing CD |
| **Dose** | Continue immunomodulatory treatment (azathioprine, 6-MP, or methotrexate) Infliximab 5 mg/kg i.v. in 250 ml 0.9% NaCl over (at least) 2 hours Infusion solution in glass infusion bottle, or polypropylene or polyolefin infusion bag; use low protein binding filter (1.2 micron pore size) and polyethylene-lined pump set Infusions every 8 weeks, or tailored to individual response First 3 infusions: Calculate CDAI and PCDAI prior to, 2, 4 and 8 weeks after infusion, in order to assess individual response |
| **Check before and during treatment** | **Before treatment**, evaluate for latent tuberculosis: PPD** if PPD was not done prior to infusion(s): PPD and chest X-ray |

**Before each infusion:**
1. Vital signs (T, P, R and BP), height and weight
2. Record symptoms (for calculation of PCDAI and CDAI)
3. Record possible adverse effects from prior infusion
4. Record Prednisolone dose
5. Obtain lab work with IV placement: CBC with diff, platelets, ESR, alb, BUN, Creatinine, GGT, ALT
6. Premedicate with:
   - Diphenhydramine hydrochloride (Benadryl) i.v.
   - Acetaminophen (Paracetamol or Tylenol) p.o.
   - *If prior hypersensitivity reaction:* Solumedrol i.v.
7. At bedside prn anaphylaxis:
   - Diphenhydramine hydrochloride (Benadryl) 1mg/kg i.v. (max. dose 50mg)
   - Epinephrine 1:1000 (0.01 ml/kg/dose) (max. dose .35ml) s.c.

**During infusion:**
- vital signs 15 minutes after start of infusion, every 30 minutes throughout, and 30 minutes after infusion

**During and after infusion:** record adverse effects

---

*References are given for pediatric studies. If no reference is provided, data were extrapolated from adult studies;**

**In patients receiving immunosuppressive or immunomodulatory treatment, PPD (purified protein derivative test (tuberculin)) is positive if the induration is ≥ 5 mm.
New therapies

An extensive review of new therapies for IBD has been published elsewhere. Biological treatment may be targeted at TNFα (infliximab, humanized anti-TNFα antibody CDP571, thalidomide), at interferon (IFN)-γ, at interleukin (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 for 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. None of the therapies (except infliximab) have been approved for clinical use in patients with IBD.

Thalidomide, tacrolimus (FK-506) and growth hormone have been studied in children with IBD, and these pioneer trials are summarized in Table 15. It seems however that all clinical studies of biological 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 longstanding Crohn’s disease) may be the more appropriate group to study; in 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, 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.
Table 15. New therapies studied in children

<table>
<thead>
<tr>
<th>Treatment and Action</th>
<th>Clinical studies</th>
<th>Ref(s)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus (FK-506): Tacrolide, comparable to cyclosporine, inhibition of T-cell proliferation; blocking of IL-2 production</td>
<td>Case report of 1 child with severe UC</td>
<td>Bousvaros 1996</td>
<td>Side effects profile similar to cyclosporine, oral absorption better than cyclosporine</td>
</tr>
<tr>
<td></td>
<td>Open label, 14 children with severe UC, oral treatment, 2-3 months: response 69%, longterm remission &lt; 50%</td>
<td>Bousvaros 2000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Open label, 8 children with oral or perianal CD, topical (ointment 0.5 mg/g); marked improvement in 7/8 pts</td>
<td>Casson 2000</td>
<td></td>
</tr>
<tr>
<td>Thalidomide, Downregulation of TNFα production; inhibition of IL-12 production</td>
<td>Case report 1 child (age 8 y) oral CD, oral 50-100 mg/d: remission oral ulcers &lt; 2 wks</td>
<td>Odeka 1997</td>
<td>Known severe teratogenicity; mild and transient side effects (drowsiness, peripheral neuropathy, edema, dermatitis) especially with higher doses; correct dosing needs further study.</td>
</tr>
<tr>
<td></td>
<td>Case report 1 child (age 13 y) oral CD, oral 25 mg/d: remission &lt; 1 months, sustained remission during 1 year of continued treatment</td>
<td>Weinstein 1998</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Case report 1 child (age 12 y) oral CD, oral 100 mg/d: remission oral ulcers &lt; 3 days, sustained for 9 months, but axonal degeneration and remaining partial sensory loss</td>
<td>Strauss 2001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Open label, 5 children (mean age 17 y) with refractory CD 1.5-2 mg/kg/d; PCDAI decrease after 3 months, steroids tapered and stopped in 4/5 patients</td>
<td>Facchini 2001</td>
<td></td>
</tr>
<tr>
<td>Recombinant human growth hormone (rhGH, somatotropin), Counteraction of catabolic process of inflammation; trophic effect on intestinal mucosa</td>
<td>Open label, 10 children with IBD, on chronic prednisone 0.05 mg/kg/d s.c. 6-12 mths: Linear growth velocity↑, CDAI unchanged</td>
<td>Maura 2002</td>
<td></td>
</tr>
</tbody>
</table>
References


16. Department of Health and Human Services, Food and Drug Administration. 21 CFR, parts 201, 312,314 and 601: Regulations Requiring Manufacturers to Assess the Safety
and Effectiveness of New Drugs and Biological Products in Pediatric Patients.
http://www.fda.gov/cber/gdlns/pedrul.htm 1999. Electronic Citation


126. Ferry GD, Kirchner BS, Grand RJ, Issenman RM, Griffiths AM, Vanderhoof JA et al. Olsalazine versus sulfasalazine in mild to moderate childhood ulcerative colitis: results of


Medical treatment 3.3


154. Sutherland LR. Mesalamine for the prevention of postoperative recurrence: is nearly there the same as being there? Gastroenterology 2000;118:436-38.


Medical treatment 3.3


230

Medical treatment 3.3


Medical treatment 3.3


340. Actis GC, Ottobrelli A, Pera A, Barletti C, Ponti V, Pinna-Pintor M et al. Continuously infused cyclosporine at low dose is sufficient to avoid emergency colectomy in acute


Medical treatment 3.3


382. Vinton NE and Shaffer SE. An open trial of oral methotrexate (MTX) therapy (RX) in severe pediatric inflammatory bowel disease (IBD). Gastroenterology 1997;112:A1113. Abstract


