

# Meeting the needs of parenteral nutrition patients

Standardised parenteral nutrition formulations are recommended in current guidelines and can be safely provided for adult and paediatric patients in hospital and at home, according to experts speaking at a Fresenius Kabi satellite symposium held during the recent EAHP congress

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➤➤ There is a place for both standardisation and personalisation in the provision of parenteral nutrition (PN) solutions, said Irene Krämer (Director of Pharmacy, Johannes Gutenberg University Hospital, Mainz, Germany) in opening the symposium.

## Practice standards

Standardised nutrition solutions can be used to meet the needs of about 75% of hospital patients, according to Mariola Sirvent (Hospital HLA-Vistahermosa, Alicante, Spain). PN is a type of therapy that is widely used but is expensive and complex and is associated with a high risk of complications. The Institute for Safe Medication Practices (ISMP) classifies parenteral nutrition as a 'high alert' treatment, she noted.

Patient outcomes are directly related to the quality of practice and therefore measures to improve the safety and adequacy of nutritional treatment and also measures to maximise the efficient use of resources have a positive impact on patients' outcomes. A number of statements and guidelines have been published by professional organisations including the British Association for Parenteral and Enteral Nutrition (BAPEN), the American Society for Parenteral and Enteral Nutrition (ASPEN), the Spanish Society of Hospital Pharmacy (SEFH) and the Spanish Society for Clinical Nutrition and Metabolism (SENPE). A working group of the SEFH has defined standards of practice for specialised nutritional support in hospitals. The standards describe the performance of competent care that should be provided to assure the safe and efficient provision of nutritional support. A total of 97 standards has been compiled, covering the process from nutritional screening to completing the treatment. They are accompanied by grades of

recommendation: 1- essential, 2- advisable and 3 - permissible. For example, under the standard for 'Formulation and Compounding', criteria are set out under the headings of facilities and equipment, work practices, personnel training, environmental monitoring and quality control.

Other important aspects include standardisation of the process for ordering PN, pharmaceutical validation of PN formulations, implementation of standardised PN formulations and development mechanisms to allow the safe individualisation of PN formulations.

"Standardisation of PN formulations is one of the most important aspects of this work", said Dr Sirvent. The products are pharmaceutically complex, there is always a risk of microbiological contamination and of mistakes during compounding because of the complexity of the task. "With more than 40 components, it is one of the most complex pharmaceutical products", she explained. There are risks of interactions, precipitation of components and lipid emulsion stability concerns, she added. Dr Sirvent said that the report of nine



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patients' deaths in Alabama (US) after being given contaminated IV nutrition bags served to underline the dangers of microbiological contamination. Over a two-year period, some 1311 errors with PN were reported to MedMarx (a database that tracks both adverse drug reactions and medication errors submitted by participating hospitals in the USA). Of these, 92 were related to compounding errors, including incorrect quantities, wrong drug and incorrect preparation, she said.

Turning to formulation, she said that five issues concerned pharmacists. They are: chemical interactions between components, lipid emulsion stability, inorganic salt precipitation, microbial



Joeri de Cloet



Irene Krämer



Magdalena Piętko



Mariola Sirvent

contamination and mixing errors. Standardisation improves the safety of all these aspects, she emphasised.

The added value of standardisation lies in the fact that it reduces the risk of transcription errors, minimises problems with omissions or inappropriate doses of nutrients, improves the chance of providing a balanced nutritional mixture, and allows professionals with limited knowledge of clinical nutrition to provide good quality care. It also allows automation of the compounding process and consequent reduction in the chances of error or contamination.

A Spanish study had shown that just three formulations could be used to meet the needs of 75% of adult, metabolically-stable patients, said Dr Sirvent. They are not suitable for some groups such as those with organ failure, glucose intolerance or body mass indices above 30. These groups would still need individually-tailored formulations, she acknowledged.

### Standardised paediatric nutrition

It has been possible to develop standardised, all-in-one (AIO) paediatric parenteral nutrition solutions that are safe and effective in both home and hospital settings, Joeri de Cloet (Research Pharmacist, University Hospital, Ghent, Belgium) told the audience.

Malnutrition in children presents special problems, for example, it increases the risks of infections and poor wound healing. It is often undetected, even in a hospital setting, he added. A well-balanced nutrition formula is important for children because growth is fast (compared with adults), nutritional requirements are high and body reserves are limited. Proper tissue and organ development depends on adequate nutrition.

An unbalanced or inadequate nutrient supply can effectively “programme” an individual to develop some diseases, such as diabetes or obesity, in adulthood, he said.

Standardised PN products are of known quality, are available ‘off the shelf’ and may cost less than patient-specific solutions. Individualised PN can be tailored to suit specific needs and is suitable for critically ill patients with conditions such as hyperkalaemia.

Before 2008 there were no commercially available, standard, AIO PN mixtures. Formulations were ‘binary’ (glucose, electrolytes and amino acids) and lipids had to be administered using a Y-connector. “This represented a major challenge”, said Mr de Cloet. What was needed was a solution that conformed to the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)/ESPEN 2005 guidelines and that combined high calcium and phosphate concentrations with lipids. The product had to allow dosage based on ideal body weight and had to have adequate stability, he explained.

Three standard formulations were designed to meet these criteria. They were suitable for children from 3kg to more than 31kg. One was a hospital inpatient formulation designed to provide AIO TPN via a central line, one was a ‘binary’ solution that provided no lipids and the third was a formulation suitable for home administration.

The PN formulation was packed in ethyl vinyl acetate copolymer (EVAM) two-compartment bags (lipid in one compartment and other ingredients in the other compartment). Stability studies showed that the product remained stable for three months.

The paediatric AIO mixture for hospitalised patients was then studied in three clinical situations. The first study was a retrospective, observational study in non-ICU patients with body weights ranging from 3–40kg who received PN for more than five days. It included 85 patients with 123 episodes of PN. The mean duration of PN was 16.3 days. All the patients gained weight and there were few complications. There were two catheter-related infections.

The next study examined, prospectively, the use of AIO mixtures in the paediatric intensive care unit (PICU). The patients’ ages ranged from one month to 15 years. The main findings were that the tailored AIO PN provided inadequate macronutrients supply on days 1–3, resulting in a cumulative energy deficit after day 3. There was also excessive fluid administration in 21% of patients. A standardised formulation could have met the requirements from day 1 and would have been suitable for 76% of PICU patients. The standard admixtures would have complied with the ESPGHAN/ESPEN guidelines.

The third study was a retrospective cohort study that examined the safety and effectiveness of PN therapy in infants and children receiving home PN. Patients under 18 years of age who were discharged on home PN between January 2000 and April 2016 were included. Before 2008, individually compounded solutions were provided (Cohort 1) and after that date standard AIO mixtures were supplied (Cohort 2). The median duration of home PN was 11 months and the most common indication was short bowel syndrome (47%). The results showed that both cohorts gained weight but there was a higher positive evolution of BMI in Cohort 2. There were fewer catheter-related blood stream infections and fewer catheter occlusions when the standardised mixture was used. There was also a higher frequency of electrolyte disturbances in the tailored PN vs standard PN group – most commonly hyperkalaemia and hypomagnesaemia.

Mr de Cloet concluded that a standard paediatric AIO mixture was safe and effective both in hospital and home settings. It complied with the ESPGHAN/ESPEN guidelines and had a positive impact on the number of IV line manipulations, resource efficiency, time and cost. Moreover, it made it possible to provide a stable, off-the-shelf product. Future research will examine the possibility of providing standardised AIO mixtures for NICU patients, he said.

### Automated preparation of PN

Home parenteral nutrition is a life-saving therapy for patients with irreversible intestinal failure, said Magdalena Piętka (Director of Pharmacy, Stanley Dudrick Hospital, Skawina, Poland). Comparing multi-chamber bags (MCBs) and tailor-made bags, Mrs Piętka said that MCBs are usually industrially-manufactured, standard AIO solutions provided as two- or three-chambered bags. They have to be mixed prior to administration. Currently, MCBs are used for the majority of PN patients. The shelf-life of commercially manufactured MCBs is usually longer than 12 months and they can be stored before mixing at room temperature.

In contrast, tailor-made PN bags must be aseptically compounded from various components, usually in hospital pharmacy aseptic units. They are



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most suitable for patients with rapidly changing requirements such as neonates, PICU patients and long-term home PN patients. Such bags are usually manufactured on either a daily or weekly basis due to their limited stability. They require storage in a refrigerator at 2–8°C.

One study showed that nearly 50% of patients with benign chronic intestinal failure needed personalised parenteral nutrition mixtures compared with 20% of cancer patients.<sup>1</sup> The authors concluded that standardised mixtures could not completely replace personalised mixtures because of special needs for micronutrients and frequent changes of requirements due to unstable clinical or metabolic status. Another study showed that the use of premixed PN was associated with increased use of supplemental intravenous electrolytes.<sup>2</sup> The more infusions, the greater the risk of catheter-related sepsis, warned Mrs Piętka. A cost analysis conducted in Turkey showed that when more than 15 bags per day were compounded, hospital-compounded parenteral nutrition bags showed a cost advantage.<sup>3</sup>

At the Stanley Dudrick hospital, 130 HPN patients are managed and the hospital pharmacy prepares more than 900 tailor-made bags each week, and so compounding in the hospital pharmacy is cost-effective, said Mrs Piętka. In order to streamline this labour-intensive process, automatic compounders are used. This improves accuracy and efficiency and minimises the need for manual additions, thereby reducing the risk of microbial and particulate contamination, she said. This makes it possible to compound a large number of bags safely in a short time, she added.

The biggest problem with home PN is always the question of stability. Lack of stability is one of the highest risk factors in this field because of the “unlimited numbers of combinations of components that are possible”. For this reason a ‘matrix approach’ is used when selecting a formulation, explained Mrs Piętka. This involves ensuring that all the starting materials are within predefined [concentration] limits. When doing this, it is critically important to ensure that the solutions used for the macro-ingredients are the same (that is, same manufacturer) as those used for the original stability testing, she warned.

Comprehensive stability testing of PN solutions is beyond the capabilities of most hospital pharmacies, however, some general principles can be applied. The lipid emulsions are the most vulnerable component of the mixture. The physico-chemical stability of lipid emulsions is such that a one-week shelf life can safely be assigned to compounded mixtures, she said. A more subtle hazard is presented by the formation of reactive lipid peroxides when polyunsaturated omega-3- and omega-6-fatty acids are exposed to oxygen. Peroxide products can damage other PN components and can even be harmful for patients in some circumstances. For this reason multi-layer bags are used. The extent of lipid peroxidation is dependent on storage time and the presence of vitamins. Many vitamins are also prone to degradation and special attention should be paid to vitamins A, C and E, she said.

In summary, Mrs Piętka said that AIO admixtures are complex formulations with limited stability and short shelf lives. They should be used within 24 hours if stored at room temperature or within seven days if stored in a refrigerator.

## Discussion

During the discussion, further details of the practicalities of standardisation were explored. Dr

Sirvent said that standardisation was sometimes misunderstood and it is important to realise that standardised PN solutions can be commercially supplied, as ready-to-use MCBs, or made in the pharmacy aseptic unit, under ISO 5 conditions.

Commenting on the wider use of standardised PN bags, Mrs Piętka said it might be possible to use them for some of the cancer patients. She also agreed that 75% of hospital inpatients could probably use standardised PN bags. “However, the needs of many home patients are more complex. Many of our home PN patients have been receiving PN from birth and consequently we are very focussed in the possibility of long-term complications”, she said. Professor Krämer added that cancer patients are easier to manage because they do not normally have intestinal failure and they can have oral electrolyte supplements.

Asked about the feasibility of implementing standardised formulations for paediatric patients, Mr de Cloet said that before standardised bags were introduced physico-chemical incompatibilities were a frequent cause of problems. When designing standard bags it is important to have enough bags for the different weight categories. “We have 12 formulas – three types for four weight categories – and this enables us to meet most needs”, he said. At first physicians were worried about possible electrolyte problems but the clinical results soon showed the effectiveness of the scheme. “No physician wants to go back to the old way now”, he said.

“We do not encounter calcium and phosphate precipitation any more, we have more flexibility and also at weekends when the pharmacy is closed, PN can still be started. You just have to add vitamins and trace elements at the point of use. We have done this for ten years now and we have seen the results”, he said.

Concerning the possibility of standardised PN bags for neonates, Mr de Cloet said that one such product was already commercially available but many additives are required because it is a ‘one for all’ formulation. “I think it would be possible to standardise with a range of three or four different bags. This would be in line with the new ESPEN guideline which recommends the use of standardised bags as first choice, even for very low birthweight neonates”, he said.

He added, “Physicians do not always know the current ESPEN guidelines – prescribing often follows old (internal) protocols – sometimes as much as 20 years old!”

Asked what percentage of home PN bags were returned unused and whether the costs of preparing these were factored into the overall costs. Mrs Piętka said she did not know the exact numbers but they were likely to be low – in the region of 1% – because good communications between patients, doctors and pharmacy meant that PN bags were rarely over-supplied. The maximum loss would be seven bags because they are supplied on a weekly basis, she added.

Both Mrs Piętka and Mr de Cloet confirmed that PN is usually administered overnight, over 12–16 hours. Some PN bags can be given over an eight-hour period, but this is for supplemental feeding.

The satellite symposium, *The pharmacist's role in meeting the needs of every parenteral nutrition patient*, was held on 28 March 2019 during the 24th EAHP Congress in Barcelona, Spain.

## References

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