COMMENTARY

Toward enteral nutrition in the treatment of pediatric Crohn disease in Canada: A workshop to identify barriers and enablers

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The treatment armamentarium in pediatric Crohn disease (CD) is very similar to adult-onset CD with the notable exception of the use of exclusive enteral nutrition (EEN [the administration of a liquid formula diet while excluding normal diet]), which is used more frequently by pediatric gastroenterologists to induce remission. In pediatric CD, EEN is now recommended by the pediatric committee of the European Crohn's and Colitis Organisation and the European Society for Paediatric Gastroenterology Hepatology and Nutrition as a first-choice agent to induce remission, with remission rates in pediatric studies consistently >75%. To chart and address enablers and barriers of use of EEN in Canada, a workshop was held in September 2014 in Toronto (Ontario), inviting pediatric gastroenterologists, nurses and dietitians from most Canadian pediatric IBD centres as well as international faculty from the United States and Europe with particular research and clinical expertise in the dietary management of pediatric CD. Workshop participants ranked the exclusivity of enteral nutrition; the health care resources; and cost implications as the top three barriers to its use. Conversely, key enablers mentioned included: standardization and sharing of protocols for use of enteral nutrition; ensuring sufficient dietetic resources; and reducing the cost of EEN to the family (including advocacy for reimbursement by provincial ministries of health and private insurance companies). Herein, the authors report on the discussions during this workshop and list strategies to enhance the use of EEN as a treatment option in the treatment of pediatric CD in Canada.

Key Words: *Crohn disease; Exclusive enteral nutrition; Nutritional therapy; Pediatrics*

Vers l'alimentation entérique pour le traitement de la maladie de Crohn en pédiatrie au Canada : un atelier pour déterminer les obstacles et les catalyseurs

L'arsenal thérapeutique de la maladie de Crohn (MC) pédiatrique est très similaire à celui de la MC qui se déclare chez les adultes, à l'exception importante de l'alimentation entérale exclusive (AEE [l'administration d'une préparation liquide qui exclut un régime normal]), plus utilisée par les gastroentérologues pédiatres pour induire une rémission. En cas de MC pédiatrique, l'AEE est désormais recommandée comme agent de première intention pour induire une rémission par le comité pédiatrique de l'*European Crohn's and Colitis Organisation* et par la Société européenne de gastroentérologie, d'hépatologie et de nutrition pédiatrique. Selon des études en pédiatrie, le taux de rémission est constamment supérieur à 75 %. Afin de décrire et d'examiner les catalyseurs et les obstacles à l'utilisation de l'AEE au Canada, un atelier a eu lieu en septembre 2014 à Toronto, en Ontario, auquel était invités les gastroentérologues, les infirmières et les diététistes spécialisés en pédiatrie de la plupart des centres de MII pédiatriques du Canada, ainsi que des conférenciers internationaux des États-Unis et de l'Europe ayant des compétences de recherche et de clinique dans la prise en charge diététique de la MC pédiatrique. Les participants à l'atelier ont classé l'exclusivité de l'alimentation entérale, les ressources en santé et les coûts comme les trois principaux obstacles à son utilisation. En revanche, les principaux catalyseurs étaient la standardisation et le partage des protocoles sur l'utilisation de l'alimentation entérale, l'assurance de ressources alimentaires suffisantes et la réduction des coûts de l'AEE pour les familles (y compris la promotion de son remboursement par les ministères de la santé provinciaux et les sociétés d'assurance privées). Dans le présent article, les auteurs rendent compte des échanges pendant l'atelier et dressent une liste des stratégies visant à améliorer l'utilisation de l'AEE comme option thérapeutique de la MC pédiatrique au Canada.

Crohn disease (CD) presents during childhood or adolescence in up to 25% of patients and is typically more extensive than adult-onset disease (1,2). Incidence rates in Canada are among the highest reported worldwide (3). Whereas teenagers with CD often progress toward penetrating complications in a rate similar to adult-onset CD, very early onset CD (<6 years of age at diagnosis, excluding monogenic forms of very early onset inflammatory bowel disease [IBD]) is associated with fewer hospitalizations and surgery (2,4). The treatment armamentarium

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in pediatric CD is very similar to adult-onset CD with the exception of the frequent use of exclusive enteral nutrition (EEN [the administration of a liquid formula diet while excluding normal diet]), which is used more often by pediatric gastroenterologists. In pediatric CD, EEN is now recommended by the pediatric committee of the European Crohn's and Colitis Organisation (ECCO), and the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) as a first-choice agent to induce remission, with remission rates in pediatric studies consistently >75%, and is also commonly used in Japan and Australasia (5). The effectiveness of EEN was first described in adult patients with severe disease (6-9). In view of safety concerns of combination immunosuppressive therapy and because of increasing patient interest in dietary therapy, EEN is now also regaining momentum as a treatment option in adult CD (10-16).

Long-term dietary patterns and specific food items have been shown to influence risk of CD development in all age groups (17-19). Nutritional approaches once CD is established have included total parenteral nutrition, specific dietary exclusions, partial enteral nutition (EN) and avoidance of all dietary intake using EEN (19-22). Avoidance of all dietary intake using a complete nutritional alternative, such as EEN, has been shown to be superior to partial EN when the additional oral dietary intake is not controlled (23). Recent case series of successful use of specific exclusion diets (alone or in combination with EN) as well as requests from many patients to further develop evidence-based dietary therapy, require confirmation by controlled dietary intervention studies (24,25).

Achieving mucosal healing (or endoscopic improvement) has gained support as therapeutic target in CD and may dramatically reduce the risk for long-term disease complications including surgery (26). In small controlled studies, EEN has been shown to be superior to steroids in achieving mucosal healing, while being notably free from important adverse events (20,27-29). EEN has demonstrated efficacy at first induction of clinical remission as well as for subsequent flares, even in patients who have lost response to anti-tumour necrosis factor (TNF) therapy (20,25,29,30). Recently, the GROWTH CD study (a prospective, outcome-based study in newly diagnosed untreated pediatric patients with CD, conducted in Europe and Israel, established by the Porto Group of ESPGHAN, NIH NCT00711945) showed that in mild-to-moderate CD, EEN was superior to steroids both when considering remission according to the Pediatric Crohn's Disease Activity Index (PCDAI) (OR 5.8 [95% CI 1.8 to 18.3]) or combined normal PCDAI and C-reactive protein (OR 3.4 [95% CI 1.3 to 9]) (31).

The use of EN for maintenance of remission varies across IBD centres in terms of strategies used (eg, overnight versus supplemental day time, percentage of total daily calories, as monotherapy or in combination with immunomodulators/anti-TNF) (10,12,15,32-37). Research is ongoing with regard to the optimal maintenance strategy (eg, Cyclic Exclusive Enteral Nutrition as Maintenance Therapy for Pediatric Crohn's Disease [CD-HOPE; NCT02201693] by GETAID pédiatrique) but uncertainty with regard to its use during maintenance of remission could deter from using EEN as induction therapy. In adults and children with CD alike, quality of life using EEN improves even before mucosal healing is obtained (38-40).

The phenotype of CD that is suitable to be treated with EEN, particularly whether isolated colonic disease will respond, has long been a subject of debate (22,28,29,41-44). Clearly, any liquid diet may cause difficulties in terms of stool consistency and frequency, which can be troublesome in the presence of left-sided colonic disease (and, therefore, increase the PCDAI subscore). Afzal et al (42) reported that the achieved remission rate for isolated colonic disease (50% [seven of 14]) was less than in ileal (92% [11 of 12]) or ileocolonic disease (82% [32 of 39]) (P=0.02). However, subsequent case series did not report this different remission rate (22,41). In the study by Buchanan et al (41), isolated colonic disease (without upper gastrointestinal disease, as categorized according to the Vienna classification) achieved a remission rate of 79%, although not assessed prospectively by customary disease activity measures. Given these discrepancies, it would appear reasonable to consider use of EEN for all patients with luminal CD. Perianal CD or the presence of severe colonic disease are listed in the ECCO/ESPGHAN guidelines as factors that warrant consideration of other induction therapy (5).

In this era of balancing treatment-associated risks with maximum effectiveness, yet with appropriate attention for patient-reported outcomes, it is timely to address why EEN is not used more widely across North America (9,45). In fact, there are significant variations in the patterns of use and the acceptance of EEN by physicians between Canada and the United States: Canadian physicians show a greater use of EEN (46). Despite growing concerns about the safety profile of corticosteroids, these geographical variations have not changed over the past 15 years (45,46). The use of EEN appears to be influenced by the extent to which physicians are exposed to its use both in their training and in their current practice setting (46,47). To chart and address enablers and barriers of use of EEN in Canada, a workshop was held in September 2014 in Toronto (Ontario), inviting pediatric gastroenterologists, nurses and dietitians from most Canadian pediatric inflammatory bowel disease centres as well as international faculty from the United States and Europe with particular research and clinical expertise in the dietary management of pediatric CD. In the present report, we discuss the findings of this workshop dedicated to enhancing the use of EEN as a treatment option in the treatment of pediatric CD in Canada.

Preworkshop findings

Before the workshop, individual telephone interviews were conducted by a consumer insights professional with 11 patient families from various clinics across Canada to begin to explore the patient and family experience of choosing a treatment option. Of the 11 patients, seven had received some form of EN as part of their initial treatment. These data were grouped according to theme (Table 1) and formed part of the workshop discussions.

Workshop

Twenty pediatric stakeholders attended the one-day workshop, including three nurses, two dietitians and 15 pediatric gastroenterologists. Participants completed a premeeting assignment identifying experience in their pediatric practice with barriers and enablers to using EEN related to the following influencers: health system (internal and external), patient/family, EN, physician/care team-related or other. During the workshop, participants worked in groups and further refined and categorized the submitted responses, and discussed potential solutions to barriers and ways to enhance enablers (Table 2). These results were further ranked according to priority, highlighting similar barriers and enablers to the use of EEN as described in the literature.

Significant barriers to the use of EEN can be related to:

1. EEN mechanism of action: requirement of exclusivity
2. Patient/family adherence: oral versus nasogastric (NG) tube
3. Health care team/health care system/insurance

Consideration of priority of barriers and enablers to the use of EEN

After an iterative process of discussion, health care participants of the workshop consistently ranked: the exclusivity of EN; the health care resources; and cost implications as the top three barriers to its use (Table 2). Conversely, key enablers repeatedly mentioned included: standardization and sharing of protocols for use of EN (including approach in clinic to EEN, which is heavily influenced by the exposure of the health care team to the benefits of EEN during their training) as well as mode of delivery; ensuring sufficient dietetic resources; and reducing the cost of EEN to the family (including advocacy for reimbursement by provincial ministries of health and private insurance companies). As will be discussed below, emphasizing the need to completely avoid the prediagnosis oral diet by means of EEN, as a requirement to achieve successful induction of remission, can help address some of these barriers and enablers.

TABLE 1
Thematic summary of patient and family interviews

Factors/themes (with examples)	Considerations and impact on practice after discussion in workshop
Messaging from health care team	
• "Pharmacist said incidence of most side effects from steroids were 10% or lower". • Family opted for the steroid because they did not feel the efficacy of the EEN was explained	• Need for multidisciplinary education and conviction; ensure accurate and consistent messaging • Written information to ensure accurate recall by families
Parental assumptions and expectations	
• "at 14, no way would she do that" • "12 is a difficult, in-between age. Maybe if he was younger or older he would (been convinced to) have tried the [formula]."	• Importance of connecting parents with experienced parents • Involve social work or health psychology
Social concerns	
• Integration into school, activities, not eating • "EEN would be socially isolating" • "patient became emotional about not eating (worried about missing the food he liked; being different from his friends)"	• Importance of connecting patients to youth with EEN experience, use available resources (videos, camp/ social experience)
Guilt	
• Parents felt that he had already been through so much that they did not want to upset him further • "At 10 or 11, it was hard to imagine that he could only drink when his friends were eating"	• Focus on benefits of EEN, not only challenges • Importance of connecting parents with experienced parents • Involve social work or health psychology
Child as the decision maker	
• "Parents have to respect the wishes of their children (even very young children). The option of a steroid was the only one our son wanted to look at, so we had to go with his wishes." (Pt was 10 years old when EEN was offered) • "You can't make your teen do what they don't want to do"	• Be sure child is present and actively engaged in discussions regarding treatment • The child is a key player in the decision making, but they are not the only player – parental involvement is also important; a difficult decision to make alone • Engage supports – such as peers – connect with patient who has been on EEN
Adaptation	
• "It seems so traumatic at first, but you have to look ahead. There are so many possibilities for a good outcome." • "it is hard, but it will get a lot better" • "nervous but relieved [at decision to place NG tube]". The tube was in for 10½ weeks… Stayed in; changed 3 times. Very successful. She gained weight."	• Have families share their experiences and strategies

EEN Exclusive enteral nutrition; NG Nasogastric

TABLE 2
Summarized barriers and enablers from group exercise

Factor	Barriers	Enablers
Health system internal (hospital/ health authority)	• Insufficient clinic resources: allied health staff, knowledge, space*	• Adequate numbers of trained team members (nurses, dietitians, social work/psychology/child health) and dedicated space for teaching*
Health system external (provincial/ regional)	• Funding for supplies, formula	• Coverage for EEN supplies and formula* • Supportive home services
Patient/family	• Fear of NG tube and/or loss of food • Difficulty sustaining diet • Limited support to family/socialization	• Involving parents/family in feeding choice • Support of diet, acknowledging it may be difficult • Supportive dietitian throughout process
Enteral nutrition	• Exclusivity of enteral nutrition with no/ limited oral intake* • Cost of enteral nutrition* • Taste • NG tube	• Evidence-based/reduced need for steroids • Few side effects • Oral option possible; recipes
Physician/care team-related	• Lack of institutional experience or critical mass to "keep it going"* • Lack of standardization of enteral nutrition approach*	• Consistent and systematic approach to EEN (protocols, tools, talking points, defined roles for team members)* • Conviction of physician and team to support EEN • Quality review process • Resource sharing

**Barriers and enablers identified as highest priority. EEN Exclusive enteral nutirition; NG Nasogastric*

The mechanism of action of EEN remains conjectural, but is suggested to involve modulation of gut microbial community (microbiota) composition, which is considered a critical factor in CD pathogenesis (40,48). Although the microbiota is rapidly altered to a limited degree by dietary changes, the overall community structure (and presumed metabolic function) has been shown to be resilient to short-term dietary interventions (eg, 10 days in the CAFE study by Wu et al [49]) and is linked with long-term dietary patterns (49-52). Although the clinical and biochemical parameters of disease remission are often achieved by four weeks of induction treatment, the relapse rates of up to 60% by the end of the first year may suggest that the 'state' of the microbiome was not sufficiently shifted (34,53,54). The duration of EEN varies substantially across published reports (9). This variation in practice can be linked with preferential use of oral versus NG tube-delivered EEN; although strict compliance with oral EEN (and avoidance of dietary intake) is achieved by many patients, for others it may be easier to sustain EEN via NG tube, with optimization of benefits beyond achieving normalization of inflammatory markers and clinical remission. The question of whether establishment of a new stable microbiome, away from the inflammation-associated 'state', can become a therapeutic goal, will need to be studied in prospective microbiome-focused trials. Gerasimidis et al (48) showed that EEN paradoxically reduces some of the presumed 'protective' features of the gut microbiota, such as community diversity and even particular bacterial species (eg, *Firmicutes*), making its mode of action difficult to infer (25,48). Recent reports describing specific exclusion diets have rekindled the debate of whether the strong therapeutic effect of EEN is mediated largely by the avoidance of putative dietary triggers (24,25). In other words, rather than actively inducing 'protective' microbiota changes, EEN may mediate remission by excluding dietary products that elicit pathological changes in gut microbiota composition/function and promote dysfunctional host-microbe interactions in the gut mucosa. Earlier trials of partial EN (50% of total daily calories) were not successful in inducing clinical remission; however, more recent evidence indicates that this is perhaps because no dietary changes were made in the remaining 50% of non-EN calories (23,55). Further support for the crucial role of exclusion of normal diet comes

from the comparison of different types of dietary intervention (28). Although trials were not powered to the level of confirming noninferiority, comparison of remission rates for different compositions of formula used (eg, elemental versus polymeric, more/less long-chain triglycerides, etc) or additional additives (eg, glutamine), have not shown one type of formula to be superior (28). There is now an ongoing multicentre, randomized dietary intervention trial studying EEN versus EN plus a specific CD exclusion diet (NCT01728870 – clinicaltrials.gov) (25). Until the efficacy of these novel dietary interventions is shown, considering the benefits of EEN in terms of exclusion of other dietary intake can help overcome several barriers to its use.

To improve patient/family adherence, EEN could, thus, be presented as an effective treatment option by exclusion of the normal dietary intake, in addition to being an alternative to corticosteroid therapy. A consistent approach to discussing EEN in clinic significantly improves acceptance and compliance, as evident from the experience in many European centres (34,41,53). Furthermore, achieving steroid-free maintenance of remission has become an accepted treatment goal in pediatric CD due to its multitude of beneficial effects on growth, nutritional status, bone health and avoiding infectious adverse events, particularly in combination with other immunosuppressive agents (56-58). Clinicians, patients and their families embark on steroid-based induction therapy with a view to early discontinuation but, without anti-TNF therapy, 30% to 40% are steroid dependent after one year of follow-up in referral centre reports from the United States and Canada (56,57). Krupoves et al (57) showed there were no temporal differences in the rates of corticosteroid dependency in pediatric CD before 2000 (43.9%) and in subsequent years (39.4%; P=0.411), and no differences between the two pediatric IBD centres contributing to this study (Montreal [St-Justine Hospital]) and Ottawa), although anti-TNF therapy was used in only 5% of this cohort.

Clearly, choosing an alternative to steroids as induction therapy then becomes a logical approach to avoid steroid dependence. For induction, EEN may be administered orally or via NG tube. Oral feedings are more common in Europe, Australia and some United States centres, whereas many Canadian centres use NG tube (however, for example, at *Centre hospitalier universitaire Sainte-Justine* [Montreal, Quebec] the majority of patients successfully adhere to oral EEN) (9). In a retrospective comparative study on mode of delivery of EEN (based on physician preference), there was no difference in clinical outcome: both were equally effective (22,59). Up to 50% of patients may require an NG tube to complete a course of EN >6 weeks (41). It is important to discuss treatment options in case of difficulty with adherence or failure of EEN, as well as planning for the strategy to maintain remission. The guidelines of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) IBD Committee refer to an induction period of at least eight weeks with EEN (9). Given that both the time to initial benefit and then to clinical remission can vary, the NASPGHAN report also suggests a period of three to four weeks of EEN before a decision is made about effectiveness (9).

Because the majority of treatment for pediatric CD occurs outside the hospital, the success of EEN therapy is highly dependent on adequate health care resources needed for a home EN program, notably the composition and commitment of a multidisciplinary team. Explaining how lifestyle choices (including diet) impact on general health and development of disease has become accepted practice. Dietary changes impacting on the family and social life are already part of living with IBD for many patients (19,60). Increasingly, patients and their families request, expect and accept dietary management as part of the treatment of IBD (60,61). Attitudes among health care staff to promote the use of EEN, the attending physician's exposure to dietary therapy during her/his training and the centre's experience are all key determinants of success of EEN (9,46,56,57). Nursing and dietitian support to deliver this evidence-based dietary management is, therefore, ideal for a successful EEN program. Access to psychological support can also be important for many patients and families to increase coping skills with the disease in general and EEN treatment in particular (9). Planning and discussing strategies to integrate EEN into the family, school and social life, significantly increase adherence to EEN.

The practical considerations of any successful home EN program include the determination of caloric and other nutrient requirements, determining the best method of administration (oral versus NG, also depending on health care system/insurance stipulation as discussed below), scheduled support during the induction period (eg, by means of a care pathway identifying the role of each team member), and addressing expectations around the time to clinical benefits and total duration of therapy (9).

EEN and its administration (formula, NG tube, and supplies and feeding pump) can be an expensive intervention. Differences in health care systems in each province of Canada affect at-home reimbursement coverage for the formula and supplies, with different programs often required for each. There are well-established programs in some provinces (eg, Alberta, Ontario and Quebec); however, restrictions, such as administration via NG tube (eg, Alberta and Ontario) or the need for home care nursing support can be a condition/barrier to funding. In turn, individual hospitals may operate their own programs in provinces in which a provincial home EN program is lacking. Because funding for health care is provincially managed, there is significant variation across Canada, which affects the uptake of EEN as a therapeutic option.

There has been some limited success in obtaining coverage with private insurance in Canada, but the process is often cumbersome and lengthy. For instance, clinics are required to write individual letters for patients to insurance companies to request financial support. This often requires two to three letters to receive what may still be limited coverage. Clearly, a positive response may justify the effort needed to seek support for home EN, but this often adds considerably to the workload of the multidisciplinary team delivering EEN. In cases where coverage is disputed, it has often been helpful to emphasize the role of the formula as the therapeutic intervention, and the therapeutic requirement for a six- to 12-week period to exclude all other dietary intake to achieve clinical remission.

CONCLUSIONS

EEN is an extremely safe but underused treatment for induction of remission in pediatric CD in North America. Guidelines from both the NASPGHAN IBD Committee as well as the recent ECCO/ESPGHAN guidelines recommend use of EEN as first-line induction therapy in pediatric CD. During this thematic workshop focused on improving the framework for successful implementation of EEN therapy in pediatric CD in Canada, the panel ranked the need for EEN, the health care resources needed for a home EN program and cost implications as the top three barriers to its use. Identifying and understanding the barriers enables us to work on targeted strategies to overcome them, and help clinics implement and improve their success using EEN. Overcoming the barriers is the next step in the process.

Until we improve our understanding of the environmental and dietary triggers of CD, the effectiveness of EN will continue to rely on exclusion of the 'prediagnosis' diet. A standardized yet individualized approach (ie, by considering the caloric and other nutrient requirements of each patient) will optimize the use of limited dietetic resources, ideally with additional support for home nutrition programs. Polymeric formulas (which tend to be less expensive and more palatable) may be better suited if the oral route is chosen, with the option of dietetic guidance to flavour the formula used to avoid taste fatigue. Reducing the cost of EEN to the family will require ongoing advocacy for reimbursement by provincial ministries of health and private insurance companies. Further research to enhance our understanding of the mechanisms of action and the optimal application of EEN (or partial EN with additional dietary modifications) is necessary. Until such time, EEN should be recommended and supported as a highly effective and safe treatment modality in CD.

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