Quality of newborn care: Adherence to guidelines for parenteral nutrition in preterm infants in in Four European Countries

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ARTICLE SUMMARY –

'Article focus':

- Optimal nutritional care is critical for neonatal intensive care unit patients and associated with improved outcomes in later life.
- Clinical practice guidelines for parenteral nutrition exist, however, current clinical practice in Europe and compliance with these recommendations is unknown.
- The main objective was to assess the adherence to guidelines for parenteral nutrition in preterm infants in Four European Countries.

'Key messages'

- The initiation of PN is still frequently not compliant with current recommendations, with the main differences observed during the first days of life.
- There is an urgent need to improve dissemination of guidelines and to facilitate translation of knowledge into clinical practice.
- Web-based standard reporting systems that determine the actual compliance of in-house protocols with guidelines should be developed in parallel to determine to what extent new guidelines are translated into clinical practice.

'Strengths and limitations of this study' section.

Strengths:

- Nutrition for preterm infants is a hot topic in the field of neonatology.
- Large survey in 4 European countries that included 74% of the units of the 4 countries
- Surveys reflect one of the first steps of the dissemination of guidelines and, thus, provides insight on compliance to guidelines

Limitations

- Surveys reflect the intention to treat of the personnel from the NICU that respond to the survey, and may not reflect the actual clinical practice within the unit

ABSTRACT

Objective: Level of adherence to guidelines is often not known and should be explored particularly in preterm infants for which poor nutrition has major effects on outcomes in later life. The main objective was to evaluate compliance to international guidelines for parenteral nutrition (PN) in preterm infants across Neonatal intensive care units (NICUs) of four European countries.

Design: Clinical practice survey by the mean of a questionnaire addressing routine PN protocols, awareness and implementation of guidelines.

Setting: NICUs in the United Kingdom, Italy, Germany and France.

Participants: One senior physician per unit; 199 units which represent 74% of the NICUs of the 4 countries.

Primary outcome measure: Adherence of unit protocol to international guidelines; **Secondary outcome measure**: Factors that influence adherence to guidelines.

Results: Eighty percent of the respondents stated that they were aware of some PN clinical practice guidelines. For amino acid infusion (AA), 63% of the respondents initiate AA on D0, 38% administer an initial dose of ≥ 1.5 g/kg/d to prevent a negative balance and 91% aim for a target dose for AA of 3 or 4 g/kg/d, as recommended. For lipid administration, 90% of the respondents initiate parenteral lipids during the first 3 days of life, 39% use an initial dose ≥ 1.0 g/kg/d, and 76% define the target dose for lipids as 3 to 4 g/kg/d, as recommended. Significant variations in PN protocols were observed among countries but the type of hospital or the number of admissions per year had only a marginal impact on the PN protocols.

Conclusions: Clinicians initiate PN earlier than in the past but the initiation of PN is still frequently not compliant with international guidelines. Continuous education focusing on parenteral nutrition practice is needed, and greater efforts are required to disseminate and implement international guidelines.

Abbreviations:

AA – amino acids; D0 – the first day of life; ELBW – extremely low birth weight; EN – enteral nutrition; NICU – neonatal intensive care unit; PN – parenteral nutrition; UK – United Kingdom; US – United States of America; VLBW – very low birth weight

INTRODUCTION

Poor nutrition in preterm infants has major effects on outcomes in later life, including physical growth, intellectual development and, possibly, cardiovascular and metabolic effects.[1, 2] The quality and quantity of daily nutritional intake is critical particularly during the first weeks of life since amino acid, energy and lipid intake from parenteral nutrition have been shown to be associated with later development.[3, 4] Reports from neonatal intensive care units (NICUs) worldwide have shown that nutritional intake in preterm infants is inadequate.[5, 6] The causes of this inadequate intake, particularly in the early neonatal phase, may be multifactorial and partly iatrogenic. It may depend not only on the infant's metabolic capacities, but also on the availability and safety of the solutions used, the type of venous access, the department's usual practice, and the prescriber's knowledge of the infant's nutritional needs.[7]

Clinical practice guidelines for the nutritional needs of preterm infants have been regularly revised over recent decades, leading to the development of the most recent international guidelines on pediatric parenteral nutrition (PN) in Europe from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN) in 2005 [8] and globally in the book entitled "Nutritional needs of the preterm infant: Scientific basis and practical guidelines" also published in 2005.[9] (Table 1) Previous studies, especially those performed before current clinical practice guidelines were available, demonstrated large differences in both the nutritional protocols applied in clinical practice and the resulting clinical outcomes.[6, 10, 11] A recent systematic review showed that large differences are observed in the nutritional protocols both among the NICUs in the individual surveys and among surveys.[12]

Level of adherence to guidelines is often not known and it remains unclear to what extent recommendations for early parenteral nutrition in NICU patients have been translated into routine clinical care in Europe. Therefore, we performed a clinical practice survey among NICU physicians in

four European countries to evaluate compliance to international guidelines for parenteral nutrition (PN) in preterm infants and to determine factors that influence compliance to guidelines.

METHODS

The survey questionnaire was developed under the lead of AL together with the coauthors. The survey was implemented in a web-based format by an independent company (GfK SE Division HealthCare, Nürnberg, Germany). It was conducted in a blinded manner between October 2009 and April 2010 among NICU physicians in Germany, the United Kingdom (UK), France and Italy in order to survey ~50 units per country. One author from each country provided a list of the largest NICUs using available data and their own knowledge of national and regional units, with at least one senior physician's name per unit. NICUs were selected for the study if they had high acuity or intensive care beds and >5 infants per week requiring parenteral nutrition. The senior physician from each NICU was contacted and asked to complete the survey questionnaire or delegate the task to a colleague devoting ≥20% of their time to patient care and with >3 years of clinical experience in neonatal intensive care. Where a response was not obtained other physicians from the same unit were approached, if available. The identity of the physicians contacted and requested to complete the survey remained blinded for the analysis and to all authors.

The survey questionnaire was developed in English and translated into German, French and Italian for use in the national language of each country. For the purpose of the survey, PN was defined as intravenous nutrition given via a central or peripheral line and containing fluids and any macro- or micronutrients. Respondents were instructed to consider only in-hospital neonatal intensive care patients. D0 was defined as the first day of life, D1 for the subsequent 24 h, and D2 and D3 the following days. The survey comprised sections to characterize the profile of the NICU, and routine clinical practice with respect to PN between D0 and D3. The survey assessed the logistical organization of PN within the hospital, the types of PN available and prescribed, and some of the

reasons for use or non-use of standard formulations, preferred product characteristics and awareness and implementation of local and international clinical practice guidelines. Only the unit profile, clinical practice parameters and awareness and implementation of guidelines were analyzed for this report.

Statistical analyses were restricted to completed questionnaires with evaluable results. Data were split to cross tabs with respect to various grouping variables. First class split variables consisted of tertiles or quartiles, which were computed on the average number of admissions to the neonatal intensive care unit per year by birth weight up to 1500 g. The second class of grouping factors comprised categorical variables such as hospital type or country. The goal was to examine the null hypothesis "No pairwise differences in proportions across subgroups". Null hypotheses were tested using χ^2-tests and rejected at the 5% error level.

RESULTS

Profile of the NICUs surveyed

A total of 199 NICUs were surveyed (45 from the UK, 55 from Germany, 49 from France and 50 from Italy) and their characteristics are presented in table 2. Overall, we surveyed 74% of the units of the 4 countries: 45/64 (70%) in the UK; 55/78 (71%) in Germany; 49/66 (74%) in France; 50/60 (83%) in Italy). One hundred sixty one of the 199 (81%) surveys were included in the analysis as 38 surveys were excluded due to invalid responses. The majority of invalid surveys came from units with less than 4 beds of high acuity care.

Awareness of nutritional guidelines

Eighty percent of physicians across all countries reported an awareness of nutritional guidelines, but less than 50% gave a source or specification (Table 3). There were inter-country differences for physicians reporting an awareness of clinical practice guidelines for neonatal or pediatric PN (Table 2). Respondents indicated that they agreed with most of the recommendations, with 66% and 70% of physicians from Germany and France and 46% and 53% in UK and Italy in strong agreement

(Figure 1). Overall, the physicians agreed less strongly with the statement "I obtain a copy, read and follow guidelines for parenteral nutrition in pediatric patients as soon as they become available" (Figure 1). When asked whether the lack of robust evidence on which the guidelines are based presented a barrier to implementation, 3% and 7% of the physicians from France and Italy agreed, in comparison to 9% and 12% of the respondents from Germany and the UK (Figure 2). About 60-70% of the physicians did not find current guidelines too complex and those from both the UK and Italy more often found the guidelines to be too theoretical to be used in clinical practice than respondents from Germany or France. Respondents from Germany were most likely to report relying on internal clinical practice protocols (Figure 2).

Adherence of unit protocol to international guidelines

Survey respondents were requested to provide information on the timing and composition of PN as summarized in table 4. With regards to initiation of PN, amino acids are initiated by 63% of the responding units on the first day of life (D0) and by 32% on D1. Amino acids were reported to be started at a dose of 1.0 g/kg/d or less by 60% overall. Glucose was administered at a starting dose of 6 or 7 g/kg/d by 71% of the NICUs surveyed. Lipid emulsions were initiated by 20% of the units on D0 and by an additional 48% on D1. Initial lipid dose was reported to be 0.5 or 1.0 g/kg/d by 98% of respondents. With regards to full parenteral nutrition, most NICUs (91%) reported a target dose for amino acids of 3 or 4 g/kg/d. Overall, 66% of the units administered a target dose of glucose of 15 or 16 g/kg/d, and 76% of the units administered a target dose of lipids of 3 or 4 g/kg/d.

Factors that influence adherence to guidelines

There was a significant effect of countries on parenteral nutrition practices (Table 4).

When the PN results were stratified by hospital type, no differences were observed in the initiation, starting or target dose of amino acids (Data not shown). University or teaching hospitals reported higher starting doses of glucose than other types of hospital (40% vs. 56% at 6 g/kg/d and 32% vs. 13% at 7 g/kg/d; p=0.022), but there was no significant difference in the target dose between the two types of institution. University or teaching hospitals also report initiation of lipid feeding earlier

than other institutions (initiation on D3 or later 5% vs. 20%; p=0.015), but with no significant difference in starting or target dose. The caloric targets between the two types of hospital were similar, but the normal maximal caloric intake prescribed were significantly different (p=0.008).

When the data were stratified by the number of admissions, the only category in which a significant difference was apparent was the day on which lipid feeding was initiated. Units with lower admissions rates were more likely to report initiation on D3 or later (p=0.011) (Data not shown).

DISCUSSION

This study represents the first survey of neonatal PN clinical practice behavior undertaken at the European level. This type of survey emphasizes how current practices differ from recommended guidelines and encourage clinicians to be aware of the potential for improvement. Since the objective of the study was to compare the data with international guidelines (table 4) we did not report and/or use local guidelines, if any, and for consistency, we mainly used for comparison the European guidelines which are widely available.[8]

Despite demonstrating apparent improvement in PN practices, the results presented here shows that 37% of neonatal units in Europe initiate amino acid feeding on D1 or later and not on D0 as recommended.[8] Moreover, 60% of the European respondents administer an initial dose of less than the required 1.5 g/kg/d to prevent a negative balance.[8] The apparent higher compliance with guideline recommendations to initiate amino acid infusion on D0 and a target dose of 3-4 g/kg/d in France may be attributable to a combination of commercially available binary standard solutions and/or awareness of a national survey on this topic and widely disseminated at the country level.[13]

Our study shows that whilst 90% of the NICUs surveyed provide early lipids, 21% of them provide a maximum dose lower than recommended. This is similar to other surveys suggesting that physicians do not comply easily with the guideline defining the optimal dose for parenteral lipids. Previous surveys have shown that the timing and dose of parenteral lipids vary between surveys to a scale

which is larger than that for amino acids.[12] It was also found that there was a lack of consensus between surveys on the contraindications for lipids and/or indication for stopping lipids. This may reflect the lack of scientific data and absence of clear guidance on this topic.

Awareness of some guidelines was reported by the majority of physicians completing the survey, although 21% claimed not to be aware of any guidelines. This may be of relevance when the 40% of respondents who do not provide amino acids on the first day of life are considered, highlighting a potential deficit in implementation of the guidelines. Limited access to standard solutions and specific country regulations on preparation may also be possible alternative explanations why guidelines have not been translated into clinical practice.

University/teaching hospitals provided a higher starting dose of glucose and initiated lipid and amino acid infusion earlier compared to other institutions. Similarly, late initiation of lipid infusion (D3 or later) was less common in NICUs with a highest number of admissions per year. While these results may suggest better adherence to treatment guidelines at hospitals with a high number of admissions, the existing data are unclear as to whether high numbers of admissions are also associated with lower rates of mortality or morbidity.[14, 15]

The methodological limitations of using surveys for the assessment of nutritional protocols have been previously discussed in detail [13] and it should be reiterated that these surveys reflect the intention to treat of the personnel from the NICU that respond to the survey, and may not reflect the actual clinical practice within the unit. Nevertheless, intention to treat reflects one of the first steps of the dissemination of guidelines and, thus, provides insight on compliance to guidelines. The number of countries participating in our survey was limited to 4 for practical reasons and, therefore, the results obtained do not permit conclusions that apply to other European countries. The number of surveys received represents a substantial proportion of NICUs in each of the 4 countries; however, the number of invalid surveys indicates that there may have been some confusion with respect to terminology or intent. Interestingly, the invalid responses were mainly seen in smaller units which

are less likely to prescribe PN. This is in line with the observation that larger units prescribe PN that are more likely compliant with guidelines.

Finally, our results allow comparison of current practices among countries but also historical comparison with similar surveys published earlier.[12] When compared to studies performed in the United States [16] or individual European countries [17-20], our study shows that PN in preterm neonates is provided earlier and in higher volumes than in the past, reflecting changing clinical practice in response to increased knowledge about parenteral feeding in neonates, even if the practices are still not perfectly in line with guidelines.

In conclusion, most respondents indicated that their clinical practice was based on common guidelines. They are initiating parenteral nutrition earlier and in larger volumes than in the past, reflecting increased knowledge about best nutritional practices in very preterm neonates. However, the initiation of PN is still frequently not compliant with current recommendations, with the main differences observed during the first days of life. Our study shows that there is an urgent need to improve dissemination of guidelines and to facilitate translation of knowledge into clinical practice. Given the need for continuous monitoring, it would be of value for scientific societies (particularly those that publish guidelines) to develop web-based standard reporting systems that determine the actual compliance of in-house protocols with guidelines. In the case of the nutrition for preterm infants, a limited number of questions on access to PN and the dose of nutrients given would be sufficient to provide insight on the implementation of guidelines at a local level.

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CONFLICT OF INTEREST STATEMENT:

The authors have no conflicts of interest relevant to this article to disclose.

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Figure legends

Figure 1. Use of international clinical practice recommendations to guide neonatal parenteral nutrition by country.

Figure 2. Justification for non-implementation of international clinical practice guidelines by country.

Tables

Table 1. International recommendations for parenteral nutrition in preterm infants.

	Tsang et al., 2005[9]	ESPEN/ESPGHAN/ESPR guidelines, 2005[8]
Amino acids		
initiation	1st day of life	1st day of life
initial dose, g/kg/d	2	≥1.5
target dose, g/kg/d	3.5-4 (ELBW) 3.2-3.8 (VLBW)	maximum 4
Glucose		
initiation	1st day of life	1st day of life
initial dose, g/kg/d	7	5.8-11.5
target dose, g/kg/d	13-17 (ELBW) 9.7-15 (VLBW)	--
Lipids		
initiation	1st day of life (VLBW) Cautious support for ELBW	No later than 3rd day
initial dose, g/kg/d	≥1	Linoleic acid >0.25
target dose, g/kg/d	3-4	3-4
Energy		
caloric target, g/kg/d	105-115 (ELBW) 90-100 (VLBW)	110-120

VLBW: very low birth weight infants; ELBW: extremely low birth weight infants; --, no recommendation provided
ESPEN/ESPGHAN/ESPR, European Society for Clinical Nutrition and Metabolism, European Society of Paediatric Gastroenterology, Hepatology and Nutrition, European Society of Paediatric Research

Table 2. Characteristics of participating NICUs.

Characteristic	TOTAL	Germany	UK	France	Italy
Questionnaires received, n	199	55	45	49	50
Questionnaires analyzed, n	161	54	39	49	19
Type of hospital, n (%)					
University/teaching hospital	106 (66)	44 (82)	27 (69)	31 (63)	4 (21)
Non-university	55 (34)	10 (19)	12 (31)	18 (37)	15 (79)
Bed capacity per unit, n (%)					
1-5	19 (12)	2 (4)	8 (21)	3 (6)	6 (32)
6-10	73 (45)	22 (41)	21 (54)	23 (47)	7 (37)
11-15	45 (28)	18 (33)	5 (13)	19 (39)	3 (16)
≥16	24 (15)	12 (22)	5 (13)	4 (8)	3 (16)
Intermediate care beds per unit, n (%)					
1-5	30 (19)	13 (24)	5 (13)	4 (8)	8 (42)
6-10	56 (35)	16 (30)	15 (39)	17 (35)	8 (42)
11-15	33 (21)	9 (17)	6 (15)	15 (31)	3 (16)
≥16	38 (24)	14 (26)	13 (33)	11 (22)	6 (12)
NR	4 (3)	2 (4)	0 (0)	2 (4)	0 (0)
VLBW infants per year, median (IQR)	90.0 (129.00-60.00)	64 (86.25-40.00)	105 (160.00-80.00)	125 (195.00-98.00)	75 (90.00-55.00)

NR, no response
IQR, interquartile range
(Percentages do not necessarily sum up to 100% due to rounding)

Table 3. Guideline awareness by country.

Question	TOTAL	Germany	UK	France	Italy
	n (%)	n (%)	n (%)	n (%)	n (%)
Are you aware of guidelines for use of neonatal / pediatric parenteral nutrition? (asymptotic significance 0.073)					
Yes	128 (80)	47 (87)	33 (85)	33 (67)	15 (79)
No	33 (21)	7 (13)	6 (15)	16 (33)	4 (21)
Of which guidelines are you aware?*					
International[8, 21]	33 (26)	10 (21)	9 (27)	10 (30)	4 (27)
National	24 (19)	16 (34)	2 (6)	0 (0)	6 (40)
In-house guidelines	8 (6)	4 (9)	2 (6)	0 (0)	2 (13)
None specifically named/other	66 (52)	19 (40)	17 (52)	24 (73)	6 (40)

*More than one answer per questionnaire possible.

(Percentages do not necessarily sum up to 100% due to rounding)

Table 4. Current practice for parenteral nutrition in NICU patients.

Nutrient	TOTAL n (%)	Germany n (%)	UK n (%)	France n (%)	Italy n (%)
Amino acids					
Initiation (p=0.005)					
D0	101 (63)	32 (59)	21 (54)	41 (84)	7 (37)
D1	51 (32)	19 (35)	15 (39)	8 (16)	9 (47)
D2 or later	9 (6)	3 (6)	3 (8)	0 (0)	3 (16)
Initial dose (p=0.001)					
0.5 g/kg/d	44 (27)	20 (37)	11 (28)	5 (10)	8 (42)
1.0 g/kg/d	53 (33)	14 (26)	9 (23)	24 (49)	6 (32)
1.5 g/kg/d	34 (21)	5 (9)	11 (28)	15 (31)	3 (16)
2 g/kg/d or higher	27 (17)	15 (28)	5 (13)	5 (10)	2 (11)
Do not know	3 (2)	0 (0)	3 (8)	0 (0)	0 (0)
Target dose (p<0.001)					
1 or 2 g/kg/d	11 (7)	6 (11)	3 (8)	0 (0)	2 (11)
3 or 4 g/kg/d	146 (91)	48 (89)	34 (87)	49 (100.0)	15 (79)
5 g/kg/d or higher / Do not know	4 (3)	0 (0)	2 (5)	0 (0)	2 (11)
Glucose					
Initial dose (p<0.001)					
6 g/kg/d	73 (45)	27 (50)	12 (31)	19 (39)	15 (79)
7 g/kg/d	41 (26)	18 (33)	3 (8)	18 (37)	2 (11)
8 g/kg/d	28 (17)	6 (11)	9 (23)	12 (25)	1 (5)
9 g/kg/d or higher	17 (11)	3 (6)	13 (33)	0 (0)	1 (5)
Do not know	2 (1)	0 (0)	2 (5)	0 (0)	0 (0)
Target dose (p<0.001)					
15 g/kg/d	68 (42)	22 (41)	21 (54)	8 (16)	17 (90)

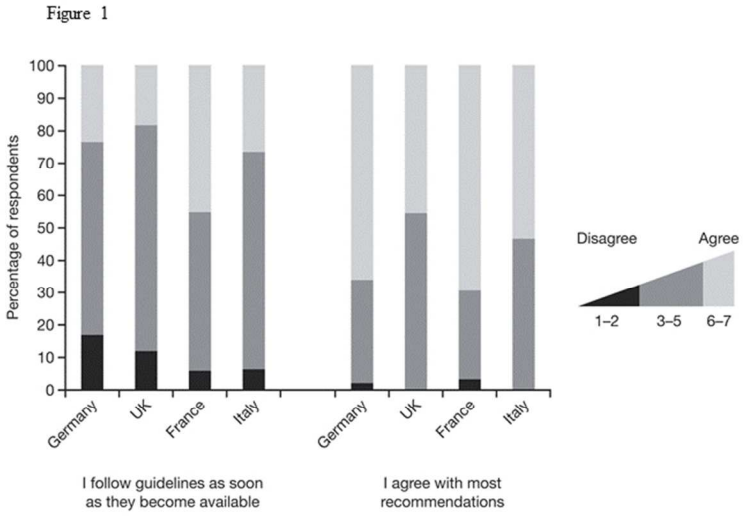
16 g/kg/d	38 (24)	14 (26)	5 (13)	18 (37)	1 (5)
17 g/kg/d	12 (8)	5 (9)	2 (5)	5 (10)	0 (0)
18 g/kg/d or higher	32 (20)	10 (19)	3 (8)	18 (37)	1 (5)
Do not know	11 (7)	3 (6)	8 (21)	0 (0)	0 (0)
Lipids					
Initiation (p=0.160)					
D0	32 (20)	12 (22)	12 (31)	3 (6)	5 (26)
D1	77 (48)	24 (44)	17 (44)	28 (57)	8 (42)
D2	36 (22)	11 (20)	9 (23)	11 (22)	5 (26)
D3 or later	16 (10)	7 (13)	1 (3)	7 (14)	1 (5)
Do not know	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Initial dose (p<0.001)					
0.5 g/kg/d	98 (61)	34 (63)	11 (28)	36 (74)	17 (90)
1.0 g/kg/d	59 (37)	18 (33)	27 (70)	13 (27)	1 (5)
1.5 g/kg/d or higher	3 (2)	2 (4)	0 (0)	0 (0)	1 (5)
Do not know	1 (1)	0 (0)	1 (3)	0 (0)	0 (0)
Target dose (p= 0.028)					
1 or 2 g/kg/d	34 (21)	15 (28)	3 (8)	9 (18)	7 (37)
3 or 4 g/kg/d	123 (76)	38 (70)	33 (85)	40 (82)	12 (63)
5 g/kg/d or higher / Do not know	4 (3)	1 (2)	3 (8)	0 (0)	0 (0)
Caloric target (p<0.001)					
90 or 100 kcal/kg/d	29 (18)	3 (6)	15 (39)	3 (6)	8 (42)
110 kcal/kg/d	28 (17)	8 (15)	6 (15)	11 (22)	3 (16)
120 kcal/kg/d	65 (40)	25 (46)	10 (26)	26 (53)	4 (21)
130 or more	35 (22)	18 (33)	4 (10)	9 (18)	4 (21)
Do not know	4 (3)	0 (0)	4 (10)	0 (0)	0 (0)
Maximal caloric intake prescribed (p<0.001)					
110 kcal/kg/d	13 (8)	1 (2)	7 (18)	3 (6)	2 (11)

120 kcal/kg/d	36 (22)	9 (17)	12 (31)	9 (18)	6 (32)
130 kcal/kg/d	32 (20)	10 (19)	4 (10)	12 (25)	6 (32)
140 kcal/kg/d	37 (23)	16 (30)	2 (5)	18 (37)	1 (5)
150 kcal/kg/d or more	34 (21)	18 (33)	6 (15)	6 (12)	4 (21)
Do not know	9 (6)	0 (0)	8 (21)	1 (2)	0 (0)

D0, D1, D2; day 0, day 1, day 2

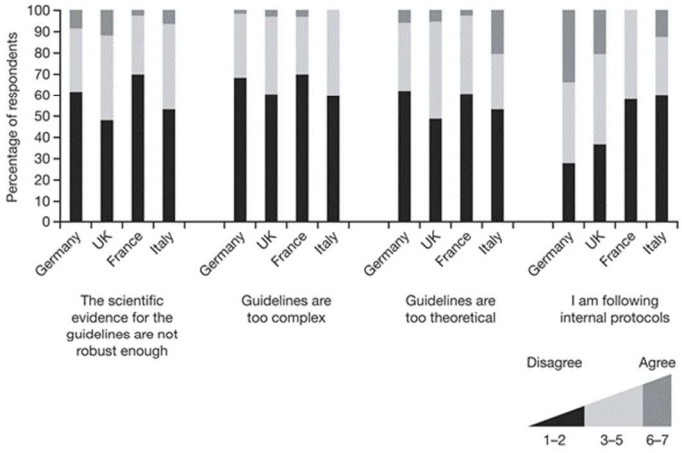
(Percentages do not necessarily sum up to 100% due to rounding)

Figure 1



Use of international clinical practice recommendations to guide neonatal parenteral nutrition by country.
254x366mm (72 x 72 DPI)

Figure 2



Justification for non-implementation of international clinical practice guidelines by country
254x366mm (72 x 72 DPI)

Table S1. PN with amino acids, glucose and lipids by type of hospital.

Nutrient	TOTAL n (%)	University/teaching hospital n (%)	Other hospital types n (%)
Amino acids			
Initiation (p=0.069)			
D0	101 (63)	71 (67)	30 (55)
D1	51 (32)	32 (30)	19 (35)
D2 or later	9 (6)	3 (3)	6 (11)
Initial dose (p=0.656)			
0.5 g/kg/d	44 (27)	28 (26)	16 (29)
1.0 g/kg/d	53 (33)	34 (32)	19 (35)
1.5 g/kg/d	34 (21)	23 (22)	11 (20)
2 g/kg/d or higher	27 (17)	20 (19)	7 (13)
Do not know	3 (2)	1 (1)	2 (4)
Target dose (p=0.213)			
1 or 2 g/kg/d	11 (7)	7 (7)	4 (7)
3 or 4 g/kg/d	146 (91)	98 (93)	48 (87)

5 g/kg/d or higher / Do not know	4 (3)	1 (1)	3 (6)
Glucose			
Initial dose (p=0.022)			
6 g/kg/d	73 (45)	42 (40)	31 (56)
7 g/kg/d	41 (26)	34 (32)	7 (13)
8 g/kg/d	28 (17)	19 (18)	9 (16)
9 g/kg/d or higher	17 (11)	11 (10)	6 (11)
Do not know	2 (1)	0 (0)	2 (4)
Target dose (p=0.160)			
15 g/kg/d	68 (42)	40 (38)	28 (51)
16 g/kg/d	38 (24)	29 (27)	9 (16)
17 g/kg/d	12 (8)	8 (8)	4 (7)
18 g/kg/d or higher	32 (20)	24 (23)	8 (15)
Do not know	11 (7)	5 (5)	6 (11)
Lipids			
Initiation (p=0.015)			
D0	32 (20)	24 (23)	8 (15)

D1	77 (48)	54 (51)	23 (42)
D2	36 (22)	23 (22)	13 (24)
D3 or later	16 (10)	5 (5)	11 (20)
Do not know	0 (0)	0 (0)	0 (0)
Initial dose (p=0.126)			
0.5 g/kg/d	98 (61)	60 (57)	38 (69)
1.0 g/kg/d	59 (37)	43 (41)	16 (29)
1.5 g/kg/d or higher	3 (2)	3 (3)	0 (0)
Do not know	1 (1)	0 (0)	1 (2)
Target dose (p= 0.372)			
1 or 2 g/kg/d	34 (21)	19 (18)	15 (27)
3 or 4 g/kg/d	123 (76)	84 (79)	39 (71)
5 g/kg/d or higher / Do not know	4 (3)	3 (3)	1 (2)
Caloric target (p=0.155)			
90 or 100 kcal/kg/d	29 (18)	14 (13)	15 (27)
110 kcal/kg/d	28 (17)	20 (19)	8 (15)
120 kcal/kg/d	65 (40)	44 (42)	21 (38)

130 or more	35 (22)	24 (23)	11 (20)
Do not know	4 (3)	4 (4)	0 (0)
Maximal caloric intake prescribed (p=0.008)			
110 kcal/kg/d	13 (8)	11 (10)	2 (4)
120 kcal/kg/d	36 (22)	22 (21)	14 (26)
130 kcal/kg/d	32 (20)	14 (13)	18 (33)
140 kcal/kg/d	37 (23)	28 (26)	9 (16)
150 kcal/kg/d or more	34 (21)	22 (21)	12 (22)
Do not know	9 (6)	9 (9)	0 (0)

(Percentages do not necessarily sum up to 100% due to rounding)

Table S2. PN with amino acids, glucose and lipids by number of admissions.

Nutrient	TOTAL	Number of admissions 0 - 65	66 - 111	≥ 112
	n (%)	n (%)	n (%)	n (%)
Amino acids				
Initiation (p=0.262)				
D0	101 (63)	24 (52)	43 (69)	34 (64)
D1	51 (32)	17 (37)	17 (27)	17 (32)
D2 or later	9 (6)	5 (11)	2 (3)	2 (4)
Initial dose (p=0.611)				
0.5 g/kg/d	44 (27)	17 (37)	15 (24)	12 (23)
1.0 g/kg/d	53 (33)	16 (35)	19 (31)	18 (34)
1.5 g/kg/d	34 (21)	8 (17)	14 (23)	12 (23)
2 g/kg/d or higher	27 (17)	5 (11)	13 (21)	9 (17)
Do not know	3 (2)	0 (0)	1 (2)	2 (4)
Target dose (p=0.343)				

1 or 2 g/kg/d	11 (7)	6 (13)	3 (5)	2 (4)
3 or 4 g/kg/d	146 (91)	39 (85)	58 (94)	49 (93)
5 g/kg/d or higher / Do not know	4 (3)	1 (2)	1 (2)	2 (4)
Glucose				
Initial dose (p=0.504)				
6 g/kg/d	73 (45)	26 (57)	23 (37)	24 (45)
7 g/kg/d	41 (26)	8 (17)	21 (34)	12 (23)
8 g/kg/d	28 (17)	6 (13)	11 (18)	11 (21)
9 g/kg/d or higher	17 (11)	6 (13)	6 (10)	5 (9)
Do not know	2 (1)	0 (0)	1 (2)	1 (2)
Target dose (p=0.320)				
15 g/kg/d	68 (42)	24 (52)	24 (39)	20 (38)
16 g/kg/d	38 (24)	9 (20)	14 (23)	15 (28)
17 g/kg/d	12 (8)	6 (13)	4 (7)	2 (4)
18 g/kg/d or higher	32 (20)	5 (11)	14 (23)	13 (25)
Do not know	11 (6.8)	2 (4.3)	6 (9.7)	3 (5.7)
Lipids				

Initiation (p=0.011)				
D0	32 (20)	10 (22)	16 (26)	6 (11)
D1	77 (48)	16 (35)	31 (50)	30 (57)
D2	36 (22)	11 (24)	9 (15)	16 (30)
D3 or later	16 (10)	9 (20)	6 (10)	1 (2)
Do not know	0 (0)	0 (0)	0 (0)	0 (0)
Initial dose (p=0.246)				
0.5 g/kg/d	98 (61)	31 (67)	37 (60)	30 (57)
1.0 g/kg/d	59 (37)	15 (33)	22 (36)	22 (42)
1.5 g/kg/d or higher	3 (2)	0 (0)	3 (5)	0 (0)
Do not know	1 (1)	0 (0)	0 (0)	1 (2)
Target dose (p= 0.224)				
1 or 2 g/kg/d	34 (21)	15 (33)	10 (16)	9 (17)
3 or 4 g/kg/d	123 (76)	30 (65)	51 (82)	42 (79)
5 g/kg/d or higher / Do not know	4 (3)	1 (2)	1 (2)	2 (4)
Caloric target (p=0.107)				
90 or 100 kcal/kg/d	29 (18)	12 (26)	6 (10)	11 (21)

110 kcal/kg/d	28 (17)	11 (24)	7 (11)	10 (19)
120 kcal/kg/d	65 (40)	13 (28)	32 (52)	20 (38)
130 or more	35 (22)	10 (22)	14 (23)	11 (21)
Do not know	4 (3)	0 (0)	3 (5)	1 (2)
Maximal caloric intake prescribed (p=0.199)				
110 kcal/kg/d	13 (8)	5 (11)	3 (5)	5 (10)
120 kcal/kg/d	36 (22)	10 (22)	10 (16)	16 (30)
130 kcal/kg/d	32 (20)	12 (26)	11 (18)	9 (17)
140 kcal/kg/d	37 (23)	7 (15)	19 (31)	11 (21)
150 kcal/kg/d or more	34 (21)	12 (26)	13 (21)	9 (17)
Do not know	9 (6)	0 (0)	6 (10)	3 (6)

(Percentages do not necessarily sum up to 100% due to rounding)

Quality of newborn care: Adherence to guidelines for parenteral nutrition in preterm infants in in Four European Countries

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Quality of newborn care: Adherence to guidelines for parenteral nutrition in preterm infants in Four European Countries

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ARTICLE SUMMARY –

'Article focus':

- Optimal nutritional care is critical for neonatal intensive care unit patients and associated with improved outcomes in later life.
- Clinical practice guidelines for parenteral nutrition exist, however, current clinical practice in Europe and compliance with these recommendations is unknown.
- The main objective was to assess the adherence to guidelines for parenteral nutrition in preterm infants in four European Countries.

'Key messages'

- The initiation of PN is frequently not compliant with current recommendations, with the main differences observed during the first days of life.
- There is an urgent need to improve dissemination of guidelines and to facilitate translation of knowledge into clinical practice.
- Web-based standard reporting systems that determine the actual compliance of in-house protocols with guidelines should be developed in parallel to determine to what extent new guidelines are translated into clinical practice.

'Strengths and limitations of this study' section.

Strengths:

- Nutrition for preterm infants is a hot topic in the field of neonatology.
- Large survey in 4 European countries that included 74% of the units of the 4 countries
- Surveys reflect one of the first steps of the dissemination of guidelines and, thus, provides insight on compliance to guidelines

Limitations

- Surveys reflect the intention to treat of the personnel from the NICU that respond to the survey, and may not reflect the actual clinical practice within the unit

ABSTRACT

Objective: Level of adherence to guidelines should be explored particularly in preterm infants for which poor nutrition has major effects on outcomes in later life. The objective was to evaluate compliance to international guidelines for parenteral nutrition (PN) in preterm infants across Neonatal intensive care units (NICUs) of four European countries.

Design: Clinical practice survey by the mean of a questionnaire addressing routine PN protocols, awareness and implementation of guidelines.

Setting: NICUs in the United Kingdom, Italy, Germany and France.

Participants: One senior physician per unit; 199 units which represent 74% of the NICUs of the 4 countries.

Primary outcome measure: Adherence of unit protocol to international guidelines; **Secondary outcome measure**: Factors that influence adherence to guidelines.

Results: 80% of the respondents stated that they were aware of some PN clinical practice guidelines. For amino acid infusion (AA), 63% of the respondents aim to initiate AA on D0, 38% aim to administer an initial dose ≥1.5 g/kg/d and 91% aim for a target dose of 3 or 4 g/kg/d, as recommended. For parenteral lipids, 90% of the respondents aim to initiate parenteral lipids them during the first 3 days of life, 39% aim to use an initial dose ≥1.0 g/kg/d, and 76% define the target dose as 3 to 4 g/kg/d, as recommended. Significant variations in PN protocols were observed among countries but the type of hospital or the number of admissions per year had only a marginal impact on the PN protocols.

Conclusions: Most respondents indicate that their clinical practice was based on common guidelines. However, the initiation of PN is frequently not compliant with current recommendations, with the main differences observed during the first days of life. Continuous education focusing on parenteral nutrition practice is needed, and greater efforts are required to disseminate and implement international guidelines.

Abbreviations:

AA – amino acids; D0 –day of birth; ELBW – extremely low birth weight; EN – enteral nutrition; NICU – neonatal intensive care unit; PN – parenteral nutrition; UK – United Kingdom; US – United States of America; VLBW – very low birth weight

INTRODUCTION

Poor nutrition in preterm infants has major effects on outcomes in later life, including physical growth, intellectual development and, possibly, cardiovascular and metabolic effects.[1, 2] The quality and quantity of daily nutritional intake is critical particularly during the first weeks of life since amino acid, energy and lipid intake from parenteral nutrition have been shown to be associated with later development.[3, 4] Reports from neonatal intensive care units (NICUs) worldwide have shown that nutritional intake in preterm infants is inadequate.[5, 6] The causes of this inadequate intake, particularly in the early neonatal phase, may be multifactorial and partly iatrogenic. It may depend not only on the infant's metabolic capacities, but also on the availability and safety of the solutions used, the type of venous access, the department's usual practice, and the prescriber's knowledge of the infant's nutritional needs.[7]

Clinical practice guidelines for the nutritional needs of preterm infants have been regularly revised over recent decades, leading to the development of the most recent international guidelines on pediatric parenteral nutrition (PN) in Europe from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN) in 2005 [8], and globally in the book entitled "Nutritional needs of the preterm infant: Scientific basis and practical guidelines" also published in 2005.[9] (Table 1) Previous studies, especially those performed before current clinical practice guidelines were available, demonstrated large differences in both the nutritional protocols applied in clinical practice and the resulting clinical outcomes.[6, 10, 11] A recent systematic review showed that large differences are observed in the nutritional protocols both among the NICUs in the individual surveys and among surveys.[12]

Level of adherence to guidelines is often not known and it remains unclear to what extent recommendations for early parenteral nutrition in NICU patients have been translated into routine clinical care in Europe. Therefore, we performed a clinical practice survey among NICU physicians in

four European countries to evaluate compliance to international guidelines for parenteral nutrition (PN) in preterm infants and to determine factors that influence compliance to guidelines.

METHODS

The survey questionnaire was developed under the lead of AL together with the coauthors. The survey was conducted between October 2009 and April 2010 among NICU physicians in Germany, the United Kingdom (UK), France and Italy in order to survey ~50 units per country. One author from each country provided a list of the largest NICUs using available data and their own knowledge of national and regional units, with at least one senior physician's name per unit. NICUs were selected for the study if they had high acuity/intensive care beds, and >5 infants per week requiring parenteral nutrition. The senior physician from each NICU was contacted and asked to complete the survey questionnaire or delegate the task to a colleague devoting ≥20% of their time to patient care and with >3 years of clinical experience in neonatal intensive care. Where a response was not obtained other physicians from the same unit were approached, if available. The identity of the physicians contacted and requested to complete the survey remained blinded for the analysis and to all authors.

The survey questionnaire was developed in English and translated into German, French and Italian for use in the national language of each country. For the purpose of the survey, PN was defined as intravenous nutrition given via a central or peripheral line and containing fluids and any macro- or micronutrients. Respondents were instructed to consider only in-hospital neonatal intensive care patients. D0 was defined as the day of birth, D1 for the subsequent 24 h, and D2 and D3 the following days. The survey comprised sections to characterize the profile of the NICU, and routine clinical practice with respect to PN. The survey assessed the logistical organization of PN within the hospital, the types of PN available and prescribed, and some of the reasons for use or non-use of standard formulations, preferred product characteristics and awareness and implementation of local

and international clinical practice guidelines. Only the unit profile, the routine clinical practice with respect to PN, and awareness and implementation of guidelines were analyzed for this report.

The survey was implemented in a web-based format by an independent company (GfK SE Division HealthCare, Nürnberg, Germany). The authors and the sponsor were blinded with regard to the respondents' identities and with regard to the individual questionnaires. To best describe the macronutrient or energy provision, single choice questions were asked offering 6 possible answers, 5 with plausible intakes and one "do not know" response. To assess the extent of agreement with statements related to awareness and implementation of guidelines, questions were asked using a 7-point bipolar scale, 1 meant "do not agree at all" and 7 meant "fully agree".

Compliance to international guidelines for PN in preterm infants was made mainly by using the European ones since they have been published in a journal widely disseminated [8] and since they are also easily and freely accessible through the ESPEN website (http://espen.anavajo.com/espencms/index.php/education/espen-guidelines). NICUs were considered compliant to guidelines if: for amino acids, initiation = day of birth, initiation dose ≥1.5 g/kg/d, target dose = 3 to 4 g/kg/d; for glucose, initiation dose ≥7 g/kg/d, target dose = 10 to 17 g/kg/d; for lipids, initiation ≤day 3 of life, initiation dose ≥1 g/kg/d, target dose = 3 to 4 g/kg/d; energy, target dose = 110 to 120 kcal/kg/d.

Statistical analysis

Analyses were restricted to completed questionnaires with evaluable results. Data were split to cross tabs with respect to various grouping variables. Since infants with a birth weight below 1500g are those more likely receiving PN, splitting the data using this parameter was consider to better reflect the experience in prescribing PN than using the whole population of newborn admitted in a NICU. Therefore, first class split variables consisted of tertiles or quartiles, which were computed on the average number of admissions to the neonatal intensive care unit per year by birth weight up to 1500 g. The second class of grouping factors comprised categorical variables such as hospital type or

country. The goal was to examine the null hypothesis "No pairwise differences in proportions across subgroups". Null hypotheses were tested using χ^2-tests and rejected at the 5% error level.

Ethics

This study was conducted according to the guidelines in the Declaration of Helsinki. Since this study did not involve human subjects/patients or handling of medical records, ethical approval was not required.

RESULTS

Profile of the NICUs surveyed

A total of 199 NICUs were surveyed (45 from the UK, 55 from Germany, 49 from France and 50 from Italy) and their characteristics are presented in table 2. Overall, we surveyed 74% of the units of the 4 countries: 45/64 (70%) in the UK; 55/78 (71%) in Germany; 49/66 (74%) in France; 50/60 (83%) in Italy). One hundred sixty one of the 199 (81%) surveys were included in the analysis as 38 surveys were excluded due to invalid responses. The majority of invalid surveys came from units with the lower number of high acuity care beds (i.e., 50% of them had ≤ 5 high acuity care beds vs. 12%; $p<0.001$). The number of years of practice in neonatology of the physicians who completed the survey questionnaire was more than 10 years for 141 of them (71%), 5 to 9 years for 40 of them (20%), 3 to 5 years for 17 of them (8.5%) and 1 to 3 years for 1 of them (0.5%).

Adherence of unit protocol to international guidelines

Survey respondents were requested to provide information on the timing and composition of PN as summarized in table 3. Level of adherence of unit protocols to international guidelines was highly variable and varied according to the type of macronutrient (Figure 1). With regards to initiation of PN, amino acids were often initiated late, and both lipids and amino acids were initiated at a lower dose than recommended (Figure 1). With regards to full parenteral nutrition (i.e., target dose), most NICUs reported an adequate target dose for amino acids, lipids and glucose. In contrast, only half of

the units reported a target energy intake compliant with guidelines; ~20% reported a lower higher target than recommended and a similar percentage a higher target than recommended.

Factors that influence adherence to guidelines

Country, hospital type and size of unit.

There was a significant effect of countries on PN practices (Table 3). The patterns observed were the following: with regards to early PN, amino acids were started sooner and at a higher dose in France than in the other countries. A similar trend was seen for lipids in the UK where the starting dose of glucose was also higher than in the other countries. With regards to full PN (i.e., target dose), amino acid target dose was more likely within the recommendations in France than in other countries whereas glucose target dose was more likely within the recommendations in the UK and in Italy. The distribution for caloric target was wide; the units in France and Germany were more likely prescribing higher energy intake than recommended whereas lower energy intake was more likely seen in the UK and Italy.

When the PN results were stratified by hospital type, no differences were observed in the initiation, starting or target dose of amino acids (Data not shown). University or teaching hospitals reported higher starting doses of glucose than other types of hospital (40% vs. 56% at 6 g/kg/d and 32% vs. 13% at 7 g/kg/d; p=0.022), but there was no significant difference in the target dose between the two types of institution. University or teaching hospitals also reported initiation of lipid feeding earlier than other institutions (initiation on D3 or later 5% vs. 20%; p=0.015), but with no significant difference in starting or target dose. The caloric targets between the two types of hospital were similar, but the normal maximal caloric intake prescribed were significantly different (p=0.008).

When the data were stratified by the number of admissions, the only category in which a significant difference was apparent was the day on which lipid feeding was initiated. Units with lower admissions rates were more likely to report initiation on D3 or later (p=0.011) (Data not shown).

Awareness of nutritional guidelines

Eighty percent of physicians across all countries reported an awareness of nutritional guidelines, but less than 50% gave a source or specification (Table 4). There were inter-country differences for physicians reporting an awareness of clinical practice guidelines for neonatal or pediatric PN (Table 4). There was no significant association between being aware of guidelines for use of neonatal / pediatric PN and being compliant with international guidelines, but there was a trend for an association between being aware of guidelines and being compliant for the lipid target dose (p=0.054) and for the initiation of amino acids (p=0.070).

Respondents indicated that they agreed with most of the recommendations, with 66% and 70% of physicians from Germany and France and 46% and 53% in UK and Italy in strong agreement (Figure 2). Overall, the physicians agreed less strongly with the statement "I obtain a copy, read and follow guidelines for parenteral nutrition in pediatric patients as soon as they become available" (Figure 2). When asked whether the lack of robust evidence on which the guidelines are based presented a barrier to implementation, 3% and 7% of the physicians from France and Italy agreed, in comparison to 9% and 12% of the respondents from Germany and the UK (Figure 3). About 60-70% of the physicians did not find current guidelines too complex and those from both the UK and Italy more often found the guidelines to be too theoretical to be used in clinical practice than respondents from Germany or France. Respondents from Germany were most likely to report relying on internal clinical practice protocols (Figure 3).

DISCUSSION

This study represents the first survey of neonatal PN clinical practice behavior undertaken at the European level. This type of survey emphasizes how current practices differ from recommended guidelines and encourage clinicians to be aware of the potential for improvement. Since the objective of the study was to compare the data with international guidelines we did not report and/or use local guidelines, if any, and for consistency, we mainly used for comparison the European

guidelines which are widely available through both a publication widely referenced [8] and a website.

Despite demonstrating apparent improvement in PN practices, the results presented here shows that 37% of neonatal units in the 4 European countries surveyed initiate amino acid feeding on D1 or later and not on D0 as recommended.[8] Moreover, 60% of the European respondents administer an initial dose of less than the required 1.5 g/kg/d to prevent a negative balance.[8] The apparent higher compliance with guideline recommendations to initiate amino acid infusion on D0 and a target dose of 3-4 g/kg/d in France may be attributable to a combination of commercially available binary standard solutions and/or awareness of a national survey on this topic and widely disseminated at the country level.[13]

Our study shows that whilst 90% of the NICUs surveyed provide early lipids, 21% of them provide a maximum dose lower than recommended. This is similar to other surveys suggesting that physicians do not comply easily with the guideline defining the optimal dose for parenteral lipids. Previous surveys have shown that the timing and dose of parenteral lipids vary between surveys to a scale which is larger than that for amino acids.[12] It was also found that there was a lack of consensus between surveys on the contraindications for lipids and/or indication for stopping lipids. This may reflect the lack of scientific data and absence of clear guidance on this topic.

Awareness of some guidelines was reported by the majority of physicians completing the survey, although 21% claimed not to be aware of any guidelines. This may be of relevance when the 40% of respondents who do not provide amino acids on the day of birth are considered, highlighting a potential deficit in implementation of the guidelines. Limited access to standard solutions and specific country regulations on preparation may also be possible alternative explanations why guidelines have not been translated into clinical practice.

University/teaching hospitals provided a higher starting dose of glucose and initiated lipid and amino acid infusion earlier compared to other institutions. Similarly, late initiation of lipid infusion (D3 or later) was less common in NICUs with a highest number of admissions per year. While these results

may suggest better adherence to treatment guidelines at hospitals with a high number of admissions, the existing data are unclear as to whether high numbers of admissions are also associated with lower rates of mortality or morbidity.[14, 15]

The methodological limitations of using surveys for the assessment of nutritional protocols have been previously discussed in detail [13] and it should be reiterated that these surveys reflect the intention to treat of the personnel from the NICU that respond to the survey, and may not reflect the actual clinical practice within the unit. Nevertheless, intention to treat reflects one of the first steps of the dissemination of guidelines and, thus, provides insight on compliance to guidelines. The number of countries participating in our survey was limited to 4 for practical reasons and, therefore, the results obtained do not permit conclusions that apply to other European countries. The number of surveys received represents a substantial proportion of NICUs in each of the 4 countries; however, the number of invalid surveys indicates that there may have been some confusion with respect to terminology or intent. Interestingly, the invalid responses were mainly seen in the smaller units which are less likely to prescribe PN.

Finally, our results allow comparison of current practices among countries but also historical comparison with similar surveys published earlier.[12] When compared to studies performed in the United States [16] or individual European countries [17-20], our study shows that PN in preterm neonates is provided earlier and in higher volumes than in the past, reflecting changing clinical practice in response to increased knowledge about parenteral feeding in neonates, even if the practices are still not perfectly in line with guidelines.

In conclusion, most respondents indicate that their clinical practice was based on common guidelines. However, the initiation of PN in the 4 countries surveyed is frequently not compliant with current recommendations, with the main differences observed during the first days of life. Our study shows that there is an urgent need to improve dissemination of guidelines and to facilitate translation of knowledge into clinical practice. Given the need for continuous monitoring, it would be of value for scientific societies (particularly those that publish guidelines) to develop web-based

standard reporting systems that determine the actual compliance of in-house protocols with guidelines. In the case of the nutrition for preterm infants, a limited number of questions on access to PN and the dose of nutrients given would be sufficient to provide insight on the implementation of guidelines at a local level.

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CONFLICT OF INTEREST STATEMENT:

The authors have no conflicts of interest relevant to this article to disclose.

CONTRIBUTORSHIP

Alexandre Lapillonne served as one of the coordinators for the survey and participated in two face-to-face meetings to discuss the results. The manuscript was drafted by Alexandre Lapillonne. He also participated in the review, revision and approval of the manuscript and had access to all of the primary data.

Virgilio P. Carnielli served as one of the coordinators for the survey and participated in two face-to-face meetings to discuss the results. He also participated in the review, revision and approval of the manuscript and had access to all of the primary data.

Nicholas D. Embleton served as one of the coordinators for the survey and participated in two face-to-face meetings to discuss the results. He also participated in the review, revision and approval of the manuscript and had access to all of the primary data.

Walter Mihatsch served as one of the coordinators for the survey and participated in two face-to-face meetings to discuss the results. He also participated in the review, revision and approval of the manuscript and had access to all of the primary data.

DATA SHARING

See materiels et methods section: "The survey assessed the logistical organization of PN within the hospital, the types of PN available and prescribed, and some of the reasons for use or non-use of standard formulations, preferred product characteristics and awareness and implementation of local and international clinical practice guidelines. Only the unit profile, clinical practice parameters and awareness and implementation of guidelines were analyzed for this report."

The data are available to the authors and the sponsor.

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Figure legends

Figure 1. Percentage of NICUs (n=161) in Germany, France Italy and the United Kingdom compliant to guidelines for parenteral nutrition in preterm infants. NICUs were considered compliant to guidelines if: for amino acids, initiation = day of birth, initiation dose ≥1.5 g/kg/d, target dose = 3 to 4 g/kg/d; for glucose, initiation dose ≥7 g/kg/d, target dose = 10 to 17 g/kg/d; for lipids, initiation ≤day 3 of life, initiation dose ≥1 g/kg/d, target dose = 3 to 4 g/kg/d; energy, target dose = 110 to 120 kcal/kg/d.

Figure 2. Use of international clinical practice recommendations to guide neonatal parenteral nutrition by country.

Figure 3. Justification for non-implementation of international clinical practice guidelines by country.

Tables

Table 1. International recommendations for parenteral nutrition in preterm infants.

	Tsang et al., 2005[9]	ESPEN/ESPGHAN/ESPR guidelines, 2005[8]
Amino acids		
initiation	day of birth	day of birth
initial dose, g/kg/d	2	≥1.5
target dose, g/kg/d	3.5-4 (ELBW) 3.2-3.8 (VLBW)	maximum 4
Glucose		
initiation	day of birth	day of birth
initial dose, g/kg/d	7	5.8-11.5
target dose, g/kg/d	13-17 (ELBW) 9.7-15 (VLBW)	--
Lipids		
initiation	day of birth (VLBW) Cautious support for ELBW	No later than 3rd day
initial dose, g/kg/d	≥1	Linoleic acid >0.25 mg/kg/d
target dose, g/kg/d	3-4	3-4
Energy		
caloric target, g/kg/d	105-115 (ELBW) 90-100 (VLBW)	110-120

VLBW: very low birth weight infants; ELBW: extremely low birth weight infants; --, no recommendation provided
ESPEN/ESPGHAN/ESPR, European Society for Clinical Nutrition and Metabolism, European Society of Paediatric Gastroenterology, Hepatology and Nutrition, European Society of Paediatric Research

Table 2. Characteristics of participating NICUs.

Characteristic	TOTAL	Germany	UK	France	Italy
Questionnaires received, n	199	55	45	49	50
Questionnaires analyzed, n	161	54	39	49	19
Type of hospital, n (%)					
University/teaching hospital	106 (66)	44 (82)	27 (69)	31 (63)	4 (21)
Non-university	55 (34)	10 (19)	12 (31)	18 (37)	15 (79)
Highest acuity beds per unit, n (%)					
1-5	19 (12)	2 (4)	8 (21)	3 (6)	6 (32)
6-10	73 (45)	22 (41)	21 (54)	23 (47)	7 (37)
11-15	45 (28)	18 (33)	5 (13)	19 (39)	3 (16)
≥16	24 (15)	12 (22)	5 (13)	4 (8)	3 (16)
Intermediate care beds per unit, n (%)					
1-5	30 (19)	13 (24)	5 (13)	4 (8)	8 (42)
6-10	56 (35)	16 (30)	15 (39)	17 (35)	8 (42)
11-15	33 (21)	9 (17)	6 (15)	15 (31)	3 (16)
≥16	38 (24)	14 (26)	13 (33)	11 (22)	6 (12)
NR	4 (3)	2 (4)	0 (0)	2 (4)	0 (0)
VLBW infants per year, median (IQR)	90 (129-60)	64 (86-40)	105 (160-80)	125 (195-98)	75 (90-55)

NR, no response
VLBW, very low birth weight
IQR, interquartile range
(Percentages do not necessarily sum up to 100% due to rounding)

Table 3. Current practice for parenteral nutrition in NICU patients by country.

Nutrient	TOTAL n (%)	Germany n (%)	UK n (%)	France n (%)	Italy n (%)
Amino acids					
Initiation (p=0.005)					
D0	**101 (63)**	**32 (59)**	**21 (54)**	**41 (84)**	**7 (37)**
D1	51 (32)	19 (35)	15 (39)	8 (16)	9 (47)
D2 or later	9 (6)	3 (6)	3 (8)	0 (0)	3 (16)
Initial dose (p=0.001)					
0.5 g/kg/d	44 (27)	20 (37)	11 (28)	5 (10)	8 (42)
1.0 g/kg/d	53 (33)	14 (26)	9 (23)	24 (49)	6 (32)
1.5 g/kg/d	**34 (21)**	**5 (9)**	**11 (28)**	**15 (31)**	**3 (16)**
2 g/kg/d or higher	**27 (17)**	**15 (28)**	**5 (13)**	**5 (10)**	**2 (11)**
Do not know	3 (2)	0 (0)	3 (8)	0 (0)	0 (0)
Target dose (p<0.001)					
1 or 2 g/kg/d	11 (7)	6 (11)	3 (8)	0 (0)	2 (11)
3 or 4 g/kg/d	**146 (91)**	**48 (89)**	**34 (87)**	**49 (100.0)**	**15 (79)**
5 g/kg/d or higher / Do not know	4 (3)	0 (0)	2 (5)	0 (0)	2 (11)
Glucose					
Initial dose (p<0.001)					
6 g/kg/d	73 (45)	27 (50)	12 (31)	19 (39)	15 (79)
7 g/kg/d	**41 (26)**	**18 (33)**	**3 (8)**	**18 (37)**	**2 (11)**
8 g/kg/d	**28 (17)**	**6 (11)**	**9 (23)**	**12 (25)**	**1 (5)**
9 g/kg/d or higher	**17 (11)**	**3 (6)**	**13 (33)**	**0 (0)**	**1 (5)**
Do not know	2 (1)	0 (0)	2 (5)	0 (0)	0 (0)
Target dose (p<0.001)					
15 g/kg/d	**68 (42)**	**22 (41)**	**21 (54)**	**8 (16)**	**17 (90)**

16 g/kg/d	**38 (24)**	**14 (26)**	**5 (13)**	**18 (37)**	**1 (5)**
17 g/kg/d	**12 (8)**	**5 (9)**	**2 (5)**	**5 (10)**	**0 (0)**
18 g/kg/d or higher	32 (20)	10 (19)	3 (8)	18 (37)	1 (5)
Do not know	11 (7)	3 (6)	8 (21)	0 (0)	0 (0)
Lipids					
Initiation (p=0.160)					
D0	**32 (20)**	**12 (22)**	**12 (31)**	**3 (6)**	**5 (26)**
D1	**77 (48)**	**24 (44)**	**17 (44)**	**28 (57)**	**8 (42)**
D2	**36 (22)**	**11 (20)**	**9 (23)**	**11 (22)**	**5 (26)**
D3 or later	16 (10)	7 (13)	1 (3)	7 (14)	1 (5)
Do not know	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Initial dose (p<0.001)					
0.5 g/kg/d	98 (61)	34 (63)	11 (28)	36 (74)	17 (90)
1.0 g/kg/d	**59 (37)**	**18 (33)**	**27 (70)**	**13 (27)**	**1 (5)**
1.5 g/kg/d or higher	**3 (2)**	**2 (4)**	**0 (0)**	**0 (0)**	**1 (5)**
Do not know	1 (1)	0 (0)	1 (3)	0 (0)	0 (0)
Target dose (p= 0.028)					
1 or 2 g/kg/d	34 (21)	15 (28)	3 (8)	9 (18)	7 (37)
3 or 4 g/kg/d	**123 (76)**	**38 (70)**	**33 (85)**	**40 (82)**	**12 (63)**
5 g/kg/d or higher / Do not know	4 (3)	1 (2)	3 (8)	0 (0)	0 (0)
Caloric target (p<0.001)					
90 or 100 kcal/kg/d	29 (18)	3 (6)	15 (39)	3 (6)	8 (42)
110 kcal/kg/d	**28 (17)**	**8 (15)**	**6 (15)**	**11 (22)**	**3 (16)**
120 kcal/kg/d	**65 (40)**	**25 (46)**	**10 (26)**	**26 (53)**	**4 (21)**
130 or more	35 (22)	18 (33)	4 (10)	9 (18)	4 (21)
Do not know	4 (3)	0 (0)	4 (10)	0 (0)	0 (0)
Maximal caloric intake prescribed (p<0.001)					
110 kcal/kg/d	13 (8)	1 (2)	7 (18)	3 (6)	2 (11)

120 kcal/kg/d	36 (22)	9 (17)	12 (31)	9 (18)	6 (32)
130 kcal/kg/d	32 (20)	10 (19)	4 (10)	12 (25)	6 (32)
140 kcal/kg/d	37 (23)	16 (30)	2 (5)	18 (37)	1 (5)
150 kcal/kg/d or more	34 (21)	18 (33)	6 (15)	6 (12)	4 (21)
Do not know	9 (6)	0 (0)	8 (21)	1 (2)	0 (0)

D0, D1, D2; day 0, day 1, day 2

(Percentages do not necessarily sum up to 100% due to rounding)

Recommended intakes as defined in the methods section are highlighted in bold

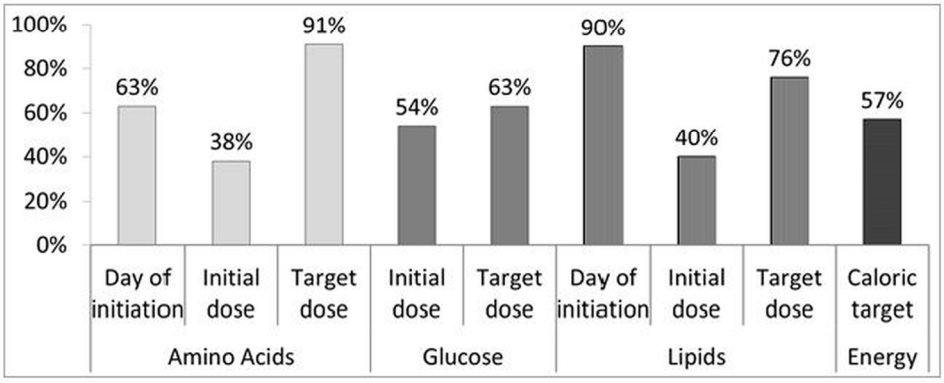
Table 4. Guideline awareness by country.

Question	TOTAL	Germany	UK	France	Italy
	n (%)	n (%)	n (%)	n (%)	n (%)
Are you aware of guidelines for use of neonatal / pediatric parenteral nutrition?					
Yes	128 (80)	47 (87)	33 (85)	33 (67)	15 (79)
No	33 (21)	7 (13)	6 (15)	16 (33)	4 (21)
Of which guidelines are you aware?*					
International [8, 21]	33 (26)	10 (21)	9 (27)	10 (30)	4 (27)
National	24 (19)	16 (34)	2 (6)	0 (0)	6 (40)
In-house guidelines	8 (6)	4 (9)	2 (6)	0 (0)	2 (13)
None specifically named/other	66 (52)	19 (40)	17 (52)	24 (73)	6 (40)

*More than one answer per questionnaire possible.

(Percentages do not necessarily sum up to 100% due to rounding)

Figure 1



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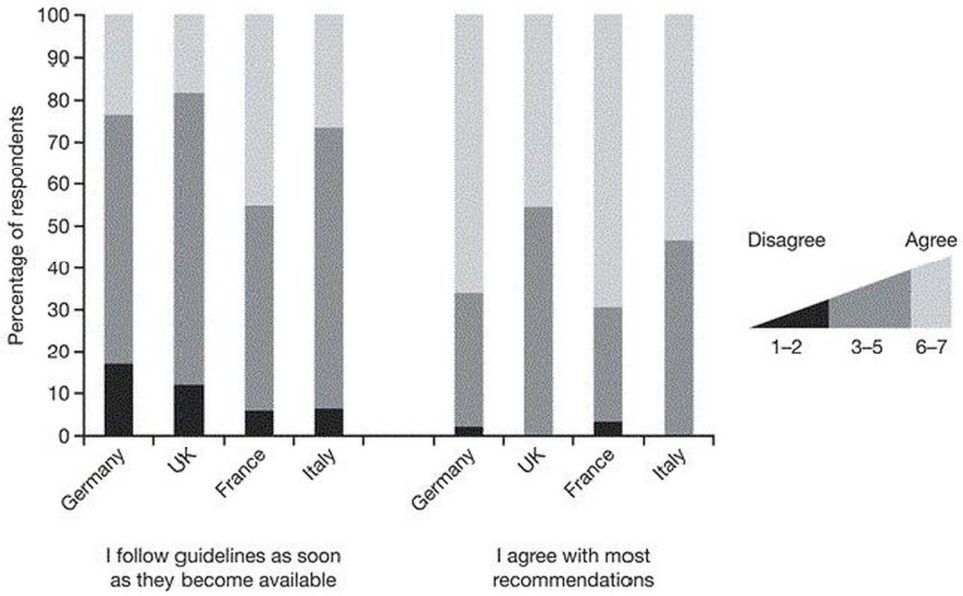

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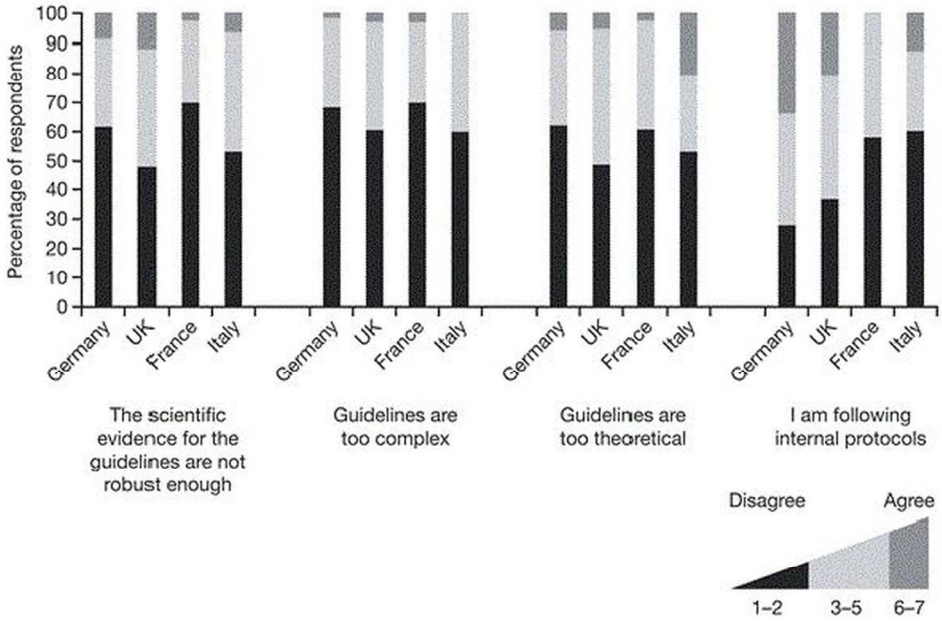

131x90mm (300 x 300 DPI)

Table S1. Current practice for parenteral nutrition in NICU patients by type of hospital (University/teaching hospital vs. other hospital types)

Nutrient	TOTAL n (%)	University/teaching hospital n (%)	Other hospital types n (%)
Amino acids			
Initiation (p=0.069)			
D0	101 (63)	71 (67)	30 (55)
D1	51 (32)	32 (30)	19 (35)
D2 or later	9 (6)	3 (3)	6 (11)
Initial dose (p=0.656)			
0.5 g/kg/d	44 (27)	28 (26)	16 (29)
1.0 g/kg/d	53 (33)	34 (32)	19 (35)
1.5 g/kg/d	34 (21)	23 (22)	11 (20)
2 g/kg/d or higher	27 (17)	20 (19)	7 (13)
Do not know	3 (2)	1 (1)	2 (4)
Target dose (p=0.213)			
1 or 2 g/kg/d	11 (7)	7 (7)	4 (7)
3 or 4 g/kg/d	146 (91)	98 (93)	48 (87)

5 g/kg/d or higher / Do not know	4 (3)	1 (1)	3 (6)
Glucose			
Initial dose (p=0.022)			
6 g/kg/d	73 (45)	42 (40)	31 (56)
7 g/kg/d	41 (26)	34 (32)	7 (13)
8 g/kg/d	28 (17)	19 (18)	9 (16)
9 g/kg/d or higher	17 (11)	11 (10)	6 (11)
Do not know	2 (1)	0 (0)	2 (4)
Target dose (p=0.160)			
15 g/kg/d	68 (42)	40 (38)	28 (51)
16 g/kg/d	38 (24)	29 (27)	9 (16)
17 g/kg/d	12 (8)	8 (8)	4 (7)
18 g/kg/d or higher	32 (20)	24 (23)	8 (15)
Do not know	11 (7)	5 (5)	6 (11)
Lipids			
Initiation (p=0.015)			
D0	32 (20)	24 (23)	8 (15)

D1	77 (48)	54 (51)	23 (42)
D2	36 (22)	23 (22)	13 (24)
D3 or later	16 (10)	5 (5)	11 (20)
Do not know	0 (0)	0 (0)	0 (0)
Initial dose (p=0.126)			
0.5 g/kg/d	98 (61)	60 (57)	38 (69)
1.0 g/kg/d	59 (37)	43 (41)	16 (29)
1.5 g/kg/d or higher	3 (2)	3 (3)	0 (0)
Do not know	1 (1)	0 (0)	1 (2)
Target dose (p= 0.372)			
1 or 2 g/kg/d	34 (21)	19 (18)	15 (27)
3 or 4 g/kg/d	123 (76)	84 (79)	39 (71)
5 g/kg/d or higher / Do not know	4 (3)	3 (3)	1 (2)
Caloric target (p=0.155)			
90 or 100 kcal/kg/d	29 (18)	14 (13)	15 (27)
110 kcal/kg/d	28 (17)	20 (19)	8 (15)
120 kcal/kg/d	65 (40)	44 (42)	21 (38)

130 or more	35 (22)	24 (23)	11 (20)
Do not know	4 (3)	4 (4)	0 (0)
Maximal caloric intake prescribed (p=0.008)			
110 kcal/kg/d	13 (8)	11 (10)	2 (4)
120 kcal/kg/d	36 (22)	22 (21)	14 (26)
130 kcal/kg/d	32 (20)	14 (13)	18 (33)
140 kcal/kg/d	37 (23)	28 (26)	9 (16)
150 kcal/kg/d or more	34 (21)	22 (21)	12 (22)
Do not know	9 (6)	9 (9)	0 (0)

(Percentages do not necessarily sum up to 100% due to rounding)

Table S2. Current practice for parenteral nutrition in NICU patients by number of admissions per year of infants with a birth weight ≤1500g.

Nutrient	TOTAL	Number of admissions		
		0 - 65	66 - 111	≥ 112
	n (%)	n (%)	n (%)	n (%)
Amino acids				
Initiation (p=0.262)				
D0	101 (63)	24 (52)	43 (69)	34 (64)
D1	51 (32)	17 (37)	17 (27)	17 (32)
D2 or later	9 (6)	5 (11)	2 (3)	2 (4)
Initial dose (p=0.611)				
0.5 g/kg/d	44 (27)	17 (37)	15 (24)	12 (23)
1.0 g/kg/d	53 (33)	16 (35)	19 (31)	18 (34)
1.5 g/kg/d	34 (21)	8 (17)	14 (23)	12 (23)
2 g/kg/d or higher	27 (17)	5 (11)	13 (21)	9 (17)
Do not know	3 (2)	0 (0)	1 (2)	2 (4)
Target dose (p=0.343)				

1 or 2 g/kg/d	11 (7)	6 (13)	3 (5)	2 (4)
3 or 4 g/kg/d	146 (91)	39 (85)	58 (94)	49 (93)
5 g/kg/d or higher / Do not know	4 (3)	1 (2)	1 (2)	2 (4)
Glucose				
Initial dose (p=0.504)				
6 g/kg/d	73 (45)	26 (57)	23 (37)	24 (45)
7 g/kg/d	41 (26)	8 (17)	21 (34)	12 (23)
8 g/kg/d	28 (17)	6 (13)	11 (18)	11 (21)
9 g/kg/d or higher	17 (11)	6 (13)	6 (10)	5 (9)
Do not know	2 (1)	0 (0)	1 (2)	1 (2)
Target dose (p=0.320)				
15 g/kg/d	68 (42)	24 (52)	24 (39)	20 (38)
16 g/kg/d	38 (24)	9 (20)	14 (23)	15 (28)
17 g/kg/d	12 (8)	6 (13)	4 (7)	2 (4)
18 g/kg/d or higher	32 (20)	5 (11)	14 (23)	13 (25)
Do not know	11 (6.8)	2 (4.3)	6 (9.7)	3 (5.7)
Lipids				

Initiation (p=0.011)				
D0	32 (20)	10 (22)	16 (26)	6 (11)
D1	77 (48)	16 (35)	31 (50)	30 (57)
D2	36 (22)	11 (24)	9 (15)	16 (30)
D3 or later	16 (10)	9 (20)	6 (10)	1 (2)
Do not know	0 (0)	0 (0)	0 (0)	0 (0)
Initial dose (p=0.246)				
0.5 g/kg/d	98 (61)	31 (67)	37 (60)	30 (57)
1.0 g/kg/d	59 (37)	15 (33)	22 (36)	22 (42)
1.5 g/kg/d or higher	3 (2)	0 (0)	3 (5)	0 (0)
Do not know	1 (1)	0 (0)	0 (0)	1 (2)
Target dose (p= 0.224)				
1 or 2 g/kg/d	34 (21)	15 (33)	10 (16)	9 (17)
3 or 4 g/kg/d	123 (76)	30 (65)	51 (82)	42 (79)
5 g/kg/d or higher / Do not know	4 (3)	1 (2)	1 (2)	2 (4)
Caloric target (p=0.107)				
90 or 100 kcal/kg/d	29 (18)	12 (26)	6 (10)	11 (21)

110 kcal/kg/d	28 (17)	11 (24)	7 (11)	10 (19)
120 kcal/kg/d	65 (40)	13 (28)	32 (52)	20 (38)
130 or more	35 (22)	10 (22)	14 (23)	11 (21)
Do not know	4 (3)	0 (0)	3 (5)	1 (2)
Maximal caloric intake prescribed (p=0.199)				
110 kcal/kg/d	13 (8)	5 (11)	3 (5)	5 (10)
120 kcal/kg/d	36 (22)	10 (22)	10 (16)	16 (30)
130 kcal/kg/d	32 (20)	12 (26)	11 (18)	9 (17)
140 kcal/kg/d	37 (23)	7 (15)	19 (31)	11 (21)
150 kcal/kg/d or more	34 (21)	12 (26)	13 (21)	9 (17)
Do not know	9 (6)	0 (0)	6 (10)	3 (6)

(Percentages do not necessarily sum up to 100% due to rounding)

Table S3: Questions of the survey questionnaire used for this report

Q1. Function:
[1] Consultant
[2] Higher Specialist Trainee
[3] Specialist Registrar
[4] Other: _____

Q2. Years of practice:
[1] less than 1 year
[2] 1 to less than 3 years
[3] 3 to less than 5 years
[4] 5 to less than 7 years
[5] 7 to less than 10 years
[6] 10 years and more

Q3. Type of hospital:
[1] University / teaching hospital
[2] General hospital
[3] Specialist hospital
[4] Private hospital

For the questions below, if you do not have the exact numbers readily available, please provide your best estimates.

Q4. How many beds are there in your neonatal intensive care unit?
…… # highest acuity beds
…… # intermediate care beds

Q5. What is the average number of admissions to your neonatal intensive care unit per year, by birth weight?
…… # <1000g
…… # 1001-1500g
…… # 1501g-2500g
…… #>250

Parenteral nutrition in this survey refers to intravenous nutrition given via a central or peripheral line. Along with fluids and micronutrients, it contains macronutrients such as amino acids/protein, glucose and lipids. In all of the questions of this survey, please consider only the neonatal intensive care patients that you see as in-patients in the hospital.

Objective 1: to understand the current treatment practices associated with neonatal Parenteral Nutrition; for example: nutritional objectives (target values); initiation of PN (first day of administration of AA, lipids, etc.)
Important definition: in this survey D0 stands for the first day of life.

Q6. Amino acid provision – please chose the respective values, which best describe your current, standard practice:

When do you start amino acids?	D0	D1	D2	D3	D4	D5 or later	Do not know
What is your starting dose? (g/kg/day)	0,5	1,0	1,5	2	2,5	>2,5	Do not know
What is your usual target dose? (g/kg/day)	1	2	3	4	5	>5	Do not know

Q7. Glucose treatment – please chose the respective categories, which best describe your current, usual practices:

Which is your starting dose? (g/kg/day)	6	7	8	9	10	>10	Do not know
What is your usual target dose? (g/kg/day)	15	16	17	18	19	>19	Do not know

Q8. Lipid treatment – please chose the respective categories, which best describe your current, usual practices:

When do you start lipid?	D0	D1	D2	D3	D4 or later	D5 or later	Do not know
Which is your starting dose? (g/kg/day)	0,5	1	1,5	2	2,5	>2,5	Do not know
What is your usual target dose? (g/kg/day)	1	2	3	4	5	>5	Do not know

Q9. Caloric targets – please chose the respective categories, which best describe your current, usual practices:

What is your usual caloric target? (kCal/kg/day)	90	100	110	120	130	>130	Do not know
What is the maximum caloric intake normally prescribed? (kCal/kg/day)	110	120	130	140	150	>150	Do not know

Objective 2: To learn about the acceptance and utilisation of local and international guideline recommendations, specifically

- awareness about local and international guidelines
- level of acceptance of the recommendations
- implementation of the recommendations - role of the guidelines
- objections and obstacles hindering the use of guidelines

Q10. Are you aware of guidelines for use of neonatal / pediatric parenteral nutrition?
[1] Yes
[2] No

⌦ Ask only, if "1" in Q10 selected

Q11. Which local and international guidelines for the use of parenteral nutrition in neonatal / pediatric patients are you aware of? Please list the type of guideline and the name of the scientific society or authority who published or issued it.

……

⌦ Ask only, if "1" in Q10 selected

Q12. **To what extent do you agree or disagree with the following statements?** (Please indicate your answer on a scale of 1 to 7 where 1 means "do not agree at all" and 7 means "fully agree")

	do not agree at all						fully agree
I agree with most of the recommendations given in the guidelines for parenteral nutrition in pediatric patients.	1	2	3	4	5	6	7
I obtain a copy, read and follow guidelines for parenteral nutrition in pediatric patients as soon as they become available.	1	2	3	4	5	6	7
The scientific evidence that guidelines are based on, are not robust enough to be convincing and to follow them	1	2	3	4	5	6	7

⌦ Ask only, if "1" in Q10 selected

Q13. What might prevent you from following guidelines for parenteral nutrition in pediatric patients? (Please indicate your answer on a scale of 1 to 7, where 1 means "do not agree at all" and 7 means "fully agree")

	do not agree at all fully agree						
Guidelines are too complex	1	2	3	4	5	6	7
Guidelines are too theoretical	1	2	3	4	5	6	7
I am following our internal protocols, which are not always aligned with the guideline recommendations	1	2	3	4	5	6	7

Quality of newborn care: Adherence to guidelines for parenteral nutrition in preterm infants in Four European Countries

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Running title: Adherence to guidelines for parenteral nutrition in preterm infants

Key Words: infant, premature, nutrition survey, feeding methods, parenteral nutrition, guideline

Word count (text) = ~~23832~~2822

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Number of tables = ~~4~~3

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ARTICLE SUMMARY –

'Article focus':

- Optimal nutritional care is critical for neonatal intensive care unit patients and associated with improved outcomes in later life.
- Clinical practice guidelines for parenteral nutrition exist, however, current clinical practice in Europe and compliance with these recommendations is unknown.
- The main objective was to assess the adherence to guidelines for parenteral nutrition in preterm infants in ~~f~~Four European Countries.

'Key messages'

- The initiation of PN is ~~still~~ frequently not compliant with current recommendations, with the main differences observed during the first days of life.
- There is an urgent need to improve dissemination of guidelines and to facilitate translation of knowledge into clinical practice.
- Web-based standard reporting systems that determine the actual compliance of in-house protocols with guidelines should be developed in parallel to determine to what extent new guidelines are translated into clinical practice.

'Strengths and limitations of this study' section.

Strengths:

- Nutrition for preterm infants is a hot topic in the field of neonatology.
- Large survey in 4 European countries that included 74% of the units of the 4 countries
- Surveys reflect one of the first steps of the dissemination of guidelines and, thus, provides insight on compliance to guidelines

Limitations

- Surveys reflect the intention to treat of the personnel from the NICU that respond to the survey, and may not reflect the actual clinical practice within the unit

ABSTRACT

Objective: Level of adherence to guidelines ~~is often not known and~~ should be explored particularly in preterm infants for which poor nutrition has major effects on outcomes in later life. The ~~main~~ objective was to evaluate compliance to international guidelines for parenteral nutrition (PN) in preterm infants across Neonatal intensive care units (NICUs) of four European countries.

Design: Clinical practice survey by the mean of a questionnaire addressing routine PN protocols, awareness and implementation of guidelines.

Setting: NICUs in the United Kingdom, Italy, Germany and France.

Participants: One senior physician per unit; 199 units which represent 74% of the NICUs of the 4 countries.

Primary outcome measure: Adherence of unit protocol to international guidelines; **Secondary outcome measure**: Factors that influence adherence to guidelines.

Results: ~~Eighty percent~~80% of the respondents stated that they were aware of some PN clinical practice guidelines. For amino acid infusion (AA), 63% of the respondents aim to initiate AA on ~~D0~~D0, 38% aim to administer an initial dose ~~of~~ ≥ 1.5 g/kg/d ~~to prevent a negative balance~~ and 91% aim for a target dose ~~for AA~~ of 3 or 4 g/kg/d, as recommended. For parenteral lipids~~lipid administration~~, 90% of the respondents aim to initiate parenteral lipids them during the first 3 days of life, 39% aim to use an initial dose ≥ 1.0 g/kg/d, and 76% define the target dose ~~for lipids~~ as 3 to 4 g/kg/d, as recommended. Significant variations in PN protocols were observed among countries but the type of hospital or the number of admissions per year had only a marginal impact on the PN protocols.

Conclusions: Most respondents indicate that their clinical practice was based on common guidelines. However, the initiation of PN is frequently not compliant with current recommendations, with the main differences observed during the first days of life. ~~Clinicians initiate PN earlier than in the past but the initiation of PN is still frequently not compliant with international guidelines.~~ Continuous education focusing on parenteral nutrition practice is needed, and greater efforts are required to disseminate and implement international guidelines.

Abbreviations:

AA – amino acids; D0 – ~~the first~~ day of ~~life~~birth; ELBW – extremely low birth weight; EN – enteral nutrition; NICU – neonatal intensive care unit; PN – parenteral nutrition; UK – United Kingdom; US – United States of America; VLBW – very low birth weight

INTRODUCTION

Poor nutrition in preterm infants has major effects on outcomes in later life, including physical growth, intellectual development and, possibly, cardiovascular and metabolic effects.[1, 2] The quality and quantity of daily nutritional intake is critical particularly during the first weeks of life since amino acid, energy and lipid intake from parenteral nutrition have been shown to be associated with later development.[3, 4] Reports from neonatal intensive care units (NICUs) worldwide have shown that nutritional intake in preterm infants is inadequate.[5, 6] The causes of this inadequate intake, particularly in the early neonatal phase, may be multifactorial and partly iatrogenic. It may depend not only on the infant's metabolic capacities, but also on the availability and safety of the solutions used, the type of venous access, the department's usual practice, and the prescriber's knowledge of the infant's nutritional needs.[7]

Clinical practice guidelines for the nutritional needs of preterm infants have been regularly revised over recent decades, leading to the development of the most recent international guidelines on pediatric parenteral nutrition (PN) in Europe from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN) in 2005 [8], and globally in the book entitled "Nutritional needs of the preterm infant: Scientific basis and practical guidelines" also published in 2005.[9] (Table 1) Previous studies, especially those performed before current clinical practice guidelines were available, demonstrated large differences in both the nutritional protocols applied in clinical practice and the resulting clinical outcomes.[6, 10, 11] A recent systematic review showed that large differences are observed in the nutritional protocols both among the NICUs in the individual surveys and among surveys.[12]

Level of adherence to guidelines is often not known and it remains unclear to what extent recommendations for early parenteral nutrition in NICU patients have been translated into routine clinical care in Europe. Therefore, we performed a clinical practice survey among NICU physicians in

four European countries to evaluate compliance to international guidelines for parenteral nutrition (PN) in preterm infants and to determine factors that influence compliance to guidelines.

METHODS

The survey questionnaire was developed under the lead of AL together with the coauthors. ~~The survey was implemented in a web-based format by an independent company (GfK SE Division HealthCare, Nürnberg, Germany). It~~ The survey was conducted ~~in a blinded manner~~ between October 2009 and April 2010 among NICU physicians in Germany, the United Kingdom (UK), France and Italy in order to survey ~50 units per country. One author from each country provided a list of the largest NICUs using available data and their own knowledge of national and regional units, with at least one senior physician's name per unit. NICUs were selected for the study if they had high acuity~~/ or~~ intensive care beds, and >5 infants per week requiring parenteral nutrition. The senior physician from each NICU was contacted and asked to complete the survey questionnaire or delegate the task to a colleague devoting ≥20% of their time to patient care and with >3 years of clinical experience in neonatal intensive care. Where a response was not obtained other physicians from the same unit were approached, if available. The identity of the physicians contacted and requested to complete the survey remained blinded for the analysis and to all authors.

The survey questionnaire was developed in English and translated into German, French and Italian for use in the national language of each country. For the purpose of the survey, PN was defined as intravenous nutrition given via a central or peripheral line and containing fluids and any macro- or micronutrients. Respondents were instructed to consider only in-hospital neonatal intensive care patients. D0 was defined as the ~~first~~ day of ~~life~~birth, D1 for the subsequent 24 h, and D2 and D3 the following days. The survey comprised sections to characterize the profile of the NICU, and routine clinical practice with respect to PN ~~between D0 and D3~~. The survey assessed the logistical organization of PN within the hospital, the types of PN available and prescribed, and some of the

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reasons for use or non-use of standard formulations, preferred product characteristics and awareness and implementation of local and international clinical practice guidelines. Only the unit profile, the routine clinical practice with respect to PN, ~~clinical practice parameters~~ and awareness and implementation of guidelines were analyzed for this report.

The survey was implemented in a web-based format by an independent company (GfK SE Division HealthCare, Nürnberg, Germany). The authors and the sponsor were blinded with regard to the respondents' identities and with regard to the individual questionnaires. To best describe the macronutrient or energy provision, single choice questions were asked offering 6 possible answers, 5 with plausible intakes and one "do not know" response. To assess the extent of agreement with statements related to awareness and implementation of guidelines, questions were asked using a 7-point bipolar scale, 1 meant "do not agree at all" and 7 meant "fully agree".

Compliance to international guidelines for PN in preterm infants was made mainly by using the European ones since they have been published in a journal widely disseminated [8] and since they are also easily and freely accessible through the ESPEN website (http://espen.anavajo.com/espencms/index.php/education/espen-guidelines). NICUs were considered compliant to guidelines if: for amino acids, initiation = day of birth, initiation dose ≥1.5 g/kg/d, target dose = 3 to 4 g/kg/d; for glucose, initiation dose ≥7 g/kg/d, target dose = 10 to 17 g/kg/d; for lipids, initiation ≤day 3 of life, initiation dose ≥1 g/kg/d, target dose = 3 to 4 g/kg/d; energy, target dose = 110 to 120 kcal/kg/d.

Statistical analysis~~es~~

Analyses were restricted to completed questionnaires with evaluable results. Data were split to cross tabs with respect to various grouping variables. Since infants with a birth weight below 1500g are those more likely receiving PN, splitting the data using this parameter was consider to better reflect the experience in prescribing PN than using the whole population of newborn admitted in a NICU. Therefore, ~~F~~first class split variables consisted of tertiles or quartiles, which were computed on

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the average number of admissions to the neonatal intensive care unit per year by birth weight up to 1500 g. ~~.~~ The second class of grouping factors comprised categorical variables such as hospital type or country. The goal was to examine the null hypothesis "No pairwise differences in proportions across subgroups". Null hypotheses were tested using χ^2-tests and rejected at the 5% error level.

Ethics

This study was conducted according to the guidelines in the Declaration of Helsinki. Since this study did not involve human subjects/patients or handling of medical records, ethical approval was not required.

RESULTS

Profile of the NICUs surveyed

A total of 199 NICUs were surveyed (45 from the UK, 55 from Germany, 49 from France and 50 from Italy) and their characteristics are presented in table 2. Overall, we surveyed 74% of the units of the 4 countries: 45/64 (70%) in the UK; 55/78 (71%) in Germany; 49/66 (74%) in France; 50/60 (83%) in Italy). One hundred sixty one of the 199 (81%) surveys were included in the analysis as 38 surveys were excluded due to invalid responses. The majority of invalid surveys came from units with ~~less~~ the lower number of ~~than 4 beds of~~ high acuity care beds (i.e., 50% of them had ≤ 5 high acuity care beds vs. 12%; p<0.001). The number of years of practice in neonatology of the physicians who completed the survey questionnaire was more than 10 years for 141 of them (71%), 5 to 9 years for 40 of them (20%), 3 to 5 years for 17 of them (8.5%) and 1 to 3 years for 1 of them (0.5%).

Adherence of unit protocol to international guidelines

Survey respondents were requested to provide information on the timing and composition of PN as summarized in table 3. Level of adherence of unit protocols to international guidelines was highly variable and varied according to the type of macronutrient (Figure 1). With regards to initiation of PN, amino acids were often initiated late, and both lipids and amino acids were initiated at a lower

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dose than recommended (Figure 1). With regards to full parenteral nutrition (i.e., target dose), most NICUs reported an adequate target dose for amino acids, lipids and glucose. In contrast, only half of the units reported a target energy intake compliant with guidelines; ~20% reported a lower higher target than recommended and a similar percentage a higher target than recommended.

~~**Awareness of nutritional guidelines**~~

~~Eighty percent of physicians across all countries reported an awareness of nutritional guidelines, but less than 50% gave a source or specification (Table 3). There were inter-country differences for physicians reporting an awareness of clinical practice guidelines for neonatal or pediatric PN (Table 2). Respondents indicated that they agreed with most of the recommendations, with 66% and 70% of physicians from Germany and France and 46% and 53% in UK and Italy in strong agreement (Figure 1). Overall, the physicians agreed less strongly with the statement "I obtain a copy, read and follow guidelines for parenteral nutrition in pediatric patients as soon as they become available" (Figure 1). When asked whether the lack of robust evidence on which the guidelines are based presented a barrier to implementation, 3% and 7% of the physicians from France and Italy agreed, in comparison to 9% and 12% of the respondents from Germany and the UK (Figure 2). About 60-70% of the physicians did not find current guidelines too complex and those from both the UK and Italy more often found the guidelines to be too theoretical to be used in clinical practice than respondents from Germany or France. Respondents from Germany were most likely to report relying on internal clinical practice protocols (Figure 2).~~

~~**Adherence of unit protocol to international guidelines**~~

~~Survey respondents were requested to provide information on the timing and composition of PN as summarized in table 4. With regards to initiation of PN, amino acids are initiated by 63% of the responding units on the first day of life (D0) and by 32% on D1. Amino acids were reported to be started at a dose of 1.0 g/kg/d or less by 60% overall. Glucose was administered at a starting dose of 6 or 7 g/kg/d by 71% of the NICUs surveyed. Lipid emulsions were initiated by 20% of the units on D0 and by an additional 48% on D1. Initial lipid dose was reported to be 0.5 or 1.0 g/kg/d by 98% of~~

~~respondents. With regards to full parenteral nutrition, most NICUs (91%) reported a target dose for amino acids of 3 or 4 g/kg/d. Overall, 66% of the units administered a target dose of glucose of 15 or 16 g/kg/d, and 76% of the units administered a target dose of lipids of 3 or 4 g/kg/d.~~

Factors that influence adherence to guidelines

Country, hospital type and size of unit.

There was a significant effect of countries on ~~parenteral nutrition~~PN practices (Table 3~~4~~). The patterns observed were the following: with regards to early PN, amino acids were started sooner and at a higher dose in France than in the other countries. A similar trend was seen for lipids in the UK where the starting dose of glucose was also higher than in the other countries. With regards to full PN (i.e., target dose), amino acid target dose was more likely within the recommendations in France than in other countries whereas glucose target dose was more likely within the recommendations in the UK and in Italy. The distribution for caloric target was wide; the units in France and Germany were more likely prescribing higher energy intake than recommended whereas lower energy intake was more likely seen in the UK and Italy.

When the PN results were stratified by hospital type, no differences were observed in the initiation, starting or target dose of amino acids (Data not shown). University or teaching hospitals reported higher starting doses of glucose than other types of hospital (40% vs. 56% at 6 g/kg/d and 32% vs. 13% at 7 g/kg/d; p=0.022), but there was no significant difference in the target dose between the two types of institution. University or teaching hospitals also reported initiation of lipid feeding earlier than other institutions (initiation on D3 or later 5% vs. 20%; p=0.015), but with no significant difference in starting or target dose. The caloric targets between the two types of hospital were similar, but the normal maximal caloric intake prescribed were significantly different (p=0.008).

When the data were stratified by the number of admissions, the only category in which a significant difference was apparent was the day on which lipid feeding was initiated. Units with lower admissions rates were more likely to report initiation on D3 or later (p=0.011) (Data not shown).

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Awareness of nutritional guidelines

Eighty percent of physicians across all countries reported an awareness of nutritional guidelines, but less than 50% gave a source or specification (Table 4). There were inter-country differences for physicians reporting an awareness of clinical practice guidelines for neonatal or pediatric PN (Table 4). There was no significant association between being aware of guidelines for use of neonatal / pediatric PN and being compliant with international guidelines, but there was a trend for an association between being aware of guidelines and being compliant for the lipid target dose (p=0.054) and for the initiation of amino acids (p=0.070).

Respondents indicated that they agreed with most of the recommendations, with 66% and 70% of physicians from Germany and France and 46% and 53% in UK and Italy in strong agreement (Figure 2). Overall, the physicians agreed less strongly with the statement "I obtain a copy, read and follow guidelines for parenteral nutrition in pediatric patients as soon as they become available" (Figure 2). When asked whether the lack of robust evidence on which the guidelines are based presented a barrier to implementation, 3% and 7% of the physicians from France and Italy agreed, in comparison to 9% and 12% of the respondents from Germany and the UK (Figure 3). About 60-70% of the physicians did not find current guidelines too complex and those from both the UK and Italy more often found the guidelines to be too theoretical to be used in clinical practice than respondents from Germany or France. Respondents from Germany were most likely to report relying on internal clinical practice protocols (Figure 3).

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DISCUSSION

This study represents the first survey of neonatal PN clinical practice behavior undertaken at the European level. This type of survey emphasizes how current practices differ from recommended guidelines and encourage clinicians to be aware of the potential for improvement. Since the objective of the study was to compare the data with international guidelines ~~(table 4)~~ we did not

report and/or use local guidelines, if any, and for consistency, we mainly used for comparison the European guidelines which are widely available through both a publication widely referenced [8] and a website. ~~[8]~~

Despite demonstrating apparent improvement in PN practices, the results presented here shows that 37% of neonatal units in the 4 E~~e~~uropean countries surveyed initiate amino acid feeding on D1 or later and not on D0 as recommended.[8] Moreover, 60% of the European respondents administer an initial dose of less than the required 1.5 g/kg/d to prevent a negative balance.[8] The apparent higher compliance with guideline recommendations to initiate amino acid infusion on D0 and a target dose of 3-4 g/kg/d in France may be attributable to a combination of commercially available binary standard solutions and/or awareness of a national survey on this topic and widely disseminated at the country level.[13]

Our study shows that whilst 90% of the NICUs surveyed provide early lipids, 21% of them provide a maximum dose lower than recommended. This is similar to other surveys suggesting that physicians do not comply easily with the guideline defining the optimal dose for parenteral lipids. Previous surveys have shown that the timing and dose of parenteral lipids vary between surveys to a scale which is larger than that for amino acids.[12] It was also found that there was a lack of consensus between surveys on the contraindications for lipids and/or indication for stopping lipids. This may reflect the lack of scientific data and absence of clear guidance on this topic.

Awareness of some guidelines was reported by the majority of physicians completing the survey, although 21% claimed not to be aware of any guidelines. This may be of relevance when the 40% of respondents who do not provide amino acids on the ~~first~~ day ~~of life~~ of birth are considered, highlighting a potential deficit in implementation of the guidelines. Limited access to standard solutions and specific country regulations on preparation may also be possible alternative explanations why guidelines have not been translated into clinical practice.

University/teaching hospitals provided a higher starting dose of glucose and initiated lipid and amino acid infusion earlier compared to other institutions. Similarly, late initiation of lipid infusion (D3 or

later) was less common in NICUs with a highest number of admissions per year. While these results may suggest better adherence to treatment guidelines at hospitals with a high number of admissions, the existing data are unclear as to whether high numbers of admissions are also associated with lower rates of mortality or morbidity.[14, 15]

The methodological limitations of using surveys for the assessment of nutritional protocols have been previously discussed in detail [13] and it should be reiterated that these surveys reflect the intention to treat of the personnel from the NICU that respond to the survey, and may not reflect the actual clinical practice within the unit. Nevertheless, intention to treat reflects one of the first steps of the dissemination of guidelines and, thus, provides insight on compliance to guidelines. The number of countries participating in our survey was limited to 4 for practical reasons and, therefore, the results obtained do not permit conclusions that apply to other European countries. The number of surveys received represents a substantial proportion of NICUs in each of the 4 countries; however, the number of invalid surveys indicates that there may have been some confusion with respect to terminology or intent. Interestingly, the invalid responses were mainly seen in the smaller units which are less likely to prescribe PN. ~~This is in line with the observation that larger units prescribe PN that are more likely compliant with guidelines.~~

Finally, our results allow comparison of current practices among countries but also historical comparison with similar surveys published earlier.[12] When compared to studies performed in the United States [16] or individual European countries [17-20], our study shows that PN in preterm neonates is provided earlier and in higher volumes than in the past, reflecting changing clinical practice in response to increased knowledge about parenteral feeding in neonates, even if the practices are still not perfectly in line with guidelines.

In conclusion, most respondents indicate~~d~~ that their clinical practice was based on common guidelines. ~~They are initiating parenteral nutrition earlier and in larger volumes than in the past, reflecting increased knowledge about best nutritional practices in very preterm neonates.~~ However, the initiation of PN in the 4 countries surveyed i~~i~~s ~~still~~ frequently not compliant with current

recommendations, with the main differences observed during the first days of life. Our study shows that there is an urgent need to improve dissemination of guidelines and to facilitate translation of knowledge into clinical practice. Given the need for continuous monitoring, it would be of value for scientific societies (particularly those that publish guidelines) to develop web-based standard reporting systems that determine the actual compliance of in-house protocols with guidelines. In the case of the nutrition for preterm infants, a limited number of questions on access to PN and the dose of nutrients given would be sufficient to provide insight on the implementation of guidelines at a local level.

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The authors have no conflicts of interest relevant to this article to disclose.

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Figure legends

Figure 1. Percentage of NICUs (n=161) in Germany, France Italy and the United Kingdom compliant to guidelines for parenteral nutrition in preterm infants. NICUs were considered compliant to guidelines if: for amino acids, initiation = day of birth, initiation dose ≥1.5 g/kg/d, target dose = 3 to 4 g/kg/d; for glucose, initiation dose ≥7 g/kg/d, target dose = 10 to 17 g/kg/d; for lipids, initiation ≤day 3 of life, initiation dose ≥1 g/kg/d, target dose = 3 to 4 g/kg/d; energy, target dose = 110 to 120 kcal/kg/d.

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Figure 2~~1~~. Use of international clinical practice recommendations to guide neonatal parenteral nutrition by country.

Figure 3~~2~~. Justification for non-implementation of international clinical practice guidelines by country.

Tables

Table 1. International recommendations for parenteral nutrition in preterm infants.

	Tsang et al., 2005[9]	ESPEN/ESPGHAN/ESPR guidelines, 2005[8]
Amino acids		
initiation	~~1~~st ~~life~~birth	~~1~~st ~~life~~birth
initial dose, g/kg/d	2	≥1.5
target dose, g/kg/d	3.5-4 (ELBW) 3.2-3.8 (VLBW)	maximum 4
Glucose		
initiation	~~1~~st ~~life~~birth	~~1~~st ~~life~~birth
initial dose, g/kg/d	7	5.8-11.5
target dose, g/kg/d	13-17 (ELBW) 9.7-15 (VLBW)	--
Lipids		
initiation	~~1~~st ~~life~~ birth (VLBW) Cautious support for ELBW	No later than 3rd day
initial dose, g/kg/d	≥1	Linoleic acid >0.25 mg/kg/d
target dose, g/kg/d	3-4	3-4
Energy		
caloric target, g/kg/d	105-115 (ELBW) 90-100 (VLBW)	110-120

VLBW: very low birth weight infants; ELBW: extremely low birth weight infants; --, no recommendation provided
ESPEN/ESPGHAN/ESPR, European Society for Clinical Nutrition and Metabolism, European Society of Paediatric Gastroenterology, Hepatology and Nutrition, European Society of Paediatric Research

Table 2. Characteristics of participating NICUs.

Characteristic	TOTAL	Germany	UK	France	Italy
Questionnaires received, n	199	55	45	49	50
Questionnaires analyzed, n	161	54	39	49	19
Type of hospital, n (%)					
University/teaching hospital	106 (66)	44 (82)	27 (69)	31 (63)	4 (21)
Non-university	55 (34)	10 (19)	12 (31)	18 (37)	15 (79)
~~Bed capacity~~Highest acuity beds per unit, n (%)					
1-5	19 (12)	2 (4)	8 (21)	3 (6)	6 (32)
6-10	73 (45)	22 (41)	21 (54)	23 (47)	7 (37)
11-15	45 (28)	18 (33)	5 (13)	19 (39)	3 (16)
≥16	24 (15)	12 (22)	5 (13)	4 (8)	3 (16)
Intermediate care beds per unit, n (%)					
1-5	30 (19)	13 (24)	5 (13)	4 (8)	8 (42)
6-10	56 (35)	16 (30)	15 (39)	17 (35)	8 (42)
11-15	33 (21)	9 (17)	6 (15)	15 (31)	3 (16)
≥16	38 (24)	14 (26)	13 (33)	11 (22)	6 (12)
NR	4 (3)	2 (4)	0 (0)	2 (4)	0 (0)
VLBW infants per year, median (IQR)	90~~.0~~ (129~~.00~~-60~~.00~~)	64 (86~~.25~~-40~~.00~~)	105 (160~~.00~~-80~~.00~~)	125 (195~~.00~~-98~~.00~~)	75 (90~~.00~~-55~~.00~~)

NR, no response
VLBW, very low birth weight
IQR, interquartile range

(Percentages do not necessarily sum up to 100% due to rounding)

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Table 3. Guideline awareness by country.

Question	TOTAL	Germany	UK	France	Italy
	n (%)	n (%)	n (%)	n (%)	n (%)
Are you aware of guidelines for use of neonatal / pediatric parenteral nutrition? (asymptotic significance 0.073)					
Yes	128 (80)	47 (87)	33 (85)	33 (67)	15 (79)
No	33 (21)	7 (13)	6 (15)	16 (33)	4 (21)
Of which guidelines are you aware?*					
International[8, 21]	33 (26)	10 (21)	9 (27)	10 (30)	4 (27)
National	24 (19)	16 (34)	2 (6)	0 (0)	6 (40)
In-house guidelines	8 (6)	4 (9)	2 (6)	0 (0)	2 (13)
None specifically named/other	66 (52)	19 (40)	17 (52)	24 (73)	6 (40)

*More than one answer per questionnaire possible.

(Percentages do not necessarily sum up to 100% due to rounding)

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Table 34. Current practice for parenteral nutrition in NICU patients by country.

Nutrient	TOTAL n (%)	Germany n (%)	UK n (%)	France n (%)	Italy n (%)
Amino acids					
Initiation (p=0.005)					
D0	**101 (63)**	**32 (59)**	**21 (54)**	**41 (84)**	**7 (37)**
D1	51 (32)	19 (35)	15 (39)	8 (16)	9 (47)
D2 or later	9 (6)	3 (6)	3 (8)	0 (0)	3 (16)
Initial dose (p=0.001)					
0.5 g/kg/d	44 (27)	20 (37)	11 (28)	5 (10)	8 (42)
1.0 g/kg/d	53 (33)	14 (26)	9 (23)	24 (49)	6 (32)
1.5 g/kg/d	**34 (21)**	**5 (9)**	**11 (28)**	**15 (31)**	**3 (16)**
2 g/kg/d or higher	**27 (17)**	**15 (28)**	**5 (13)**	**5 (10)**	**2 (11)**
Do not know	3 (2)	0 (0)	3 (8)	0 (0)	0 (0)
Target dose (p<0.001)					
1 or 2 g/kg/d	11 (7)	6 (11)	3 (8)	0 (0)	2 (11)
3 or 4 g/kg/d	**146 (91)**	**48 (89)**	**34 (87)**	**49 (100.0)**	**15 (79)**
5 g/kg/d or higher / Do not know	4 (3)	0 (0)	2 (5)	0 (0)	2 (11)
Glucose					
Initial dose (p<0.001)					
6 g/kg/d	73 (45)	27 (50)	12 (31)	19 (39)	15 (79)
7 g/kg/d	**41 (26)**	**18 (33)**	**3 (8)**	**18 (37)**	**2 (11)**
8 g/kg/d	**28 (17)**	**6 (11)**	**9 (23)**	**12 (25)**	**1 (5)**
9 g/kg/d or higher	**17 (11)**	**3 (6)**	**13 (33)**	**0 (0)**	**1 (5)**
Do not know	2 (1)	0 (0)	2 (5)	0 (0)	0 (0)
Target dose (p<0.001)					
15 g/kg/d	**68 (42)**	**22 (41)**	**21 (54)**	**8 (16)**	**17 (90)**

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16 g/kg/d	**38 (24)**	**14 (26)**	**5 (13)**	**18 (37)**	**1 (5)**
17 g/kg/d	**12 (8)**	**5 (9)**	**2 (5)**	**5 (10)**	**0 (0)**
18 g/kg/d or higher	32 (20)	10 (19)	3 (8)	18 (37)	1 (5)
Do not know	11 (7)	3 (6)	8 (21)	0 (0)	0 (0)
Lipids					
Initiation (p=0.160)					
D0	**32 (20)**	**12 (22)**	**12 (31)**	**3 (6)**	**5 (26)**
D1	**77 (48)**	**24 (44)**	**17 (44)**	**28 (57)**	**8 (42)**
D2	**36 (22)**	**11 (20)**	**9 (23)**	**11 (22)**	**5 (26)**
D3 or later	16 (10)	7 (13)	1 (3)	7 (14)	1 (5)
Do not know	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Initial dose (p<0.001)					
0.5 g/kg/d	98 (61)	34 (63)	11 (28)	36 (74)	17 (90)
1.0 g/kg/d	**59 (37)**	**18 (33)**	**27 (70)**	**13 (27)**	**1 (5)**
1.5 g/kg/d or higher	**3 (2)**	**2 (4)**	**0 (0)**	**0 (0)**	**1 (5)**
Do not know	1 (1)	0 (0)	1 (3)	0 (0)	0 (0)
Target dose (p= 0.028)					
1 or 2 g/kg/d	34 (21)	15 (28)	3 (8)	9 (18)	7 (37)
3 or 4 g/kg/d	**123 (76)**	**38 (70)**	**33 (85)**	**40 (82)**	**12 (63)**
5 g/kg/d or higher / Do not know	4 (3)	1 (2)	3 (8)	0 (0)	0 (0)
Caloric target (p<0.001)					
90 or 100 kcal/kg/d	29 (18)	3 (6)	15 (39)	3 (6)	8 (42)
110 kcal/kg/d	**28 (17)**	**8 (15)**	**6 (15)**	**11 (22)**	**3 (16)**
120 kcal/kg/d	**65 (40)**	**25 (46)**	**10 (26)**	**26 (53)**	**4 (21)**
130 or more	35 (22)	18 (33)	4 (10)	9 (18)	4 (21)
Do not know	4 (3)	0 (0)	4 (10)	0 (0)	0 (0)
Maximal caloric intake prescribed (p<0.001)					
110 kcal/kg/d	13 (8)	1 (2)	7 (18)	3 (6)	2 (11)

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120 kcal/kg/d	36 (22)	9 (17)	12 (31)	9 (18)	6 (32)
130 kcal/kg/d	32 (20)	10 (19)	4 (10)	12 (25)	6 (32)
140 kcal/kg/d	37 (23)	16 (30)	2 (5)	18 (37)	1 (5)
150 kcal/kg/d or more	34 (21)	18 (33)	6 (15)	6 (12)	4 (21)
Do not know	9 (6)	0 (0)	8 (21)	1 (2)	0 (0)

D0, D1, D2; day 0, day 1, day 2

(Percentages do not necessarily sum up to 100% due to rounding)

Recommended intakes as defined in the methods section are highlighted in bold

Table 4. Guideline awareness by country.

Question	TOTAL n (%)	Germany n (%)	UK n (%)	France n (%)	Italy n (%)
Are you aware of guidelines for use of neonatal / pediatric parenteral nutrition?					
Yes	128 (80)	47 (87)	33 (85)	33 (67)	15 (79)
No	33 (21)	7 (13)	6 (15)	16 (33)	4 (21)
Of which guidelines are you aware?*					
International [8, 21]	33 (26)	10 (21)	9 (27)	10 (30)	4 (27)
National	24 (19)	16 (34)	2 (6)	0 (0)	6 (40)
In-house guidelines	8 (6)	4 (9)	2 (6)	0 (0)	2 (13)
None specifically named/other	66 (52)	19 (40)	17 (52)	24 (73)	6 (40)

*More than one answer per questionnaire possible.

(Percentages do not necessarily sum up to 100% due to rounding)