

Standardized and Individualized Parenteral Nutrition Mixtures in a Pediatric Home Parenteral Nutrition Population

*Sjoerd C.J. Nagelkerke, *Cora F. Jonkers-Schuitema, †Wendy L.M. Kastelijn, ‡Anne-Loes E. Gerards, *Marc A. Benninga, †Barbara A.E. de Koning, and *Merit M. Tabbers

See “Use of Standard Parenteral Nutrition Bags in a Paediatric Home Parenteral Nutrition Population” by Hill on page 160.

ABSTRACT

Objectives: Studies evaluating efficacy or safety of standardized parenteral nutrition (PN) versus individualized PN are lacking. We aimed to assess effects on growth and safety of standardized PN compared with individualized PN in our Home PN group.

Methods: Descriptive cohort study in Dutch children on Home PN, in which standardized PN was compared with individualized PN. Both groups received similar micronutrient-supplementation. Primary outcome was growth over 2 years, secondary outcomes were electrolyte disturbances and biochemical abnormalities. Additionally, patients were matched for age to control for potential confounding characteristics.

Results: Fifty patients (50% girls, median age 6.5 years) were included, 16 (32%) received standardized PN mixtures. Age (11 vs 5 years), gestational age (39.2 vs 36.2 weeks) and PN duration (97 vs 39 months) were significantly higher in the group receiving standardized PN ($P: \leq 0.001$; 0.027; 0.013 respectively). The standardized PN group showed an increase in weight-for-age (WFA), compared with a decrease in the individualized PN group (+0.38 SD vs -0.55 SD, $P: 0.003$). Electrolyte disturbances and biochemical abnormalities did not differ. After matching for age, resulting in comparable groups, no significant differences were demonstrated in WFA, height-for-age, or weight-for-height SD change.

Conclusions: In children with chronic IF, over 2.5 years of age, standardized PN mixtures show a comparable effect on weight, height, and weight for height when compared with individualized PN mixtures. Also, standardized PN mixtures (with added micronutrients) seem noninferior to individualized PN mixtures in terms of electrolyte disturbances and basic biochemical abnormalities. Larger studies are needed to confirm these conclusions. **Trial Registration:** Academic Medical Center medical ethics committee number W18_079 #18.103.

Key Words: electrolytes, growth, home parenteral nutrition, pediatric intestinal failure, standardized mixtures

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From the *Department of Pediatric Gastroenterology, Hepatology and Nutrition, Emma Children’s Hospital, University of Amsterdam, Amsterdam UMC, Amsterdam, the †Erasmus Medical Center, Department of Pediatric Gastroenterology, Sophia Children’s Hospital, Erasmus University Rotterdam, Rotterdam, and the ‡Department of Hospital Pharmacy, University of Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands.

Address correspondence and reprint requests to Sjoerd C.J. Nagelkerke, Department of Pediatric Gastroenterology, Hepatology and Nutrition, Emma Children’s Hospital/Amsterdam UMC, Meibergdreef 9 (room C2–312), 1105 AZ Amsterdam, The Netherlands (e-mail: sjoerd.nagelkerke@amsterdamumc.nl).

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What Is Known

- Current guidelines on pediatric parenteral nutrition conclude that standardized parenteral nutrition mixtures are not suitable for children with chronic intestinal failure on home parenteral nutrition.
- Studies evaluating efficacy or safety of standardized parenteral nutrition are lacking.

What Is New

- In children over 2.5 years of age with chronic intestinal failure and stable nutritional need, standardized parenteral nutrition mixtures show comparable growth (weight, height, and weight for height) when compared with individualized parenteral nutrition mixtures.
- Standardized parenteral nutrition mixtures are at least noninferior to individualized parenteral nutrition mixtures in terms of electrolyte disturbances and basic biochemical abnormalities in a home parenteral nutrition cohort. As both groups received similar amounts of micronutrients, micronutrients were not analyzed.

Intestinal failure (IF) is defined as a critical reduction of functional gut mass below the minimum necessary for adequate digestion and absorption to satisfy body nutrient and fluid requirements for adequate growth and development in children (1,2). Causes of IF in children consist of short bowel syndrome (SBS), intestinal neuromuscular motility, and intrinsic epithelial disorders (3–5). Children with IF are (partly) dependent on parenteral nutrition (PN) to achieve adequate growth, and fluid and electrolyte

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homeostasis (1). Goal is to achieve intestinal autonomy, meaning there is no longer need for Home PN administration (6). Prevalence of Home PN use varies across studies, ranging from 9.6 to 14.1 children per million (7,8).

In children, PN requirements vary, depending on age, weight, nutritional and hydration status, underlying disease, daily activity level, and environmental conditions. Regarding PN, both standardized formulations compounded by pharmaceutical companies and individualized formulations compounded by a pharmacy are available. According to the recently updated Guidelines on Pediatric PN uncritical use of standardized formulations particularly over longer periods of time, may be less than optimal for growth and development (9,10). However, data are lacking supporting this conclusion. Apart from possibly not being optimal for growth and development, concerns can also be raised about potential electrolyte imbalances when standardized PN mixtures are prescribed. In contrast, possible advantages of standardized PN solutions could be a reduction in costs and a longer shelf life than individualized PN solutions. A longer shelf life could, for example, enable patients and parents to go on vacations for longer duration.

As all published studies on the effects of standardized PN mixtures have been performed in hospitalized children, we aimed to investigate the effects and safety of standardized and individualized PN on growth in a pediatric Home PN population.

METHODS

Subjects

All children (0–18 years of age) receiving Home PN from 2 Dutch dedicated pediatric Home PN centers visiting the outpatient clinic between June 2017 and July 2018 were eligible for inclusion (Emma Children's Hospital/Amsterdam University Medical Center and Sophia Children's Hospital/Erasmus Medical Center). Patients were excluded if they received PN for less than 6 months.

Measurements

Study data were collected via chart review, including demographic and clinical patient characteristics (including the number of central line-associated bloodstream infections (CLABSI), number of hospital admissions and the frequency of comorbidities). Bowel characteristics, nutritional data, growth measurements and laboratory data were noted. Date of inclusion was defined as date of visit at the Home PN-outpatient clinic in the period between June 2017 and July 2018. When 2 or more outpatient visits were made in this period, the visit with complete laboratory data was included. Primary outcome measure was growth (Weight-For-Age [WFA], Height-For-Age [HFA] and Weight For Height [WFH]) after 24 months. Secondary outcome measures were electrolyte disturbances and biochemical abnormalities including liver function. All outcome measures were assessed for the period patient received either standardized or individualized PN.

Growth

Weight and height were measured using standard measuring equipment. With the Growth Analyzer VE version 1.5.1 (Growth Analyzer BV, The Netherlands), using up-to-date Dutch national reference standards, sex- and age-adjusted standard deviation scores (SDS) were obtained for WFA, HFA, and WFH (11). Measurements were retrieved at the date of inclusion and 6, 12, and 24 months before date of inclusion. Growth was assessed by calculating the

difference in age-adjusted SDS between date of inclusion and previous measurement at minus 6, 12, and 24 months. This difference indicated a change in growth chart position.

Parenteral Nutrition Mixtures and Oral/enteral Intake

Patients were either coded as receiver of standardized (commercially available bag with additions) or individualized PN mixtures when they received this type of mixture for at least 6 months at inclusion. If patients switched from individualized PN to standardized PN during the study period, or vice versa, growth was only assessed from the moment of the switch till the date of inclusion. In our practice, a single bag of PN per day is provided in order to lighten the burden of care on parents and prevent compounding errors. Patients were prescribed standardized PN when nutritional need was stable over at least 3 months and the composition of an available mixture met their nutritional need. Fluids and electrolytes were added to the standardized PN if this did not exceed the limitations imposed by the manufacturer. When patient's nutritional need was not met by the available mixtures, for example, because of intestinal losses requiring the compensation of large volumes of fluids and/or electrolytes, individualized PN was prescribed. Individualized PN mixtures were compounded by the hospital pharmacy. Compounding of these mixtures is done under stringent conditions and the composition is frequently checked. Different standardized PN mixtures were prescribed to patients (Table 1). If patients received standardized PN mixtures, parents added all micronutrient additions before infusion. Both groups received the same amount of vitamin and trace elements per bag, therefore, micronutrient levels were not analyzed. Composition of PN was recorded for all mixtures as well as the number of PN days per week. Amount of infused lipids (all patients received mixed lipid preparations), amino acids, and carbohydrates per week was calculated and recorded as grams/day. Furthermore, if patients received enteral nutrition (EN), the amount of macronutrients was recorded as grams/day. Finally, it was noted if patients were partially fed orally. Detailed and reliable information regarding oral intake is not available because of the retrospective character of this study. Furthermore, it is unknown to which degree enteral provided nutrients are absorbed. The prescribed PN and EN reflect the response of the treating physician to the patient's weight gain and growth over time.

All patients received Taurolidine locks for the prevention of CLABSI.

TABLE 1. Types of prescribed standardized parenteral nutrition formula

PN brand, manufacturer	Number of prescriptions (number of exclusive prescriptions*)
Smofkabiven Central, Fresenius Kabi	6 (4)
Aminomix 1 Novum, Fresenius Kabi	3 (0)
Olimel N5E, Baxter	1 (1)
Olimel N7E, Baxter	5 (5)
Olimel N9E, Baxter	2 (1)
Numeta G16%E, Baxter	1 (1)
Numeta G19%E, Baxter	1 (1)

PN = parenteral nutrition.

*Three patients received both Aminomix 1 Novum (without lipids) and either Smofkabiven Central or Olimel N9E (with lipids). If patients solely received 1 mixture, they were coded as exclusive prescription.

Patients' nutritional need at time of inclusion was calculated according to the hospital's protocol by a dietician, using the Schofield formula and adding the increased energy expenditure associated with activity, disease state and growth (12,13).

Biochemical Values

Serum glucose, triglyceride, and electrolyte concentrations at time of inclusion were studied. Liver function (albumin, prothrombin time and bilirubin [total and conjugated]) and liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], γ -glutamyl transferase [GGT] and alkaline phosphatase [AP]) were noted. Additionally, we recorded whether patients were admitted because of electrolyte abnormalities in the 24 months previous to date of inclusion.

Statistical Analysis

Statistical analyses were performed using SPSS version 24.0.0.1 (IBM corporation, Armonk NY). Continuous data are summarized as median and interquartile range (IQR), categorical data are presented as frequencies and percentages. Mann-Whitney *U* test and Fisher Exact test were used to assess differences between patients receiving standardized or individualized PN mixtures for continuous

data and categorical data, respectively. A 2 sided *P* value ≤ 0.05 was considered as statistically significant. As an additional analysis, to compensate for differences in baseline characteristics, one-to-one case control matching on age was performed leading to an even distribution of potential confounding baseline characteristics.

As differences between nutritional need and caloric intake could be a possible confounder for weight gain, this difference was calculated. For both groups, Kendall tau was used to investigate the correlation of this difference with weight gain.

The Institutional Review Board/Independent Ethics Committee of the Academic Medical Center declared that this study did not have to be reviewed by a medical ethics board according to Dutch Law on Medical Research with Humans (WMO).

RESULTS

Patient Characteristics

In total, 56 patients received Home PN. Of these, 50 patients (50% girls) were included for analysis, of whom 16 (32%) received standardized PN mixtures. Six patients were not included because PN was used less than 6 months. Median age at inclusion was 6.5 years (IQR: 3.5–10.5, minimum 0.5 years) and median PN duration was 62 months (IQR: 18–99). Patient characteristics are shown in Table 2. Age, gestational age (GA), and PN duration were

TABLE 2. Demographic patient characteristics

	Before matching			After matching		
	Standard (n = 16)	Individualized (n = 34)	<i>P</i>	Standard (n = 10)	Individualized (n = 10)	<i>P</i>
Sex (female)	8 (50)	17 (50)	1.000*	7 (70)	5 (50)	0.650*
Age (years)	11 (8.5–14)	5 (2.5–7.5)	$\leq 0.001^\dagger$	9 (5–11)	8 (6–11)	0.796 [†]
Gestational age (weeks)	39.2 (35.3–41)	36.2 (34.3–37.8)	0.027[†]	38.8 (34.9–40.3)	36.2 (34.5–38.8)	0.315 [†]
Gestational age <37.0 weeks	4 (25)	22 (65)	0.015*	2 (20)	7 (70)	0.070 [†]
Birth weight (SD-score)	0.07 (–0.88 to 0.29)	–0.32 (–1.51–.54)	0.793 [†]	0.06 (–1.13–.14)	0.11 (–1.04–.63)	0.661 [†]
Underlying disease			0.601*			0.307*
Short bowel syndrome	7 (44)	15 (44)		5 (50)	3 (30)	
Small bowel length (cm)	43 (26–54)	32 (15–60)	0.620 [†]	45 (35–57)	8 (0–35)	0.063 [†]
Bowel lengthening procedure	3 (19)	6 (18)	1.000*	3 (30)	2 (20)	1.000*
Motility disorder	7 (44)	11 (32)		4 (40)	5 (50)	
Microvillus Inclusion disease	0	4 (12)		0	2 (20)	
Other	2 (13)	4 (12)		1 (10)	0	
Ileocecal valve in situ	8 (50)	25 (74)	0.121*	4 (40)	6 (60)	0.656*
Colon in situ	9 (56)	26 (77)	0.191*	5 (50)	7 (70)	0.650*
Comorbidity [‡]	7 (44)	19 (59)	0.366*	4 (40)	8 (80)	0.170*
CLABSI (/1000 PNdays) [§]	2.7 (1.4–5.1)	2.7 (1.4–4.8)	0.497 [†]	2.7 (1.4–4.1)	2.7 (1.4–4.7)	0.968 [†]
Hospital [§] Admission (/1000 PNdays)	2.1 (0–5.1)	1.4 (1–4.1)	0.890 [†]	2.7 (0–4.1)	2.7 (1.4–4.1)	0.877 [†]
Hospital Admission (days)	9.5 (0–23.5)	8 (1.5–46.25)	0.563 [†]	9.5 (0–26)	7.5 (3–17)	0.879 [†]
PN duration (months)	97 (40–134)	39 (13–80)	0.013[†]	66 (26–113)	81 (25–137)	0.631 [†]
Total PN Infusion (kCal/day)	1213 (1057–1471)	1125 (765–1372)	0.417 [†]	1163 (524–1235)	1500 (959–1902)	0.143 [†]
Days PN infusion at inclusion (/week) [§]	7 (4–7)	7 (7–7)	0.002[†]	7 (4–7)	7 (7–7)	0.247 [†]
Days PN infusion at T minus 24 months (/week) [§]	7 (5–7)	7 (7–7)	0.001[†]	7 (5–7)	7 (7–7)	0.143 [†]
Days PN fat infusion at inclusion (/week) [§]	5.5 (3–7)	5 (4–7)	0.741 [†]	5 (2–7)	7 (4–7)	0.247 [†]
Days PN fat infusion at T minus 24 months (/week) [§]	5.5 (3–7)	5 (4–7)	0.741 [†]	5 (2–7)	7 (4–7)	0.247 [†]
ECH/AUMC	11 (69)	24 (71)	1.000*	7 (70)	10 (100)	0.211*

All continuous data are presented as median (interquartile range), all categorical data is presented as n (%). AUMC = Amsterdam University Medical Centre; CLABSI = central line-associated bloodstream infection; ECH = Emma Children's Hospital; PN = parenteral nutrition; SD = standard deviation.

*Fisher exact test was used to determine *P* value.

[†]Mann-Whitney *U* test was used to determine *P* value.

[‡]Comorbidity defined as any disease other than underlying disease or PN-associated complication, such as intestinal failure associated-liver disease or CLABSI.

[§]Number of.

^{||}During study period of 24 months.

Bold indicates a statistically significant difference between groups.

TABLE 3. Median change in standard deviation score over 6, 12, and 24 months

		Before matching					After matching				
		Standard	n	Individualized	n	P	Standard	n	Individualized	n	P
Weight	6 months	0.07 (−0.01 to 0.30)	15	−0.02 (−0.28 to 0.63)	32	0.592	0.19 (−0.01 to 0.50)	10	0.19 (−0.16 to 0.52)	10	0.842
	12 months	0.16 (−0.04 to 0.46)	15	−0.19 (−0.59 to 0.30)	25	0.047	0.16 (−0.04 to 0.46)	10	0.22 (−0.17 to 0.47)	10	0.721
	24 months	0.38 (−0.34 to 0.80)	12	−0.55 (−1.11 to −0.07)	20	0.003	0.80 (−0.12 to 1.40)	10	−0.42 (−1.17 to −0.26)	10	0.051
Height	6 months	−0.04 (−0.09 to 0.22)	15	−0.07 (−0.33 to 0.23)	30	0.700	−0.08 (−0.31 to 0.16)	10	−0.26 (−0.40 to 0.01)	10	0.277
	12 months	−0.11 (−0.28 to 0.53)	15	−0.23 (−0.39 to 0.14)	25	0.410	−0.21 (−0.45 to 0.06)	9	−0.45 (−0.70 to −0.06)	9	0.234
	24 months	−0.15 (−0.65 to 0.39)	12	−0.30 (−0.86 to 0.35)	20	0.580	−0.24 (−0.79 to −0.05)	9	−0.78 (−0.89 to −0.12)	9	0.445
Weight for height	6 months	0.12 (−0.19 to 0.58)	15	0.16 (−0.34 to 0.73)	30	0.819	0.40 (−0.05 to 0.66)	10	0.35 (−0.31 to 0.78)	10	0.963
	12 months	0.10 (−0.49 to 1.12)	15	−0.19 (−0.50 to 0.28)	25	0.288	0.39 (−0.11 to 1.04)	9	0.21 (−0.15 to 1.10)	9	0.798
	24 months	0.54 (−0.50 to 1.52)	12	−0.18 (−0.99 to 0.50)	20	0.071	1.38 (−0.89 to 2.20)	9	−0.11 (−1.04 to 1.96)	9	0.101

All data are presented as median (interquartile range). Mann-Whitney U test was used to determine P value. Bold indicates a statistically significant difference between groups.

significantly higher in the group receiving standardized PN (P: ≤0.001; 0.027; 0.013, respectively). The amount of PN infusions per week was significantly lower in the standardized group (P: 0.002).

Growth

After 24 months, median change in WFA SDS in the standardized PN group was +0.38 SD (−0.34 to 0.80), whereas in the individualized PN group, a median decrease in WFA SDS was seen: −0.55 SD (−1.11 to −0.07). The difference between these groups reached statistical significance (P: 0.003). No statistical differences at 24 months were seen regarding change in HFA SDS or change in WFH SDS between the 2 groups (Table 3).

At all time points, WFA, HFA, and WFH did not significantly differ between the groups (Supplemental Table 1, Supplemental Digital Content, <http://links.lww.com/MPG/B729>).

Intake

Six patients received total PN without any oral or enteral intake, 1 (6%) in the standardized PN group versus 5 (15%) in the individualized PN group (P: 0.65). In the standardized PN group, 19% (3/16) received EN compared with 38% (13/34) in the individualized PN group (P: 0.218). As stated in the “Method section”, reliable data on amount of oral intake was not available.

Difference in nutritional need and caloric provision of enteral and parenteral nutrition was calculated for both groups. The standardized PN group showed a median deficit of 17 calories/kg/day

(−20 to −11). This was significantly different compared with the individualized PN group where a deficit of 4 calories/kg/day per day was observed (−15 to 6, P: 0.029).

No significant relationship between this calculated difference and change in WFA SDS was seen in both groups: $r_{\tau} = -0.121$, P: 0.583 for the standardized PN group and $r_{\tau} = 0.148$, P: 0.363 for the individualized PN group.

Biochemical Values

No statistical differences in abnormal values for sodium (Na), potassium (K), magnesium (Mg), calcium (Ca), and phosphorus (P) were observed between the 2 groups (Table 4). Also, no statistical differences in abnormal liver tests were found between both groups. Median total and conjugated bilirubin were 6.0 μmol/L (5.0–13.0) and 4.0 μmol/L (2.3–6.0), respectively in the standardized PN group and 5.0 μmol/L (4.0–9.0) and 3.0 μmol/L (2.0–4.0), respectively in the individualized PN group. Both total and conjugated bilirubin concentrations did not statistically differ between both groups (P: 0.473 and P: 0.662, respectively). Neither hyperglycemia (defined as ≥6.1 mmol/L) nor hypertriglyceridemia (≥2.1 mmol/L) were seen in this cohort. No child was admitted because of abnormal electrolyte concentrations.

Age-matched Cohort

Twenty patients were included for analysis after matching for age. Median age of these 20 patients at inclusion was 9 years (IQR: 6–11, minimum 2.5 years) and median PN duration was 75 months

TABLE 4. Number of electrolyte disturbances

	Before matching			After matching		
	Standard	Individualized	P	Standard	Individualized	P
Sodium	0	0	—	0	0	—
Potassium	1 (6.3%)	3 (9.4%)	1.000	1 (10%)	0	1.000
Calcium	0	3 (9.1%)	0.542	0	1 (10%)	1.000
Magnesium	1 (6.7%)	3 (10%)	1.000	0	1 (10%)	1.000
Phosphorus	4 (25%)	9 (28.1%)	1.000	2 (20%)	0	0.474
Chloride	2 (14.3%)	5 (16.7%)	1.000	1 (10%)	2 (20%)	0.582

Normal laboratory range: sodium 135–145 mmol/L, potassium 3.5–5 mmol/L, calcium 2.15–2.75 mmol/L, magnesium 0.68–0.88 mmol/L, phosphorus 1.00–2.05 mmol/L, chloride 98–107 mmol/L.

(IQR: 29–128). Groups were comparable on all baseline characteristics (Table 2).

After 24 months, median change in WFA SDS in the standardized PN group was +0.80 SD (−0.12–1.40), whereas in the individualized PN group, a median decrease in WFA SDS was seen: −0.42 SD (−0.17 to 0.47). The difference between these groups did not reach statistical significance (P : 0.051). No statistical differences were seen regarding change in HFA SDS or WFH SDS between the 2 groups (Table 3).

The standardized PN group showed a median deficit of 17 calories/kg/day (−27 to 3). This was significantly different compared with the individualized PN group where a surplus of 1 calorie/kg/day per day was observed (−18 to 12; P : 0.247).

No significant relationship between this calculated difference and change in WFA SDS was seen in both groups: $r_{\tau} = -0.067$, P : 0.851 for the standardized PN group and $r_{\tau} = 0.048$, P : 0.881 for the individualized PN group.

No statistical differences were observed between both groups in any biochemical value.

DISCUSSION

This is the first study assessing the effects of standardized and individualized PN formulations in a pediatric home PN population. In this cohort, standardized PN mixtures in children with chronic IF facilitated an increase in WFA SD score whereas a decrease in WFA SDS was seen in the individualized PN group. The same observation was made after age matching; however, the difference between groups did not reach statistical significance. No statistical differences in HFA Z-score and WFH Z-score were observed between groups. Children receiving standardized PN mixtures did not have a higher number of electrolyte or liver test abnormalities (including total and conjugated bilirubin concentrations) compared with the individualized PN group.

The observed differences in potential confounders on growth (i.e. gestational age and number of nights on PN) in our cohort impose a possible risk of bias. To correct for the observed differences in potential confounders on growth, and reduce the risk of bias, patients were age-matched, which resulted in an even distribution of these potential confounders between groups. Of note, patients included in the age-matched cohort were older than patients in the original cohort with a minimum age of 2.5 years.

Children in our cohort receiving standardized PN mixtures showed an average increase in WFA SDS over 24 months. This in contrast to the group receiving individualized PN mixtures where a decrease in WFA SDS was seen. No statistical difference was observed for height gain or change in WFH SDS. The observed change in WFA SDS cannot be explained by catch-up growth as the standardized group was not lighter than the individualized PN group at t minus 24 months. A possible explanation for the observed decrease in WFA SDS in the individualized PN group could be the lower gestational age in this group. Several studies report that preterm children are at increased risk of impaired growth in childhood (14,15). We did not see a statistically significant difference in the length of hospital admissions, as a surrogate marker for disease activity, that could explain the observed decrease in WFA SDS in the individualized PN group. As body composition was not measured in this study, it should be emphasized that the observed increase in WFA SDS in the standardized group might be because of an undesirable increase in fat mass.

After age matching, we also observed an increase in WFA SDS in the standardized group over 24 months and a decrease in the individualized group. However, the observed differences did not reach statistical significance.

The standardized PN group received 17 calories/kg/day less than their calculated nutritional need via parenteral and enteral nutrition combined. In the individualized PN group, the deficit was 4 calories/kg/day. These findings contradict the differences in WFA SDS change described. The nutritional deficit did not statistically correlate with WFA SDS change. These findings were also observed in the age-matched cohort. Therefore, it seems reasonable to exclude the deficit of provided (par)enteral nutrients as a reason for the observed weight loss in this cohort. A possible explanation could be the fact that the physician, in reaction to an increase in WFH SDS, decreased the amount of prescribed calories. The amount of oral intake was not noted in patient medical charts. Furthermore, it is not known to which degree enterally provided nutrients are absorbed. As such the observed discrepancy between intake and weight gain could not be elucidated by the available data. These findings imply that the group receiving standardized PN mixtures had less 'severe' IF, which could explain the observed difference in weight gain.

In recent studies in neonates, similar results were seen regarding growth difference between infants receiving either individualized or standardized PN mixtures. For example, Evering et al found that premature infants (GA < 32 weeks) receiving standardized PN mixtures had the highest cumulative weight gain compared with infants receiving individualized or partially standardized mixtures. Authors stated that (partially) standardized PN mixtures were at least noninferior to individualized PN mixtures (16).

Regarding electrolyte abnormalities, we found no significant differences between the 2 groups (entire cohort and age-matched cohort). In both groups, no child needed to be admitted to hospital because of electrolyte imbalances. Also, we did not see a difference in the amount of abnormal liver tests or total and conjugated bilirubin concentrations between the groups. This is in accordance with several other studies, which also did not report an increase in biochemical abnormalities in patients receiving standardized PN mixtures (17,18). Micronutrient supplementation was similar in both groups, and therefore, not analyzed.

Strength of this study is that this is the first study investigating the efficacy and safety of standardized and individualized PN mixtures in home PN patients with a follow-up of 2 years. As stated by the Cochrane handbook, adverse events can generally best be assessed over a longer time period than most randomized clinical trials report (19).

There are some methodological limitations to this study. First, because of the retrospective character of this study, results concerning nutritional intake should be interpreted with caution. Second, the amount of included subjects is low and heterogeneous, which is common in studies concerning the pediatric chronic IF population because of the low prevalence (7,8). Additionally, the 2 groups of patients differ on the duration of PN therapy, age, gestational age, and the amount of days PN is infused. Age matching resulted in 2 comparable groups, however, the sample size in the age-matched cohort is small, which reduced the power of statistical tests in finding a significant difference. Finally, as mentioned before, some possible confounders for weight gain could not be taken into account.

Future studies should be done in an international collaboration initiative, such as the European reference network on rare inherited and congenital anomalies (ERNICA) or by the European society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN).

Studies should also assess the amount of oral caloric intake and investigations of nutrient losses by bomb calorimetry to be able to calculate the absorption of enteral nutrition. Furthermore, the measurement of energy expenditure by indirect calorimetry could provide useful data in assessing the role of underfeeding as a

possible confounder. Lastly, data on body composition could give interesting insights in the effects of both types of nutrition on the child receiving home PN (20).

CONCLUSIONS

In children with chronic IF over 2.5 years of age, standardized PN mixtures (with added micronutrients) show a comparable effect on WFA, HFA, and WFH compared with individualized PN. Furthermore, standardized PN mixtures are at least noninferior to individualized PN mixtures in terms of basic biochemical abnormalities in a home PN cohort. Therefore, standardized PN mixtures can be considered for patients with chronic IF older than 2.5 years who have stable nutritional needs if the composition of this mixture meets the nutritional need of the patient.

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REFERENCES

- Goulet O, Ruemmele F. Causes and management of intestinal failure in children. *Gastroenterology* 2006;130:S16–28.
- Pironi L. Definitions of intestinal failure and the short bowel syndrome. *Best Pract Res Clin Gastroenterol* 2016;30:173–85.
- Abi Nader E, Lambe C, Talbotec C, et al. Outcome of home parenteral nutrition in 251 children over a 14-y period: report of a single center. *Am J Clin Nutr* 2016;3:1327–36.
- D'Antiga L, Goulet O. Intestinal failure in children: the European view. *J Pediatr Gastroenterol Nutr* 2013;56:118–26.
- Diamanti A, Basso MS, Castro M, et al. Irreversible intestinal failure: prevalence and prognostic factors. *J Pediatr Gastroenterol Nutr* 2006;47:450–7.
- Mangalat N, Teckman J. Pediatric intestinal failure review. *Child* 2018;5:E100.
- Neelis EG, van Oers HA, Escher JC, et al. Treatment of children with intestinal failure: intestinal rehabilitation, home parenteral nutrition or small intestine transplantation? *Ned Tijdschr Geneesk* 2014;158:A7771.
- Diamanti A, Capriati T, Gandullia P, et al. Pediatric chronic intestinal failure in Italy: report from the 2016 survey on behalf of Italian Society for Gastroenterology, Hepatology and Nutrition (SIGENP). *Nutrients* 2017;9:pii: E1217.
- Riskin A, Picaud JC, Shamir R. ESPGHAN/ESPEN/ESPR guidelines on pediatric parenteral nutrition: standard versus individualized parenteral nutrition. *Clin Nutr* 2018;37 (6 Pt B):2409–17.
- Hill S, Ksiazek J, Prell C, et al., ESPGHAN/ESPEN/ESPR/CSPEN working group on pediatric parenteral nutrition. ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition: home parenteral nutrition. *Clin Nutr* 2018;37 (6 Pt B):2401–8.
- Schonbeck Y, Talma H, van Dommelen P, et al. The world's tallest nation has stopped growing taller: the height of Dutch children from 1955 to 2009. *Pediatr Res* 2013;73:371–7.
- Joosten K, Embleton N, Yan W, et al., ESPGHAN/ESPEN/ESPR/CSPEN working group on pediatric parenteral nutrition. ESPGHAN/ESPEN/ESPR guidelines on pediatric parenteral nutrition: energy. *Clin Nutr* 2018;37 (6 Pt B):2309–14.
- Mirtallo J, Canada T, Johnson D, et al. Safe practices for parenteral nutrition. *JPEN J Parenter Enter Nutr* 2004;28:S39–70.
- Pampanini V, Boiani A, De Marchis C, et al. Preterm infants with severe extrauterine growth retardation (EUGR) are at high risk of growth impairment during childhood. *Eur J Pediatr* 2015;174:33–41.
- Ford GW, Doyle LW, Davis NM, et al. Very low birth weight and growth into adolescence. *Arch Pediatr Adolesc Med* 2000;154:778–84.
- Evering VH, Andriessen P, Duijsters CE, et al. The effect of individualized versus standardized parenteral nutrition on body weight in very preterm infants. *J Clin Med Res* 2017;9:339–44.
- Iacobelli S, Bonsante F, Vintejeux A, et al. Standardized parenteral nutrition in preterm infants: early impact on fluid and electrolyte balance. *Neonatology* 2010;98:84–90.
- Krohn K, Babl J, Reiter K, et al. Parenteral nutrition with standard solutions in paediatric intensive care patients. *Clin Nutr* 2005;24:274–80.
- Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions. *The Cochrane Collaboration* 2011.
- Neelis E, Olieman J, Rizopoulos D, et al. Growth, body composition and micronutrient abnormalities during and after weaning off home parenteral nutrition. *J Pediatr Gastroenterol Nutr* 2018;67:e95–100.