

RESEARCH PAPER

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

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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 cow's milk allergy; aiming to describe the population, growth parameters and micronutrient status.

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

Results: One hundred-and-ninety-one children were included with a median age of 19 months (interquartile range 4–63]. Seventeen percent (33/191) were on AAFs and 83% (158/191) were on EHFs. The feeds were commonly used in cancer for 26% and in critical illness for 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. 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% confidence interval (CI) with a challenge proven

CMA. In addition manufacturers need to also demonstrate safety and efficacy with regard to normal physical growth in infants ⁽⁶⁾. However, as a result of 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 EHF 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⁾. The present survey therefore aimed to describe 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 EHF beyond food allergy.

Materials and methods

In the UK, 20 tertiary National Health Service centres are responsible for the majority of complex paediatric patients. To include a wide range of diagnostic categories, a spread across the UK was considered desirable, and 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, comprising 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 because this was classified as a practice survey. An anonymised EXCEL spreadsheet (version 2016; Microsoft Corp., Redmond, WA, USA) 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 were 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 the 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 EHF/AAF; (ii) indications for use of EHF/AAF; (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. As a result of similarities in protein hydrolysis, glucose polymer and lipid content of semi-elemental and extensively hydrolysed feeds, for the purpose of the present study, all semi-elemental feeds (as long as they were extensively hydrolysed) were grouped under EHF and all elemental feeds under AAFs (Table 1). EHF and AAFs included did not require hypoallergenicity testing for suitability for the management of CMA because this survey excluded patients with a CMA.

Inclusion criteria

Children between 0 and 18 years consuming an EHF ⁽¹⁷⁾ or 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 immunoglobulin (Ig)E or non-IgE mediated CMA or multiple food allergies which resulted in the prescription of EHF or AAFs

Table 1 Feeds that were included in this survey

Extensively hydrolysed (semi-elemental) feeds	Amino acid (elemental) feeds
Nutramigen LGG (Mead Johnson, Uxbridge, UK)	E028 (Nutricia Medical Trowbridge, UK)
Pregestimil Lipil (Mead Johnson, Uxbridge, UK)	PurAmino (Mead Johnson, Uxbridge, UK)
Similac Alimentum (Abbott Laboratories, Maidenhead, UK)	Alfamino (Nestle Health Science, Vevey, Switzerland)
Althera (Nestle Health Science, Vevey, Switzerland)	Neocate LCP (Nutricia Medical Trowbridge, UK)
Aptamil Pepti (Nutricia Medical Trowbridge, UK)	Neocate Junior (Nutricia Medical Trowbridge, UK)
Aptamil Pepti Junior (Nutricia Medical Trowbridge, UK)	
Infatrini Peptisorb (Nutricia Medical Trowbridge, UK)	

- 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
- 4 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 (IQRs) 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 versus EHF, gender, time on formula (</> 3 months), medications and symptoms. Pearson's chi-squared test with continuity corrections or Fisher's exact test were used, where appropriate, to compare rates of children in outpatient/inpatient setting and rates of improved growth, as well as assess vitamin/mineral deficiencies and vitamin/mineral supplementation between children on either EHF 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, and anthropometric measures with adjustment for potential confounders of age and gender. Only variables that had a statistically significant impact are reported. $P < 0.05$ (two-tailed) was considered statistically significant.

ANTHRO (<5 years of age) and ANTHRO PLUS (>5 years of age) software [World Health Organization (WHO), Geneva, Switzerland] was used to convert growth parameters into *Z*-scores and malnutrition was expressed in accordance with 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 = 4–63] and median gestational age of ex-preterm infants at birth was 30 weeks gestational age (IQR = 26–33.1). With regard to prescribed feeds, 17% (33/191) were on an AAF

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 years of age Converting data to <i>Z</i> -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 <i>Z</i> -score moderate malnutrition <–2 <i>Z</i> -score weight for age (21) – underweight <–2 <i>Z</i> -score weight for height (WHZ) – wasted <–2 <i>Z</i> -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 ^{–1} 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	Amino acid formula (AAF) (including elemental feeds) Extensively hydrolysed formula (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

Table 2 Continued

Parameter	Description
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

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 paediatric intensive care unit (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 EHF to all infants/children on admission⁽²⁰⁾. The second most common reason for use of EHF 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

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 extensively hydrolysed formula (EHF) or amino acid formula (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. PICU, paediatric intensive care unit; GI, gastrointestinal.

95% of cases, feeds were reconstituted in accordance with the manufacturer's 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, EHF 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 EHF (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 extensively hydrolysed formula and amino acid formula

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 considered not to tolerate standard whole protein paediatric feeds, as a result of vomiting 12%, congenital/acquired

Figure 1 Contribution of extensively hydrolysed formulas (EHFs) and amino acid formulas (AAFs) expressed as percentage of total energy requirements, stratified by feed type.

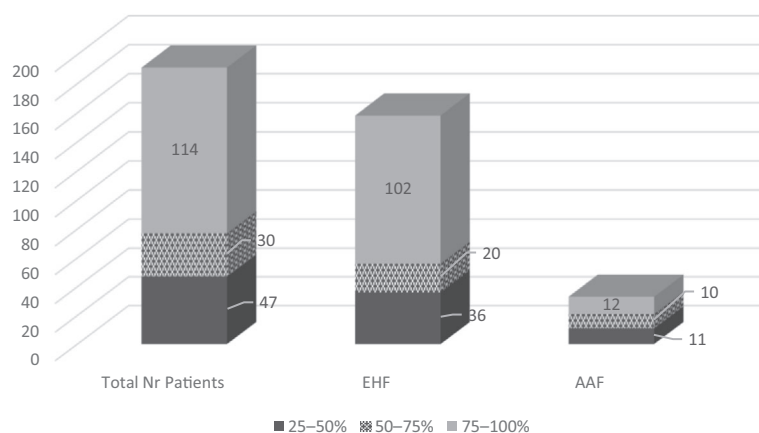


Table 5 Feeding route stratified by extensively hydrolysed formula (EHF) and amino acid formula (AAF)

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 parenteral nutrition: Overall 11% (21/191), EHF 48% (10/21) and AAF 52% (11/21).

Reason for admission	Total	<1 week	1-4 weeks	1-3 months	3-12 months	>12 months
PICU ALL	60	17%	70%	3%	8%	2%
PICU / Other	45	20%	69%	4%	4%	2%
PICU / Cardiac	11	9%	64%	0%	27%	0%
PICU / Prematurity	4	0%	100%	0%	0%	0%
Cancer	49	4%	18%	24%	53%	0%
GI disease	34	9%	24%	12%	35%	21%
Liver	18	17%	39%	6%	22%	17%
Other	12	25%	8%	17%	33%	17%
Prematurity	10	10%	40%	30%	20%	0%
Cardiac disease	8	38%	0%	25%	38%	0%

Figure 2 Heat map displaying the length of time feeds were used, stratified by reason for admission.

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 the 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 EHF 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 (WAZ) ⁽²¹⁾ for the population was -1.2 (IQR = -2.1 to -0.1), height-for-

Reason for admission	Grand Total	Standard clinical Practice	Not tolerating Standard feeds	Vomiting	Other	Congenital/Acquired GI pathology	Malabsorption	Diarrhoea	Constipation	Reflux
PICU ALL	60	85%	3.3%	0%	10%	1.7%	0%	0%	0%	0%
PICU/Other	45	80%	4.4%	0%	13.3%	2.2%	0%	0%	0%	0%
PICU/Cardiac	11	100%	0%	0%	0%	0%	0%	0%	0%	0%
PICU/Prematurity	4	100%	0%	0%	0%	0%	0%	0%	0%	0%
Cancer	49	12.2%	57.1%	28.6%	2.0%	0%	0%	0%	0%	0%
GI disease	34	2.9%	47.1%	2.9%	5.9%	23.5%	5.9%	8.8%	2.9%	0%
Liver	18	11.1%	0%	0%	50%	5.6%	33.3%	0%	0%	0%
Other	12	8.3%	25%	41.7%	0%	0%	8.3%	0%	8.3%	8.3%
Prematurity	10	0%	10%	0%	10%	40.0%	10%	20%	0%	10%
Cardiac disease	8	0%	62.5%	25%	0%	0%	0%	12.5%	0%	0%

Figure 3 Heatmap of primary indications for use of formula.

Table 6 Variables significantly contribute towards the likelihood of being on either extensively hydrolysed formula (EHF) or amino acid formula (AAF)

Variable 1	Variable 2	Variable 3	Variable 4	Probability of being on an EHF (%)	Probability of being on an AAF (%)
			Diarrhoea	95	5
			Malabsorption	94	6
		Vomiting		93	7
			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

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 ⁽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-pre-term infants in the 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) versus -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,

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

Diagnostic category	WAZ	HAZ	WHZ	Body mass index
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%

GI, gastrointestinal; HAZ, height-for-age Z-score; PICU, paediatric intensive care unit; WAZ, weight-for-age Z-score; WHZ, weight-for-length/height.

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)	–	–

AAF, amino acid formula; EHF, extensively hydrolysed formula.

Table 9 Medication use stratified by extensively hydrolysed formula (EHF) or amino acid formula (AAF)

	Overall percentage	EHF	AAF
Proton pump inhibitor	40% (77/191)	40% (63/158)	42% (14/33)
Antiemetics	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)
Anticonvulsant	4% (7/191)	4% (6/158)	3% (1/33)

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) were prescribed two and 21% (41/191) were on three or more medications. Forty percent of children (77/191) were prescribed a proton pump inhibitor (PPI), followed by antiemetics (30%; 58/191) and diuretics (28%; 53/191) (Table 9). 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 EHF 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, although 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 EHF 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⁾ reported a lower incidence of feed intolerance, such as vomiting, high gastric residual volumes and diarrhoea in critically ill children, when meeting the prescribed energy requirements when using these feeds. This participating centre in the present study admitted 50% of children for planned cardiac surgery. Dysmotility is well documented not only in children with this diagnosis⁽²⁶⁾, but also 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, and 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 underlying diagnosis⁽¹²⁾. The evidence for either EHF or AAF alleviating these symptoms and improving the 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 as a result of 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). Despite its frequent use in gastrointestinal disorders including short gut syndrome, there are only a limited number of studies, often of poor quality⁽³¹⁾, evaluating EHF/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 also in combination. In addition, the heterogeneity of gastrointestinal diagnoses and medical management make it really difficult to establish the efficacy of these feeds.

The use of EHF 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 EHF 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 because 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 hospitalised children where 7.9% were stunted and 5% had a body mass index < -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, although the 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, particularly in the presence of malnutrition (which was common in our cohort) and during admission to the PICU. We consider 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, because PPI and other medications are known to 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 with 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 3 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 also after this when clinically indicated (no time interval suggested)⁽⁴⁶⁾. Assessment of zinc, copper and selenium levels is recommended only when clinically indicated (no time interval suggested) and vitamin D should be performed every 6 months⁽⁴⁶⁾. In light of the limited data on nutritional adequacy when using either EHF/AAF in children with complex disease, it is prudent that children who are on these feeds for >3 months are monitored at least to the standard set by the 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 the 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 EHF and AAFs. Because this was a survey, we also did not control for growth measurement accuracy, nor 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.

Conclusions

This practice survey found that EHF and AAFs are commonly used in a variety of children with complex medical conditions, most of whom are 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 light of the limited evidence supporting the

routine use of these feeds in a variety of conditions, further research is required with respect to better defining the 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 (Box 1).

Box 1. Key learning points for healthcare professionals

- When an extensively hydrolysed formula (EHF) or amino acid formula (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

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RM was responsible for the design of survey, support to collecting centres, help with data analysis and writing the article. CS, LS, SM and LM were responsible for the collection of data and writing the article. All authors critically reviewed the manuscript and approved the final version submitted for publication.

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.

References

- World Health Organization (2002) The WHO: Guiding principles for complementary feeding of the breastfed child. Available at: https://www.who.int/nutrition/publications/guiding_principles_compfeeding_breastfed.pdf
- Fiocchi A, Brozek J, Schunemann H *et al.* (2010) World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guidelines. *Pediatr Allergy Immunol* **21**(Suppl 21), 1–125.
- Muraro A, Werfel T, Hoffmann-Sommergruber K *et al.* (2014) EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy* **69**, 1008–1025.
- Host A, Koletzko B, Dreborg S *et al.* (1999) Dietary products used in infants for treatment and prevention of food allergy. Joint Statement of the European Society for Paediatric Allergology and Clinical Immunology (ESPACI) Committee on Hypoallergenic Formulas and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition. *Arch Dis Child* **81**, 80–84.
- Pediatrics AAP (2000) Hypoallergenic infant formulas. *Pediatrics* **106**, 346–349.
- European Commission. Food for infants and young children. Available at: https://ec.europa.eu/food/safety/labelling_nutrition/special_groups_food/children_en (accessed April 2020).
- Brun AC, Stordal K, Johannesdottir GB *et al.* (2012) The effect of protein composition in liquid meals on gastric emptying rate in children with cerebral palsy. *Clin Nutr* **31**, 108–112.
- Minor G, Ochoa JB, Storm H *et al.* (2016) Formula switch leads to enteral feeding tolerance improvements in children with developmental delays. *Glob Pediatr Health* **3**, 2333794X16681887.
- Macias-Rosales R, Larrosa-Haro A, Ortiz-Gabriel G *et al.* (2016) Effectiveness of enteral versus oral nutrition with a medium-chain triglyceride formula to prevent malnutrition and growth impairment in infants with biliary atresia. *J Pediatr Gastroenterol Nutr* **62**, 101–109.
- Norman K & Pirlich M (2008) Gastrointestinal tract in liver disease: which organ is sick? *Curr Opin Clin Nutr Metab Care* **11**, 613–619.
- Taylor RM, Bjarnason I, Cheeseman P *et al.* (2002) Intestinal permeability and absorptive capacity in children with portal hypertension. *Scand J Gastroenterol* **37**, 807–811.
- Royal College of Nursing (2014) *Nutrition in Children and Young People with Cancer - RCN Guidance*. London: Royal College of Nursing.
- Joosten KFM, Eveleens RD & Verbruggen S (2019) Nutritional support in the recovery phase of critically ill children. *Curr Opin Clin Nutr Metab Care* **22**, 152–158.
- Eveleens RD, Joosten KFM, de Koning BAE *et al.* (2020) Definitions, predictors and outcomes of feeding intolerance in critically ill children: a systematic review. *Clin Nutr* **39**, 685–693.
- Marino IR & Lauro A (2018) Surgeon's perspective on short bowel syndrome: where are we? *World J Transplant* **8**, 198–202.
- Vandenplas Y, Plaskie K & Hauser B (2010) Safety and adequacy of a semi-elemental formula for children with gastro-intestinal disease. *Amino Acids* **38**(3), 909–914.
- Asai Y, Yanishevsky Y, Clarke A *et al.* (2014) Rate, triggers, severity and management of anaphylaxis in adults treated in a Canadian emergency department. *Int Arch Allergy Immunol* **164**, 246–252.
- World Health Organization (2012) Global Database on Child Growth and Malnutrition: Child growth indicators and their interpretation. Available at: www.who.int/nutgrowthdb/about/introduction/en/index2html
- Fenton TR, Nasser R, Eliasziw M *et al.* (2013) Validating the weight gain of preterm infants between the reference growth curve of the fetus and the term infant. *BMC Pediatr* **13**, 92.
- Marino LV, Eveleens RD, Morton K *et al.* (2019) Peptide nutrient-energy dense enteral feeding in critically ill infants: an observational study. *J Hum Nutr Diet* **32**, 400–408.
- Awazuhara H, Kawai H, Baba M *et al.* (1998) Antigenicity of the proteins in soy lecithin and soy oil in soybean allergy. *Clin Exp Allergy* **28**, 1559–1564.
- Meyer R, Groetch M & Venter C (2018) When should infants with cow's milk protein allergy use an amino acid formula? A practical guide. *J Allergy Clin Immunol Pract* **6**, 383–399.
- Tume LN & Valla FV (2018) A review of feeding intolerance in critically ill children. *Eur J Pediatr* **177**(11), 1675–1683.
- Han-Markey T (2000) Nutritional considerations in pediatric oncology. *Semin Oncol Nurs* **16**, 146–151.
- Romano C, van Wyncel M, Hulst J *et al.* (2017) European Society for Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for the evaluation and treatment of gastrointestinal and nutritional complications in children with neurological impairment. *J Pediatr Gastroenterol Nutr* **65**, 242–264.
- Cavell B (1981) Gastric emptying in infants with congenital heart disease. *Acta Paediatr Scand* **70**, 517–520.

27. Duncan M & Grant G (2003) Oral and intestinal mucositis - causes and possible treatments. *Aliment Pharmacol Ther* **18**, 853–874.
28. de Koning BA, van der Schoor SR, Wattimena DL *et al.* (2007) Chemotherapy does not influence intestinal amino acid uptake in children. *Pediatr Res* **62**, 195–199.
29. Gonzalez Ballesteros LF, Ma NS, Gordon RJ *et al.* (2017) Unexpected widespread hypophosphatemia and bone disease associated with elemental formula use in infants and children. *Bone* **97**, 287–292.
30. Uday S, Sakka S, Davies JH *et al.* (2018) Elemental formula associated hypophosphataemic rickets. *Clin Nutr* **38**, 2246–2250.
31. Barclay AR, Beattie LM, Weaver LT *et al.* (2011) Systematic review: medical and nutritional interventions for the management of intestinal failure and its resultant complications in children. *Aliment Pharmacol Ther* **33**, 175–184.
32. Ksiazek J, Piena M, Kierkus J *et al.* (2002) Hydrolyzed versus nonhydrolyzed protein diet in short bowel syndrome in children. *J Pediatr Gastroenterol Nutr* **35**, 615–618.
33. Olieman JF, Penning C, Ijsselstijn H *et al.* (2010) Enteral nutrition in children with short-bowel syndrome: current evidence and recommendations for the clinician. *J Am Diet Assoc* **110**, 420–426.
34. Meyer R, Foong RX, Thapar N *et al.* (2015) Systematic review of the impact of feed protein type and degree of hydrolysis on gastric emptying in children. *BMC Gastroenterol* **15**, 137.
35. Baker A, Stevenson R, Dhawan A *et al.* (2007) Guidelines for nutritional care for infants with cholestatic liver disease before liver transplantation. *Pediatr Transplant* **11**(8), 825–834.
36. Mouzaki M, Bronsky J, Gupte G *et al.* (2019) Nutrition support of children with chronic liver diseases: a joint position paper of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* **69**, 498–511.
37. Wahid AM, Powell CV, Davies IH *et al.* (2017) Intestinal failure in children and young people with neurodisabling conditions. *Arch Dis Child* **102**, 475–476.
38. Sullivan P (2009) *Feeding and Nutrition in Children with Neurodisability*. [Hillary MH, editor]. London: Mac Keith Press.
39. Brun AC, Stordal K, Johannesdottir GB *et al.* (2013) Nissen fundoplication in children with cerebral palsy: influence on rate of gastric emptying and postprandial symptoms in relation to protein source in caloric liquid meals. *Clin Nutr* **32**, 619–623.
40. Savage K, Kritas S, Schwarzer A *et al.* (2012) Whey- vs casein-based enteral formula and gastrointestinal function in children with cerebral palsy. *JPEN J ParenterEnteral Nutr*. **36**(1 Suppl), 118S–123S.
41. Khoshoo V & Brown S (2002) Gastric emptying of two whey-based formulas of different energy density and its clinical implication in children with volume intolerance. *Eur J Clin Nutr* **56**, 656–658.
42. Hecht C, Weber M, Grote V *et al.* (2015) Disease associated malnutrition correlates with length of hospital stay in children. *Clin Nutr* **34**, 53–59.
43. Marino LV & Magee A (2016) A cross-sectional audit of the prevalence of stunting in children attending a regional paediatric cardiology service. *Cardiol Young* **26**, 787–789.
44. Michel KE & Higgins C (2002) Nutrient-drug interactions in nutritional support. *J Vet Emerg Crit Care* **12**, 163–167.
45. Yadlapati R & Kahrilas PJ (2018) The "dangers" of chronic proton pump inhibitor use. *J Allergy Clin Immunol* **141**, 79–81.
46. British Association for Enteral and Parenteral Nutrition (2016) Enteral Feed Monitoring. Available at: <https://www.bapen.org.uk/nutrition-support/enteral-nutrition/enteral-feed-monitoring> (accessed April 2020).