The use of extensively hydrolysed and amino acid feeds beyond cow's milk allergy – a national survey

Short title: Specialist feeds beyond cow's milk allergy

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Abstract

Background

Extensively hydrolysed formulas (EHFs) and amino acid formulas (AAFs) with proven hypoallergenicity are used for children suffering from cow's milk allergy, when breast milk is not available. However, these feeds are often used in other medical conditions where tolerance and absorption of whole protein is affected, frequently without assessment of efficacy. This practice survey assessed the use of these feeds in paediatric conditions other than CMA; aiming to describe the population, growth parameters and micronutrient status.

Methodology

Four National Health Service tertiary paediatric centres participated in this practice survey. Inclusion: children between 0-18 years, consuming >25% of their estimated energy requirements of an EHF/AAF for any condition other than allergic disease. Anonymised data was collected: (i) descriptive information (ii) indications (iii) type and route of feeding (iv) growth status and nutritional deficiencies (v) medication and vitamin and mineral supplementation.

Results

One hundred-and-ninety-one children were included with a median age of 19 months [IQR: 4 to 63]. Seventeen percent (33/191) were on AAFs and 83% (158/191) on EHFs. The feeds were commonly used in cancer 26% and critical illness 31%. The majority (73%) of children had enteral feeds via a nasogastric tube. Nutritional biomarkers were performed in 29% of children and 83% were on a vitamin or mineral supplement.

Conclusions

This practice survey found that EHFs and AAFs were used in a variety of medical conditions. Indications for feed choice varied, and evidence-based research supporting the use was scarce. Whilst awaiting further research, children on these types of feeds should have regular nutritional monitoring.

Introduction

Breast milk represents the optimal source of nutrition for all infants, including those with medical conditions.(1) However, for certain conditions, when breast milk is not available or insufficient, specialist feeds may be recommended, which include extensively hydrolysed formulas (EHFs) and amino acid formulas (AAFs).(2) When these feeds are intended for the management of cow's milk allergy (CMA) they have to be assessed according to the criteria by the European Academy for Allergy and Clinical Immunology [EAACI](3, 4)and the American Academy of Paediatrics [AAP] (5) to be tolerated by 90% of children at a 95% CI with a challenge proven CMA. In addition manufacturers need to also demonstrate safety and efficacy with regards to normal physical growth in infants.(6) However, due to the characteristics of EHF and AAF, including peptides, amino-acids, glucose polymers and varying levels of medium chain and long chain fatty acids, they are also commonly used in the nutritional support of a variety of acute and chronic childhood illnesses affecting the gastrointestinal tract and are chosen to manage symptoms of gastrointestinal dysmotility,(7, 8) malabsorption,(9-11) drug induced mucositis (12) and feed intolerance,(13) using a wide variety of definitions to characterise an intolerance to a standard feed.(14) The evidence to recommend the use of AAFs and EHFs in many of these conditions is limited,(14-16) in addition to lack of defined criteria for the assessment and monitoring of tolerance, efficacy or adequacy. Nutritional requirements differ depending on the clinical diagnosis for both macro and micronutrients, complicated further by the feeding route (i.e. nasogastric) and polypharmacy.(14) This survey was therefore aimed at describing current clinical practice, including when, how and for whom these feeds were used, to better inform future research and guidelines on use of AAFs and EHFs beyond food allergy.

Methods

In the United Kingdom (UK) 20 tertiary National Health Service centres are responsible for the majority of complex paediatric patients. In order to include a wide range of diagnostic categories, a spread across the UK was considered desirable, so for this practice survey a convenience sample of eight centres with specialist paediatric dietitians was selected, of which four agreed to participate. These were University Hospital Southampton Hospital NHS Foundation Trust, University Hospitals Bristol NHS Foundation Trust, Royal Alexandra Children's Hospital, Brighton University Hospital NHS

Trust and King's College Hospital NHS Foundation Trust in London. These centres provide specialist regional services to a variety of children with complex diseases including, children with congenital heart disease requiring surgery, critically ill children, infants with gastrointestinal disorders including congenital or acquired intestinal failure, and those with neurodisabilities, cholestatic liver disease and various cancers.

NHS Health Research Authority waived the need for consent as this was classified as a practice survey. An anonymised excel spreadsheet (Version 2016) was developed by the lead researcher and statistician, and circulated to the four centres with iterative changes until all centres agreed on both the survey data collection sheet and information required. Data was collected from February to October 2018. For this survey, no patient identifiable information was collected and no additional tests, interventions or information was required outside of what was recorded in medical notes at routine clinic appointments or during hospital stays. Data collection was designed to capture information in the following domains: (i) descriptive information on children prescribed EHFs/AAFs (ii) indications for use of EHFs/AAFs (iii) type of feed including feed concentration and route of feeding (e.g. oral, nasogastric) (iv) growth status, (v) nutritional deficiencies as measured by biomarkers and (vi) medications and vitamin and mineral supplementation. Due to the similarities in protein hydrolysis, glucose polymer and lipid content of semi-elemental and extensively hydrolysed feeds for the purpose of this study all semi elemental feeds, as long as they were extensively hydrolysed, were grouped under EHFs and all elemental feeds under AAFs (Table 1). EHFs and AAFs included did not required hypoallergenicity testing for suitability for the management of CMA as this survey excluded patients with a CMA.

The following inclusion and exclusion criteria were used:

Inclusion criteria:

1. Children between 0-18 years consuming an extensively hydrolysed formula (EHF) (17) or amino acid formula (AAF) as part of their enteral nutrition (including oral and/or tube feeding) providing >25% of estimated energy requirements for any condition other than allergic disease

Exclusion criteria

1. Children with confirmed IgE or non-IgE mediated CMA or multiple food allergies which resulted in the prescription of EHFs or AAFs
2. Children on an elimination diet to confirm suspected non-IgE mediated CMA or multiple food allergy
3. Confirmed (by endoscopy with biopsy) eosinophilic gastrointestinal disease (EGID)

Dietitians from survey centres received a protocol to reflect the survey spreadsheet, with further details on data collection and also describing parameters in more detail to reduce data collection bias (Table 1).

Statistical Analysis

Statistical analysis was performed using R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are presented as medians with interquartile ranges and categorical variables as frequencies and percentages. The Mann-Whitney U test was used to examine the differences in z-scores between groups including: AAF vs EHF, gender, time on formula (</> 3 months), medications and symptoms. Pearson's chi square test with continuity corrections or Fisher's Exact test were used, where appropriate, to compare rates of children in outpatient/inpatient setting, rates of improved growth, assess vitamin/mineral deficiencies and vitamin/mineral supplementation between children on either EHFs or AAFs.

Multiple logistic regression was used to investigate the probability of being prescribed an AAF versus EHF based on diagnoses/symptoms, prematurity, time on the feed, anthropometric measures with adjustment for potential confounders of age and gender. Only variables that had a statistically significant impact are reported in this study. All tests were two-tailed and significance level was set to 0.05.

The WHO Anthro (< 5 years of age) and Anthro Plus (> 5 years of age) software was used to convert growth parameters into z-scores and malnutrition was expressed as per WHO definitions (Table 2).(18) For ex-preterm infants z-scores were corrected using the Fenton growth charts for preterm infants.(19)

Results

Subjects

One hundred-and-ninety-one children from the four centres (Table 3) were included: 71% (136/191) inpatients and 29% (55/191) outpatients. Fifty five percent (106/191) were male and 21% of children (40/191) were born preterm (< 37 weeks gestational age). The median age at the time of data collected was 19 months [IQR: 4 to 63] and median gestational age of ex-preterm infants at birth was 30 weeks gestational age [IQR: 26 to 33.1]. With regards to prescribed feeds, 17% (33/191) were on an AAF and 83% (158/191) on an EHF. Most of the children on an EHF in this practice survey [36%

(57/158)] were critically ill on a PICU, where half of children were admitted following planned cardiac surgery for congenital heart disease or as a result of acute admission for respiratory failure. The standard practice of this PICU (University Hospital Southampton Hospital NHS Foundation Trust) was to provide nutrient-energy dense whey based EHFs to all infants/ children on admission.(20) The second most common reason for use of EHFs was a diagnosis of cancer [25% (39/158)], including neuroblastoma, osteosarcoma, rhabdomyosarcoma and acute myeloid leukaemia) (Table 4).

This practice survey found no significant difference (p = 0.99) in the proportion of prescribed AAFs for an inpatient 17.6% (24/136) or outpatient 16.4% (9/55). In 95% of cases, feeds were reconstituted according to manufacturer recommendations. Only 5% (9/191) of cases had the feed reconstituted at a higher concentration and 1% (1/191) at a lower concentration. In 60% (114/191) of the population surveyed, EHFs and AAFs contributed > 75% of energy requirements (Figure 1).

Seventy three percent of patients (139/191) received nasogastric tube feeds and 14% had a percutaneous gastrostomy (Table 5). In addition, 10% (20/191) of feeds were used to supplement an oral diet, the majority of which were on EHFs [80% (16/20)]. In 11% (21/191) of cases, these feeds were used (via a variety of enteral routes) to supplement parenteral nutrition, of which 52% [(11/21)] were prescribed an AAF.

Most children were on either EHF or AAF for 1-4 weeks (37%). However, in 29% and 7% of recruited patients these feeds were used for 3-12 months and > 12 months respectively. A heat map stratified by reason for admission and time on the feed, found that children on the PICU, where 50% of patients had a planned admission for cardiac surgery, were on the feed for 1-4 weeks and those remaining on these feeds for a longer period of time (3-12 months) were those with cancer and gastrointestinal diseases (Figure 2).

Indications for using an EHF and AAF

When assessing the indications for using an EHF or AAF, 32% responded that the use of these feeds was part of their standard practice protocol in their unit and 29% used these feeds when children were deemed not to tolerate standard whole protein paediatric feeds, due to vomiting 12%, congenital/acquired gastrointestinal pathology 7%, malabsorption 5%, diarrhoea 3%, reflux 1% and constipation 1%. In addition, 10% marked “other” reasons for using an EHF or AAF. Figure 3, summarises the combined indications for AAF and EHF into a heat map (Figure 3). Outside of PICU, these feeds were more commonly used in cancer and gastrointestinal diseases, including congenital/acquired gastrointestinal pathology, in addition to children with liver disease.

Variables that significantly increased the likelihood of children being on either EHFs or AAFs were assessed using multiple logistic regression analysis and results are reported as percentage probability in Table 6. Diarrhoea, vomiting or malabsorption as a single variable increased the use of an EHF, but in combination and increased numbers, in particular in association with male gender, the higher the probability of using an AAF.

Nutritional Status

The median weight-for-age z-score (21) (21) for the population was -1.2 [IQR:-2.1 to -0.1], height-for-age z-score (HAZ) -1.3 [IQR: -2.7 to 0] and weight-for-length/height (WHZ) z-score was -0.2 [IQR:-1-1 to 0.8]. Moderate malnutrition, as defined by a z-score <-2 z scores,(18) was present in 29.8% for WAZ (underweight), 10.7% for WHZ (wasted), and 36.4% for HAZ (stunted). When malnourished children were stratified by diagnosis, we found that children with cardiac disorders and ex-preterm infants both in PICU as well as on the wards particularly had poor growth parameters as highlighted in Table 7.

No statistical difference was found in WAZ (p = 0.97), HAZ (p = 0.54) and WAZ (p=0.51) between children on an EHF versus an AAF. However, children who were on these feeds (EHF or AAF) for >3 months (compared to < 3 months) had an improved WHZ z-score: 0.0 [IQR:-0.5 to 0.9] vs. -0.3 [IQR:-1.4 to 0.6], (p=0.02). The presence of reflux (p=0.04) and malabsorption (p=0.003) had a statistically significant negative impact on WAZ and HAZ respectively.

Vitamins, minerals and medications

From the patients surveyed, 83% (159/191) were on either a single vitamin/mineral supplement or a multivitamin and mineral supplement (Table 8). However, only 29% (55/191) of children vitamin and mineral status was assessed during the study period. These assessments were more commonly performed in children on an AAF [45% (15/33)] than an EHF [25% (40/158)]. Low vitamin D status was most frequently documented (5%), followed by zinc, vitamin A and phosphate each at 3%. Numbers were too small to perform further statistical analysis to assess any association of vitamin and mineral deficiencies on either EHF/AAF.

In this practice survey, 30.4% (58/191) were prescribed one medication, 29.8% (57/191) two and 21% (41/191) three or more medications. Forty percent of children (77/191) were prescribed a proton pump inhibitor (PPI), followed by anti-emetics [30% (58/191)] and diuretics [28% (53/191)] (Table 8). The only medication that had an impact on growth was PPI use, which was negative for both WAZ (p=0.02) and HAZ (p=0.001).

Discussion

This practice survey, set out to describe the use of EHFs and AAFs in children with various diagnoses to establish when, how and for whom these feeds were used. We found that 83% of children were prescribed an EHF and only 17% an AAF, also reflective of practice for CMA, where AAF is reserved for the more severe cases.(22) The most common diagnostic category where these feeds were used were in critically ill children, followed by cancer and gastrointestinal diseases. A higher percentage (39%) of children with gastrointestinal diagnoses (which included congenital gastrointestinal pathology) were on an AAF, followed by children with cancer diagnoses, prematurity and liver disease. Children on PICU tended to stay on either of these feeds for less than 4 weeks, but those with cancer, gastrointestinal diseases and congenital cardiac disorders remained on either EHF or AAF for a longer period of time. This reflects the nature of the diagnosis and course of disease.

The most common clinical motivation for using either EHFs or AAFs in conditions other than CMA, is to improve perceived feed intolerance, which may include vomiting, raised gastric residual volumes, abdominal distention, diarrhoea and constipation.(14) Our findings indicate that poor tolerance of standard feeds, reflected by vomiting and diarrhoea are common reasons for choosing an EHF or AAF, when not using these feeds as standard practice. Although feeding intolerance is well documented in many paediatric diagnoses,(8, 23-25) quantifying the severity or frequency of intolerance that requires a feed change is ambiguous and varies between centres and diagnoses. In our practice survey, an energy-dense whey-based EHF was used by one centre as routine practice in their young critically ill children. Marino *et al* (20) showed lower incidence of feed intolerance, such as vomiting, high gastric residual volumes and diarrhoea in critically ill children, whilst meeting prescribed energy requirements when using these feeds. This participating centre, admitted 50% of children for planned cardiac surgery. Dysmotility is not only well documented in children with this diagnosis,(26) but in critically ill children *per se*.(23) Nutritional characteristics of the EHF, including the type of protein, the extent of hydrolysis, the osmolality and fat content, pre and probiotics may have all contributed to this positive finding.

Children with cancer commonly have gastrointestinal symptoms including diarrhoea, abdominal pain and vomiting related to both the treatment, as well as the the underlying diagnosis.(12) The evidence for either EHF or AAF to alleviate these symptoms to improve delivery of nutrients is limited and mainly consensus based.(12) Chemotherapy frequently induces intestinal mucositis, with morphological changes including the flattening of the villi, villus atrophy and down-regulation of the

enterocyte- specific gene expression that is crucial for degradation and absorption of nutrients.(27) The inflammation of the gastrointestinal tract can impact on the brush border, impacting both on the absorption of protein as well as sugars.(28) There may therefore be a role for using either EHF/AAF in paediatric cancer when gastrointestinal symptoms occur, but to date, limited clinical trials exist, supporting their routine use in this cohort.

In complex gastrointestinal disorders both EHF and AAF use is commonplace. Almost 50% of our gastrointestinal cohort, were on these feeds due to not tolerating standard protein feeds and 24% had congenital gastrointestinal pathology. The use of AAF was higher in this diagnostic category, which was also highlighted by recent publications on micronutrient adequacy in children with complex gastrointestinal disease.(29, 30) In spite of its frequent use in gastrointestinal disorders including short gut syndrome, there are only a limited number of studies, often of poor quality,(31) evaluating EHFs/AAFs in a variety of gastrointestinal disease. (16, 32, 33) The motivation for use in gastrointestinal disorders is often based on the different gastric emptying kinetics of whey versus casein,(34) peptides and/or amino acids which have different absorption patterns, type of fat and lactose content. EHF/AAF are a composite of nutrients, which potentially impact on gastrointestinal tolerance, not only as a single nutrient but in combination. In addition, the heterogeneity of gastrointestinal diagnoses and medical management, makes it really difficult to establish the efficacy of these feeds.

The use of EHFs for their medium chain triglyceride (MCT) content is common in children with cholestasis,(10) although there is little evidence of any beneficial effects of MCT on growth or other outcomes.(35) Unlike long chain triglycerides, the partial water solubility of MCT enables direct absorption into the portal system without the need for bile flow, which may be impaired or absent in cholestasis.(36) If liver disease progresses and children develop cirrhosis and portal hypertension the result may be intestinal changes such as mucosal oedema resulting in diarrhoea.(11) There may therefore, be a benefit to using EHFs if diarrhoea is suspected to be related to portal hypertension,(11) however, to date there is no convincing evidence for the routine use of an EHF in liver disease.

This practice survey also included children with other diagnoses. Within this category, most notably are children with neurodisabilities where dysmotility is well described.(37, 38) The current guidelines from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition on the nutritional management of children with neurodisabilities, suggest trialling whey-based feeds in

children with symptoms of gastro-oesophageal reflux.(25) This suggestion followed studies by Brun *et al* (7, 39) and Savage *et al* (40) on improved gastric emptying with whole whey protein in children with cerebral palsy. Khoshoo *et al* (41) also found that energy dense partially hydrolysed whey feeds were better tolerated in this population. However, the aforementioned studies assessed tolerance for partially or whole whey protein, questioning the use of either AAF or EHF in children with neurodisabilities in particular as their macro and micronutrient requirements are often very different.

Almost 10% of children in this practice survey were acutely malnourished and almost 40% had persistent malnutrition. This level of malnutrition was much higher than reported in the study by Hecht *et al* (42) on European hospitalized children where 7.9% were stunted and 5% had a BMI < -2 z-score. However, this finding is in line with prevalence of malnutrition associated with chronic diseases such as congenital heart disease.(43) There was no difference in the growth parameters between AAF and EHF, but pooled data indicated that children who remained on either feed for > 3 months had better WHZ. Data from this practice survey also found that more than 70% of our population received enteral tube feeding, which is usually started when oral intake does not meet nutritional requirements, in particular in the presence of malnutrition (which was common in our cohort) and during admission to PICU. We believe that this high prevalence of tube feeding in our practice survey reflects the medical complexity of children on these feeds and is similar to recently published studies on AAF use in children with complex gastrointestinal disease.(29) Furthermore, many of these children are on multiple medications, impacting on the ability to utilise and assimilate nutrients from feeds. Our survey has found a negative association between the PPI and some of the growth parameters. We cannot infer causality, however, as it is known that PPI and other medications impact on the bioavailability of nutrients essential for growth, (44,45) further work is required to understand the association between various medications and feed tolerance and growth.(44, 45)

We also collected data on vitamin and mineral status, where available. Recent publications have highlighted concerns in regards to phosphate levels in children with complex gastrointestinal conditions receiving an AAF as a sole source of nutrition.(29, 30) In only 29% of children, nutritional biomarkers for vitamin and minerals status were taken, although 36% were on these feeds for longer than three months. Current British Association for Parenteral and Enteral Nutrition (BAPEN) guidelines for tube fed patients in the UK suggest that electrolytes, B12, folate and a full blood count

are assessed until stable and after this when clinically indicated (no time interval suggested).(46) Assessment of zinc, copper and selenium levels are recommended only when clinically indicated (no time interval suggested) and vitamin D should be performed every 6 months.(46) In the light of the limited data on nutritional adequacy when using either EHF/AAF in children with complex disease, it seems prudent that children who are on these feeds for > 3 months, are monitored at least to the standard set by BAPEN.

This practice survey has many limitations. The most notable is the bias introduced by the selection of the population. Only eight centres were approached from across the UK and only four of these volunteered to take part and one centre contributed more than half of the patients in this survey. We can therefore not generalise our findings to all paediatric centres in the UK nor all medical conditions where these feeds may be used. In addition, our survey does not account for the severity of disease, which varies within each category recruited for this survey and may have affected choice of feed. Although we provided definitions for diarrhoea, we did not clearly define malabsorption disorders, which may have influenced our results on indications for use of EHFs and AAFs. As this was a survey, we also did not control for growth measurement accuracy and also the accuracy of nutritional biomarkers. Despite these limitations, this is the first survey to report the use of AAF and EHF in clinical practice and we believe, contributes useful information for future studies.

Conclusion

This practice survey found that EHFs and AAFs are commonly used in a variety of children with complex medical conditions, most of them receiving feeds via the enteral route. Our survey found that the primary aim of using either EHF or AAF was to improve tolerance, which may be as part of standard practice. The majority of children on these feeds are fed enterally and are on multiple medications that may impact on the bioavailability of nutrients but are not commonly monitored for vitamin and mineral status. In the light of limited evidence supporting routine use of these feeds in a variety of conditions, further research is required, on better defining composition of feeds suitable for conditions where whole protein feeds are not tolerated, including safety, indications and the cost-benefit. In the meantime, healthcare professionals need to be aware that children on either EHF/AAF with complex conditions on multiple medications should be monitored regularly to ensure adequate growth including micronutrient status.

Transparency Declaration

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported. The reporting of this work is compliant with STROBE guidelines. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

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Table 1: Feeds that were included in this survey

Extensively hydrolysed (semi-elemental) feeds	**Amino Acid (elemental) feeds**
Nutramigen (Mead Johnson)	Neocate LCP (Nutricia)
Pregestimil (Mead Johnson)	Neocate Junior (Nutricia)
Similac Alimentum (Abbott)	E028 (Nutricia)
Althera (Nestle)	PurAmino (Mead Johnson)
Aptamil Pepti (Nutricia)	Alfamino (Nestle)
Aptamil Pepti Junior (Nutricia)	
Infatrini Peptisorb (Nutricia)	

Table 2: Data collected on growth and indications for feed

Parameter	Description
Diagnostic category	Oncology and haematology (including bone marrow transplant) Paediatric Intensive Care (PICU) Congenital heart disease –pre/peri-operatively Gastrointestinal disorders including: Gastroschisis, volvulus, pseudo-obstruction, duodenal atresia, jejunal atresia, necrotising enterocolitis (NEC), intestinal failure – congenital or acquired including short bowel syndrome – defined as bowel length of < 40 cm[20] Cholestatic liver disease Prematurity: < 37 weeks gestational age Other: neurodisabilities, chromosomal disorder
Age	Converted into weeks and days Corrected for prematurity
Current growth	Weight in kg Length/height in cm/m Head circumference in cm < 2 year of age Converting data to z-scores using WHO Anthro and Anthro Plus software. <37 weeks of gestational age, Fenton Growth calculator was used(19)

Malnutrition	Defined as per WHO guidelines: <-2 z-score moderate malnutrition <-2 z-score Weight for Age (21) - underweight <-2 z - score Weight for Height (WHZ) – wasted <-2 s-score Height for Age (HAZ) - stunted
Indication for feed use	Malabsorption disorder Diarrhoea – defined as Bristol stool chart > 6 and stoma output > 30 ml/kg Gastroesophageal reflux disease – physician diagnosed Constipation – using criteria from the NICE guidelines Feed intolerance – defined as presence or worsening of diarrhoea/constipation and/or vomiting/ abdominal distention on current formula Conjugated jaundice
Feed information	AAF (including elemental feeds) EHF (including all semi-elemental feeds that are also extensively hydrolysed) Concentration of feeds: diluted, standard (as per company guidelines) or concentrated or ready to use nutrient-energy dense
Route of feeding	Oral Nasogastric feeding tube Nasojejunal feeding tube Gastrostomy Jejunostomy Parenteral nutrition
Nutritionally related medication and vitamins/minerals	Antacid medication (i.e. proton pump inhibitors and other antacids) Diuretics Antiemetics Immunomodulatory Anticonvulsants Gastric emptying agents Corticosteroids Laxatives Chemotherapy Vitamin supplement Vitamin and mineral supplement Mineral supplement Omega-3 fatty acid supplementation
Presence/ absence of vitamin or mineral deficiencies	Based on available nutritional biomarkers and judged by local cut-offs

Table 3: Numbers of patients contributed by individual centres

Hospital	Patients Number	Percentage
Brighton University Hospital NHS Trust	23	12%
Bristol University Hospitals NHS Foundation Trust	25	13%
King's College Hospital NHS Foundation Trust	33	17%
Southampton University Hospital NHS Foundation Trust	110	58%

Table 4: Pooled data of diagnostic category, stratified by use of either EHF or AAF

Diagnostic Category	Overall Percentage	EHF	AAF
PICU ALL	31% (60/191)	36% (57/158)	9% (3/33)
PICU / Other	24% (45/191)	27% (42/158)	9% (3/33)
PICU / Cardiac	6% (11/191)	7% (11/158)	0% (0/33)
PICU / Prematurity	2% (4/191)	3% (4/158)	0% (0/33)
Cancer	26% (49/191)	25% (39/158)	30% (10/33)

GI disease	18% (34/191)	13% (21/158)	39% (13/33)
Liver	9% (18/191)	9% (15/158)	9% (3/33)
Other*	6% (12/191)	6% (10/158)	6% (2/33)
Prematurity	5% (10/191)	5% (8/158)	6% (2/33)
Cardiac disease	4% (8/191)	5% (8/158)	0% (0/33)

*Neurodisabilities, bone marrow transplant, High Dependency Unit, Long Term Ventilation and chromosomal disorders

Table 5: Feeding route stratified by EHF and AAF

Route of Feeding	overall percentage	EHF	AAF
Oral	10% (20/191)	80% (16/20)	20% (4/20)
Nasogastric tube	73% (139/191)	82% (114/139)	18% (25/139)
Nasojejunal tube	2% (4/191)	75% (3/4)	25% (1/4)
Percutaneous gastrostomy	14% (27/191)	89% (24/27)	11% (3/27)

Percutaneous jejunostomy	1% (1/191)	100% (1/1)	0% (0/1)
* Supplemental to parenteral nutrition	11% (21/191)	48% (10/21)	52% (11/21)

Table 6: Variables significantly contribute towards the likelihood of being on either AAF or EHF

Variable 1	Variable 2	Variable 3	Variable 4	Probability of being on an EHF expressed in %	Probability of being on an AAF expressed in %

			Diarrhoea	95%	5%
	Malabsorption			94%	6%
		Vomiting		93%	7%
	Malabsorption		Diarrhoea	85%	15%
Male			Diarrhoea	84%	16%
		Vomiting	Diarrhoea	84%	16%
Male	Malabsorption			79%	21%
	Malabsorption	Vomiting		79%	21%
Male		Vomiting		78%	22%
	Malabsorption	Vomiting	Diarrhoea	60%	40%
Male		Vomiting	Diarrhoea	58%	42%
Male	Malabsorption	Vomiting		50%	50%
Male	Malabsorption	Vomiting	Diarrhoea	28%	72%

Table 7: Percentage of children with growth parameters of less than -2 z-scores stratified by diagnostic category

Diagnostic category	WAZ	HAZ	WHZ	BMI
PICU ALL	27%	37%	11%	24%
PICU / Cardiac	44%	55%	0%	9%
PICU / Other	19%	31%	9%	26%
PICU / Ex-preterm	75%	50%	50%	50%
Cardiac disease	63%	88%	14%	25%
GI disorders	30%	36%	13%	21%
Cholestatic liver disease	47%	60%	21%	33%
Cancer	11%	11%	0%	9%
Other	33%	63%	0%	13%
Prematurity < 37 weeks	56%	57%	17%	29%

Table 8: Vitamin and/or mineral supplementation

	Overall Percentage	EHF	AAF
Multivitamin	44% (84/191)	48% (76/158)	24% (8/33)
Vitamin D	15% (28/191)	12% (19/158)	27% (9/33)
Iron	14% (27/191)	12% (19/158)	24% (8/33)
Multivitamin and mineral	7% (14/191)	7% (11/158)	9% (3/33)
Calcium	1% (2/191)	1% (2/158)	0% (0/33)
Zinc	2% (3/191)	1% (1/158)	6% (2/33)
Probiotic	1% (1/191)	1% (1/158)	0% (0/33)
Omega 3 fatty acids	0% (0/191)	-	-

Table 9: Medication use stratified by EHF and AAF

	Overall Percentage	EHF	AAF
Proton pump inhibitor	40% (77/191)	40% (63/158)	42% (14/33)
Anti-emetics	30% (58/191)	30% (47/158)	33% (11/33)
Diuretics	28% (53/191)	33% (52/158)	3% (1/33)
Chemotherapy	25% (48/191)	24% (38/158)	30% (10/33)
Ranitidine	15% (28/191)	15% (23/158)	15% (5/33)
Gastric Emptying Agents	15% (29/191)	13% (21/158)	24% (8/33)
Laxatives	13% (25/191)	14% (22/158)	9% (3/33)
Corticosteroids	8% (16/191)	9% (14/158)	6% (2/33)
Immunomodulatory medication	7% (14/191)	6% (10/158)	12% (4/33)
Anti-convulsant	4% (7/191)	4% (6/158)	3% (1/33)

Box 1: Key learning points for healthcare professionals

- When an EHF or AAF is considered for a child that does not tolerate whole protein feeds, consider the reasons for the change of feed and published data specific to that condition.
- Consider nutritional content of the feed and whether it will meet the nutritional needs for a child with that specific condition.
- Children who do not tolerate standard feeds often have complex conditions that affect multiple organs and are on polypharmacy, which may impact on nutritional adequacy.
- Ensure that the child on either EHF or AAF is regularly monitored for both growth and targeted micronutrients.
- Audit practice of use of EHF and AAF outside of food allergy.
- Initiate research on nutritional adequacy of use of EHF and AAF outside of food allergy