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## Pharmacy practice paper

### Current clinical practice in neonatal and paediatric parenteral nutrition in Europe

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#### Abstract

**Objective:** To investigate current prescribing, compounding, and administration practice of parenteral nutrition (PN) in five European countries, and to explore the use of pre-prepared batch-manufactured standard solutions.

**Methods:** Questionnaire survey in 218 hospitals in Germany, France, Italy, Spain, and the UK.

**Results:** 98 hospitals (45%) responded to the questionnaire. Compounding practice was found to differ greatly throughout Europe. Pharmacy aseptic compounding services were usually available in Spain (64%) and the UK (87%), but less often in Germany (35%), France (40%), and Italy (50%). Pre-prepared standard parenteral nutrition solutions were used in 25% of all hospitals surveyed for neonates, and in 17% of hospitals for children. Most of the neonatal standard solutions were prepared within the hospital, whereas commercial contractors usually supplied standard solutions for children.

**Conclusions:** We found considerable differences in compounding practice in the five European countries included in the survey. Several hospitals used internally developed standard parenteral nutrition solutions. More international guidance is needed on some of the controversial issues of parenteral nutrition treatment in neonates and children, for example light protection of PN solutions during the administration process and the route of lipid emulsion administration. Also, the safety and efficacy of standard solutions requires further investigation.

#### Introduction

Parenteral nutrition (PN) plays an important role in neonatal and paediatric feeding. PN is indicated in neonates in prematurity, and in some pathologies such as congenital malformation of the gut, and necrotizing enterocolitis<sup>1</sup>. For children indications include short bowel syndrome, Crohn's disease, and malignancy<sup>2</sup>.

The prescribing, compounding, and administration of PN are complex, high-risk procedures usually requiring the

involvement of different healthcare professionals. Most hospitals use guidelines and computer programs, which have been developed to facilitate PN prescribing<sup>3,4</sup>.

PN admixtures are either prepared in pharmacy aseptic compounding units, on the ward, or are brought in from external manufacturers. Sterility and stability of the prepared solutions is an important aspect of PN support, not only during compounding and storage, but also

during administration. The use of in-line bacteriological filters has recently been advised<sup>5</sup>, and vitamin and lipid stability in PN is dependent on light protection<sup>6</sup>.

The development of multi-compartment PN bag technology, in which solutions are segregated during terminal sterilization and mixed immediately before administration, has provided a range of commercially available licensed PN solutions.

Although these are suitable for adults and children older than 2 year, these products are not appropriate for neonates, infants, and children with special nutritional requirements.

This means that for those patients, PN solutions are either prepared daily, or batch-manufactured standard solutions (StSol) are used.

Hospitals have standardized PN for paediatric patients in various different ways<sup>7-12</sup>, including:

1. Using a standard prescribing protocol
2. Prescribing according to the recommendations of a validated computer program
3. Using standard PN solutions manufactured as a batch in hospital according to an agreed formula
4. Using commercially available standard PN solutions

Therefore, in the context of this study, standardization was defined as any of the four approaches shown above. Only the last two options (3 and 4) have the potential advantage of pharmaceutical final product testing and, in the case of multi-compartment bag presentations, terminal sterilization.

StSol can offer several potential advantages: reduction of prescribing and compounding time, enhanced stability and sterility assurance, and end-product testing for correct composition. Many hospitals have introduced pre-prepared standard bags for neonatal patients for those reasons<sup>7, 8, 11, 12</sup>.

This survey was undertaken to investigate current practice in the prescribing, compounding, and administration of PN for neonates and children, with particular reference to standardisation.

## Methods

A survey was carried out in five European countries: Germany, France, Italy, Spain, and the UK. A postal questionnaire was developed, validated, and also translated, using a reverse translation validation process. The questionnaire was then sent to pharmacists, neonatologists, or paediatricians at 218 hospitals. Hospitals were included from the main cities of each country taking a geographical spread into consideration. Teaching and non-teaching hospitals were included.

Questions were asked regarding prescribing, compounding and administration of PN. The use and composition of standardized PN was also investigated. Data were analysed using SPSS 10.0 for Windows.

## Results

98 hospitals (45%) responded to the questionnaire. The response from each country was: Germany 20 (44%), France 20 (45%), Italy 16 (29%), Spain 11 (36%), and UK 31 (71%).

The number of PN bags provided on a typical day in participating hospitals varied between 1 and over 25 (Figure 1).

PN was prescribed by physicians in 81% (N=79) and by pharmacists in 6% (N=6) of hospitals. In 13% (N=13) of hospitals either physicians or pharmacists prescribed PN. Pharmacists' prescribing was only reported in the UK. There were marked differences in the preparation of PN throughout Europe.

In Germany, 35% of hospitals use pharmacy compounding units, in France 40%, in Italy 50%, in Spain 64%, and in the UK 87%. 32% of hospitals overall indicated that PN is prepared on their wards. In 38% of hospitals additions of vitamins, trace elements and other PN components or drugs are made to the PN container on the ward.

For neonatal PN, lipids were administered separately from the binary solution in 90% of hospitals (n=73), and as total nutrient admixtures (TNA), where the lipid emulsion is mixed with the binary solution in one container, in 8 hospitals (10%) (no response from 17 hospitals to this question). Lipids were given separately to children in 78% of hospitals (n=56) and in form of TNA in 16 hospitals (22%) (no response from 26 hospitals).

Vitamins were not added to the PN solution every day. Participants were asked to indicate when, after commencement of PN, vitamins and trace elements were usually initiated.

They were also asked to state how many days per week micronutrients were provided.

The addition of vitamins to PN for neonates and children is shown for water-soluble vitamins in Figure 2 and for lipid-soluble vitamins in Figure 3 (error bars represent 95% confidence interval of the mean).

Vitamins were usually added every day of the week once commenced (83 hospitals (92%)). The remaining hospitals included vitamins between six and three days a week (7 hospitals (8%)) (no response from 8 hospitals).

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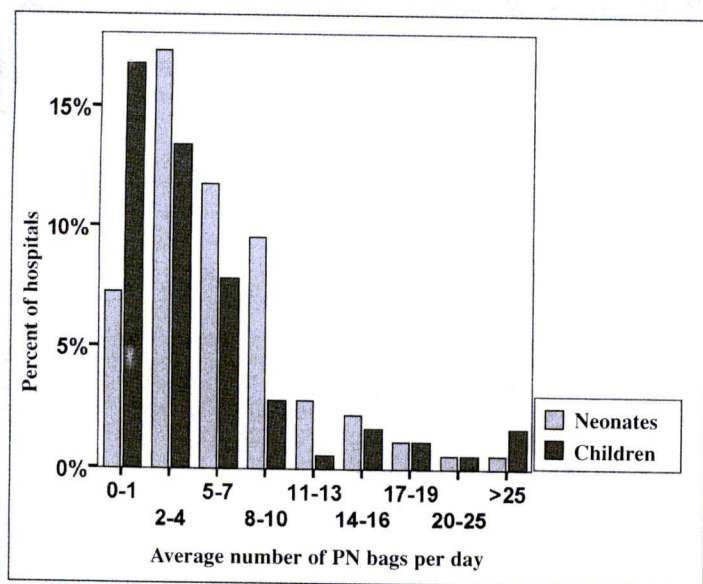


Figure 1: Number PN bags used on average per day

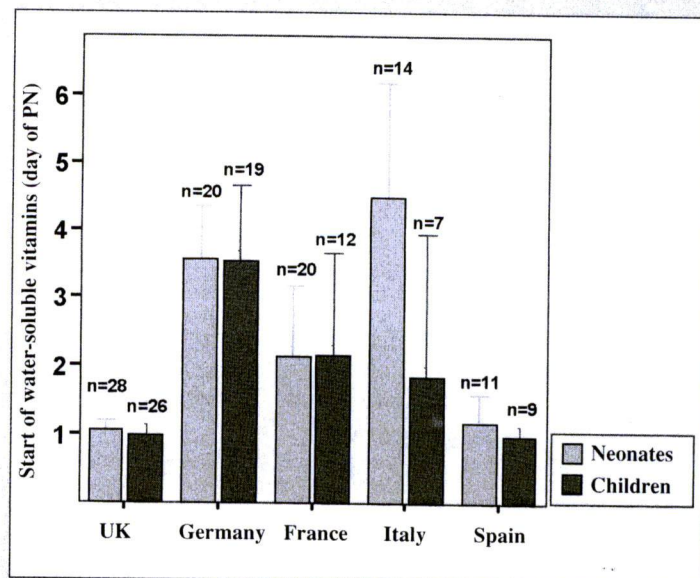


Figure 2: Start of water-soluble vitamins for neonates and children in the five countries

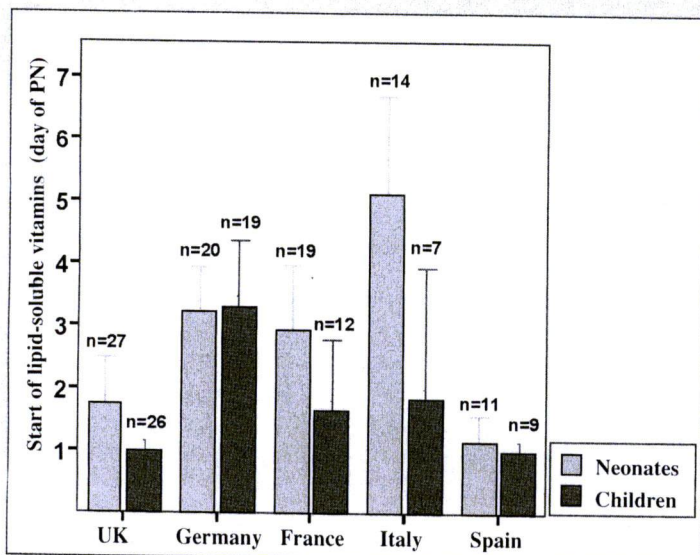


Figure 3: Start of lipid-soluble vitamins for neonates and children in the five countries

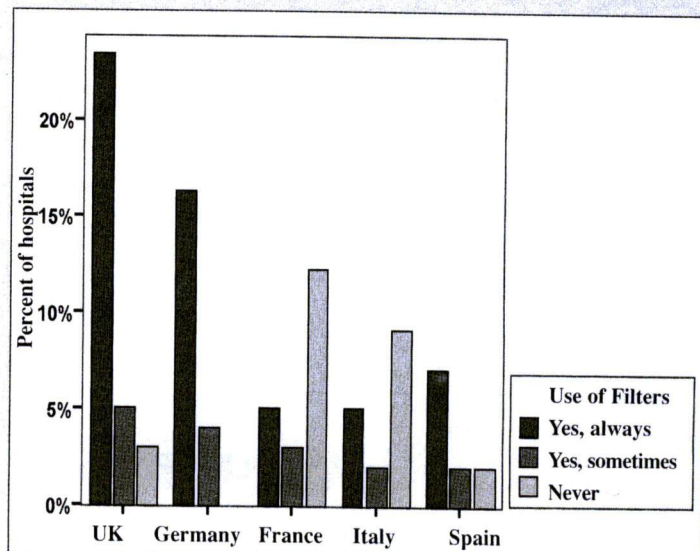


Figure 4: Use of in-line administration filters in each country

PN administration techniques also varied considerably. Figure 4 shows how often in-line administration filters were used in each of the five countries.

Light protection of PN containers and administration sets is summarised for each country in Table 1.

Among the 98 responding hospitals, 79 provided information on the use of StSol. Of these, 19 hospitals (24%) used StSol for neonates, which had been developed and compounded internally in 57% of cases, but also in conjunction with other hospitals (21%), or through commercial sup-

pliers (21%). Only 14 hospitals (18%) reported using StSol for children. Of these hospitals just one had developed an internal standard PN for paediatric patients other than neonates whereas all others used commercial suppliers.

## Discussion

Little has been published about current PN practice in Europe, and little is therefore known about the way in which PN is prescribed, prepared, and administered to neonates and paediatric patients. Our results show that physicians were mainly responsible for the prescription of PN, although in some hospitals in the UK pharmacists

**Table 1:** Frequency of light protection during the administration of PN

	Light protection during administration					
	Container			Administration tubing		
	Always n (%)	Sometimes n (%)	Never n (%)	Always n (%)	Sometimes n (%)	Never n (%)
UK	20 (65)	9 (29)	2 (7)	3 (10)	2 (7)	25 (83)
Germany	6 (30)	8 (40)	6 (30)	3 (17)	11 (61)	4 (22)
France	6 (30)	3 (15)	11 (55)	1 (5)	2 (11)	16 (84)
Italy	10 (63)	2 (13)	4 (25)	5 (31)	4 (25)	7 (44)
Spain	5 (50)	1 (10)	4 (40)	2 (22)	3 (33)	4 (44)

were also prescribing, although, at the time of this survey, there was no legal framework for this.

Compounding practice differed greatly throughout Europe. In the UK, most hospital pharmacies had aseptic compounding units, which offer comprehensive aseptic services, including PN. In Germany PN was often prepared on the ward, and in France many hospitals use commercial contractors for aseptic compounding. The increasing availability of licensed, terminally sterilised PN from industry may alter this dynamic in the near future.

Many years ago, PN was infused from three separate glass containers of amino acids, glucose, and lipids. The risk of bacterial contamination is increased if separate containers are used<sup>13</sup>, and in contemporary practice PN is usually provided in flexible plastic containers, either as TNA, which contains all macronutrients (including lipids) and electrolytes, or as binary solutions of amino acids and glucose where lipids are infused separately.

In this study, we found that lipids were usually administered separately in the surveyed hospitals, especially for neonates. This might be due to concerns about possible instabilities of lipid emulsions in PN solutions, especially as neonatal requirements for calcium are relatively high<sup>14,15</sup>.

This factor becomes even more important to consider, as organic phosphates are increasingly used, which allow higher concentrations of calcium to be included without a resulting calcium phosphate precipitation<sup>16</sup>. Careful consideration of emulsion stability is essential as increased concentrations of divalent ions (including Ca 2+) are used routinely in practice. Didier and co-workers have shown that lipid emulsion alone might be a better growth medium for microbial contaminants than TNA<sup>17</sup>.

Administration of lipids in the form of TNA has potential practical advantages, and Cuntz and co-workers have investigated safety and efficacy of TNA in children, and found no differences in complications between children who received lipids separately or as TNA<sup>18</sup>. Although the

use of TNA is now widespread in adults, little has been published about advantages or disadvantages of this practice for neonatal and paediatric patients, and the questions whether or not to infuse lipids separately remains a controversial issue<sup>19</sup>.

Although most hospitals gave vitamins on each day of PN, a significant number of hospitals did not start micronutrients on the first day of PN. Particularly in Germany and Italy, vitamins addition was frequently delayed until several days after commencement of PN.

Commercially available vitamin preparations are formulated to meet daily needs of paediatric patients. An insufficient provision of vitamins could potentially occur if daily administration of vitamins is not adhered to or if vitamins are added only after several days of PN.

In order to remove particles from PN solutions and reduce risk of administering microbial contaminants, the use of in-line filters during PN administration has recently been advocated<sup>5</sup>. We found that many hospitals filtered the PN solution during administration, particularly in the UK, Germany and Spain.

Light protection has been shown to reduce the formation of lipid peroxides and will also protect light sensitive vitamins from degradation<sup>20</sup>. PN solutions were protected from light in some hospitals, with the highest prevalence for protection of PN containers in the UK. Light protection of the administration set tubing was uncommon, possibly due to a lack of suitable materials. The exposure of the PN solution to light during administration, especially in neonatal care where phototherapy is used, might promote an increased degradation of vitamins, which can result in a sub-optimal provision of vitamins. It can also lead to the formation of toxic lipid peroxides<sup>6</sup>. Light protection of the PN container and the development of affordable light protective administration sets should be encouraged.

This study has shown that a significant number of hospitals use StSol. From the published literature it is known that

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some hospitals introduced pre-prepared PN solutions many years ago, and some have published the composition of their solutions<sup>7-12</sup>. StSol can provide obvious advantages in terms of reduced prescribing and compounding time and also the possibility for improved quality control through end-product testing of standard batches. Intuitively, there should be a reduced risk of prescribing, compounding, and administration errors with StSol although there is currently no published evidence for this. If commercially prepared as two- or three-compartment bags, StSol are terminally sterilized, and therefore the risk from microbial contamination and the presence of bacterial pyrogens is reduced. However, such licensed solutions are currently not available for children below the age of two years.

## Conclusions

The provision of neonatal and paediatric PN is complex and requires inter-disciplinary co-operation. There are cultural differences in Europe regarding the role of different professions in the provision of PN, especially the role of the pharmacy as the compounding and prescribing facility for PN.

The use of StSol was found to be widespread, and although this approach may offer pharmaceutical and economic advantages, and it is important that nutritional adequacy is ensured. More work is needed to investigate pharmaceutical and clinical issues regarding lipid administration, especially in term of emulsion stability, lipid peroxidation, microbial contamination, cost effectiveness, and error reduction.

We have shown that there is considerable diversity of current PN practice in Europe, and that arguably, more guidance is needed on some of the controversial issues

described above. In particular the use of pre-prepared StSol requires further investigation in terms of safety and efficacy.

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