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TITLE: Exclusive Enteral Nutrition: An optimal care pathway for use in children with active luminal Crohn's disease

Position Paper

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INTRODUCTION

Crohn's disease (CD) is a chronic relapsing inflammatory bowel disease (IBD) that may affect any portion of the gastrointestinal tract. Exclusive enteral nutrition (EEN) is recommended as a first line therapy for active luminal paediatric CD by many contemporary consensus guidelines and reportedly induces remission in up to 83% of children.[1-3] EEN involves using a nutritionally complete liquid formula as the primary source of nutrition for a defined period of time. EEN improves nutritional status, enables catch up growth in those children presenting with malnutrition, and avoids possible side effects related to corticosteroids.[4,5] Internationally, there are variations in EEN protocols between centres[6] and this was recently demonstrated in a publication surveying 37 Paediatric Gastroenterologists from Australia and New Zealand.[7]

The standardisation of EEN protocols has been identified as a key enabler for the effective use of EEN therapy, as well as sufficient dietetic resourcing, and subsidisation of costs.[8] In 2019, an optimal care pathway for EEN in adults with active CD was published[9], however one is yet to be defined for children in Australia and New Zealand.

AIM

The aim of this study was to develop an optimal care pathway for use of EEN in children with active luminal Crohn's disease, in Australia and New Zealand.

METHOD

A working group of 11 IBD paediatric dietitians and one paediatric Gastroenterologist from Australia and New Zealand was created through expression of interest within the Australasian Society of Parenteral and Enteral Nutrition (AuSPEN) Paediatric IBD

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subcommittee. Seven key areas for an optimal care pathway were identified by group consensus: clinical indications, workup assessments, EEN prescription, monitoring, food reintroduction, partial enteral nutrition (PEN) and maintenance enteral nutrition (MEN). PEN was defined as a proportion of diet provided by enteral formula that is specifically used to induce clinical remission in children with active CD.[1] MEN was defined as a proportion of diet provided by enteral formula that is specifically used to reduce the risk of subsequent relapse after successful induction treatment, usually with EEN.

The working group was divided into seven subgroups. Each subgroup conducted literature searches of Medline, Embase, and Cochrane library databases using the MeSH terms: inflammatory bowel disease, Crohn's disease, enteral nutrition, nutrition therapy, nutrition support, diet therapy, diet, nutrition assessment, and malnutrition. Subgroups considered articles for inclusion from January 1996 to June 2021, and assessed the level of evidence (LoE) according to the National Health and Medical Research Council (NHMRC) hierarchy of evidence.[10] Provisional consensus statements were developed from the supporting evidence tables, then reviewed by the working group, and voted on in two rounds.

A statement was considered accepted, if at least 80% agreement was met, with a 100% reply rate. Where literature gaps existed, group consensus and expert opinion was used. The final consensus statements informed the proposed optimal care pathway for clinicians managing EEN therapy in children with active luminal CD.

RESULTS

The consensus statements of the seven key areas of EEN therapy are presented and discussed below, and then summarised as an optimal care pathway (Figure 1).

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1. Clinical Indications for EEN

Consensus Statements

1.	EEN is recommended as first line induction therapy in children with active luminal CD (LoE II) 100% Agreement.
2.	EEN is as effective as corticosteroids for the induction of remission in children with active luminal CD (LoE I) 100% Agreement.
3.	EEN improves nutritional parameters including weight (wt), height (ht) (LoE II) and bone health when used as induction therapy in children with active luminal CD (LoE IV) 100% Agreement.
4.	EEN may effectively be used as a re-induction agent in the presence of a relapse or flare of active CD (LoE IV) 100% Agreement.
5.	EEN may reduce the need for surgical intervention (LoE IV) when used in children with complicated CD and prevent post surgical infections/complications (LoE IV) 100% Agreement.

Remission induction

EEN is widely recommended as first line induction therapy in children with active luminal CD, given both its clinical efficacy (which is comparable to corticosteroids), nutritional and growth benefits and avoids the adverse effects of corticosteroids (CS).[11-14] Reported remission rates for the use of EEN as induction therapy in patients newly diagnosed with active CD, range from 63% to 83%.[4,11-17]

The therapeutic target for CD induction therapy is to achieve mucosal healing (assessed by endoscopy), because it has been associated with reductions in relapse rate, progression of inflammation leading to complications, and need for surgery.[1] In clinical

practice, biochemical and clinical parameters are commonly used as surrogate markers to demonstrate remission in response to EEN [e.g. faecal calprotectin (FC), C-reactive protein (CRP), and Paediatric CD Activity Index (PCDAI)].[18,19]

In a Cochrane study, comparing EEN to CS for remission induction in paediatric patients with active Crohn's disease, EEN remission rates were 63-83% compared to 61-72% with corticosteroids, and no statistical difference was found.[13]

Four studies identified a significantly higher rate of mucosal healing in children who received EEN as induction therapy, compared to CS.[18,20,21,22]

EEN appears to be slightly less effective in cases of relapsed CD (compared to newly diagnosed CD), with remission rates of 58.3-80%.[5,23] When including only relapsed children in a meta-analysis, no statistically significant difference in remission rates between EEN and corticosteroids was found.[12]

Nutritional support

Children responding to EEN have a statistically significant improvement in weight and Body Mass Index (BMI) z scores over the course of therapy,[4,5] which are sustained over a 6-month period.[4] In a Chinese study, children who reached remission after an 8 week course of EEN had statistically significant improvement in weight gain, haemoglobin and serum albumin level, compared with children who did not reach remission on EEN ($p<0.05$).[22]

Werkstetter et al[24] demonstrated improvements in bone metabolism and muscle mass accrual over 12 weeks, in 10 children with newly diagnosed CD who completed 8 weeks of EEN.

Avoidance of surgery and complications

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There are very few paediatric studies in this area, and unfortunately none of high quality. However, a prospective observational study that followed 147 children with newly diagnosed CD, found a lower but insignificant rate of new complications (fibrostenotic or penetrating CD, poor height growth) if EEN was used for induction therapy compared to CS.[16]

A retrospective study of 83 adults with percutaneous undrainable abscesses in CD showed a significantly lower cumulative surgical rate in those treated with EEN (mean duration 5.9 weeks) compared with those not receiving EEN (p=0.001), with 15% of patients who received EEN completely avoiding surgery.[25] Further, the risk of post-operative septic intra-abdominal complications was significantly lower (p=0.036) in those patients receiving EEN.[25]

A recent review of paediatric case reports and adult studies investigating the role of EEN in complicated CD, showed that EEN may have beneficial effects in patients with structuring and penetrating CD.[26] The duration of EEN in these studies was either 8 or 12 weeks, highlighting the need for more research into the optimal EEN duration to reduce CD complications and the need for surgery.

2 Workup Assessment prior to EEN commencement

Consensus Statements

1.	To optimise implementation and adherence to EEN, a Multi-Disciplinary Team (MDT) approach is recommended, including a gastroenterologist, dietitian and IBD nurse. Availability of a social worker and/or psychologist is also recommended to support the psychological wellbeing and resourcing of children (LoE V) 100% Agreement.

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2	A Dietitian should undertake a comprehensive growth and nutritional assessment, including assessment of refeeding risk and diagnosed food allergies, prior to commencing EEN (LoE V) 100% Agreement.

MDT support is essential for adherence to EEN therapy and optimal outcomes.[27,28] A Canadian study determined that the conviction of the MDT to support EEN is an enabler of EEN success, and that it is important to involve the child as a decision maker, and actively engage them in treatment discussions.[8]

CD can have a negative impact on psychological wellbeing, therefore access to a psychologist or social worker is helpful in maximising treatment outcomes[29]

IBD nurses are the main liaison between child and treating team, and provide ongoing support regarding symptom management, medication, and appointments.

The initial nutritional assessment should consider past medical history including diagnosed allergies, anthropometric measures[30], biochemical parameters, clinical symptoms, nutrition intake in previous two weeks, emotional wellbeing, and family supports. A risk assessment of malnutrition and refeeding syndrome (RFS) is also necessary to guide medical therapy.[31]

3 Prescribing EEN Therapy

Consensus Statements

1.	A Dietitian should be involved in prescribing EEN in paediatric CD (LoE V) 100% Agreement.

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2	Polymeric formulas should be used for EEN to maximise adherence, unless otherwise indicated (eg cow's milk allergy) (LoE I) 100% Agreement.
3	To induce remission in children with active paediatric CD, duration of EEN should be 6 to 8 weeks (LoE IV) 92% Agreement.
4	There is insufficient evidence to make recommendations about concomitant food and fluids allowed during EEN (LoE V) 100% Agreement.
5	Standard predictive equations should be used when calculating nutritional requirements in paediatric CD. There is sufficient evidence that children with active CD have increased energy requirements compared with healthy controls (LoE III-2) 92% Agreement.
6.	If a child is at risk of refeeding syndrome, a slower rate of increase in EEN formula is recommended, and regular blood monitoring, in accordance with local refeeding syndrome guidelines (LoE V) 100% Agreement.

Practice points;

*EEN may be graded up over a period of days, to minimise gastrointestinal side effects.

*If a child is unable to meet their recommended volume orally, nasogastric feeding should be considered.

The prescription of formula is based on the estimated energy requirement (EER) of the child, which takes into account the energy costs of injury or disease, activity level and resting energy expenditure (REE). Recent studies show that REE is not increased in children with active CD, therefore standard predictive equations are appropriate.[3, 32,,33] The Schofield equation best predicts the measured REE in children with CD (3-18 yrs).[34]

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Actual body weight should be used, or adjusted body weight for height if the child is underweight,[30] or overweight.

The protein requirement may vary from 1.2 to 1.5g/kg/day in active inflammation, especially in the setting of weight loss or poor nutritional state. Subsequently, the protein requirement may decrease to 1g/kg/d once remission is achieved.[3, 22]

A Cochrane analysis showed that there was no difference in efficacy between elemental and non elemental formulas.[13] Polymeric formula should be chosen considering the advantages in palatability, availability, and cost.[23] In cases of cow's milk protein allergy an appropriate alternative should be prescribed.

Recent studies have also found that EEN efficacy at inducing remission as defined by reduction in FC, CRP, and PCDAI is not significantly reduced when negligible amounts of specific concomitant foods (e.g. clear fluids, chewing gum, boiled sweets) are consumed.[4, 15, 35-37] A recent survey of dietitians found that this is common practice in Australia, but not in New Zealand.[38]

Insufficient evidence exists to inform our EEN consensus statements around concomitant foods. The optimal duration of EEN to induce remission in patients with active Crohn's disease is not known. However, mucosal remission has been demonstrated by endoscopy after 8 weeks of EEN.[21,22,31] The majority of consensus guidelines suggest 6-8 weeks of EEN, and surveys of gastroenterology unit practices show that 6-8 weeks is most commonly prescribed.[1-3,24,31,39,40]

4. Monitoring of EEN

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Consensus Statements

1.	Throughout the course of EEN, regular review of a child's clinical, biochemical, and nutritional status is recommended (LoE V) 100% Agreement.
2	An MDT review is needed to assess response to EEN, and should be undertaken after 2 to 4 weeks, then children should continue on EEN and consideration be given to commencement of maintenance therapy by the medical team. If EEN is being adhered to and has not induced a clinical response after 2 to 4 weeks, an alternative induction therapy should be considered (LoE V) 100% Agreement.

Practice points

*The MDT (ideally the dietitian) should monitor adherence to treatment and address barriers to EEN success (taste fatigue, gut side effects, access to formula, emotional support).

The MDT (ideally the dietitian) should regularly complete a nutritional assessment, review family supports and response to treatment, ensure growth and satiety are achieved, side effects minimised and adherence maximised. Fortnightly dietetic review is common practice in Australia and NZ for children undertaking EEN.[38,39]

Dietitians play an instrumental role in the implementation and monitoring of EEN, and children with more dietetic contacts during treatment have been shown to have higher rates of remission.[15]

The MDT should assess the child's clinical response to EEN at week 2-4, as a clinical improvement usually occurs within days.[40] Dziechciarz et al[11] reported that the time to remission was within 11 days to 2.5 weeks, however it is likely that some children require longer than 2.5 weeks to achieve remission.

An alternative treatment should be considered by the medical team in the absence of response after 2-4 weeks of EEN.[28]

5. Reintroduction of Food after EEN

Consensus Statement

1.	There is insufficient evidence to guide the reintroduction of food after EEN (LoE III-3) 92% Agreement.

Practice point

* In the absence of high quality evidence, our consensus group and other expert consensus guidelines[2,23,29] suggest the gradual reintroduction of nutritionally balanced meals with a corresponding decrease in formula over one to two weeks, after a course of EEN.

Faiman et al[41] conducted a retrospective single centre study comparing rapid reintroduction over 3 days compared to slow reintroduction over five weeks in 39 patients with newly diagnosed CD. No significant differences were observed in terms of relapse rate and maintenance of remission over one year, proposing that rapid food

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reintroduction is tolerated. However this study has a number of limitations and has not been replicated.

Gkikas et al[42] have described several food reintroduction protocols (post EEN) with the aim of preventing exacerbation of CD symptoms, that have demonstrated limited efficacy. One study suggested recommencing EEN for an unspecified time if symptoms reoccur.[43] However, further high quality research is needed before recommendations can be made.

6. Partial Enteral Nutrition (PEN) in induction of remission

Consensus Statement

1.	There is insufficient evidence to recommend partial enteral nutrition for induction of remission in children with active CD (LoE II) 100% Agreement.

Prospective cohort studies have demonstrated mixed results when comparing PEN to EEN for the induction of remission, with many studies limited by small sample sizes.[44-47] Recently, one randomized controlled trial (RCT) demonstrated a positive clinical response for PEN coupled with CD exclusion diet (CDED) in a direct comparison to EEN in children with mild-moderate luminal CD.[48] More children tolerated PEN with CDED compared to EEN (defined as continuation of therapy) at week 6, with no significant difference in remission (defined as PCDAI ≤ 10) at week 6 between the two groups. Further large prospective randomized trials (that include endoscopic assessment), are needed to demonstrate the efficacy and safety of PEN as an EEN alternative.

7. Role of Maintenance Enteral Nutrition (MEN) in prolonging remission

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Consensus Statements

1.	There is insufficient evidence to recommend the routine use of MEN as a sole maintenance therapy (LoE III-2) 100% Agreement.
2.	MEN (at >35% of EER) may have a role, in conjunction with other treatments, to optimise nutrition and support growth and the maintenance of remission, although further studies are required (LoE III-2) 100% Agreement.

In a recent literature review of 16 studies (adult and paediatric), MEN intakes of greater than 35% EER demonstrated significant efficacy in maintaining clinical remission, and had significantly lower one year relapse rates.[42] The use of MEN has been associated with further clinical benefits such as improved endoscopic indices and weight z-scores[49], and reduced mucosal cytokine levels.[50]

A recent pilot study proposed that cyclical EEN may be a potential maintenance therapy. Pigneur Arnaud et al[51] randomised patients with clinical remission after EEN, to either cyclical EEN (100% EER 2 weeks in every 8 weeks) or daily supplemental EN (25% EER). A significantly greater proportion of the cyclical EEN group remained in remission (51%) compared with the supplemental EN group (24%) at 12 months (p=0.0051).

Conclusion

EEN protocols vary widely throughout the world, however the development of Australian and New Zealand evidence based consensus statements should facilitate standardisation of paediatric EEN therapy in this region. The consensus statements have been summarised in the optimal care pathway (Figure 1), to provide practical guidance for clinicians managing children with active luminal CD. The development of a consistent

EEN management pathway may enhance the uptake, acceptance and efficacy of this first line therapy, and lead to more rigorous research in the future.

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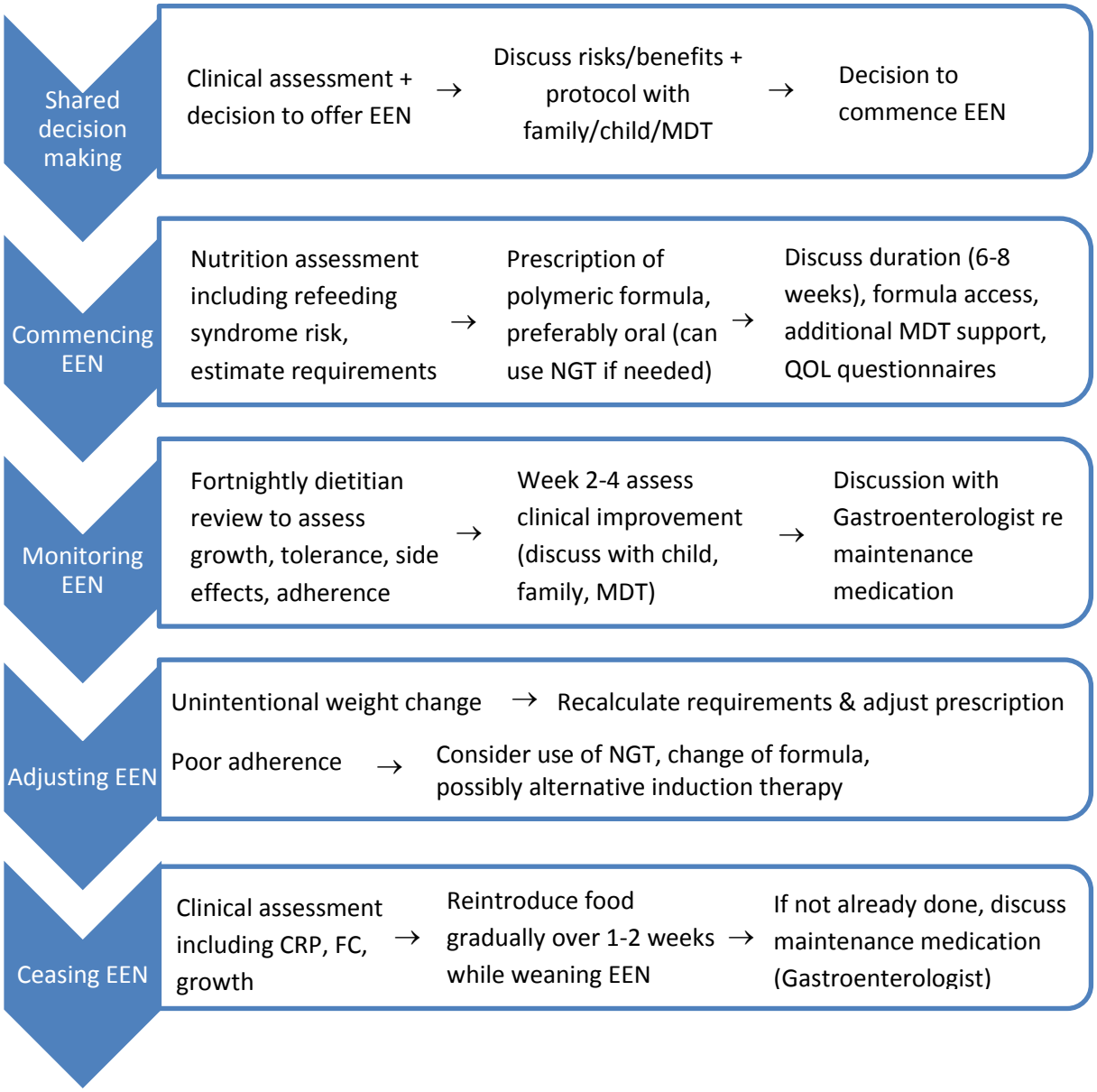
Figure 1. Optimal Care Pathway for using EEN in children with active luminal CD



EEN = exclusive enteral nutrition, CD = Crohn's disease, MDT = multidisciplinary team, NGT = naso-gastric tube, QOL = quality of life, CRP = C-reactive protein, FC= faecal calprotectin.

The format is consistent with the AuSPEN adult CD optimal care pathway for EEN (Day A, et al 2019 JGH online), reprinted with permission from the authors. *Not permitted for commercial use.*

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TITLE: Exclusive Enteral Nutrition: An optimal care pathway for use in children with active luminal Crohn's disease

Position Paper

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