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# Systematic review: nutritional therapy in paediatric Crohn's disease

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## SUMMARY

### Background
At least 25% of individuals diagnosed with Crohn's disease (CD) have onset of disease in childhood. Almost all children with CD have nutritional impairments, such as weight loss or stunting, at diagnosis or subsequently. Nutritional therapy (exclusive enteral nutrition) is established as a valid and effective treatment in paediatric CD. The advantages of this approach are induction of remission and control of inflammatory changes, mucosal healing, positive benefits to growth and overall nutritional status, and avoidance of other medical therapies.

### Aim
To provide a comprehensive up-to-date review of the roles of nutritional therapy in CD and of the data supporting this therapy.

### Methods
A search of PubMed was performed with search terms 'enteral nutrition', 'nutritional therapy', 'Crohn disease' and 'children'. Relevant articles were selected from this search. In addition, the reference lists of available articles were reviewed for further relevant articles.

### Results
Nutritional therapy offers numerous benefits in the management of CD. Recent work has begun to elucidate the likely mechanisms of this therapy. These include direct mucosal anti-inflammatory effects and alteration of intestinal microflora.

### Conclusion
Further studies are required to define longer-term effects of nutritional therapy in patients with CD.

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## INTRODUCTION

The inflammatory bowel diseases (IBD), which include ulcerative colitis (UC) and Crohn's disease (CD), can be diagnosed and defined on the basis of endoscopic, radiological and histological features.[1] Characteristically, UC involves the colon only with superficial acute and chronic inflammatory changes. CD, on the other hand, can involve any part of the gastrointestinal tract and features include full-thickness acute and chronic inflammation, along with non-caseating granulomas.

Children with IBD can present with various typical symptoms, but some individuals may have subtle symptoms or be asymptomatic.[1] In CD, the most frequently presenting symptoms are abdominal pain, diarrhoea and weight loss.[1] Bloody diarrhoea is more commonly seen in children presenting with UC. Weight loss may also occur in both groups, but is generally seen more frequently in children with CD: published patient series define weight loss of 50–65% in UC and up to 85% in children diagnosed with CD.[1]

In addition to interruption of normal weight gains prior to diagnosis in children with IBD, there may be impaired linear growth at diagnosis and subsequently. Given that many children with IBD are diagnosed in adolescence (prior to or during puberty), disturbed growth is therefore a major complication of paediatric IBD. Attention to growth and nutrition at diagnosis, and during ongoing management, is of critical importance in children and adolescents with IBD.

Both CD and UC are life-long conditions, which commonly run relapsing and remitting courses. Various therapies, including medical, surgical and nutritional therapies, are available to manage CD and UC.[1] With the exception of colectomy for UC, none of these therapies is able to cure or eradicate disease. Current therapies, however, help manage inflammatory processes, eliminate symptoms, and prevent complications. Although new therapies are increasingly available, such as biological agents like Infliximab, each of these may also result in significant side effects and complications.

A nutritional approach to the management of IBD has great merits, as it permits control of inflammation, resolution of symptoms and optimization of growth through childhood. Furthermore, although there is increasing use of biological and immunomodulatory therapies, we must not lose sight of the absolute importance of growth and nutrition in children and of the relevance of avoiding side effects in children who are likely to have many decades of disease and exposure to medications ahead of them. This study reviews the nutritional impact of IBD, establishes the rationale for considering nutritional management of IBD in children and adolescents, and delineates the current understanding of the mechanisms of this therapy.

## METHODS

A search of the literature was performed in May 2007 using PubMed from 1966 to May 2007. Search terms used were 'enteral nutrition', 'nutritional therapy', 'Crohn disease' and 'children'. Relevant articles were selected from this search. In addition, the reference lists of available published articles were reviewed for further relevant references.

## NUTRITIONAL IMPACT OF IBD

Children diagnosed with IBD commonly have a history of weight loss, especially in CD. In various series, up to 85% of children and adolescents with CD have lost weight in the period prior to diagnosis.[1] Over a 4-year period from 1999 to 2003, only half (31 of 61) of the children we diagnosed with CD at Sydney Children's Hospital gave a history of weight loss.[2] Weight loss was generally seen less frequently in children diagnosed with UC than in those with CD.

Although a number of factors may contribute to altered weight gains in children with CD, the primary reason is thought to be protein-energy malnutrition caused by reduced caloric intake and anorexia.[1, 3] For instance, Thomas and investigators[4] ascertained that the average energy intake of a group of 24 children with active CD was lower than that of control children by 400 kcal per day. Reduced intake was also illustrated in a group of eight growth-retarded adolescents with CD: these individuals ingested only 55–80% of their expected caloric intake.[5] Cytokines, such as tumour necrosis factor (TNF)-$\alpha$, originating in the inflamed gut probably also contribute to anorexia. Nausea, abdominal discomfort, or enhanced gastro-colic reflex may be additional factors leading to diminished intake. Malabsorption is a further factor that may contribute to weight loss or impaired weight gains.

In addition to altered weight gains, children with IBD can have impaired linear growth. Impaired linear growth is recognized in both UC and CD but is present

at a substantially greater frequency in children with CD. Interrupted linear growth may be present at diagnosis in up to 50% of patients with CD.[3, 6, 7] This altered growth pattern also may cause an impact upon the final height acquired by these patients. Furthermore, impaired linear growth through adolescence and diminished final adult height acquisition may cause impact upon both quality of life and psychological status of the patient.

The cause of poor linear growth in children with IBD is also multifactorial. Along with malnutrition, proinflammatory cytokines also have significant independent effects. Animal studies demonstrate that around 40% of growth impairment is consequent to inflammatory proteins, including interleukin (IL)-6.[8, 9] These factors, together with other potential factors, can cause adverse impact upon linear growth in children with IBD.

A recent report evaluated the final adult height in a group of 123 patients with CD, all of whom were diagnosed prior to 16 years of age.[10] The mean final height of these individuals was 2.4 cm less than the parental or target height (range of −20.0 to +9.0 cm). Almost one-fifth of these patients had a final height that was >8.0 cm below their target height. The two factors that influenced reduced final adult height in this cohort were the presence of jejunal disease and the period of symptoms prior to diagnosis.[10] Factors that were not linked to final height acquisition were the use of corticosteroids, prepubertal diagnosis, parental heights and the requirement for surgery. Interestingly, this report included patients from two British gastroenterology units where enteral nutrition is used frequently. Although specific data on the use of enteral nutrition in these individuals were not available, one could speculate that the use of exclusive enteral nutrition (EEN) in at least some of these patients may have decreased or delayed the requirements for steroids over the period of follow-up. Other reports also suggest that jejunal disease is linked to impaired growth.[11, 12] Other putative factors that have been suggested are male gender, severity of illness, age of onset of symptoms, and therapies.

A recent report from a large population-based assessment of growth in Danish children with IBD highlights the impact of IBD, especially CD, upon growth.[13] This cohort comprised 50 children with UC, four with indeterminate colitis and 44 with CD. Growth parameters were evaluated and contrasted with Danish reference values. The children with UC had height-for-age and BMI-for-age similar to standard values. In contrast, the children with CD had lower height-for-age than the population of normal children ($Z$ score −0.77) and were shorter than those with UC ($P = 0.005$). Half of the children with CD had height below the 25th centile. Furthermore, the children with CD had mean BMI $Z$ score of −1.15, and again differed from those with UC ($P = 0.001$). One advantage of the analysis of this particular cohort is the un-selected population from which the patients were drawn. Nonetheless, the findings are similar to those of previous selected groups of children with IBD.

In addition to the impact of IBD upon linear growth and weight, IBD may lead to secondary micronutrient deficiencies.[14] The spectrum of these deficiencies was emphasized recently.[15] This report evaluated the micronutrient status of 54 adult patients in remission from CD, with comparison to 25 healthy controls. Intakes of various micronutrients were lower in patients with CD. Over half the patients had decreased serum levels of zinc, niacin, copper and vitamin C.[15] Detailed studies of the levels of these micronutrients and minerals in children have not yet been conducted.

Because of the prevalence of nutritional impairments in children and adolescents with IBD, management principles need to include a focus upon nutritional recovery during therapy. Accurate and comprehensive nutritional assessment is required in all children at diagnosis. This includes collection of as much data about growth prior to diagnosis as possible (to establish previous growth patterns) along with family growth patterns. Close attention to growth is required during treatment and regular review or reassessment is necessary. A therapeutic intervention in a child with IBD cannot be judged successful unless growth is normalized and proceeding satisfactorily. Furthermore, the effects of therapies (such as corticosteroids) upon nutrition and growth also need to be taken into account.

A therapy that leads to resolution of gut inflammation (with healing of mucosal disease), whilst improving nutrition and growth could therefore be seen as an ideal therapy for the management of CD in children. EEN provides these advantages, whilst also potentially leading to avoidance or delay in the use of drug therapies.

## EXCLUSIVE ENTERAL NUTRITION

The term EEN refers to the use of an enteral formula, either elemental or polymeric, which is given

exclusively (instead of normal diet) as a distinct therapy. Enteral nutrition (EN) may be provided as a supplement solely for nutritional support; the use of supplementary nutrition in this manner is not further considered in this review. EEN is proven to have roles in the treatment of CD, but is not shown to have a particular role for the management of UC.[16]

## EEN in adults

Initial reports of the use of EN in the management of IBD came from Europe over 30 years ago. Parenteral nutrition provided along with bowel rest had previously been demonstrated to have benefits in some individuals with severe colitis.[17] In the 1970s, several reports illustrated the benefits of enteral formulae in CD.[18–21] These initial case reports and case series involved the use of elemental feeds in adults and demonstrated improvements in gut inflammation consequent to the use of formulae.

O'Morain *et al.* formally evaluated an elemental formula in adults with active CD.[22] This study randomized patients to receive either elemental formula or corticosteroids and demonstrated benefits for elemental feeding. Further studies have confirmed these findings in other adult populations.[23–25] However, one European multicentre study involving 55 adults with CD treated with an elemental formula showed that this approach was less effective than oral corticosteroids in the induction of remission.[26] Although differing in terms of criteria and the numbers of included studies, subsequent meta-analyses show that corticosteroids are more effective in inducing remission than enteral feeding with elemental formulae.[27–29] Similar conclusions were reached in the Cochrane review of this topic[30]: a conclusion that was reaffirmed in the recent update of this review.[31]

Elemental formulae alone were utilized in the initial studies evaluating EEN in adults with IBD. In studies comparing elemental formulae to polymeric (whole protein) drinks, polymeric feeds are shown to be equally efficacious.[32, 33] Similar conclusions were reached in the Cochrane reviews.[30, 31] Polymeric formulae, however, have the advantage of lesser cost as well as enhanced taste and palatability, thereby improving tolerance and compliance. Most patients are able to take polymeric feeds orally without insertion of a nasogastric (NG) tube, which is usually required when elemental feeds are prescribed.[32] Although polymeric formulae have various benefits over elemental feeds, elemental formulae continue to be used in both adult and paediatric settings.

## EEN in children

Many randomized and non-randomized studies have evaluated EEN or aspects in children (summarized in Table 1). A meta-analysis of five of these paediatric studies (not including any adult studies) using EEN for CD in a total of 147 children has ascertained that EEN and steroids were of equal efficacy in the induction of remission in children with active CD.[34] Although opposite conclusions were reached in the Cochrane reviews,[30, 31] these systematic reviews were based principally upon adult studies, with only a small number of paediatric studies. The benefits of EEN do appear to differ between paediatric and adult populations.

Paediatric studies show that treatment with EEN can induce remission in up to 85% of newly diagnosed patients. One multi-centre North American study using a semi-elemental formula showed a remission rate of 83% in children newly diagnosed with CD.[35] In children with previously diagnosed CD (with relapsing disease), the rate of reinduction of remission was 50%. We have demonstrated a very similar pattern upon reviewing our experience with EEN over a 2-year period.[36] Thirteen (80%) of 15 children with newly diagnosed CD managed with EEN, as sole therapy, attained remission. In this group of children, the mean Pediatric Crohn's disease activity index (PCDAI), a validated marker of disease activity,[37] fell from $37.1 \pm 10.8$ to $6.7 \pm 5.1$ after 8 weeks of therapy. Data were also analysed in a second group of children with previously diagnosed CD who also received EEN; on average, these children had been diagnosed with CD for more than 3 years. Remission was achieved with EEN in 58% of this cohort. Of interest, even the children in this group, who did not achieve remission, had decreased PCDAI and nutritional improvements following treatment with EEN.[36]

Exclusive enteral nutrition leads to rapid onset of clinical benefits in many cases. For instance, in a group of 12 children treated with a standard polymeric formula, PCDAI and C-reactive protein (CRP) decreased promptly with EEN.[38] In some of the subjects, CRP fell within the first 7 days of therapy. Although some children do have very early changes in standard inflammatory markers, others have slower improvements. For many children, some of the initial responses to EN include improved energy and mood.[36]

**Table 1.** Clinical trials of exclusive enteral nutrition (EEN) in children with Crohn's disease (CD). The principle features of studies of EEN in children with CD are provided. All published randomized controlled trials (RCT) are included, along with non-RCT (prospective or retrospective) studies published over the last 7 years. Formula type included elemental (E), semi-elemental (SE) or polymeric (P) formula. Patient numbers in RCT studies are those who received EEN. Patient numbers are those that received EEN in the respective study. Remission rates are as detailed by the authors: these may be clinical remission or defined by disease activity scores. Comments detail key aspects of the studies

| Author | Reference | Year | RCT | Patients (*n*) | Formula | Length (weeks) | Remission (%) | Comments |
|---|---|---|---|---|---|---|---|---|
| Sanderson | 55 | 1987 | Y | 9 | SE | 6 | 89 | RCT comparing EEN to corticosteroids and sulphasalazine |
| Seidman | 86 | 1991 | Y | 10 | E | 3 | 80 | RCT comparing EEN to corticosteroids |
| Seidman | 87 | 1993 | Y | 34 | SE | 4 | 76 | RCT comparing EEN to corticosteroids |
| Thomas | 4 | 1993 | Y | 12 | E | 4 | 100 | RCT comparing EEN to corticosteroids and sulphasalazine |
| Ruuska | 88 | 1994 | Y | 10 | P | 8 | 90 | RCT comparing EEN to corticosteroids |
| Akobeng | 89 | 2000 | Y | 18 | P | 4 | 50 | Comparison between formulae of different glutamine content |
| Fell | 52 | 2000 | N | 29 | P | 8 | 79 | Prospective evaluation of polymeric formula: assessment of mucosal cytokines |
| Terrin | 90 | 2002 | Y | 20 | SE | 8 | 90 | RCT comparing EEN to corticosteroids and mesalazine |
| Gailhoustet | 72 | 2002 | N | 15 | N/A | N/A | N/A | Prospective evaluation of impact upon quality of life (compared to steroids) |
| Ludvigsson | 91 | 2004 | Y | 33 | E/P | 6 | 76 | Comparison between two formula types (SE and P) |
| Afzal | 71 | 2004 | N | 26 | P | 8 | 88 | Prospective evaluation of effect of EEN upon quality of life |
| Bannerjee | 38 | 2004 | N | 12 | P | 6 | N/A | Prospective assessment of inflammatory cytokines and growth factors |
| Gavin | 54 | 2005 | N | 40 | P | 6–8 | 78 | Evaluation of energy intake in cohort receiving EEN |
| Afzal | 44 | 2005 | N | 65 | P | 8 | 77 | Review of remission rates according to disease location |
| Knight | 43 | 2005 | N | 44 | E/P | 6–8 | 90 | Retrospective analysis of cohort with focus on outcomes over 1–7 years |
| Johnson | 53 | 2006 | Y | 50 | E | 6 | 28 | Comparison between partial EN and total EN |
| Borrelli | 51 | 2006 | Y | 19 | P | 10 | 79 | EEN vs. steroids: mucosal healing in 74% |
| Berni Canani | 69 | 2006 | N | 37 | SE/E/P | 8 | 86.5 | Retrospective analysis of cohort: mucosal healing in 64.8% |
| Day | 36 | 2006 | N | 27 | P | 6–8 | 79 | Case series including newly or previously diagnosed patients |
| Akobeng | 92 | 2007 | Y | 15 | P | 4 | N/A | Study compared two polymeric formula: outcomes were antioxidant profiles |
| Rodrigues | 93 | 2007 | N | 98 | E/P | 6 | 58 | Retrospective assessment of adherence and response with E or P formulae |

N/A, not available.

## EEN in combination with other therapy

There are little available data on the combination of EEN with other medical therapy to induce remission. Some case series and reports include an occasional patient who had received therapy such as corticosteroids or aminosalicylates in addition to EEN. There are reports of the early addition of maintenance therapy, such as azathioprine, but there are no conclusive data yet, to support this combination. Clearly, however, the early introduction of azathioprine in children with moderate to severe CD at diagnosis is justified and well supported.[39] At present, there are no data demonstrating which patient groups would most benefit from the early introduction of azathioprine during the period of EEN.[40]

One recent report from Japan illustrates that the provision of EN may improve the response to other therapy.[41] In this instance, 110 adults with CD treated with Infliximab had greater responses, if they had also received EN.

## EEN and disease location

Initial studies demonstrated that EEN was not helpful in UC and suggested that ileal disease responded better than colonic disease.[16, 42] We have shown no difference in the remission rate of children with ileal disease and that in children with isolated colonic disease.[36] Another report also demonstrated no difference in response between colonic and ileal disease: however, the children in this series with colonic disease appeared to have earlier relapse in follow-up.[43] In contrast, Afzal *et al.*,[44] in a recent report, note a decreased response rate in isolated colonic disease without associated small bowel disease. Upon systematic review of available studies, Zachos *et al.*[31] were unable to make definite conclusions about the impact of disease location upon response because of lack of adequate data.

Exclusive enteral nutrition can also be beneficial in children with peri-anal disease, whether isolated or present in combination with luminal disease[36] and can be helpful in the management of enterovesical fistula (unpublished data). Furthermore, one recent case report has illustrated that EEN may also be beneficial for proximal small bowel CD.[45] In this case, an adult with long-standing CD who developed duodenal disease complicated by the development of a stricture was managed successfully with administration of an elemental formula. Improvement in the stricture was associated with falling mucosal levels of TNF-$\alpha$ and other pro-inflammatory cytokines.[45]

The influence of disease location and other factors upon short-term responses to EEN requires further definition. Disease location also may influence the long-term outcomes of children treated with EEN. Again, additional studies are required to define these aspects of EEN in children with CD.

## Endoscopic and mucosal healing with EEN

Mucosal healing is now recognized as an important goal in the initial management of CD. It appears that the acquisition of mucosal healing may be associated with modification of the long-term course of the disease.[46, 47] Furthermore, persistence of inflammation is likely to cause adverse impact upon growth in children and adolescents. Persistence also is associated with increased risk of subsequent relapse, particularly in adults.[48, 49]

A recent report from Japan demonstrated the clinical benefits of elemental formula in 28 adults with CD.[50] The use of this therapy in this cohort induced remission in 71%, with endoscopic healing and improvements seen in up to 44% and 78% of individuals respectively. In addition, mucosal levels of multiple proinflammatory cytokines fell to control levels, along with correction of imbalance in the ratio between IL-1$\beta$ and IL-1ra.

Borrelli *et al.*[51] recently reported the outcomes of a group of 37 children randomized to receive either 10 weeks of polymeric formula or corticosteroids. Seventy-nine per cent of the children receiving EEN entered remission in the study period, compared to 67% of the children treated with steroids ($P = 0.40$). EEN led to a reduction of PCDAI from $38.1 \pm 10$ to $6.53 \pm 1.4$. Erythrocyte sedimentation rate and CRP levels fell, whilst albumin normalized during the period of therapy. Furthermore, colonoscopy undertaken before and after the course of treatment demonstrated that 74% of the children given EEN had mucosal healing, but this was seen in only 33% of the steroid group ($P < 0.05$).

The mucosal healing associated with the administration of EEN has been correlated with reduced levels of several key inflammatory markers within the intestinal mucosa. In a group of 29 children treated with EEN, of whom 79% entered remission, endoscopic healing was commonly seen.[52] Repeat colonoscopy was conducted within 2 months of diagnosis in each of these patients and demonstrated improved endoscopic

severity scores in both the ileum and the colon. Reduced IL-1$\beta$ and interferon-$\gamma$ mRNA along with increased tumour growth factor (TGF)-$\beta$ mRNA were defined in mucosal biopsies in parallel with endoscopic and clinical improvements.[52] The full implications of achieving or not achieving mucosal healing following EEN therapy are not yet clear. Mucosal healing could influence disease progression, extra-intestinal disease, steroid requirements, growth patterns as well as other outcomes. Further long-term clinical studies are now required to elucidate the importance of establishing mucosal healing in paediatric CD.

## Why is EEN provided in an 'exclusive' manner?

Traditionally, EN, as a therapeutic manoeuvre in CD, has been provided exclusively (rather than in combination with a partial normal diet). The need to provide EN in an exclusive manner (i.e. EEN) when used to induce remission is supported by recent data from the UK. Johnson *et al.*[53] compared a group of children given EEN with a group given approximately 50% of their intake as formula with the remainder as a normal diet (partial EN group). The EEN group had a remission rate of 42%, which was superior to that of the partial EN group (remission in 15%: $P < 0.035$).

Some investigators report their use of EEN along with access to hard-boiled lollies[43] and flavouring agents.[36, 54] Although this approach may assist in compliance with administration of formula, it could also cause adverse impact upon responses and outcomes. It is not yet clear if the addition of these items to the formula alters the clinical benefits. Further studies are required to understand fully the relevance and importance of exclusive administration of EN.

## EEN and nutritional status

An additional benefit of EEN is the nutritional improvement seen during and following therapy in many clinical studies.[4, 55, 56] These benefits of EEN are especially crucial in children and adolescents.

In a cohort of 14 patients, EEN lead to increasing weight *Z* scores at 8 and 16 weeks.[57] The mean age of these patients was 12.5 years. During the period of EEN, levels of insulin-like growth factor (IGF)-1 and IGF-binding protein-3 increased. Recent data show that IGF-1 levels improve very promptly after the commencement of EEN.[38] In these 12 children studied, IGF-1 levels normalized after just 7 days of EEN.[38]

Body composition studies in children show that all body compartments improve with EEN.[58] In addition to weight gains, we have demonstrated short-term height gains.[36] Height velocity is noted to improve more rapidly in children treated with EEN than in children treated with steroids.[4, 55] These nutritional improvements do not appear to coincide with normalization of inflammation, suggesting multiple and independent activities of EEN.[36, 59]

## EEN and bone metabolism

In addition to overall nutritional benefits, it appears that the use of EEN also has specific benefits on bone nutrition. We have examined markers of bone turnover in a group of children treated for up to 8 weeks and compared these outcomes to data from control children.[60] Children with CD ($n = 17$) were managed according to standard protocol with polymeric nutrition.[36] Serum samples taken prior to commencement of EEN and after 8 weeks of therapy were used to measure serum Cross-laps and bone specific alkaline phosphatase (markers of bone breakdown and formation, respectively). Overall children at diagnosis of CD had abnormal bone markers compared to controls. After 8 weeks of therapy with EEN, both markers had returned to control levels. This finding suggests a further short-term benefit of EEN; the mechanism of this effect is likely through a reduction of pro-inflammatory cytokines leading to improved bone metabolism. It is notable that a similar short-term benefit is seen after the administration of Infliximab.[61] The long-term benefits of EEN upon bone health are yet to be fully ascertained and are the current subject of further scrutiny.

## EEN and maintenance of remission

Several paediatric and adult reports over the last decade support a role for ongoing EN in the maintenance of remission and prevention of relapse. A report from Toronto demonstrated the benefits of providing regular feeds in addition to normal diet.[62] In these children, overnight NG tube feeds with elemental formula in combination with normal diet throughout the day resulted in prolonged remission. Using a different approach, investigators from another Canadian centre showed that disease remission could be maintained by giving enteral formula as intermittent intensive periods of exclusive feeds via NG tube.[63]

Ongoing enteral formula may help maintain remission and delay the requirement for further therapy, such as corticosteroids.[43] However, in contrast to the above cohorts, we provided supplementary oral formula in combination with a normal diet throughout the day.[36] Our approach has been to recommend an ongoing supplement of between 500 ml and 1000 ml of polymeric formula each day, in conjunction with normal meals. This therapeutic strategy may also be used in combination with maintenance medical therapy, but may be limited by compliance. Further detailed analysis and study are now required to demonstrate the short and long-term benefits of this management approach in children.

Adult studies also show that oral supplements of formula in addition to an ongoing standard diet can be beneficial.[64, 65] Several recent studies have come from Japan on this topic. One report in Japanese adults with CD illustrates that maintenance EN can have a role in prevention of relapse.[66] In this study, 51 patients with CD in remission were randomized to receive either half their calories in the form of an elemental formula along with normal diet or to have an unrestricted normal diet (with no additional supplements) for up to 2 years. Although 22 of these patients had entered remission after a defined period of EEN, others ($n$ = 25) had received parenteral nutrition, five had undergone a surgical procedure ($n$ = 5) and one had received corticosteroids. The treatment group had a much lower rate of relapse (34%) than the free diet group (64%). The multivariate hazard ratio was calculated as 0.40 (0.16–0.98). Interestingly, this study was halted before the expected end of the study period, as a result of the interim analyses by the monitoring board defining a significant benefit for the use of ongoing formula.

Supplementary EN may also have benefits in preventing post-operative recurrence of CD. A group of adults who had received at least 1200 kcal of an enteral formula (polymeric or elemental) for the first 12 months following a resection had much lower risk of disease recurrence than a comparison group who were not treated with supplementary feeds ($P$ = 0.017).[67] These benefits were particularly evident in patients with penetrating disease and patients without colonic disease. Another Japanese study has shown similar findings.[68] In this study, 40 patients were allocated to either receive nocturnal elemental feeds in conjunction with a low-fat diet throughout the day for more than 12 months or to receive a standard diet. The group of 20 adults who received overnight feeds had endoscopic disease recurrence rates of 25% after 6 months and 30% after 1 year. In contrast, the group who received just a standard diet had recurrence rates of 40% and 70% after the same time intervals ($P$ = 0.027 at 12 months). Further studies evaluating EN in this post-operative role are required before this approach can be considered more widely.

## Long-term outcomes associated with EEN

Two recent reports have concentrated on longer-term outcomes of children managed with EEN to induce remission. Knight *et al.*[43] reviewed the long-term outcomes of 44 children treated with EEN over several years at a single paediatric IBD centre, with follow-up periods varying between 1 and 7 years. Most of these children ($n$ = 40) were managed with an elemental formula, and the other four were provided with a polymeric formula. Over half of the children were able to continue on maintenance formula in conjunction with normal diet after induction of remission.

Overall, 90% of these children responded to EEN with remission reached in median of 6 weeks, and a median duration of remission of 54.4 weeks (range from 4 to 312 weeks).[43] Fifteen of the children on maintenance EN had no episode of relapse after remission was established. Further, almost half of the patients have had no exposure to corticosteroids since diagnosis. In the children who did eventually require steroids, therapy was delayed by a median period of 68 weeks (range 6–190). In addition to these effects upon disease activity, the authors showed improved weight $Z$ scores to 12 months after diagnosis (compared to base-line values), but no improvement in height $Z$ scores. No long-term nutritional data were available in this group of patients.

A further paediatric report[69] has also illustrated long-term outcomes of EEN. This retrospective study looked at 37 children who had received EEN and contrasted outcomes in these children to outcomes of 10 children treated with steroids. The initial remission rate in those managed with EEN was similar to that in children treated with corticosteroids (86.8% vs. 90% respectively). Children managed with EEN achieved much greater mucosal improvements (64.8% vs. 40%) and much greater complete healing (7/37 vs. 0%). Furthermore, EEN therapy led to enhanced nutritional improvements and linear growth recovery in these children superior to those managed with steroids.

These children had been followed up for 12 months since diagnosis. After induction of remission, both

groups were managed with maintenance amino salicylic acid (ASA) therapy. The group treated initially with EEN had a much longer duration of remission in the 12-month follow-up period. No other long-term data were available in these patients.[69]

Together, these longer-term follow-up studies suggest that EEN may prompt a more prolonged remission characterized by less requirement for medicines such as corticosteroids. Maintenance EN over many months can assist in maintaining remission, help to ensure adequate and appropriate growth, in addition to postponing a requirement for steroids. Further studies of the long-term outcomes of nutritional therapy in children with CD are now required to guide more fully the practitioners and patients.

## Variations in the use of EEN

Although there are much convincing data supporting the diverse benefits of EEN in children with active CD, there are wide differences in the use of EEN between various countries and even within countries.[70] EEN is used as initial therapy in many English centres,[43, 52, 53] but not in many centres in the USA.[70] The reasons for these differences are unclear, but are the subject of current studies. Potential factors could include access to dietetic and nursing support, lack of experience with the use of EEN, lack of financial support for the provision of formula and a lack of understanding of the mechanisms of action. Improving understanding of the many roles of EEN in the management of CD in children should permit more considered decisions about the use of this therapy.

## EEN and quality of life

Exclusive enteral nutrition is felt by some to be difficult to administer successfully and felt to lead to decreased quality of life (QOL) for the patients involved. The influence of therapy upon QOL during and following EEN are shown in two recent studies of children with CD.[71, 72]

A study from the UK showed improved QOL scores in 24 of 26 children treated with EEN for active CD.[71] The validated IMPACT II questionnaire was used to define QOL and almost 90% of the children entered remission. Three of these children received their enteral formula via a NG tube: all three had overall improvements in QOL despite the need for NG feeding.

Additional data of the impact of EEN therapy upon QOL were obtained from a French cohort of 30 children.[72] Half of this cohort received EEN via NG tubes, whereas the remainder had been treated with steroids. Although a formal, validated QOL scoring system was not utilized, the authors showed that EEN leads to overall improvements, but with an adverse impact upon family functioning. The difficulties associated with use of NG tubes were again emphasized by these children.

Similar studies have not been conducted in groups of children treated with EEN given orally. However, it does appear that the improvements in day-to-day functioning, bowel symptoms and overall well-being may outweigh the negative aspects associated with a period of EEN therapy.

## Side effects of EEN

Published reports demonstrate that EEN is safe and well tolerated with few side effects. Borreli *et al.*[51] report minimal side effects with EEN. Four of the 17 patients (23.5%) in this study had side effects, including nausea, abdominal pain, flatulence, or diarrhoea. In contrast, two-thirds of the children treated with steroids had various side effects.

Loose, unformed motions and flatulence may be reported, but nausea and constipation are uncommonly reported.[36, 51] A number of children do report early satiety and nausea with feeding. These children may benefit from the addition of short period of acid suppressive therapy, particularly during the start of the feeding period.

The only reported severe adverse event associated with EEN is a single case of re-feeding syndrome.[73] This adolescent had a large weight loss prior to the start of therapy and developed classical features of re-feeding syndrome within 2 days of starting EEN. As with the commencement of nutritional resuscitation in any setting, one must consider the risk of re-feeding syndrome at the time of starting EEN and establish baseline electrolyte levels as well as monitor closely (as reviewed in Afzal *et al.*[73]). However, re-feeding during EEN is likely to be an uncommon occurrence, as evidenced by the lack of published reports.

## EEN protocols

Although EEN is well proven to have numerous benefits and is now well established in many centres

around the world, there is no consensus yet as to the optimal way in which it should be administered. These variations in protocols include the administration of different formulae, variable use of NG tubes, differing lengths of therapy, differing definitions of exclusivity and diverse approaches to the recommencement of normal diet at the end of the period of exclusive liquid diet. These variations in practice hinder the comparison of assorted patient cohorts, and impede the advance of support for the benefits of EEN as a standard practice in all paediatric gastroenterology units.

In various clinical reports, EEN has been provided for periods of between 4 and 12 weeks. Our local data demonstrate that the clinical (anti-inflammatory and nutritional) benefits continue beyond the first 4–6 weeks of treatment.[36] Although many children have improvements in energy and mood within the first 7–10 days of EEN therapy, these aspects continue to improve after this time. Furthermore, although inflammatory markers often fall within 14 days of therapy, they generally continue to improve over 6–8 weeks. Finally, we have seen further nutritional benefits beyond the sixth week of therapy.[36]

Well-designed clinical studies with consistent EEN protocols are required to ascertain the optimal length of time that EEN should continue, and to elucidate the variables that may influence this. These may include the degree of nutritional impairment at diagnosis, the location of disease and the pattern of disease. These studies may determine, for instance, that disease in one location should be treated for a longer period of time than disease in another location.

Currently, our protocol encompasses administering a 1 kcal per mL polymeric formula (Osmolite, Abbott Australasia Pty Ltd, Sydney, NSW, Australia) by mouth for 8 weeks.[36] Patients have the option of using a NG tube if unable to tolerate volumes by mouth. Only five of 49 newly diagnosed patients managed with EEN over the past 3 years have elected for NG tube insertion (unpublished data). Patient compliance may be enhanced when flavouring (e.g. Nesquik; Nestle, Sydney, Australia) is added to the formula. At diagnosis, EEN is discussed with the patient and family as the mainstay of therapy for CD by medical, nursing and dietetic staff and a nutritional assessment is conducted to calculate formula requirements.

Formula volume is prescribed to meet estimated energy requirements using ideal weight for height (with height potential used in cases of stunting/delayed height gain) and taking into account the patient's usual activity level.[36] Requirements are modified over the 8-week period as required, based on weight gains, hunger and overall progress. Regular out-patient clinical review is undertaken along with close liaison by phone to monitor progress, make any required adjustments to management and to offer regular support and motivation to patients and their family.

At the conclusion of 8 weeks of EEN, food is gradually introduced, with one meal added every 3 days. Volumes of formula are decreased by approximately 250–500 mL per meal, depending on the age and caloric requirements of the child. Children are advised to select bland or simple foods initially and to build upon food variety over the subsequent weeks.

## MECHANISMS OF ACTION OF EEN

Although there are much data supporting the various clinical roles of EEN in children and adolescents, until recently, there have been little data on the ways in which EEN exerts various anti-inflammatory benefits. Suggested mechanisms include bowel rest (by use of a simple liquid food product), nutritional improvements, modulation of immune events, direct anti-inflammatory effects and alteration of intestinal microflora. The latter two mechanisms have been supported by work conducted over the last few years.

### EEN and intestinal microflora

Many animal and human studies support the critical role the intestinal microflora play in the pathogenesis and/or perpetuation of intestinal inflammation in CD. Animal models illustrate that the presence of flora is required to lead to inflammation; an absence of flora in a germ-free environment leads to either no inflammation or delayed onset of inflammation. The use of probiotics or antibiotics modulating flora is also well demonstrated in animal models of CD.

In human studies, the presence of flora is also shown to be critical. Colonic diversion (leading to no faecal flow) often leads to amelioration or resolution of colonic inflammation. Furthermore, antibiotics can play a role in the induction of remission in individuals with CD, especially in the setting of colonic disease.

Alterations in the patterns of flora also are evident in individuals with CD.[74, 75] For example, Seksik *et al.*[75] used molecular techniques to show that the microflora of patients with CD differed from that of

normal controls and that the patterns of faecal flora changed during active disease. Despite these extensive data, there is no evidence yet supporting a role for one particular organism in these processes. It appears more likely that the altered pattern of flora prompts variations in mucosal responses, possibly in combination with other host factors, such as the decreased secretion of epithelial antibacterial proteins including defensins.[76]

With this in mind, it is reasonable to consider that EEN may prompt the observed effects via modulation of the intestinal flora.[77] Several investigators have produced data that support this hypothesis.

Preliminary data from a British study show that EEN leads to alterations in the bacterial flora present on mucosal surfaces.[78] Mucosal biopsies were obtained from children diagnosed with CD before and after EEN treatment. The nature of the mucosa-associated flora was defined using molecular techniques, and comparison made to biopsies from control patients. Over time in the subjects, EEN was seen to change markedly the bacterial populations present. In addition, EEN restored the variability of flora between intestinal sites, to that seen in the control samples.[78]

Similar effects of EEN are noted by an Italian group.[79] This clinical study included nine children with active CD, who were all treated with a polymeric formula for 8 weeks. All but one patient entered remission with EEN alone (the other child received steroids in addition to EEN). Following the period of EEN, each of the subjects continued on oral supplementary formula throughout the course of the study. The faecal flora patterns in stool samples taken regularly over the course of the study were defined using molecular studies (tissue gradient gel electrophoresis). Large changes in the faecal flora patterns were evident as a consequence of EEN. Ongoing changes were also seen beyond 8 weeks whilst children maintained supplementary formula. Samples from control subjects showed no variation over time.

Recently, we have undertaken detailed studies of the faecal flora in children treated with EEN.[80] Ten children with newly diagnosed CD were enrolled for this study, along with seven controls. Serial stool samples were collected from patients with CD prior to, during and following a period of EEN. Control children provided just two stool samples 8 weeks apart. Bacterial DNA was extracted from stool samples and then used in polymerase chain reactions to amplify the 16S rRNA gene with five primer sets. One primer set amplifies all bacterial species, but the other four sets amplify separate bacterial groups (*Bacteriodes–Prevotella* group, *Bifidobacteria* group, *Clostridium coccoides* group and the *Clostridium leptum* subgroup). Denaturing gradient gel electrophoresis was then used to define bacterial groups present. Faecal flora patterns altered shortly after the start of EEN and changes persisted throughout the period of EEN. Bacterial groups tended to return to pre-treatment patterns over the 4 months after the completion of the EEN period. The pattern of these changes varied between patients. As seen in the other studies, the faecal flora patterns were stable in the samples obtained from control patients.

At this point, it remains unclear how treatment with EEN modulates changes in faecal or mucosa-associated flora. One possibility is that this could be because of prebiotic properties of the formula used for EEN. A further explanation is that EEN alters the micro-environment in the colon, perhaps as a result of alterations in pH, short-chain fatty acids or changes in bacterial growth factors. These changes may then modulate mucosal inflammatory events as a result of interactions between bacteria and the epithelium. Alternatively, EEN may have primary effects upon the intestinal epithelium, which consequently leads to changes in the balance of the flora as a consequence of epithelial events via cross-talk. Further detailed studies are required to define these events more clearly.

Of direct relevance to this are data showing that EN provided exclusively in a non-IBD context also alters flora and the characteristics of the bacterial metabolic activity.[81] A small group of adults managed with an enteral formula as their complete nutritional intake for dysphagia were studied prospectively with assessment of bacterial flora patterns (molecular analyses) and of bacterial metabolic activity (short chain fatty acids). A multi-fibre formula resulted in increased faecal short chain fatty acid levels compared to baseline and an increase in the number of bacteria present. However, there did not appear to be a variation in the patterns of dominant bacterial groups.[81]

## EEN and epithelial interactions

Interactions between the gastro-intestinal epithelial surface and the components (nutrients) provided in EN formulae may also contribute to the benefits seen with EEN. This hypothesis seems plausible given that the

epithelial apical surface interacts directly with luminal contents, and is a main contributor to innate immune responses, leading on to activation of other immune responses as required.[82] The roles of specific components within EN formulae that may interact with the epithelial surface have not clearly been elucidated. However, the nature of the fat contained in the formula may be important.[83]

Data from Meister *et al.*[84] show that EN, provided as an elemental formula, directly inhibits mucosal inflammatory events. These investigators used a short-term tissue control model to demonstrate these anti-inflammatory effects. Mucosal biopsies were obtained endoscopically from individuals with IBD and from controls. These explants were then incubated with formula and variations in certain cytokines evaluated. In tissue obtained from patients with CD, the exposure to formula prompted an increase in the ratio of IL-1 receptor antagonist to IL-1$\beta$, which differed from that seen in control tissue. The data obtained from these *in vitro* studies are consistent with data from clinical studies showing changes in these cytokines consequent to EEN.[50, 52]

Further *in vitro* studies have also demonstrated that enteral formulae may modulate epithelial responses.[85] These studies utilized intestinal epithelial cells maintained in cell culture, which were then stimulated with proinflammatory agents (including TNF-$\alpha$) in the presence or absence of polymeric formulae. These experiments showed that the addition of formula altered epithelial cell chemokine responses to the pro-inflammatory stimulation even when the formula and the inflammatory agent were kept separate in a two-compartment model. These effects appeared to be mediated by effects of the formula upon intracellular signalling processes.[85] Further detailed *in vitro* and *in vivo* studies are required to elucidate these events fully.

## SUMMARY AND CONCLUSIONS

Although much remains unknown about the mechanisms by which EEN exerts clinical effects, it is abundantly clear that this therapy can play a key role in the management of CD in children and adolescents. Not only can EEN induce remission, it also leads to superior levels of mucosal healing, modulation of mucosal immune events, nutritional improvements and recovery of bone metabolism. There are suggestions from the published literature that EEN has greater benefits in children than in adults: there may be patient groups that respond better to EEN. Much work is now required to define further these predictors of response so that EEN is used optimally. Furthermore, elucidating the mechanisms by which EEN acts should lead us to understand better the key interactions between the host epithelium and foreign antigens in the intestinal lumen.

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## REFERENCES

1 Griffiths AM, Hugot J-P. Crohn Disease, Chapter 41. In: Walker A, Goulet O, Kleinman RE, *et al.*, eds. *Pediatric Gastrointestinal Disease*, 4th edn. BC Decker: Hamilton Ontario, 2004: 789–824.
2 Lemberg DA, Clarkson C, Bohane T, Day AS. The role of esophago-gastro-duodenoscopy in the initial assessment of children with IBD. *J Gastroenterol Hepatol* 2005; **20**: 1696–700.
3 Kirschner KS, Voinchet O, Rosenberg IH. Growth retardation in inflammatory bowel disease. *Gastroenterology* 1978; **75**: 504–11.
4 Thomas AG, Taylor F, Miller V. Dietary intake and nutritional treatment in childhood Crohn's disease. *J Pediatr Gastroenterol Nutr* 1993; **17**: 75–81.
5 Aiges H, Markowitz J, Rosa J, Daum F. Home nocturnal supplemental nasogastric feedings in growth-retarded adolescents with Crohn's disease. *Gastroenterology* 1989; **97**: 905–10.
6 Hildebrand H, Karlberg J, Kristiansson B. Longitudinal growth in children and adolescents with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 1994; **18**: 165–73.
7 Saha MT, Ruuska T, Laippala P, Lenko HL. Growth of prepubertal children with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 1998; **26**: 310–4.
8 Ballinger AB, Azooz O, El-Haj T, Poole S, Farthing MJ. Growth failure occurs through a decrease in insulin-like growth factor 1 which is independent of under nutrition in a rat model of colitis. *Gut* 2000; **46**: 694–700.
9 Sawczenko A, Azooz O, Paraszczuk J, *et al.* Intestinal inflammation-induced growth retardation acts through IL-6 in rats and depends on the -174 IL-6 G/C polymorphism in children. *Proc Natl Acad Sci USA* 2005; **102**: 13260–5.
10 Sawczenko A, Ballinger AB, Savage MO, Sanderson IR. Clinical features affecting

final adult height in patients with pediatric-onset Crohn's disease. *Pediatrics* 2006; **118**: 124–9.
11 Griffiths AM, Nguyen P, Smith C, MacMillan JH, Sherman PM. Growth and clinical course of children with Crohn's disease. *Gut* 1993; **34**: 939–43.
12 Sawczenko A, Ballinger AB, Croft NM, Sanderson IR, Savage MO. Adult height in patients with early onset of Crohn's disease. *Gut* 2003; **52**: 454–5.
13 Paerregaard A, Urne FU. Anthropometry at the time of diagnosis in Danish children with inflammatory bowel disease. *Acta Paediatr* 2005; **94**: 1682–3.
14 Geerling BJ, Badart-Smook A, Stockbrugger RW, *et al.* Comprehensive nutritional status in recently diagnosed patients with inflammatory bowel disease compared with population controls. *Eur J Clin Nutr* 2000; **54**: 514–21.
15 Filippi J, Al-Jaouni R, Wiroth JB, Hebuterne X, Schneider SM. Nutritional deficiencies in patients with Crohn's disease in remission. *Inflamm Bowel Dis* 2006; **12**: 185–91.
16 Seidman EG. Nutritional management of inflammatory bowel disease. *Gastroenterol Clin North Am* 1989; **18**: 129–55.
17 Holm I. Benefits of total parenteral nutrition (TPN) in the treatment of Crohn's disease and ulcerative colitis. A clinical review. *Acta Chir Scand* 1981; **147**: 271–6.
18 Voitk AJ, Echave V, Feller JH, Brown RA, Gurd FN. Experience with elemental diet in the treatment of inflammatory bowel disease. Is this primary therapy? *Arch Surg* 1973; **107**: 329–33.
19 Tim LO, Odes HS, Duys PJ, *et al.* The use of an elemental diet in gastrointestinal diseases. *S Afr Med J* 1976; **50**: 1752–6.
20 Younoszai MK. Growth in a teenage boy with granulomatous enteritis fed "elemental diets". *Am J Dis Child* 1977; **131**: 235–6.
21 Ricour C, Duhamel JF, Nihoul-Fekete C. Use of parenteral and elementary enteral nutrition in the treatment of Crohn's disease and ulcerative colitis in children. *Arch Fr Pediatr* 1977; **34**: 505–13.
22 O'Morain C, Segal AW, Levi AJ. Elemental diet as primary treatment of acute Crohn's disease: a controlled trial. *Br Med J (Clin Res Ed)* 1984; **288**: 1859–62.
23 Malchow H, Lorenz-Meyer H, Steinhardt HJ, *et al.* Defined formula diet in the treatment of active Crohn disease. *Beitr Infusionther Klin Ernahr* 1986; **14**: 216–31.
24 Lindor KD, Fleming CR, Burnes JU, Nelson JK, Ilstrup DM. A randomized prospective trial comparing a defined formula diet, corticosteroids and a defined formula diet plus corticosteroids in active Crohn's disease. *Mayo Clin Proc* 1992; **67**: 328–33.
25 Gorard DA, Hunt JG, Payne-James JJ, *et al.* Initial response and subsequent course of Crohn's disease treated with elemental diet or prednisolone. *Gut* 1993; **34**: 1198–202.
26 Lochs H, Steinhardt HJ, Klaus-Wentz B, *et al.* Comparison of enteral nutrition and drug treatment in active Crohn's disease. Results of the European Cooperative Crohn's disease Study IV. *Gastroenterology* 1991; **101**: 881–8.
27 Griffiths AM, Ohlsson A, Sherman PM, Sutherland LR. Meta-analysis of enteral nutrition as a primary treatment of active Crohn's disease. *Gastroenterology* 1995; **108**: 1056–67.
28 Fernandez-Banares F, Cabre E, Esteve-Comas M, Gassull MA. How effective is enteral nutrition in inducing clinical remission in active Crohn's disease? A meta-analysis of the randomized clinical trials. *J Parenter Enter Nutr* 1995; **19**: 356–64.
29 Messori A, Trallori G, D'Albasio G, *et al.* Defined-formula diets versus steroids in the treatment of active Crohn's disease: a meta-analysis. *Scand J Gastroenterol* 1996; **31**: 267–72.
30 Zachos M, Tondeur M, Griffiths AM. Enteral nutritional therapy for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2001; **3**: CD000542.
31 Zachos M, Tondeur M, Griffiths AM. Enteral nutritional therapy for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2007; **1**: CD000542.
32 Gonzalez-Huix F, de Leon R, Fernandez-Banares F, *et al.* Polymeric enteral diets as primary treatment of active Crohn's disease: a prospective steroid controlled study. *Gut* 1993; **34**: 778–82.
33 Verma S, Brown S, Kirkwood B, Giaffer MH. Polymeric versus elemental diet as primary treatment in active Crohn's disease: a randomized, double-blind trial. *Am J Gastroenterol* 2000; **95**: 735–9.
34 Heuschkel RB, Menache CC, Megerian JT, Baird AE. Enteral nutrition and corticosteroids in the treatment of acute Crohn's disease in children. *J Pediatr Gastroenterol Nutr* 2000; **31**: 8–15.
35 Seidman EG, Jones A, Issenman R, Griffiths A. Relapse prevention/growth enhancement in pediatric Crohn's disease: multi-centre randomized controlled trial of intermittent enteral nutrition versus alternate day prednisone. *J Pediatr Gastroenterol Nutr* 1996; **23**: A344.
36 Day AS, Whitten KE, Lemberg DA, *et al.* Exclusive enteral feeding as primary therapy for Crohn's disease in Australian children and adolescents: a feasible and effective approach. *J Gastroenterol Hepatol* 2006; **21**: 1609–14.
37 Hyams JS, Ferry GD, Mandel FS, *et al.* Development and validation of a pediatric Crohn's disease activity index. *J Pediatr Gastroenterol Nutr* 1991; **12**: 439–47.
38 Bannerjee K, Camacho-Hubner C, Babinska K, *et al.* Anti-inflammatory and growth-stimulating effects precede nutritional restitution during enteral feeding in Crohn disease. *J Pediatr Gastroenterol Nutr* 2004; **38**: 239–41.
39 Markowitz J, Grancher K, Kohn N, *et al.* A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. *Gastroenterology* 2000; **119**: 895–902.
40 Heuschkel R. Synergy between immunosuppressive therapy and enteral nutrition in the management of childhood Crohn's disease. *J Parent Enteral Nutr* 2005; **29**(Suppl. 4): S160–5.
41 Tanaka T, Takahama K, Kimura T, *et al.* Effect of concurrent elemental diet on infliximab treatment for Crohn's disease. *J Gastroenterol Hepatol* 2006; **21**: 1143–9.
42 Seidman EG. Nutritional therapy for Crohn's disease: lessons from the Ste-Justine Hospital experience. *Inflamm Bowel Dis* 1997; **3**: 49–53.
43 Knight C, El-Matary W, Spray C, Sandhu BK. Long-term outcome of nutritional therapy in paediatric Crohn's disease. *Clin Nutr* 2005; **24**: 775–9.
44 Afzal NA, Davies S, Paintin M, *et al.* Colonic Crohn's disease in children does not respond well to treatment with enteral nutrition if the ileum is not involved. *Dig Dis Sci* 2005; **50**: 1471–5.
45 Yamamoto T, Nakahigashi M, Umegae S, Kitagawa T, Matsumoto K. Acute duodenal Crohn's disease successfully managed with low-speed elemental diet infusion via nasogastric tube – a case

report. *World J Gastroenterol* 2006; **12**: 649–51.
46 Hanauer SB. Hit me with your best shot...Fire away! *Nat Clin Pract Gastroenterol Hepatol* 2006; **3**: 473.
47 D'Haens G. Mucosal healing in pediatric Crohn's disease. *Inflamm Bowel Dis* 2004; **10**: 479–80.
48 Wyatt J, Vogelsang H, Hubl W, Waldhoer T, Lochs H. Intestinal permeability and the prediction of relapse in Crohn's disease. *Lancet* 1993; **341**: 1437–9.
49 Tibble JA, Sigthorsson G, Bridger S, Fagerhol MK, Bjarnason I. Surrogate markers of intestinal inflammation are predictive of relapse in patients with inflammatory bowel disease. *Curr Gastroenterol Rep* 2000; **2**: 353.
50 Yamamoto T, Nakahigashi M, Umegae S, Kitagawa T, Matsumoto K. Impact of elemental diet on mucosal inflammation in patients with active Crohn's disease: cytokine production and endoscopic and histological findings. *Inflamm Bowel Dis* 2005; **11**: 580–8.
51 Borrelli O, Cordischi L, Cirulli M, *et al.* Polymeric diet alone versus corticosteroids in the treatment of active pediatric Crohn's disease: a randomised controlled open-label trial. *Clin Gastroenterol Hepatol* 2006; **4**: 744–53.
52 Fell JM, Paintin M, Arnaud-Battandier F, *et al.* Mucosal healing and a fall in mucosal pro-inflammatory cytokine mRNA induced by a specific oral polymeric diet in paediatric Crohn's disease. *Aliment Pharmacol Ther* 2000; **14**: 281–9.
53 Johnson T, MacDonald S, Hill SM, Thomas A, Murphy MS. Treatment of active Crohn's disease in children using partial enteral nutrition with liquid formula: a randomised controlled trial. *Gut* 2006; **66**: 356–61.
54 Gavin J, Anderson CE, Bremner AR, Beattie RM. Energy intakes of children with Crohn's disease treated with enteral nutrition as primary therapy. *J Hum Nut Dietet* 2005; **18**: 337–42.
55 Sanderson IR, Udeen S, Davies PS, *et al.* Remission induced by an elemental diet in small bowel Crohn's disease. *Arch Dis Child* 1987; **61**: 123–7.
56 Azcue M, Rashid M, Griffiths A, Pencharz PB. Energy expenditure and body composition in children with Crohn's disease: effect of enteral nutrition and treatment with prednisolone. *Gut* 1997; **41**: 203–8.
57 Beattie RM, Camacho-Hubner C, Wacharasindhu S, *et al.* Responsiveness of IGF-1 and IGFBP3 to therapeutic intervention in children and adolescents with Crohn's disease. *Clin Endocrinol (Oxf)* 1998; **49**: 483–9.
58 Royall D, Greenberg GR, Allard JP, *et al.* Total enteral nutrition support improves body composition of patients with active Crohn's disease. *J Parenter Enter Nutr* 1995; **19**: 95–9.
59 Teahon K, Pearson M, Smith T, Bjarnason I. Alterations in nutritional status and disease activity during treatment of Crohn's disease with elemental diet. *Scand J Gastroenterol* 1995; **30**: 54–60.
60 Whitten KE, Leach S, Bohane TD, Woodhead H, Day AS. The effect of exclusive enteral nutrition on bone metabolism in children with active Crohn's disease. *J Gastroenterol Hepatol* 2006; **21**: A351.
61 Franchimont N, Putzeys V, Collette J, *et al.* Rapid improvement of bone metabolism after infliximab treatment in CD. *Aliment Pharmacol Ther* 2004; **20**: 607–14.
62 Wilschanski M, Sherman P, Pencharz P, *et al.* Supplementary enteral nutrition maintains remission in paediatric Crohn's disease. *Gut* 1996; **38**: 543–8.
63 Belli DC, Seidman E, Bouthillier L, *et al.* Chronic intermittent elemental diet improves growth failure in children with Crohn's disease. *Gastroenterology* 1988; **94**: 603–10.
64 Verma S, Kirkwood B, Brown S, Giaffer MH. Oral nutritional supplementation is effective in the maintenance of remission in Crohn's disease. *Dig Liver Dis* 2000; **32**: 769–74.
65 Harries AD, Jones LA, Danis V, *et al.* Controlled trial of supplemented oral nutrition in Crohn's disease. *Lancet* 1983; **1**: 887–90.
66 Takagi S, Utsunomiya K, Kuriyama S, *et al.* Effectiveness of an ''half elemental diet'' as maintenance therapy for Crohn's disease: a randomised-controlled trial. *Aliment Pharmacol Ther* 2006; **24**: 1333–40.
67 Esaki M, Matsumoto T, Hizawa K, *et al.* Preventative effect of nutritional therapy against postoperative recurrence of Crohn's disease, with reference to findings determined by intraoperative enteroscopy. *Scand J Gastroenterol* 2005; **40**: 1431–7.
68 Yamamoto T, Nakahigashi M, Umegae S, Kitagawa T, Matsumoto K. Impact of long-term enteral nutrition on clinical and endoscopic recurrence after resection for Crohn's disease: a prospective, non-randomised, parallel, controlled study. *Aliment Pharmacol Ther* 2006; **25**: 67–72.
69 Berni Canani R, Terrin G, Borrelli O, *et al.* Short and long-term therapeutic efficacy of nutritional therapy and corticosteroids in paediatric Crohn's disease. *Dig Liver Dis* 2006; **38**: 381–7.
70 Levine A, Milo T, Buller H, Markowitz J. Consensus and controversy in the management of pediatric Crohn disease: an international survey. *J Pediatr Gastroenterol Nutr* 2003; **36**: 464–9.
71 Afzal NA, Van Der Zaag-Loonen HJ, Arnaud-Battandier F, *et al.* Improvement in quality of life of children with acute Crohn's disease does not parallel mucosal healing after treatment with exclusive enteral nutrition. *Aliment Pharmacol Ther* 2004; **20**: 167–72.
72 Gailhoustet L, Goulet O, Cachin N, Schmitz J. Study of psychological repercussions of 2 modes of treatment of adolescents with Crohn's disease. *Arch Pediatr* 2002; **9**: 110–6.
73 Afzal NA, Addai S, Fagbeni A, *et al.* Refeeding syndrome with enteral nutrition in children: a case report, literature review and clinical guidelines. *Clin Nutr* 2002; **21**: 515–20.
74 Swidsinski A, Ladhoff A, Pernthaler A, *et al.* Mucosal flora in Inflammatory Bowel Disease. *Gastroenterology* 2002; **122**: 44–54.
75 Seksik P, Rigottier-Gois L, Gramet G, *et al.* Alterations of the dominant faecal bacterial groups in patients with Crohn's disease of the colon. *Gut* 2003; **52**: 237–42.
76 Wehkamp J, Salzman NH, Porter E, *et al.* Reduced Paneth cell alpha-defensins in ileal Crohn's disease. *Proc Natl Acad Sci USA* 2005; **102**: 18129–34.
77 Seidman E. Gastrointestinal benefits of enteral feeds. In: Baker S, Baker R, David A, eds. *Pediatric Enteral Nutrition*. New York: Chapman and Hall, 1994: 46–66.
78 Pryce-Millar E, Murch SH, Heuschkel RB, *et al.* Enteral nutrition therapy in Crohn's disease changes the mucosal flora. *Pediatr Gastroenterol Nutr* 2004; **39**(Suppl. 1): S289.
79 Lionetti P, Callegari M, Cavicchi M, *et al.* Enteral nutrition-induced remission is associated with profound modification of the intestinal microflora in Crohn's disease. *J Pediatr Gastroenterol Nutr* 2004; **39**(Suppl. 1): S106.
80 Eng WR, Day AS, Leach S, Whitten KE, Zhang L, Mitchell HM. Exclusive enteral

nutrition alters the intestinal microbiota of children with Crohn's Disease. *Gastroenterology* 2005; **128**: A511.
81 Schneider SM, Giraud-Pipau F, Anty R, *et al.* Effects of total enteral nutrition supplemented with a multi-fibre mix on faecal short-chain fatty acids and microbiota. *Clin Nutr* 2006; **25**: 82–90.
82 Sanderson IR. Short chain fatty acid regulation of signalling genes expressed by the intestinal epithelium. *J Nutr* 2004; **134**: 2450S–4S.
83 Gorard DA. Enteral nutrition in Crohn's disease: fat in the formula. *Eur J Gastroenterol Hepatol* 2003; **15**: 115–8.
84 Meister D, Bode J, Shand A, Ghosh S. Anti-inflammatory effects of enteral diet components on Crohn's disease-affected tissues *in vitro*. *Dig Liver Dis* 2002; **34**: 430–8.
85 de Jong NSH, Leach ST, Day AS. Polymeric formula has direct anti-inflammatory effects on enterocytes in an *in vitro* model of intestinal inflammation. *Dig Dis Sci* 2007; **52**: 2029–36.
86 Seidman EG, Lohouses MJ, Turgeon J, Bouthillier L, Morin CL. Elemental diet versus prednisone as initial therapy in Crohn's disease: early and long term results. *Gastroenterology* 1991; **100**: A250.
87 Seidman E, Griffiths A, Jones A, Issenman R. Semi-elemental (S-E) diet versus prednisone in pediatric Crohn's disease. *Gastroenterology* 1993; **104**: A778.
88 Ruuska T, Savilahti E, Maki M, Ormala T, Visakorpi JK. Exclusive whole protein enteral diet versus prednisolone in the treatment of acute Crohn's disease in children. *J Pediatr Gastroenterol Nutr* 1994; **19**: 175–80.
89 Akobeng AK, Miller V, Stanton J, Elbadri AM, Thomas AG. Double-blind randomized controlled trial of glutamine-enriched polymeric diet in the treatment of active Crohn's disease. *J Pediatr Gastroenterol Nutr* 2000; **30**: 78–84.
90 Terrin G, Canani RB, Ambrosini A, *et al.* A semielemental diet (Pregomin) as primary therapy for inducing remission in children with active Crohn's disease. *Ital J Pediatr* 2002; **28**: 401–5.
91 Ludvigsson JF, Krantz M, Bodin L, Stenhammar L, Lindquist B. Elemental versus polymeric enteral nutrition in paediatric Crohn's disease: a multicentre randomized controlled trial. *Acta Paediatr* 2004; **93**: 327–35.
92 Akobeng AK, Richmond K, Miller V, Thomas AG. Effect of exclusive enteral nutritional treatment on plasma antioxidant concentrations in childhood Crohn's disease. *Clin Nutr* 2007; **26**: 51–6.
93 Rodrigues AF, Johnson T, Davies P, Murphy MS. Does polymeric formula improve adherence to liquid diet therapy in children with active Crohn's disease? *Arch Dis Child* 2007; **92**: 767–70.