World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v21.i22.6809

World J Gastroenterol 2015 June 14; 21(22): 6809-6816
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

EDITORIAL

Exclusive enteral nutrition in children with Crohn's disease

Andrew S Day, Robert N Lopez

Andrew S Day, Robert N Lopez, Department of Paediatrics, University of Otago, Christchurch 8140, New Zealand
Andrew S Day, Robert N Lopez, Paediatrics Department, Christchurch Hospital, Christchurch 8140, New Zealand

Author contributions: Day AS and Lopez RN contributed equally to this paper.

Conflict-of-interest: The authors have no conflicts of interest to declare.

Correspondence to: Andrew S Day, Professor, Department of Paediatrics, University of Otago, P.O. Box 4345, Christchurch, 8140, New Zealand. andrew.day@otago.ac.nz
Telephone: +64-3-3640747
Fax: +64-3-3640919

Received: January 19, 2015
Peer-review started: January 20, 2015
First decision: March 10, 2015
Revised: March 26, 2015
Accepted: April 16, 2015
Article in press: April 17, 2015
Published online: June 14, 2015

Abstract

Exclusive enteral nutrition involves the use of a complete liquid diet, with the exclusion of normal dietary components for a defined period of time, as a therapeutic measure to induce remission in active Crohn's disease (CD). This very efficacious approach leads to high rates of remission, especially in children and adolescents newly diagnosed with CD. This intervention also results in mucosal healing, nutritional improvements and enhanced bone health. Whilst several recent studies have provided further elaboration of the roles of exclusive enteral nutrition in the management of CD, other reports have provided new understanding of the mechanisms by which this intervention acts.

Key words: Children; Crohn's disease; Exclusive enteral nutrition; Nutrition; Outcomes; Mechanisms

Core tip: Exclusive enteral nutrition is well-established as a key therapy in children with active Crohn's disease. Recent studies increasingly support this role, whilst other data has illustrated key mechanisms of action.

Day AS, Lopez RN. Exclusive enteral nutrition in children with Crohn's disease. *World J Gastroenterol* 2015; 21(22): 6809-6816 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i22/6809.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i22.6809

INTRODUCTION

Crohn's disease (CD), one of the inflammatory bowel diseases (IBD), is a chronic inflammatory condition that may involve any part of the gastrointestinal tract (GIT) commonly leading to symptoms such as abdominal pain, diarrhoea and nutritional impairments[1]. CD may present at any age, with up to one quarter of cases being diagnosed during childhood. In recent years, rates of CD have been increasing in many countries. Recent Australian data, for instance, shows a ten-fold increase in the incidence of CD over the first decade of the 21st century[2]. Other reports also demonstrate increasing incidence of CD in various countries and indicate that this condition is often presenting at younger ages[3].

The best accepted hypothesis for the pathogenesis of CD is that uncontrolled inflammation in the GIT follows a dysregulated immune response to environmental triggers in individuals with a genetic susceptibility[1]. Environmental factors implicated include diet and the intestinal microflora. Some dietary factors, such as breast-feeding in infancy are protective, whilst others (for example, a high fat diet) are associated with increased risk.

Onset of CD in children and adolescents is commonly associated with weight loss, and may also lead to impaired linear growth and pubertal delay. Consequently, the management of CD in this age group requires close attention to nutrition, with frequent assessment of weight, height and weight for height measurements[1,4]. Exclusive enteral nutrition (EEN) provides a way to induce remission and optimise nutrition following diagnosis. EEN involves the administration of a liquid diet formulation for a defined period of time as the sole intervention to induce remission[4]. EEN has essentially no side-effects and is associated with high rates of mucosal healing. However, similar to all other currently-available therapies for CD, EEN is not curative. This article focuses upon the roles of EEN in paediatric CD, with particular regards to new understandings of the role of EEN as well as the mechanisms of this therapy.

CD AND NUTRITIONAL CONSEQUENCES

CD is characterised by the finding of acute and chronic inflammatory changes in any section of the GIT. CD can be distinguished from ulcerative colitis (another form of IBD) by disease location, extent of involvement through the bowel wall, its patchy nature and the finding of non-caseating granuloma[5]. CD in childhood is typically extensive with pan-enteric involvement commonly seen; more than half of children have disease involvement proximal to the terminal ileum[1,6]. The initial features of CD also may include perianal, perioral or extra-intestinal features.

Many children diagnosed with CD present with classical symptoms of diarrhoea, abdominal pain and weight loss. Others, however, may present with less obvious symptoms such as lethargy, isolated joint symptoms, or oral findings.

Many reports indicate that almost all children presenting with CD have a history of either weight loss or plateauing of weight gain: in some studies more than 85% of children have these features[1,7]. This likely reflects early satiety or post-prandial abdominal discomfort. Circulating pro-inflammatory cytokines [for example, tumour necrosis factor (TNF)-α] also contribute to anorexia[8]. Consequent to changes in weight, a number of children may also have impaired linear growth. These changes in normal growth patterns may exist for many months prior to diagnosis, sometimes preceding any specific gastrointestinal symptoms[9]. Measurement of weight, height and weight for height assessments is essential at diagnosis. Review of historical growth patterns and interpretation of linear growth in the context of familial growth patterns are also important. Subsequent to diagnosis close attention to growth patterns and to the velocity of linear growth is required to ensure that adequate growth is attained and then maintained.

In addition to altered weight and height, impaired nutrition and uncontrolled inflammation also leads to delayed pubertal development[8]. In past generations, the combined effects of these growth impairments commonly resulted in reduced final adult height. Consequently, assessment of pubertal status in adolescents and calculation of bone age are important aspects of the ongoing care of children with CD, from diagnosis onwards.

Micronutrient deficiencies are also seen in children with CD. Although deficiencies of iron and vitamin D are seen most commonly, vitamin B12, zinc and selenium may also be low[10]. Although the nutritional impacts of CD may be most pronounced at diagnosis (when inflammation is uncontrolled prior to the commencement of therapy), these adverse effects also can occur at any subsequent stage.

Given that CD can have adverse nutritional consequences in children, it is not surprising that close ongoing attention to nutrition is a critical aspect of patient management. The use of EEN provides an important and vital role in managing many of the negative nutritional impacts of CD in children as well as inducing remission[4]. Although the main focus of EEN is upon the induction of remission and initial control of disease, further benefits may follow. Additionally, ongoing maintenance enteral nutrition (MEN) after initial EEN may assist in the maintenance of remission[11,12].

EFFICACY OF EEN IN INDUCTION OF REMISSION

A number of studies published over the last 15 years have demonstrated the efficacy of EEN in children with active CD. Generally EEN leads to the induction of remission in approximately 85% of patients. A meta-analysis of paediatric studies indicated that EEN had equivalent response to corticosteroids in children with active CD[13]. Although still involving relatively small cohorts, studies published in the last year or so confirm and build upon previous data.

A prospective Australian study involving 34 children demonstrated clinical remission in 84% and biochemical remission in 76%, whilst 58% had early endoscopic response[14]. A subset of this group also had small bowel imaging (magnetic resonance enterography) before and after EEN: 3 of these 14 children had complete transmural healing.

A recent Spanish study evaluated the outcomes of 40 children treated with EEN[15]. On an intention to

treat basis, 80% entered remission after 6-8 wk of EEN. When the investigators evaluated the outcomes in the 34 children who had completed the full period of EEN, 32 (92.1%) entered remission.

A retrospective study conducted in the Netherlands assessed the outcomes of EEN in 77 children[16]. Of the children who completed a course of EEN, 71% had complete remission whilst 26% had partial remission. The investigators noted that ileal or ileo-colonic disease location and poor nutritional status at baseline were important determinants of outcome in this series.

The impact of disease location upon outcomes has been variable in reported studies.

One study conducted in the United Kingdom showed a marked disparity between colonic disease (50% response rate) and ileal or ileo-colonic disease (remission rate between 92% and 83% respectively)[17]. In contrast, a subsequent report from Scotland involving 114 children showed that those with isolated terminal ileal disease had a lower remission rate, but that location did not otherwise influence outcome[18]. When evaluated in a Cochrane analysis, there was felt to be insufficient evidence to clearly elucidate the impact of location upon outcome[19].

Exclusivity is an important determinant of efficacy for EEN as illustrated in two separate reports. Johnson *et al*[20] demonstrated that almost three times as many children managed with EEN entered remission compared to a group of children managed with Partial EN (half of daily calories provided with normal diet and half as formula). More recently, Gupta *et al*[21] reported that 65% of 23 children entered remission when managed with a novel Partial EN regimen (comprising 90% of intake as overnight enteral feeds and 10% as normal diet during the day).

To date there has been little consideration of how factors such as disease location or disease severity might influence outcomes in an individual patient. One study demonstrates that an early fall in faecal calprotectin levels corresponded with response to EEN one month later[22]. Further evaluation of faecal markers or other specific indicators might permit the development of predictive algorithms that lead to a more individualised application of EEN in children.

EEN may have roles in the perioperative period in children with CD. Preoperative nutritional support may enhance weight and improve nutritional parameters (*e.g.*, serum albumin) leading to enhanced operative outcomes. Extensive data from clinical trials conducted in Japan also show the benefits of enhanced nutritional support post-operatively. These studies demonstrated that the use of maintenance enteral nutrition to provide up to 50% of caloric requirements in adults with surgically-induced remission delayed recurrence in these individuals[23,24].

SIDE-EFFECTS OF EEN

Few significant side-effects are seen with EEN[4]. Whilst some children may have nausea or loose motions initially, others may have constipation. Transient elevation of hepatic transaminases were noted in one case series[25], but was not observed in a second series[26]. Refeeding syndrome has also been reported following EEN[27,28]. The three children reported in these reports had moderate/severe malnutrition, placing them at increased risk of refeeding syndrome. Consequently, when commencing EEN in children with significant malnutrition, a routine approach should be utilised to identify those at greater risk and to commence enteral nutrition slowly and carefully along with close monitoring of electrolytes.

EEN AND MUCOSAL HEALING

Evidence in recent years has emphasised the importance of mucosal healing as a primary outcome measure in children with CD. The disconnect between clinical improvement in patients with active CD and lack of endoscopic change, particularly following corticosteroid treatment, has been shown in a number of studies[14,29,30]. While improved patient well-being is a useful and satisfying marker of disease control, the role of mucosal healing as a predictor for long-term CD burden has become very clear[14,31].

The inherent difficulty in documenting mucosal response to therapy is the need to repeat endoscopy, often times in patients who have noted a significant clinical improvement in their symptoms following treatment. A few studies in recent years have managed to document important endoscopic, histologic and biological findings before and after treatment with EEN in children with CD - invaluable evidence to further encourage this therapy as the mainstay towards achieving disease remission.

An English case-controlled study documented a 79% rate of clinical remission in children with CD following an eight-week course of EEN[31]. Further to that, they showed improvements in median endoscopic and histologic scores in both ileal and colonic disease following treatment. Of particular significance, this study showed a fall in ileal interferon (INF)-γ mRNA and a rise in transforming growth factor (TGF) β1 mRNA, whereas in the colon interleukin (IL)-8 mRNA fell following treatment.

A number of studies have shown early mucosal healing with EEN at 8-10 wk following commencement of therapy[14,29,30]. In addition, EEN has consistently outperformed corticosteroids in achieving mucosal healing in cases of active CD when the two different therapies have been directly compared. Perhaps most encouragingly, early mucosal healing as a result of EEN has been shown to result in improved outcomes at one year - specifically, in terms of reduced rates of endoscopic relapse, hospitalisation and need for anti-TNF agents[14]. As a corollary however, poor initial, mucosal response following a course of EEN can be viewed as an indicator of more severe disease course,

which may warrant earlier introduction of other medical therapies.

Grover *et al*[14] extended the impact of EEN on mucosal healing to further demonstrate that EEN is also able to lead to resolution of transmural inflammation. Follow-up magnetic resonance imaging was utilised to demonstrate improvements and resolution of inflammatory changes in this series of children with newly diagnosed CD.

What is clear is that EEN is the superior therapy for inducing mucosal healing - the gold standard for disease remission. Achievement of this standard is likely to result in improved disease control for children with IBD - a cohort in whom disease phenotype is typically more aggressive.

EEN ENHANCES GROWTH AND NUTRITION

In addition to anti-inflammatory benefits, EEN also leads to important improvements in nutritional parameters. Early changes after starting EEN include rapid improvement in circulating levels of Insulin-like Growth Factor (IGF)-1, with prompt return to control values[32]. Weight is enhanced, with weight gain typically corresponding with efficacy. Some reports have also shown early height catch up during the full period of EEN.

Gerasimidis *et al*[33] recently evaluated the influence of EEN upon body composition parameters in 17 children. Body impedance analysis demonstrated marked improvement in lean mass (P = 0.0001) but not fat mass (P > 0.05) during eight weeks of EEN. During this period, levels of a number of micronutrients also improved.

An earlier report showed improved weight, lean body mass, and skin fold thickness measurements after 3 and 6 wk of EEN[34]. Similarly, a subsequent study from Toronto, Canada, showed improvements in weight and lean body mass subsequent to EEN[35]. Interestingly, this report also showed improved linear growth in comparison to height gains seen in ten children treated with corticosteroids over the same period of time.

EEN AND BONE HEALTH

It is well established that active CD negatively impacts upon bone health. Reduced bone mineral density and increased fracture risk are known complications of poorly-controlled CD[36]. Future fracture risk is associated with peak bone mass, which is acquired primarily during childhood and adolescence[37]. Among the factors leading to reduced bone mass in children with IBD are vitamin D deficiency, corticosteroid therapy, reduced sunlight exposure, decreased physical activity and uncontrolled intestinal inflammation, which directly and indirectly contributes to malnutrition[36-39].

Vitamin D deficiency is a prevalent issue amongst children with IBD. Levin *et al*[37] found that the majority of their cohort of Australian children with IBD were either vitamin D deficient (< 51 nmol/L) or insufficient (51-75 nmol/L). This report also showed that children with vitamin D deficiency had greater corticosteroid exposure than those with normal vitamin D levels. As may have been expected however, the mean serum vitamin D concentration was higher in the group treated with EEN after diagnosis compared to the group treated with corticosteroids.

An eight-week course of EEN in children newly-diagnosed with IBD has been shown to result in normalisation of bone markers indicating more new bone formation and less bone resorption[38]. Furthermore, a six-week course of EEN (followed immediately by a two-week course of partial EN) resulted in better improvements in *z*-scores (on DEXA scans) when compared to a group of Canadian children treated with corticosteroids[39].

EEN has also been shown to have more direct benefits on bone mineral density. A German study elegantly demonstrated that bone metabolism and muscle mass improved within 12 wk of commencement with EEN in children with CD[36]. The peripheral quantitative computed tomography method used in this study demonstrated improved trabecular density *z*-scores, normalisation of initially high cortical density *z*-scores and improved muscle cross-sectional area.

VARIATIONS IN EEN PRACTICE AND PROTOCOLS

Although EEN is well established as a standard and safe therapy to induce remission in active CD, there are marked differences in the application of EEN, as well as variations in individual protocols.

A trans-Atlantic study published in 2003 reported that EEN was used regularly by 62% of European paediatric gastroenterologists, whilst only 5% of practitioners in the United States used this therapy[40]. Subsequent studies have indicated that EEN was used regularly by 12% of North American and 38% of Australian paediatric gastroenterologists[41,42]. A recent Swedish report found that 96% of paediatric units in Sweden used EEN as a treatment option in active CD, whilst 68% of those respondents routinely used EEN as initial therapy in newly-diagnosed CD[43].

The reasons for these marked differences in the routine application of EEN are not fully characterised. Two studies shed some light on what influences the choice of EEN as a preferred option to treat CD in childhood. The routine use of EEN by Australian paediatric gastroenterologists appeared to be closely related to their awareness of this therapy during their training[42]. Those who were not routinely using EEN reported concerns about adherence, cost and resource requirements. When asked similar questions, North

American respondents reported similar concerns[43]. Again the routine recommendation of EEN was associated with the practitioners' previous experience with EEN.

In addition, EEN protocols vary in many regards between units and countries[44]. Variations include the duration of EEN course, the type or brand of formulation used, and the inclusion of other oral intake (such as other fluids or boiled lollies) during EEN. A number of studies demonstrate no differences between outcomes seen with elemental or polymeric enteral formulae[4], and indicate that polymeric formulae have superior taste and acceptability[45]. However, the impact of any other differences upon comparative outcomes has not yet been evaluated.

A typical regimen involves the use of a polymeric formula administered exclusively over eight weeks[4,44,46]. Formula is introduced gradually over the first three days of the course of therapy, until required daily amounts are reached (specific details of calculating caloric requirements and further practical aspects of EEN are included in reference[4]). Whilst most children are able to take the required volumes orally, some will require placement of a nasogastric tube to facilitate compliance. During the period of EEN, children are encouraged to take additional water orally and to chew small amounts of sugar-less chewing gum. At the completion of the eight week period of EEN, one small meal would typically be reintroduced every three days, whilst reducing the daily volume of formula with each added meal.

MECHANISMS OF EEN IN CD

Although EEN has been used for many years, it is only in the last few years that an understanding of the mechanisms of this therapy has emerged. Evidence now indicates three primary components to the actions of EEN: alteration of the intestinal microflora, enhancement of barrier function and direct anti-inflammatory effects. However, the relationships between these events and the triggers for these changes have yet to be elucidated.

EEN and the intestinal microbiota

Initial support for modulation of the intestinal flora by EEN came from three earlier studies, using molecular tools[47-49]. The most comprehensive of these studies used denaturing gel gradient electrophoresis to examine changes in the flora during and following a course of EEN in children[49]. In this report, EEN resulted in a marked and prolonged reduction of bacterial diversity across all bacterial groups. In particular, variations in the composition of the Bacteroides group correlated closely with reducing disease activity and inflammatory proteins.

A more recent study used a similar molecular technique (temperature gradient gel electrophoresis) to ascertain changes during and following EEN[50]. The results arising from this work again showed a reduction in diversity during EEN, with a divergence from the control setting seen in the children with CD. Interestingly, the concentrations of the putative protective *Faecalibacterium prausnitzii* species fell after 1 mo of EEN. This study also demonstrated an increase in faecal pH and a reduction in butyrate levels during EEN. In contrast, an increase in faecal butyrate levels was seen in a Swedish study of 18 children managed with EEN[51]. In these patients the induction of remission was associated with increased butyrate and decreased acetic acid in faecal samples.

A new report has employed high-throughput sequencing to delineate changes in the flora during and following EEN[52]. The number of operational taxonomic units (OTU) reduced markedly upon commencing EEN, and this correlated closely with the successful induction of remission. Furthermore, subsequent disease exacerbations occurred in conjunction with an increase in OTUs. A particular finding was that families within the Firmicutes correlated with disease activity.

Together these reports indicate that EEN leads to pronounced changes in the intestinal flora, and variations in faecal metabolic activity. The relationships between these changes and coincident improvements in mucosal inflammation are yet to be ascertained.

EEN and barrier function

The intestinal mucosa provides an essential barrier to the outside world: intestinal permeability is a central component of this activity. Increased permeability occurs secondary to active inflammation in the gut and may also be present in preclinical CD.

In elegant *in vitro* studies Nahidi *et al*[53] showed that a polymeric formula (as used in EEN) resulted in normalisation of altered permeability and migration of key tight junction proteins back to the cell membrane. This report was further supported by studies employing a murine model of gut inflammation[54]. In this model, the administration of a polymeric formula in animals with gut inflammation reversed impaired intestinal permeability and altered tight junction protein localisation, in conjunction with normalisation of inflammatory changes. Although this work is consistent and clear, these findings have not yet been complemented by *in vivo* studies in individuals with CD.

Direct anti-inflammatory effects of EEN

Numerous studies have demonstrated that the use of EEN results in reductions in mucosal levels of pro-inflammatory cytokines. Meister *et al*[55] used *ex vivo* mucosal biopsies to demonstrate that an elemental formula resulted in an increased ratio of IL-1Ra to IL-1β compared to the ratio in control samples. Using an *in vitro* model of inflammation de Jong *et al*[56] showed that polymeric formula led to a reduction in cellular production of IL-8 following stimulation

with TNF-α. Preliminary data indicated that this anti-inflammatory effect of the polymeric formula was mediated by disruption of intracellular nuclear factor (NF)-κB signalling. Subsequent experiments have demonstrated that the administration of polymeric formula results in inhibition of specific kinases in the NF-κB signal transduction pathway (unpublished observations). These findings suggest that as yet unidentified active elements within formulae used for EEN interact directly with epithelial cells leading to anti-inflammatory effects. Again, further work is required to definitively elucidate these processes.

CONCLUSION

EEN is now firmly established as a first line therapy for the induction of remission in children with active CD. Recent studies further support and clearly substantiate the added benefits of EEN. However, additional collaborative studies are now required to further progress the use and application of EEN. Hopefully, ways to optimise and individualise EEN protocols should arise from such endeavours.

A number of investigators have provided intriguing data on the mechanisms by which EEN exerts its clinical benefits. Although these include *in vitro* and animal methods, the clear implication is that EEN interacts directly with the inflamed gut. The relevant importance of the various mechanisms is not yet clarified - further elaboration of these aspects may prompt the development of novel enteral nutrition formulations for EEN that enhance outcomes. In addition, these data should further enhance our understanding of the roles that these mucosal events play in the pathogenesis of CD. In turn, these avenues of research promise to result in novel approaches that may lead to better outcomes for children with CD.

REFERENCES

1 **Lemberg DA**, Day AS. Crohn disease and ulcerative colitis in children: an update for 2014. *J Paediatr Child Health* 2015; **51**: 266-270 [PMID: 25039307 DOI: 10.1111/jpc.12685]

2 **Phavichitr N**, Cameron DJ, Catto-Smith AG. Increasing incidence of Crohn's disease in Victorian children. *J Gastroenterol Hepatol* 2003; **18**: 329-332 [PMID: 12603535]

3 **Benchimol EI**, Fortinsky KJ, Gozdyra P, Van den Heuvel M, Van Limbergen J, Griffiths AM. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. *Inflamm Bowel Dis* 2011; **17**: 423-439 [PMID: 20564651 DOI: 10.1002/ibd.21349]

4 **Critch J**, Day AS, Otley A, King-Moore C, Teitelbaum JE, Shashidhar H. Use of enteral nutrition for the control of intestinal inflammation in pediatric Crohn disease. *J Pediatr Gastroenterol Nutr* 2012; **54**: 298-305 [PMID: 22002478 DOI: 10.1097/MPG.0b013e318235b397]

5 **IBD Working Group of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition**. Inflammatory bowel disease in children and adolescents: recommendations for diagnosis--the Porto criteria. *J Pediatr Gastroenterol Nutr* 2005; **41**: 1-7 [PMID: 15990620]

6 **Van Limbergen J**, Russell RK, Drummond HE, Aldhous MC, Round NK, Nimmo ER, Smith L, Gillett PM, McGrogan P, Weaver LT, Bisset WM, Mahdi G, Arnott ID, Satsangi J, Wilson DC. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. *Gastroenterology* 2008; **135**: 1114-1122 [PMID: 18725221 DOI: 10.1053/j.gastro.2008.06.081]

7 **Vasseur F**, Gower-Rousseau C, Vernier-Massouille G, Dupas JL, Merle V, Merlin B, Lerebours E, Savoye G, Salomez JL, Cortot A, Colombel JF, Turck D. Nutritional status and growth in pediatric Crohn's disease: a population-based study. *Am J Gastroenterol* 2010; **105**: 1893-1900 [PMID: 20145606 DOI: 10.1038/ajg.2010.20]

8 **Walters TD**, Griffiths AM. Mechanisms of growth impairment in pediatric Crohn's disease. *Nat Rev Gastroenterol Hepatol* 2009; **6**: 513-523 [PMID: 19713986 DOI: 10.1038/nrgastro.2009.124]

9 **Kanof ME**, Lake AM, Bayless TM. Decreased height velocity in children and adolescents before the diagnosis of Crohn's disease. *Gastroenterology* 1988; **95**: 1523-1527 [PMID: 3181677]

10 **Gerasimidis K**, McGrogan P, Edwards CA. The aetiology and impact of malnutrition in paediatric inflammatory bowel disease. *J Hum Nutr Diet* 2011; **24**: 313-326 [PMID: 21564345 DOI: 10.1111/j.1365-277X.2011.01171.x]

11 **Wilschanski M**, Sherman P, Pencharz P, Davis L, Corey M, Griffiths A. Supplementary enteral nutrition maintains remission in paediatric Crohn's disease. *Gut* 1996; **38**: 543-548 [PMID: 8707085]

12 **Cameron FL**, Gerasimidis K, Papangelou A, Missiou D, Garrick V, Cardigan T, Buchanan E, Barclay AR, McGrogan P, Russell RK. Clinical progress in the two years following a course of exclusive enteral nutrition in 109 paediatric patients with Crohn's disease. *Aliment Pharmacol Ther* 2013; **37**: 622-629 [PMID: 23360085 DOI: 10.1111/apt.12230]

13 **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 [PMID: 10896064]

14 **Grover Z**, Muir R, Lewindon P. Exclusive enteral nutrition induces early clinical, mucosal and transmural remission in paediatric Crohn's disease. *J Gastroenterol* 2014; **49**: 638-645 [PMID: 23636735 DOI: 10.1007/s00535-013-0815-0]

15 **Navas-López VM**, Blasco-Alonso J, Lacasa Maseri S, Girón Fernández-Crehuet F, Serrano Nieto MJ, Vicioso Recio MI, Sierra Salinas C. [Exclusive enteral nutrition continues to be first line therapy for pediatric Crohn's disease in the era of biologics]. *An Pediatr* (Barc) 2014; Epub ahead of print [PMID: 24704330 DOI: 10.1016/j.anpedi.2014.02.027]

16 **de Bie C**, Kindermann A, Escher J. Use of exclusive enteral nutrition in paediatric Crohn's disease in The Netherlands. *J Crohns Colitis* 2013; **7**: 263-270 [PMID: 22820027 DOI: 10.1016/j.crohns.2012.07.001]

17 **Afzal NA**, Davies S, Paintin M, Arnaud-Battandier F, Walker-Smith JA, Murch S, Heuschkel R, Fell J. 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**: 1471-1475 [PMID: 16110838]

18 **Buchanan E**, Gaunt WW, Cardigan T, Garrick V, McGrogan P, Russell RK. The use of exclusive enteral nutrition for induction of remission in children with Crohn's disease demonstrates that disease phenotype does not influence clinical remission. *Aliment Pharmacol Ther* 2009; **30**: 501-507 [PMID: 19549288 DOI: 10.1111/j.1365-2036.2009.04067.x]

19 **Zachos M**, Tondeur M, Griffiths AM. Enteral nutritional therapy for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2007; (**1**): CD000542 [PMID: 17253452]

20 **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; **55**: 356-361 [PMID: 16162683]

21 **Gupta K**, Noble A, Baldassano R, Sreedharan R, Grossman A, Kachelries K. A Novel Enteral Nutritional Therapy Protocol for the Treatment of Pediatric Crohn's Disease. *J Pediatr Gastroenterol*

Nutr 2010; **51** (Suppl 2): E87
22 **Gerasimidis K**, Nikolaou CK, Edwards CA, McGrogan P. Serial fecal calprotectin changes in children with Crohn's disease on treatment with exclusive enteral nutrition: associations with disease activity, treatment response, and prediction of a clinical relapse. *J Clin Gastroenterol* 2011; **45**: 234-239 [PMID: 20871409 DOI: 10.1097/MCG.0b013e3181f39af5]
23 **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-randomized, parallel, controlled study. *Aliment Pharmacol Ther* 2007; **25**: 67-72 [PMID: 17229221]
24 **Esaki M**, Matsumoto T, Hizawa K, Nakamura S, Jo Y, Mibu R, Iida M. Preventive effect of nutritional therapy against postoperative recurrence of Crohn disease, with reference to findings determined by intra-operative enteroscopy. *Scand J Gastroenterol* 2005; **40**: 1431-1437 [PMID: 16316891]
25 **Schatorjé E**, Hoekstra H. Transient hypertransaminasemia in paediatric patients with Crohn disease undergoing initial treatment with enteral nutrition. *J Pediatr Gastroenterol Nutr* 2010; **51**: 336-340 [PMID: 20601906 DOI: 10.1097/MPG.0b013e3181d94f63]
26 **Lemberg DA**, Leach ST, Day AS. Transient hypertransaminasemia in pediatric patients with Crohn disease. *J Pediatr Gastroenterol Nutr* 2011; **53**: 229 [PMID: 21788771 DOI: 10.1097/MPG.0b013e31821c6497]
27 **Afzal NA**, Addai S, Fagbemi A, Murch S, Thomson M, Heuschkel R. Refeeding syndrome with enteral nutrition in children: a case report, literature review and clinical guidelines. *Clin Nutr* 2002; **21**: 515-520 [PMID: 12468372]
28 **Akobeng AK**, Thomas AG. Refeeding syndrome following exclusive enteral nutritional treatment in Crohn disease. *J Pediatr Gastroenterol Nutr* 2010; **51**: 364-366 [PMID: 20639770 DOI: 10.1097/MPG.0b013e3181e712d6]
29 **Borrelli O**, Cordischi L, Cirulli M, Paganelli M, Labalestra V, Uccini S, Russo PM, Cucchiara S. Polymeric diet alone versus corticosteroids in the treatment of active pediatric Crohn's disease: a randomized controlled open-label trial. *Clin Gastroenterol Hepatol* 2006; **4**: 744-753 [PMID: 16682258]
30 **Berni Canani R**, Terrin G, Borrelli O, Romano MT, Manguso F, Coruzzo A, D'Armiento F, Romeo EF, Cucchiara S. Short- and long-term therapeutic efficacy of nutritional therapy and corticosteroids in paediatric Crohn's disease. *Dig Liver Dis* 2006; **38**: 381-387 [PMID: 16301010]
31 **Fell JM**, Paintin M, Arnaud-Battandier F, Beattie RM, Hollis A, Kitching P, Donnet-Hughes A, MacDonald TT, Walker-Smith JA. 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**: 281-289 [PMID: 10735920]
32 **Day AS**, Aurangzeb B, Leach ST, Lemberg DA, Walker J. The effects of Exclusive Enteral Nutrition upon the Insulin-like Growth Factor pathway in children with Crohn disease. AGW October 2008. *J Gastro Hepatol* 2008; **23**: A303
33 **Gerasimidis K**, Talwar D, Duncan A, Moyes P, Buchanan E, Hassan K, O'Reilly D, McGrogan P, Edwards CA. Impact of exclusive enteral nutrition on body composition and circulating micronutrients in plasma and erythrocytes of children with active Crohn's disease. *Inflamm Bowel Dis* 2012; **18**: 1672-1681 [PMID: 22069243 DOI: 10.1002/ibd.21916]
34 **Khoshoo V**, Reifen R, Neuman MG, Griffiths A, Pencharz PB. Effect of low- and high-fat, peptide-based diets on body composition and disease activity in adolescents with active Crohn's disease. *JPEN J Parenter Enteral Nutr* 1996; **20**: 401-405 [PMID: 8950740]
35 **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**: 203-208 [PMID: 9301499]
36 **Werkstetter KJ**, Schatz SB, Alberer M, Filipiak-Pittroff B, Koletzko S. Influence of exclusive enteral nutrition therapy on bone density and geometry in newly diagnosed pediatric Crohn's disease patients. *Ann Nutr Metab* 2013; **63**: 10-16 [PMID: 23867548 DOI: 10.1159/000350369]
37 **Levin AD**, Wadhera V, Leach ST, Woodhead HJ, Lemberg DA, Mendoza-Cruz AC, Day AS. Vitamin D deficiency in children with inflammatory bowel disease. *Dig Dis Sci* 2011; **56**: 830-836 [PMID: 21222159 DOI: 10.1007/s10620-010-1544-3]
38 **Whitten KE**, Leach ST, Bohane TD, Woodhead HJ, Day AS. Effect of exclusive enteral nutrition on bone turnover in children with Crohn's disease. *J Gastroenterol* 2010; **45**: 399-405 [PMID: 19957194 DOI: 10.1007/s00535-009-0165-0]
39 **Soo J**, Malik BA, Turner JM, Persad R, Wine E, Siminoski K, Huynh HQ. Use of exclusive enteral nutrition is just as effective as corticosteroids in newly diagnosed pediatric Crohn's disease. *Dig Dis Sci* 2013; **58**: 3584-3591 [PMID: 24026403 DOI: 10.1007/s10620-013-2855-y]
40 **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**: 464-469 [PMID: 12658036]
41 **Stewart M**, Day AS, Otley A. Physician attitudes and practices of enteral nutrition as primary treatment of paediatric Crohn disease in North America. *J Pediatr Gastroenterol Nutr* 2011; **52**: 38-42 [PMID: 20975582 DOI: 10.1097/MPG.0b013e3181e2c724]
42 **Day AS**, Stephenson T, Stewart M, Otley AR. Exclusive enteral nutrition for children with Crohn's disease: use in Australia and attitudes of Australian paediatric gastroenterologists. *J Paediatr Child Health* 2009; **45**: 337-341 [PMID: 19490411 DOI: 10.1111/j.1440-1754.2009.01498.x]
43 **Gråfors JM**, Casswall TH. Exclusive enteral nutrition in the treatment of children with Crohn's disease in Sweden: a questionnaire survey. *Acta Paediatr* 2011; **100**: 1018-1022 [PMID: 21272070 DOI: 10.1111/j.1651-2227.2011.02178.x]
44 **Whitten KE**, Rogers P, Ooi CY, Day AS. International survey of enteral nutrition protocols used in children with Crohn's disease. *J Dig Dis* 2012; **13**: 107-112 [PMID: 22257479 DOI: 10.1111/j.1751-2980.2011.00558.x]
45 **Wall CL**, Day AS, Gearry RB. Use of exclusive enteral nutrition in adults with Crohn's disease: a review. *World J Gastroenterol* 2013; **19**: 7652-7660 [PMID: 24282355 DOI: 10.3748/wjg.v19.i43.7652]
46 **Day AS**, Whitten KE, Lemberg DA, Clarkson C, Vitug-Sales M, Jackson R, Bohane TD. 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**: 1609-1614 [PMID: 16928225]
47 **Pryce-Millar E**, Murch SH, Heuschkel RB. Enteral nutrition therapy in Crohn's disease changes the mucosal flora. *J Pediatr Gastroenterol Nutr* 2004; **39** (Suppl 1): 289
48 **Lionetti P**, Callegari ML, Ferrari S, Cavicchi MC, Pozzi E, de Martino M, Morelli L. Enteral nutrition and microflora in pediatric Crohn's disease. *JPEN J Parenter Enteral Nutr* 2005; **29**: S173-5; discussion S175-8, S184-8 [PMID: 15980280]
49 **Leach ST**, Mitchell HM, Eng WR, Zhang L, Day AS. Sustained modulation of intestinal bacteria by exclusive enteral nutrition used to treat children with Crohn's disease. *Aliment Pharmacol Ther* 2008; **28**: 724-733 [PMID: 19145728]
50 **Gerasimidis K**, Bertz M, Hanske L, Junick J, Biskou O, Aguilera M, Garrick V, Russell RK, Blaut M, McGrogan P, Edwards CA. Decline in presumptively protective gut bacterial species and metabolites are paradoxically associated with disease improvement in pediatric Crohn's disease during enteral nutrition. *Inflamm Bowel Dis* 2014; **20**: 861-871 [PMID: 24651582 DOI: 10.1097/MIB.0000000000000023]
51 **Tjellström B**, Högberg L, Stenhammar L, Magnusson KE, Midtvedt T, Norin E, Sundqvist T. Effect of exclusive enteral nutrition on gut microflora function in children with Crohn's disease. *Scand J Gastroenterol* 2012; **47**: 1454-1459 [PMID: 23016828 DOI: 10.3109/00365521.2012.703234]
52 **Kaakoush NO**, Day AS, Leach ST, Lemberg DA, Nielsen

S, Mitchell HM. Effect of exclusive enteral nutrition on the microbiota of children with newly diagnosed Crohn's disease. *Clin Transl Gastroenterol* 2015; **6**: e71 [PMID: 25588524 DOI: 10.1038/ctg.2014.21]

53 **Nahidi L**, Day AS, Lemberg DA, Leach ST. Differential effects of nutritional and non-nutritional therapies on intestinal barrier function in an in vitro model. *J Gastroenterol* 2012; **47**: 107-117 [PMID: 21953313 DOI: 10.1007/s00535-011-0471-1]

54 **Nahidi L**, Leach ST, Mitchell HM, Kaakoush NO, Lemberg DA, Munday JS, Huinao K, Day AS. Inflammatory bowel disease therapies and gut function in a colitis mouse model. *Biomed Res Int* 2013; **2013**: 909613 [PMID: 24027765 DOI: 10.1155/2013/909613]

55 **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**: 430-438 [PMID: 12132791]

56 **de Jong NS**, 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**: 2029-2036 [PMID: 17406842]

P- Reviewer: Freeman HJ, Hsieh CC, Romano C **S- Editor**: Ma YJ
L- Editor: A **E- Editor**: Ma S

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327