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ORIGINAL COMMUNICATION

Transition to peptide-based diet improved enteral nutrition tolerance and decreased healthcare utilization in pediatric home enteral nutrition

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Abstract

Background: Home enteral nutrition (HEN) use continues to increase in children unable to meet nutritional needs through oral intake. Some patients do not tolerate standard polymeric formula (SPF), which may lead to malnutrition. Use of peptide-based diet (PBD) has demonstrated benefits in adults, however there remains a paucity of data in pediatric population.

Methods: Retrospective review of medical records of children receiving HEN between October 2015 and October 2019 was conducted. Nutrition, tolerance, and healthcare utilization was tracked through May 2020. Children receiving PBD as initial formula or transitioned to PBD from SPF were included. Our objective was to assess gastrointestinal tolerance and impact on healthcare utilization in children receiving PBD.

Results: During study period, 30 children (mean age, 9 ± 5.44 years; 20 of 30 [66.7%] male) utilized PBDs. Twenty-one patients started PBD directly with malnutrition as primary indication. Nine patients transitioned from SPF to PBD, most often due to intolerance of SPF (66%). After transition to PBD, no symptoms were reported in 6 of 9 (66.7%) patients, and symptoms of SPF intolerance resolved in 4 of 9 (44.5%) patients. Healthcare utilization declined significantly after transition to PBD, including mean numbers of emergency room visits (0.78 ± 1.09 to 0.11 ± 0.33; $P = .025$), provider visits (1.67 ± 1.32 to 0.56 ± 0.73; $P = .007$), and phone calls (1.22 ± 1.39 to 0.33 ± 0.50; $P = .026$).

Conclusions: PBD is well tolerated and can result in significant reduction in healthcare utilization in children intolerant to SPF.

KEYWORDS
enteral, enteral feeding, healthcare utilization, home enteral nutrition, nutrition, nutrition therapy, pediatric enteral nutrition, peptide-based diet, polymeric formula

CLINICAL RELEVANCY STATEMENT

Major guidelines recommend initiation of enteral nutrition therapy with a standard polymeric formula. However, a standard approach to patients with significant enteral feeding intolerance is lacking. In children requiring long-term enteral nutrition, enteral feeding intolerance and its related healthcare utilization can be challenging. The main clinical implication of our findings is that transition to peptide-based diet in children intolerant to enteral nutrition is a safe and probably a cost-effective intervention toward achieving nutrition therapy goals.

INTRODUCTION

Prevalence of enteral nutrition (EN) and home EN (HEN) has increased significantly over the last few decades.[1,2] In children, EN is utilized for various indications, including altered digestion or absorption, increased metabolic demand, and nutrition support in disorders that affect swallowing and/or oral motor development.[3] The leading cause reported for utilization of long-term HEN in children are neurodevelopmental delay/disabilities.[4] Various pathophysiological mechanisms are thought to be involved in children requiring EN, including gastric dysrhythmia, delayed gastric emptying, and enteric nervous system malfunction.[5] Moreover, long-term HEN for children is typically overwhelming for patients and caregivers[4,6] and requires specialized care.[7] Johnson and Deitz reported in 1985 that mothers spent around 3–8 h every day to feed their children with disabilities in comparison with 50 min for children without disability.[4,8]

Enteral feeding intolerance (EFI) is a recognized challenge and a frequent cause of suboptimal HEN in adults and children.[4,9] EFI is holistically defined and characterized by the presence of gastrointestinal (GI) distress symptoms, significant gastric residual volume, and suboptimal delivery of EN.[10] However, the popular pragmatic definition of EFI as the cessation or reduction of EN because of GI dysfunction continues to be used.[9] Given the outlined complexity of HEN management in children,[3] including EFI, the need for proven strategies to address challenges of HEN delivery in children speaks for itself.

Given the availability of many standard polymeric formulas (SPFs) and specialized EN formulas,[11] the logical and practical emerging approach in managing EFI has been to transition to a specialized EN formula.[12] Recently, transition to peptide-based diet (PBD) was reported to be beneficial in adult HEN patients intolerant to SPF.[13] The transition to PBD in EFI resulted in significant reduction in healthcare utilization in addition to improvement in GI tolerance.[13,14] In the pediatric population, studies have also noted better EN tolerance with PBD, although the data have been limited to critically ill cohorts.[15,16] Data for children receiving HEN are lacking despite the need to establish meaningful intervention to help optimize nutrition support for EN-intolerant children, in order to support their growth and development.

This study aims to assess changes in GI tolerance and healthcare utilization in children receiving HEN with PBD.

METHODS

After institutional review board approval, we performed a retrospective review of electronic medical records for children 18 years old and younger, who received at least 80% of their nutrition needs from HEN and were exclusively on PBDs between October 2015 and October 2019. Nutrition, clinical, and healthcare utilization history of the study participants was tracked until May 30, 2020. The study cohort was subdivided into two groups: PBD-initiated group (PBD-i group; children who were directly started on PBD as initial formula) and PBD-transitioned group (PBD-t group; children who were initiated on SPF and later transitioned to PBD). Because of the retrospective nature of this review, the decision to transition to PBD in the PBD-t group was made and documented by the clinical providers and often based on symptoms of GI distress, including nausea, vomiting, diarrhea, abdominal pain/cramps, bloating, and constipation. There was no standardized reporting tool, and only available documented clinical judgement data were obtained. In addition to basic patient demographic data, anthropometric variables while receiving HEN were obtained, including weight, height, weight-for-age *z*-score, and change in weight-for-age *z*-score. A *z*-score is the deviation of the value for a child from the mean value of the reference population divided by the standard deviation (SD) for the reference population. Weight-for-age *z*-score is used in this study to reflect the growth of children respective to their age. Additionally, nutrition status and data on HEN support variables, such as regimen, actual consumption, tolerance, and follow-up, were also collected. Healthcare utilization data related to HEN follow-up, specifically phone calls, emergency room (ER) visits, and visits with HEN providers, were collected. Healthcare encounters not directly related to HEN were excluded.

Statistical analysis

Statistical analysis was performed using JMP Pro 14 software 2018 (SAS Institute, Cary, NC, USA). Normally distributed data are presented as mean ± SD, whereas data with non-normal distribution are presented as median and interquartile range (IQR). Parametric continuous variables were analyzed using matched-pairs Student *t*-test or Wilcoxon signed rank for nonparametric data. Nominal variables are presented in frequencies and percentages. Contingency analysis was performed to assess nominal variables, and agreement statistics was performed to assess the significance of change in these variables with intervention. Bowker and McNemar tests were performed to calculate symmetry of disagreement. A *P*-value of .05 was considered statistically significant.

RESULTS

A total of 30 children met the inclusion criteria. Twenty-one patients (70%) started directly on PBD as initial HEN formula (PBD-i), whereas nine (30%) were transitioned from SPF to PBD (PBD-t). Basic

TABLE 1 Demographic and clinical characteristics in patients receiving peptide-based diets as primary enteral nutrition formula (PBD-i) or transitioned after standard polymeric formulas (PBD-t)

Characteristic	PBD-i (n = 21)	PBD-t (n = 9)
Age, mean ± SD, years	8.42 ± 5.15	10.22 ± 6.35
Gender, %		
Male	66.7	66.7
Female	33.3	33.3
Weight at EN initiation, median (IQR), kg	20.0 (14.1–34.9)	28.4 (12.9–52.0)
Weight-for-age *z*-score at EN initiation, median (IQR), kg	0.24 (−1.00 to 1.91)	0.07 (−2.61 to 0.58)
Estimated energy need at EN initiation, mean ± SD, kcal/kg/day	61.9 ± 29.0	68.11 ± 25.12
Estimated protein need at EN initiation, mean ± SD, g/day	25.35 ± 21.04	29.72 ± 17.71
Indication for EN, n (%)		
Malnutrition	11 (52.4)	3 (33.3)
Dysphagia and SBS	3 (14.3)	2 (22.2)
Poor oral intake/feeding difficulties	4 (19)	3 (33.3)
Bridge to oral as clinically appropriate	3 (14.3)	1 (11.2)
Primary diagnosis, n (%)		
Anoxic brain injury, brain tumor, and global developmental delay	8 (38)	3 (33.3)
GI congenital anomalies/dysmotility, SBS, IBD, and gastroschisis	3 (14.3)	2 (22.3)
Skeletal anomalies; SMA syndrome and CLOVES syndrome	1 (4.8)	1 (11.1)
Cystic fibrosis	1 (4.8)	1 (11.1)
Pulmonary atresia	0	1 (11.1)
Postural orthostatic tachycardia with GI symptoms	0	1 (11.1)
Hematological malignancies	2 (9.5)	0
Other malignancies	3 (14.3)	0
CHDs, including trisomy 21 related	3 (14.3)	0

Abbreviations: CHD, congenital heart defects; CLOVES, congenital lipomatous overgrowth, vascular malformations, epidermal nevi and scoliosis/skeletal/spinal anomalies; EN, enteral nutrition; GI, gastrointestinal; IBD, inflammatory bowel disease; IQR, interquartile range; PBD-I, group initiated with peptide-based diets; PBD-t, group initiated with standard polymeric formulas and transitioned to peptide-based diets; SBS, short-bowel syndrome; SD, standard deviation; SMA, superior mesenteric artery.

demographics and clinical characteristics are shown in Table 1. In the PBD-i group (n = 21), two-thirds of patients were male (14 of 21; 66.7%), had a mean age of 8.42 ± 5.15 years, and mean weight-for-age *z*-score of 0.24 (IQR, −1.00 to 1.19). The average estimated energy need for this group was 61.9 ± 29.0 kcal/kg/day with average protein needs of 25.35 ± 21.04 g/day. Malnutrition was the leading indication to start HEN in 11 of 21 (52.4%) patients, followed by inadequate oral intake and feeding disorders in 4 of 21 (19%), GI disorders in 3 of 21 (14.3%), and bridge to oral intake as clinically indicated in 3 of 21 (14.3%). Clinical justification to start PBD included malnutrition in 14 of 21 (66.7%) patients, pancreatic insufficiency in 3 of 21 (14.3%), and distant past intolerance to SPF in 1 of 21 (4.8%). No specific reason was listed as justification to initiate PBD in 3 of 21 (14.3%) patients. The most common diagnoses were neurodevelopmental disorders/disabilities, including brain tumors in 8 of 21 (38%), followed by other malignancies in 5 of 21 (23.8%); GI conditions, including congenital anomalies, short-bowel syndrome (SBS), and inflammatory disorders in 3 of 21 (14.3%); congenital heart diseases in 3 of 21 (14.3%); and undocumented specific primary diagnosis in 4 of 21 (19.1%) patients. The most frequently chosen PBD formulas were Peptamen Jr 1.0 and Peptamen Jr 1.5, each used in 9 of 21 (42.9%) children, followed by Peptamen Prebio in 2 of 21 (9.4%) and Peptamen Jr Fiber in 1 of 21 (4.8%). By the end of the study, patients in the PBD-i group were on a PBD for a median of 62.5 (IQR, 14.7–113.2) weeks. Notably, none of patients in the PBD-t group were on blenderized tube feeding (BTF) before transition to PBD.

In the PBD-t group (n = 9), 66.7% were male (six of nine); the PBD-t group had a mean age of 10.22 ± 6.35 years and mean weight-for-age *z*-score of 0.07 (IQR, −2.61 to 0.58). Average estimated energy need for this group was 68.11 ± 25.12 kcal/kg/day with average protein needs of 29.72 ± 17.71 g/day. The most common diagnoses in this group were neurodevelopmental disorders/disabilities, including brain tumors in three patients (of nine; 33.3%), followed by GI conditions, including congenital anomalies, SBS, and inflammatory disorders in two patients (of nine; 22.3%). The most commonly used PBD formula was Peptamen Jr 1.5 in eight patients (of nine; 88.9%), whereas one (of nine; 11.1%) transitioned to Peptamen Jr 1.0. The most common standard formula used before transition

TABLE 2 Indication and EN dependency in patients receiving PBDs as primary EN formula or transitioned after SPFs

Variable	PBD-i (n = 21)	PBD-t (n = 9)
Indication for PBD, n (%)		
Malnutrition	14 (66.6)	2 (22.2)
Pancreatic insufficiency	3 (14.3)	0
Current or past intolerance to SPF	1 (4.8)	6 (66.7)
Unspecified	3 (14.3)	1 (11.1)
EN/PBD dependency		
Duration on PBD, median (IQR), weeks	62.5 (14.7–113.2)	22.2 (11.2–137.2)
Documented tolerance to PBD, %	52.4	66.7
Average consumed PBD servings out of goal, %	94.82	94.81
Remained on PBD by end of the study, %	28.5	22.2
Ability to resume satisfactory oral intake, %	14.4	44.5
Transitioned to SPF, %	4.8	22.2
Transitioned to other specialized formula, %	9.5	0
Transferred care/lost to follow-up, %	23.8	11.1
Transitioned to PN, %	9.5	0
Death, %	9.5	0
PB formula used, n (%)		
Peptamen Jr 1.0	9 (42.9)	1 (11.1)
Peptamen Jr 1.5	9 (42.9)	8 (88.9)
Peptamen Prebio	2 (9.4)	0
Peptamen Jr Fiber	1 (4.8)	0

Abbreviations: EN, enteral nutrition; IQR, interquartile range; PB, peptide-based; PBD, PB diet; PBD-i, group initiated with PBDs; PBD-t, group initiated with SPFs and transitioned to PBDs; PN, parenteral nutrition; SPF, standard polymeric formula.

to PBD was PediaSure Enteral (1.0 and 1.5) (three of nine patients; 33.3%).

At baseline, there was no statistically significant difference between groups (PBD-i and PBD-t) in terms of age, weight, weight-for-age *z*-score, estimated energy and protein needs, and duration on PBD.

Formula regimen data

By the end of study period, patients in the PBD-i group were on PBD formula for a median of 37.2 (IQR, 17.2–122.2) weeks, and 6 of 21 (28.5%) patients remained on PBD. Patients gained a median of 2.6 (IQR, −0.4 to 8.75) kg while on PBD, and weight-for-age *z*-score increased by an average of +0.18 ± 1.62.

By contrast, in patients in the PBD-t group, duration of HEN with SPF was of a median of 4.4 (IQR, 2.2–11.9) weeks, and after transitioning, they were on PBD for a median of 22.2 (IQR, 11.2–137.2) weeks. While on SPF, patients lost a median of 0.5 (IQR, −1.0 to 1.5) kg, with a median decrease in weight-for-age *z*-score at −0.13 (IQR, −0.42 to 0.30). However, while on PBD, they gained a median of 2.7 (IQR, −1.0 to 6.7) kg with a median weight-for-age *z*-score increase at 0.11 (IQR, −0.18 to 1.29). Patients were able to consume more energy from PBD compared with SPF formulas (94.8% ± 8.18% vs 73.3% ± 25.09%; $P = .0477$), which leaned toward the nutrition target.

EN/PBD dependency

At the end of the study, 6 of 21 (28.5%) patients in the PBD-i group remained on PBD, whereas 5 of 21 (23.8%) had their medical care transferred to other centers or did not show for follow-up as scheduled. Few patients were transitioned to other formulas: 1 of 21 (4.8%) transitioned to SPF and 2 of 21 (9.5%) transitioned to elemental formulas. Three patients (14.3%) achieved oral autonomy, whereas 2 of 21 (9.5%) transitioned to parenteral nutrition (PN). Death was reported in 2 of 21 (9.5%) patients; both incidents were related to underlying conditions—namely, global developmental delay with poor functional status and refractory blood malignancy.

In the PBD-t group, two of nine (22.2%) patients remained on PBD by the end of the study. Almost half (four of nine; 44.5%) achieved oral autonomy, and two of nine (22.2%) were transitioned back to SPF. One patient (11.1%) was lost to follow-up. Table 2 includes EN dependency data.

Tolerability data

In the PBD-i group, 11 of 21 (52.4%) reported no symptoms of EFI. Among those who reported symptom(s), 2 of 21 (9.5%) reported

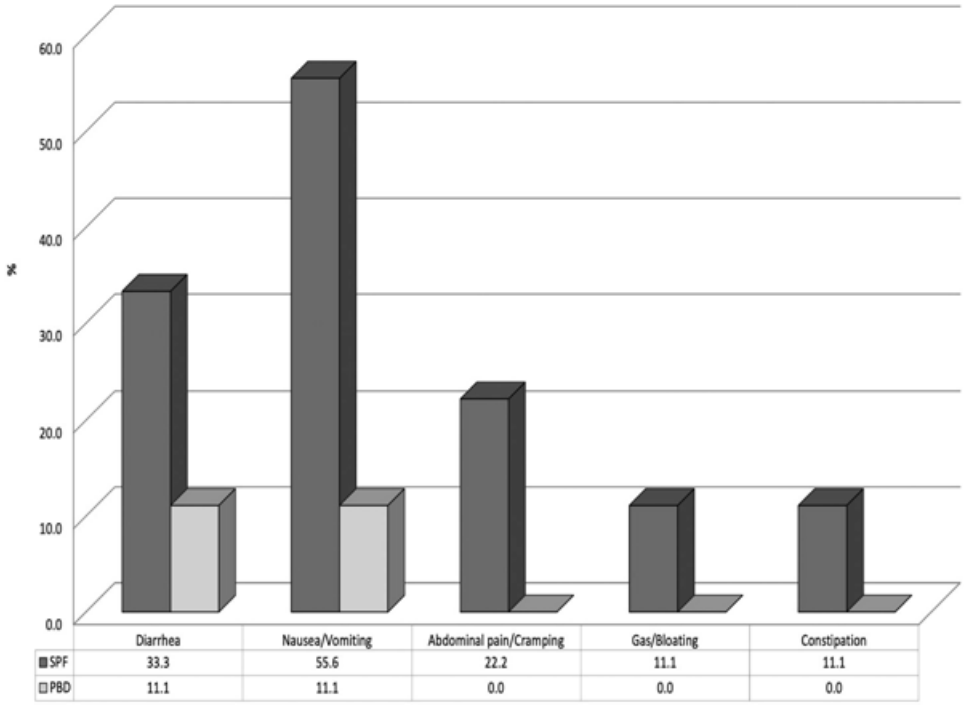

FIGURE 1 Reduction in gastrointestinal distress with transition to a PBD ($P = .045$). PBD, peptide-based diet; SPF, standard polymeric formula

diarrhea, and 10 of 21 (47.6%) had at least one episode of nausea/vomiting while on PBD.

Interestingly, in the PBD-t group, symptoms of GI distress such as diarrhea, nausea and vomiting, abdominal pain and cramping, bloating, and constipation showed a significant reduction after transition to PBD. Six (of nine; 66.6%) patients had at least one symptom of EFI while on SPF, whereas only two (of nine; 22.2%) presented with at least one symptom on EFI while on PBD. Four patients had their symptoms completely resolved after transitioning from SPF to PBD, and of those reporting no EFI symptoms while on SPF, none reported EFI onset after transition to PBD. The improvement in EN tolerance with transition to PBD in this cohort was statistically significant ($P = .0455$). Figure 1 illustrates greater tolerability for PBD compared with SPF.

Healthcare utilization

Patients in the PBD-i group had median phone communications of one (range, 0–6) call, a median number of visits to the emergency department of zero (range, 0–1), and a median number of visits to provider of zero (range, 0–4)—related to EN intolerance while on PBD.

Patients in the PBD-t group experienced a significant reduction in healthcare utilization related to EFI. The mean number of phone communications was reduced from 1.22 ± 1.39 to 0.33 ± 0.50 ($P = .026$); mean number of ER visits declined from 0.78 ± 1.09 to 0.11 ± 0.33 ($P = .025$); and mean number of provider visits declined from 1.67 ± 1.32 to 0.56 ± 0.73 ($P = .007$) (Figure 2). Given that patients were on PBD for a longer duration compared with SPF, the healthcare utilization components studied were further analyzed to assess these variables as an average per week. The reduction in healthcare utilization with transition to PBD continued to be statistically significant with a reduction in the mean number of phone communications per week (0.23 ± 0.38 to 0.01 ± 0.02; $P = .05$), reduction in the mean number of visits to the ER per week (0.09 ± 0.15 to 0.0005 ± 0.001; $P = .04$), and a decrease in the mean number of provider visits per week (0.42 ± 0.41 to 0.011 ± 0.02; $P = .01$).

DISCUSSION

Results of this study show that a PBD was well tolerated by children when started as initial HEN formula or when children transitioned to a PBD in the context of SPF intolerance. In children directly started on PBD, the majority tolerated it well and achieved their nutrition goals. In those transitioned to PBD, all symptoms of EFI (diarrhea, nausea/vomiting, abdominal pain, bloating, and constipation) improved significantly after the transition. Moreover, there was a significant reduction in healthcare utilization related to nutrition therapy in this group as well.

Several possible explanations for improved tolerance of PBD noted in our study cohort can be attributed to physiological properties of PBD as semi-elemental formulas. One unique property of PBD is that they typically contain a larger percentage of medium-chain triglycerides (MCTs) in their fat component. SPF and typical diets contain a larger percentage of long-chain triglycerides (LCTs), which are absorbed through a complex process of emulsification by bile and lipolysis by pancreatic enzymes to break them down to monoglycerides, free fatty acids, and glycerol (Figure 3).[17] Subsequently, recon-

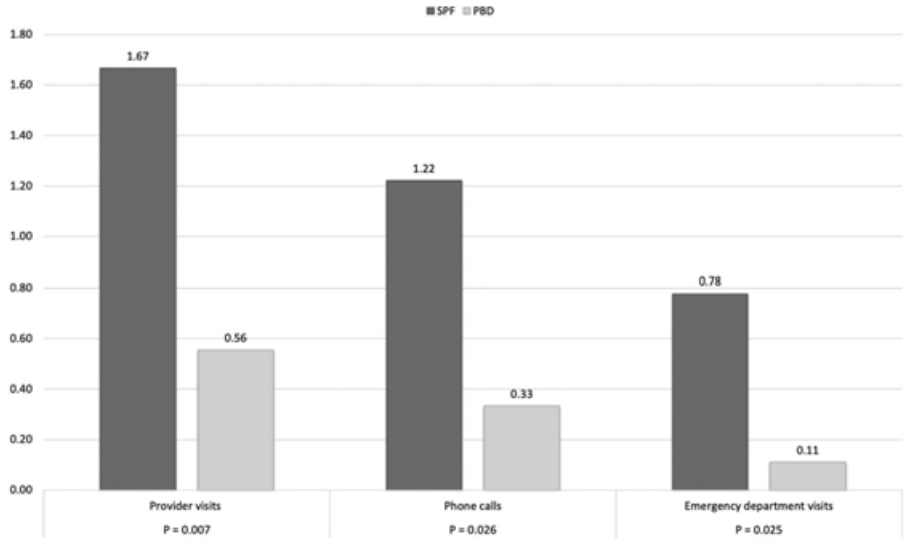

FIGURE 2 Healthcare utilization with transition to a PBD. PBD, peptide-based diet; SPF, standard polymeric formula

stitution of fatty acids after absorption into triglyceride results in the release of chylomicrons into the bloodstream.[18] MCT absorption differs in a number of ways: MCTs are passively absorbed, as they do not require bile and pancreatic enzymes for hydrolysis.[19] In contrast to LCTs, MCTs do not influence the release of cholecystokinin and therefore reduce the secretion of pancreatic enzymes and gallbladder emptying.[20] Once absorbed, MCTs can enter the hepatocyte mitochondria from the cytosol without using acylcarnitine system for transportation.[21] Another important plausible theory for greater PBD tolerance in patients is that some PBDs contain enzymatically hydrolyzed whey protein, which may lead to better protein absorption,[22] especially in those with intestinal disease and mucosal damage.[13] Figure 4 illustrates the absorption of dipeptides and tripeptides.

Transition to PBD in patients intolerant to SPF is an emerging practice.[13] In a similar study to this one, Mundi et al noted a significant reduction in healthcare utilization and symptoms of EFI with transition to PBD in a cohort of adult patients.[13] The study showed that PBDs were well tolerated in patients initiated on PBD as well as in those switched to PBD secondary to SPF intolerance. The review described that PBDs were significantly effective in helping patients achieve their nutrition goals and a significant reduction in the frequency of all EFI symptoms. In the adult cohort, these clinical benefits were also associated with a significant reduction in healthcare utilization, which translates into reduction in cost of care.

Initiation of EN with SPF remains the standard of care.[25,26] However, the importance of taking healthcare utilization into account in approaching patients who are intolerant to SPF or those presenting with diagnosis that are at high-risk of GI intolerance is crucial in holistic assessment of the cost-effectiveness of this intervention. Given that the higher cost of PBDs has always been listed as a barrier in transitioning patient from SPF to PBD,[13] a number of other interventions have been tried to reduce EFI, including using symptomatic pharmacotherapy, changing EN formula administration, or fortifying SPF with fiber. In fact, healthcare utilization related to EFI can be significant and lead to a higher cost of care and/or overwhelming nutrition care for patients and caregivers. A review of >1000 insurance claims for patients who received EN has found that transition to PBD in homecare adults previously receiving oral and enteral SPF reduced hospitalizations and overall cost of care.[14] LaValle et al noted a significant increment ($P < .001$) in EN tolerance by 18% with transition to PBD over 1 year. Moreover, a 28% reduction in at least one hospitalization over a period of 1 year was found in those who transitioned to 100% whey protein PBD. Although it is difficult to translate utilization to a dollar value, associated cost is expected to be significant. For example, in many estimates, one visit to the ER with GI symptoms may cost $2000–$3500.[13,14,27,28] LaValle et al also showed that the majority of adult patients who received PBD had commercial insurance compared with government-sponsored programs (ie, Medicare, Medicaid), which may signify reduced access to these formulas.

There is a paucity of data to guide clinicians on pediatric HEN practice, especially in the presence of EFI. In 2016, Minor et al[12] retrospectively studied the effects of transitioning a cohort of HEN-intolerant, developmentally delayed children to PBD. They noted that 92% of the study cohort had clinically evident improvement in EFI and that 75% of that improvement took place within 1 week after transition to PBD. Interestingly, all children in this study were noted to have improved weight gain after transition to PBD. Recently, Ibrahim et al[15] evenly randomized 180 critically ill children needing EN into either an SPF or PBD cohort. Children who were receiving a PBD were able to achieve their target EN volumes in shorter duration and showed significantly less symptoms of EFI. In addition, those who were randomized to PBD also showed better weight gain. However, there was no difference in mortality between the two cohorts. Similar to these reports, our study also noted an improvement in clinical symptoms after transition to PBD. Additionally, our study also investigated HEN-related healthcare utilization in the setting of transition to PBD in children intolerant to SPF and noted significant benefit there as well. We feel that this extra

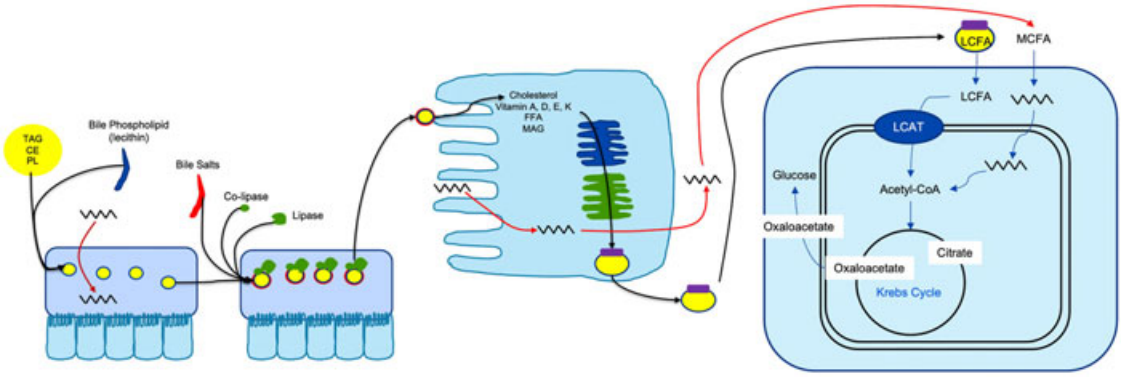

FIGURE 3 Digestion and absorption of triglycerides. CE, cholesterol esters; FFA, free fatty acids; LCAT, lecithin-cholesterol acyltransferase; LCFA, long-chain fatty acids; MAG, monoacylglycerol; MCFA, medium-chain fatty acids; PL, phospholipids; TAG, triglyceride. Reprinted with permission from Mayo Foundation for Medical Education and Research

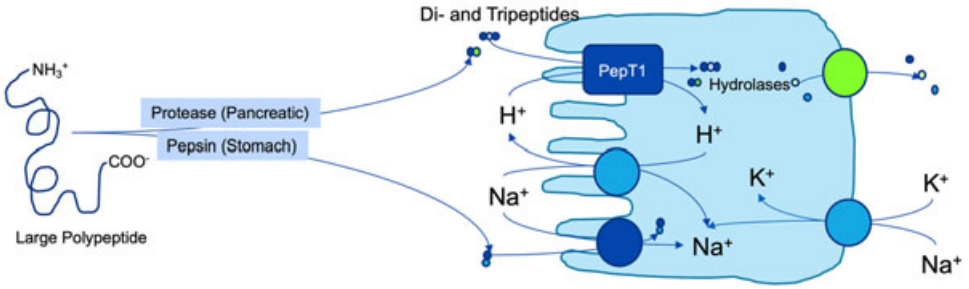

FIGURE 4 Illustration showing dipeptide and tripeptide absorption by enterocyte bypassing pancreatic and gastric enzymes. Reprinted with permission from Mayo Foundation for Medical Education and Research

layer of investigation may help clinicians in making cost-effective decisions about how they approach EFI in children.

Another emerging intervention in patients who are intolerant to HEN is transition to BTF. BTF has been used in adults and children, and it was estimated that between 30% and 89% of children receiving HEN use BTF at some point.[29] Samela et al[30] studied the transition to BTF in a cohort of 10 children with intestinal failure who were weaned off PN and were receiving elemental or semi-elemental formula–based EN but were having diarrhea or altered bowel symptoms. After transition to BTF, they noted that 90% of children tolerated the transition well, with resolution of their altered bowel symptoms and stool consistency. BTF may also provide psychological benefits to enterally fed children by giving them the sense of being normally fed.[2,31] However, concerns regarding safety and contamination, given that there are no established practices in the preparation and delivery of BTF, are valid and need to be considered.[32]

Current study limitations include the retrospective nature of chart review design. Because of this, HEN formula was preselected by the HEN team based on clinical need in an uncontrolled manner. Nevertheless, it is improbable that the clinical benefits observed by transition to PBD occurred randomly. The study's cohort size was also small, especially for the PBD-t group. However, diversity in the primary diagnosis and indication of EN suggests the ability to generalize the results to a larger real-world population. Additionally, we were able to only capture data from our institutional electronic medical records and relied on the adequacy of documentation by clinical staff. It is possible that important information with regards to the clinical evolution or healthcare utilization variables could have been missed because of patients reporting to other facilities or insufficient documentation. Given that our hospital is a referral center receiving patients globally, we also noted that a proportion of study patients had their care transferred to other institutions, usually back to their local providers. Patients in the study received one PBD brand, as that is the only PBD formula available in our center's formulary. Because of this, our findings may not be generalized to all PBD formulas.

CONCLUSIONS

The current study showed that in children requiring long-term HEN, PBD was well tolerated whether used as the initial HEN formula or when patients transitioned to PBD from SPF. Moreover, transition to PBD in children who are intolerant of SPF led to significant improvement in HEN tolerance, along with a reduction in healthcare utilization in relation to EFI. The current study replicates similar findings noted in an adult HEN cohort. These findings support that early transition

to PBD should be considered in children with documented EFI, as the cost of this transition is probably outweighed by the overall cost in healthcare utilization if EFI persists. Additional prospective studies are needed to further explore emerging approaches in the management of EFI in adult and pediatric HEN population.

CONFLICT OF INTEREST

Manpreet S. Mundi has research grants from Fresenius Kabi, Nestlé, VectivBio, and Real Food Blends and is on the advisory board of Fresenius Kabi and Baxter. Ryan T. Hurt is a consultant for Nestlé. Osman Mohamed Elfadil, Dana B. Steien, Ramya Narasimhan, Saketh R. Velapati, Lisa Epp, Ishani Patel, and Jalpan Patel have no relevant conflict of interest to report.

AUTHOR CONTRIBUTIONS

Manpreet S. Mundi, Osman Mohamed Elfadil, Lisa Epp, and Ryan T. Hurt contributed to the conception and design of the research; Osman Mohamed Elfadil, Dana B. Steien, Ramya Narasimhan, Saketh R. Velapati, Ishani Patel, and Jalpan Patel contributed to the acquisition and analysis of the data; Osman Mohamed Elfadil, Dana B. Steien, and Manpreet S. Mundi contributed to the interpretation of the data; and Osman Mohamed Elfadil, Dana B. Steien, and Manpreet S. Mundi drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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