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Tolerance, Healthcare Utilization and Cost of Enteral Peptide-Based Diets in Children in Post-Acute Care in the USA

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Abstract

Context: Peptide-Based (PB) Enteral Tube Feeding (ETF) has been shown to reduce Gastro Intestinal (GI) intolerance in paediatric patients receiving enteral nutrition. However, there are limited data on the use of these formulas in paediatric patients in the post-acute setting.

Objective: We assessed the real-world GI tolerance, healthcare utilization and resource use costs of 100% whey protein (w-)PB ETF in paediatric patients in the post-acute setting.

Design: Using medical claims data from the United States, we analysed GI intolerance events and hospital visits among paediatric patients (aged <18 years) receiving w-PB ETF for 1 year pre- and post-ETF initiation. These data were used to estimate resource use costs using a multivariate general linearized model, adjusted for age, sex, and Charlson Comorbidity Index score.

Results: The percentage of patients experiencing no GI intolerance events increased from 36% in the 1-year period pre-w-PB ETF to 53% in the 1-year period post-w-PB ETF initiation (p<0.001). The proportion of patients with at least one hospital inpatient visit decreased from 100% to 63% over the same period, and the mean number of inpatient visits per patient decreased from 16.9 to 12.5. Cost-modelling revealed that, after 180 days post ETF initiation, outpatient-, inpatient- and emergency room visits accounted for 69%, 28% and 3% of total estimated healthcare resource costs, respectively.

Conclusion: Whey protein PB ETF formulas are a valuable treatment option for paediatric patients with or at risk of malnutrition who show intolerance to standard ETF formulas. These formulas may help to reduce hospital in patient visits and associated costs.

Keywords: Enteral nutrition; Enteral feeding; Tube feeding; Diet elemental; Diet formula; Paediatrics; Gastrointestinal tract

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Introduction

Disease-related malnutrition (defined as under nutrition due to one or more diseases or injuries) in paediatric populations is a prevalent condition that negatively affects patient growth, development, and other clinical outcomes [1,2]. Disease-related malnutrition in paediatrics may be attributed to several key factors, namely decreased nutrient intake, nutrient loss, altered nutrient utilization, and increased energy expenditure [1]. Medical conditions that affect nutrient digestion, including short bowel syndrome, inflammatory bowel disease, and cystic fibrosis, can contribute to suboptimal nutrient absorption through factors such as excessive fluid loss, partial intestinal failure, or reduced delivery of digestive enzymes to the intestines [3-5].

In critically ill children, malnutrition can also adversely affect immune response, leading to poor wound healing, higher risk of infections, and complications of underlying diseases [2]. Disease-related malnutrition has also been linked to impaired quality of life in paediatric populations, with under nutrition and weight loss associated with worse physical and social functioning in children with cancer [6].

Enteral Tube Feeding (ETF) therapy may be used to help meet nutritional requirements in paediatric patients with inadequate volitional intake, and a range of formulas have been developed to support this objective [7,8]. Enteral nutrition in children with

disease-related malnutrition can be beneficial for gastrointestinal (GI) mucosal integrity and motility, improving nutritional intake and clinical outcomes [7,8]. For some paediatric patients requiring a long-term alternative or supplement to oral nutrition but who are otherwise able to receive care outside the hospital setting, Home Enteral Tube Feeding (HETF) is an option, maximizing the potential for patient and family autonomy while maintaining adequate nutritional intake [7]. It is estimated that approximately 189,000 paediatric patients receive HETF in the United States [9].

Standard polymeric ETF formulas contain complex nutrients such as whole proteins, which may not be optimal for digestion and adequate nutrient absorption in certain nutritionally high-risk patients [10-12]. Patients with intolerance to ETF formulas can experience multiple upper or lower GI symptoms, including nausea, vomiting, bloating, constipation, and diarrhoea [11,12]. GI intolerance can interrupt ETF, reducing the volume of enteral nutrition delivered, adversely affecting patient quality of life and exacerbating disease-related malnutrition [11,12]. Intolerance to enteral nutrition has been associated with increased length of hospital stay and increased mortality [13], while poor tolerance to a feeding regimen can prevent admission to an HETF program [14].

Peptide-Based (PB) ETF formulas, consisting of hydrolysed proteins and medium chain triglycerides, are designed to improve digestion and absorption and can help to reduce intolerance in patients receiving enteral nutrition who are at risk of or experiencing GI intolerance [10,12,15,16]. These formulas have proven to be efficacious and well-tolerated in various patients considered nutritionally at high-risk, including those with inflammatory bowel disease [17] as well as tube-fed children with developmental delays [16]. PB ETF formulas have demonstrated similar or improved tolerance, digestion, and nutrient assimilation compared with polymeric or amino acid formulas across multiple disease areas [10,12,15,16], as well as in patients in the post-acute care setting [16,18].

Despite the need for well-tolerated home enteral nutrition regimens, there are few published studies relating to the use of PB ETF formulas in paediatric patients in the post-acute care setting. The objective of this study was to describe the demographic, clinical and treatment characteristics of whey protein peptide-based (w-PB) ETF in paediatric patients 1 to <18 years of age in a post-acute care setting and assess the real-world tolerance and frequency of GI tolerance-related adverse events, before and after the initiation of w-PB ETF. Additionally, healthcare utilization and costs associated with the use of these formulas in this population are described.

Methods

This is a retrospective review of a single cohort of paediatric patients (1 to <18 years old) receiving w-PB ETF (Peptamen Junior® enteral nutrition formulas, Nestle Health Science, Bridgewater, NJ, USA) for any condition after hospital discharge during the period of Q1-2013 through Q4-2017. All patients meeting the criteria above and identified in the database were included in the study. The cohort of patients was observed for up to 1 year post-initiation of w-PB ETF following discharge in the post-acute care setting, and did not include patients using standard tube feeding formulas. In this study, the pre-index period is defined as the as the period of 1 year before the product (w-PB ETF) was taken for the first time (the index date), and the post-index period is defined as the period of 1 year after the index date. To the best of the authors' knowledge there is no data reporting the cost of healthcare utilization with standard formulas in the post-acute care setting.

Medical claims data were obtained from the Decision Resources Group Real World Evidence Data Repository US database [19], which links medical claims, prescription claims and electronic health records (EHRs) from government and commercial insurance plans to provide longitudinal patient-level data across both inpatient and outpatient facilities. The repository covers the majority of the US healthcare system, representing >300 million patients' medical and pharmacy claims, and electronic health record data. Claims and EHR data are sourced separately and linked together by a Health Insurance Portability and Accountability Act (HIPAA)-compliant encrypted patient key generated by a third party.

Demographic variables collected were patient age, sex, anthropometric data and clinical characteristics including medical diagnosis. Medical conditions included diseases of the digestive system, endocrine nutritional and metabolic diseases, diseases of the respiratory system and diseases of the circulatory system, among others. Evaluated outcomes (events) reported in the database were reported in either medical claims, pharmacy claims or EHRs and were recorded as binary (yes or no) values, as indicated by the caregiver or patient in the post-acute care setting. Intolerance is defined as the presence or absence of nausea/vomiting, diarrhoea, constipation, abdominal distension and gastric residual. Outcomes such as diarrhea, for example, are therefore not defined by a specific number of events (e.g. a minimum number of stools per day). Data on enteral feeding tube site, as well as timing and method of formula delivery is not available from the DRG database. Healthcare utilization data is descriptive and not designed to compare costs to other cohorts of tube fed patients.

Statistics

Univariate descriptive statistics, including means, standard deviations, and proportions were calculated for all study variables. Healthcare resource utilization and costs were estimated using multivariate general linearized models. To control for potential confounders, these models were adjusted for age at index, sex, and Charlson Comorbidity Index (CCI) score. Data were analyzed using a standard statistical software package (Stata, version 15.1, College Station, TX, USA).

Results

A total of 911 paediatric patients were eligible for inclusion in the study, with a mean (SD) age of 6.18 (4.42) years **(Table 1)**. Sex distribution was approximately equal, with 52.5% of patients being male. Of the patients in the study, 72% were insured with commercial insurers, 21% were insured through Medicaid and 6% were insured through Blue Cross providers. The remaining

patients in the study (<1%) had other or unknown health insurance arrangements.

	Patients receiving w-PB ETF (N=911)		
Number of intolerance events experienced	Pre-index (%)	Post-index (%)	p†
0	329 (36.1)	480 (52.7)	<0.001
1	278 (30.5)	232 (25.5)	0.04
2	183 (20.1)	127 (13.9)	0.001
3	93 (10.21)	52 (5.7)	0.001
4	27 (3.0)	19 (2.1)	0.2
5	1 (0.1)	1 (0.1)	1

Abbreviations: GI: Gastrointestinal; w-PB ETF, 100% whey protein peptide-based enteral tube feeding.

†Chi-square test (2 degrees of freedom), alpha=0.05 level of significance

Table 1: Number of patients experiencing GI intolerance events pre- and post-initiation of w-PB ETF.

The study population had a mean (SD) of 2.02 (1.12) Charlson comorbidities, as categorized according to the International Classification of Diseases (ICD) diagnosis codes [20]. The CCI quantifies an individual patient's disease burden and associated 1-year mortality risk. Patients had a mean (SD) CCI score of 2.65 (2.24).

The most frequently recorded underlying medical conditions in the patient population included diseases of the digestive system (31.28%), diseases of the nervous system (29.4%), diseases of the respiratory system (28.5%), endocrine nutritional and metabolic diseases (26.7%), and congenital malformations/deformations and chromosomal abnormalities (23.1%) **(Figure 1)**.

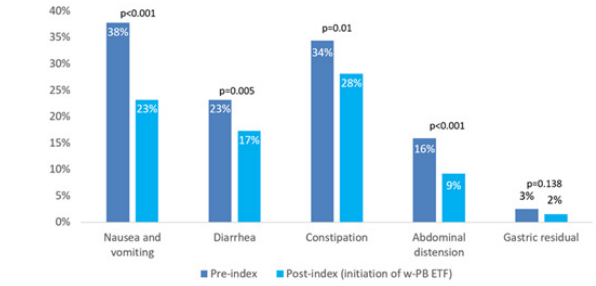

Figure 1: Prevalence of GI intolerance events pre- and post-initiation of w-PB ETF. **Abbreviations:** GI, gastrointestinal; w-PB ETF, 100% whey protein peptide-based enteral tube feeding.

Clinical patient characteristics (weight, height and body mass index [BMI]) were collected for up to 1 year prior to and 1 year after the initiation of w-PB ETF **(Table 2)**. A statistically significant increase in weight and height was observed for the paediatric patients between the pre- and post-index period, in line with expected growth for the age group.

Across the study population, the data showed a statistically significant improvement in GI tolerance after the initiation of w-PB ETF in all evaluated outcomes with the exception of gastric residual, where a numerical improvement was observed, while not statistically significant **(Figures 1 and 2)**. Comparing pre-index vs.post-index periods, the proportion of patients experiencing nausea and vomiting (37.8% vs. 23.2%, p<0.001), diarrhea (23.2% vs. 17.3%, p=0.005), constipation (34.4% vs. 28.1%, p=0.01), abdominal distension (15.9% vs. 9.2%, p<0.001), and gastric residual (2.5% vs. 1.5%, p=0.1) as an intolerance event decreased following initiation of w-PB ETF.

Across the study population, the percentage of patients experiencing one or more intolerance events also declined following initiation of w-PB ETF, from 63.9% of patients in the pre-index period to 47.3% of patients in the post-index period (p<0.001) **(Table 3 and Figures 2 and 3)**. As a result, there was a statistically significant increase in the number of patients receiving w-PB ETF experiencing no GI events during the post-index observation.

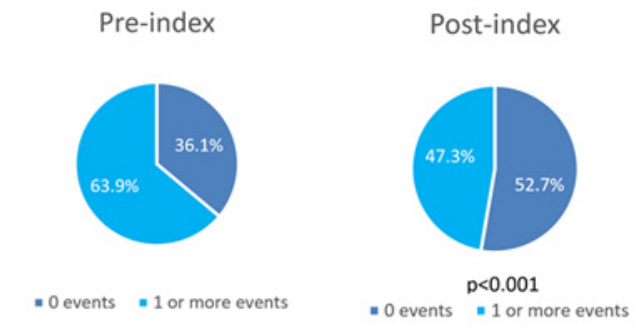

Figure 2: Percentage of patients experiencing >1 GI intolerance event pre- and post-initiation of w-PB ETF. **Abbreviations:** GI, gastrointestinal; w-PB ETF, 100% whey protein peptide-based enteral tube feeding.

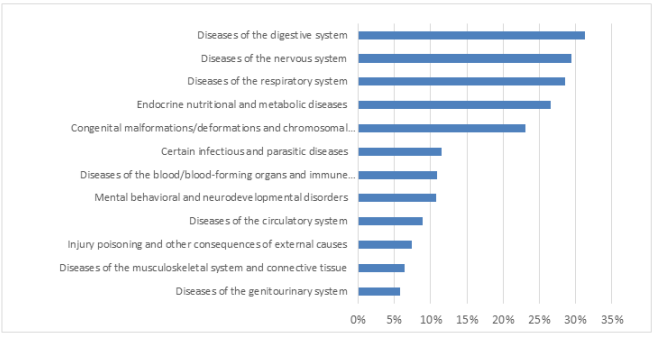

Figure 3: Clinical patient characteristics.

In the 1-year period prior to initiating w-PB ETF, 99.9% of patients recorded at least one inpatientvisit, with an average of 16.9 visits per patient **(Table 4)**. In the post-index period, there was a significant reduction in the percentage of patients recording at least one inpatient visit (99.9 vs. 62.8%), with a reduction in the mean number of visits per patient to 12.5 visits. In the first 30, 90, and 180 days following initiation of w-PB ETF, 28.8%, 43.8%, and 54.6% of patients, respectively, recorded at least one inpatient visit, while all patients at all-time points assessed had at least one outpatient visit, which is expected for this population.

Patients receiving w-PB ETF (N=911)										
	Cumulative pre-index		30 days post-index		90 days post-index		180 days post-index		Cumulative post-index	
Healthcare resource utilization										
	Patients with ≥ 1 visit (%)	Mean (SD) visits per patient	Patients with ≥ 1 visit (%)	Mean (SD) visits per patient	Patients with ≥ 1 visit (%)	Mean (SD) visits per patient	Patients with ≥ 1 visit (%)	Mean (SD) visits per patient	Patients with ≥ 1 visit (%)	Mean (SD) visits per patient
Inpatient visits†	910 (99.9)	16.88 (26.49)	262 (28.8)	3.82 (4.61)	399 (43.8)	7.02 (9.88)	497 (54.6)	9.59 (14.87)	572 (62.8)	12.51 (19.34)
Outpatient visits	905 (99.3)	40.00 (32.75)	910 (99.9)	5.51 (3.87)	911 (100)	13.77 (10.13)	911 (100)	24.36 (19.11)	911 (100)	40.06 (34.26)
Modelled healthcare resource use costs‡										
			Expected value (SE), USD		Expected value (SE), USD		Expected value (SE), USD			
			[95% CI]		[95% CI]		[95% CI]			
Inpatient visits§			1,155 (340)		2,004 (487)		2,872 (624)			
			[489–1,821]		[1,049–2,959]		[1,649–4,095]			
Outpatient visits			1,611 (97)		3,966 (213)		6,944 (363)			
			[1,422–1,801]		[3,550–4,383]		[6,233–7,656]			
Emergency room visits			165 (25)		242 (33)		302 (39)			
			[115–214]		[178–306]		[226–377]			
Total			2,931		6,212		10,118			

Abbreviations: CI: Confidence Interval; SD: Standard Deviation; SE:Standard Error; USD: United States Dollar; w-PB ETF, 100% whey protein peptide-based enteral tube feeding. †Includes hospital or ICU visits. Excludes the index visit. ‡Multivariate generalized linear model adjusted for age, sex, and CCI score. §includes hospital or intensive care unit visits.

Table 2: Healthcare resource utilization by pediatric patients receiving w-PB ETF.

Variables	Patients receiving w-PB ETF (N=911)
Age group	
0–5	468
6–10	265
11–17	178
Sex	
Male	478
Female	433
Payer	
Blue Cross	56
Commercial	657
Medicaid	191
Medicare	–
Others	6
Unknown	1

Abbreviations: w-PB ETF, 100% whey protein peptide-based enteral tube feeding.

Table 3: Patient demographic characteristics

Modelled healthcare resource use costs for paediatric patients on w-PB ETF are also presented in **Table 2**. Of the total 180-day per-patient estimated resource use costs of $10,118, 69% were attributed to outpatient visits, 28% to inpatient visits, and 3% to emergency room visits. The data highlights that outpatient visits represent the largest cost share, followed by inpatient visits, with only a small percentage of costs due to emergency room visits.

Discussion

This analysis assesses the association of GI symptoms before and after introduction of a w-PB ETF in a post-acute care setting, which indicates that w-PB ETF formulas may be used to optimize digestion and absorption of nutrients in the context of preventing

	Pre-index			Post-index		
	N	Mean (SD)	Median	Mean (SD)	Median	p†
Weight, lbs	50	47.01 (25.08)	41.95	51.09 (25.99)	44.55	<0.001
Height, in	41	42.28 (11.58)	41.34	45.04 (10.97)	44.49	0.001
BMI	31	16.67 (2.56)	16.48	16.93 (2.64)	16.72	0.431

Abbreviations: GI, gastrointestinal; SD, standard deviation; w-PB ETF, 100% whey protein peptide-based enteral tube feeding. †t-test, alpha=0.05 level of significance. †t-test, alpha=0.05 level of significance.

Table 4: Clinical patient characteristics.

or managing symptoms of feeding intolerance. The data in the home care setting shows that these formulas are most commonly prescribed to children and adolescents with medical conditions involving the digestive, nervous or respiratory systems, endocrine nutritional and metabolic diseases, and congenital malformations or chromosomal abnormalities.

w-PB ETF formulas have been shown to be more efficacious and better tolerated than intact-protein formulas for adult patients in the hospital setting, and both adult and paediatric patients in the post-acute care setting [10,11,15,16]. The data presented here show that nutritional intervention with w-PB ETF leads to a significant reduction in GI intolerance symptoms, compared with pre-index nutritional support (standard ETF or oral nutrition support). Following the initiation of w-PB ETF diets, more than half of the patients experienced no gastrointestinal intolerance events, compared with around one-third in the pre-index period.

Across the total study population, an increase in patient height was recorded over the two-year study period, in line with expected growth for the age group. Similarly, a trend towards weight gain was observed in the post-index period, indicating that w-PB ETF was a factor in the ability to support growth in paediatric patients.

Resource cost modelling of patients receiving w-PB ETF revealed that outpatient visits accounted for the largest share of healthcare resource costs, followed by inpatient visits. Only a small percentage of the total per-patient resource use costs were due to emergency room visits.

Due to the study's retrospective design and the nature of data queries, this study presents with a number of limitations. The data accessed was limited to that found in the Decision Resources Group Real World Evidence Data Repository US database. Patient data assessment was limited to those patients receiving w-PB ETF and no comparison with standard enteral nutrition formulas was established in clinical outcomes or healthcare cost. Data on the time and duration of feed delivery (24 hours vs. intermittent) and its potential association with GI symptoms is lacking from the database. Additionally, data on enteral feeding tube site and method of formula delivery is not available from the DRG database. Enteral feeding tube placement and method of formula infusion may be associated with gastrointestinal intolerance and as such, are considered potential biases [21].

Real-world data collected from routine clinical practice may be subject to coding errors, missing data and variations in reporting across clinical practices. These analyses were therefore limited by the fact that only patients with complete data were included, and the results may not represent those who disenrolled from a health plan within 12 weeks of therapy initiation and were lost to follow-up, or those not receiving necessary medical care due to a lack of insurance or resources. Due to the open network nature of the databases used in the current analysis, patients' continuous eligibility cannot be ascertained. Healthcare services provided by out-of-network providers therefore may not be captured by the databases.

These data provide valuable insight to clinicians and decision makers into the use of w-PB ETF formulas in the post-acute care setting, the paediatric populations receiving them and the associated improvement in GI tolerance symptoms. This work estimates and describes healthcare resource use and costs associated with the use of w-PB ETF formulas in the homecare setting, with the most relevant component of recorded cost of care being medical visits.

While the potential benefits of w-PB ETF formulas for paediatric patients with GI intolerance have been demonstrated [16], clear recommendations around their use are lacking. Further research and clinical and economic studies should therefore be performed in this subject area.

Conclusion

The use of w-PB ETF formulas is a valuable treatment option for enterally fed paediatric patients who experience or are at risk for gastrointestinal intolerance. Gastrointestinal intolerance with enteral feeding leads to frequent feeding interruptions and a potential reduction in delivery of daily protein and energy, which may lead to malnutrition. Malnutrition is associated with poor clinical outcomes, including longer hospitalizations, higher rates of infection and increased mortality. In children and adolescents, the use of w-PB ETF formulas is associated with improved GI tolerance, with more than one-half of paediatric patients experiencing no intolerance events following initiation of a w-PB diet. As expected, all paediatric patients receiving w-PB ETF reported at least one outpatient visit in the post-index period, while in-hospital visits were much less common. After the first 30 days following ETF initiation, outpatient visits represented the largest share of healthcare resource costs, with only a small proportion of the resource use costs due to emergency room visits.

Conflicts of Interest and Source of Funding

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