



## Parenteral Nutrition in Neonatology – To Standardize or Individualize?

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**Key words:** parenteral nutrition, computer-assisted prescribing, neonates

### Abstract

Premature very low birth weight (< 1500 g) infants comprise one of the largest groups receiving parenteral nutrition. PN should be optimized to answer their high nutritional requirements and suit their metabolic status, but should also be validated pharmaceutically. PN can be provided as a standard, usually commercial, formulation, representing the average needs of a large group of patients. Alternatively, an individualized PN compound adapted to the patient's needs can be prescribed and prepared, usually on a daily basis. The main advantage of individually prescribed PN is that it is tailored to suit a specific patient, thereby assuring the best possible nutrition and biochemical control. Batch-produced standardized PN bags can be readily available as ward stocks in neonatal intensive care units, enabling initiation of early PN immediately after the delivery of a premature infant. Moreover, standard PN solutions incorporate expert nutritional knowledge and support. A combination of standardized PN bags, prepared under strict standardization criteria, for most neonates, with a small number of specifically tailored individualized PN formulations for those in need for them, could reduce pharmacy workload and costs and increase safety, while maintaining the desired clinical flexibility. For those in need of the individualized PN formulations, a computerized ordering system can save time, decrease prescription and compounding errors, and improve quality of nutritional care.

*IMAJ 2006;8:641–645*

With the advances in neonatal care, more premature very low birth weight infants are surviving (VLBW defined as birth weight < 1500 g). This means longer hospitalization in the neonatal intensive care units and nutritional support, which in the case of the smaller premature infant means parenteral nutrition, at least for the first few weeks until enteral nutrition can be advanced to a sufficient amount [1,2]. It is therefore not surprising that neonates represent one of the largest age group of patients receiving PN today [3].

PN is an intravenous medication and thus susceptible to medication errors [4]. PN administration carries the risk of inducing metabolic derangements as well as infectious complications [5]. Also, there is the issue of compatibility and stability of addi-

tives in the PN admixture [6], and the question of how to avoid the risk of substrate precipitation.

PN admixtures consist of many different components [7]. PN should be optimized and suited to the patient's nutritional and metabolic status, but should also be validated pharmaceutically. PN can be provided as a standard, usually commercial, formulation, representing the average needs of a large group of patients. Alternatively, an individualized PN compound adapted to the patient's needs can be prescribed and prepared, usually on a daily basis and in the hospital pharmacy. For adults, there is a wide range of commercially available standard PN solutions [8] with available data on issues of stability and additives, such as trace elements, vitamins and electrolytes. Such standard PN solutions are less available and less frequently used for the pediatric population in general, and in neonates specifically [5,7-9].

### A vote for individualized PN

The main advantage of individually prescribed PN is that it is tailored to suit a specific patient to achieve the best possible nutrition with the most precise biochemical control [10]. The prescription can be changed on a daily basis, reflecting the patient's medical condition and most recent laboratory tests [3]. Standardization, in contrast to individualization, can be a threat to the clinical judgment of the patient's needs, replacing the nutritional requirements with "cookbook medicine" [4]. This is especially true when the patient is a very tiny and fragile VLBW premature infant. In this group of patients the nutritional requirements are enormous; these include sufficient protein and calories to cope with all morbidities related to prematurity (such as respiratory distress syndrome), to enable an adequate rate of accretion of nutrients that would have been reached *in utero* if premature delivery has not occurred and, eventually, to achieve proper growth [11-13]. However, this group of patients has a labile unstable metabolic control, with the tendency towards major, sometimes life-threatening, metabolic disturbances (e.g., hypo- or hyperglycemia, hypo- or hypernatremia, hypo- or hyperkalemia). Theoretically, only individually tailored PN – prescribed at least once daily and based on updated laboratory results – can meet such a nutritional challenge. Dice et al. [14]

PN = parenteral nutrition

VLBW = very low birth weight

conducted a small randomized control study and found better weight gain and higher intake of amino acids, lipids and energy when individualized PN was used in VLBW infants as compared to standardized formulations. This followed a previous study in a pediatric population where individualized PN formulations resulted in better growth and eventually also cost less than the standardized PN bags because of decreased wastage [15]. However, these studies – especially in the VLBW infants [14] – were conducted more than 25 years ago, when the standardized PN formulations were less optimal than what is available today and lipids were not routinely supplied with the standardized PN formulations, unless specifically ordered. The difference in caloric intake and weight gain therefore cannot be attributed to the administration of standard solutions, but to the better and more intensive nutritional monitoring in the group that received the individualized PN. In those settings, individually tailored PN ordered by the physician and pharmacist might have reflected the increasing knowledge of VLBW infants' nutritional requirements more than the standardized solutions that were available. Bethune [8], who surveyed some of the available standard PN formulations for neonates in the UK, found that none of them met all the nutritional requirements of neonates. In part this was because they were made for peripheral, and not only central venous administration, thus providing less glucose and calories. Also, these formulations did not provide for the increased need for electrolytes due to excessive gastrointestinal losses (generally potassium and magnesium), or for infants who were fluid restricted because of cardiac or renal failure.

Another aspect that must be considered when ordering PN is the lack of data on the stability of electrolyte additives. This limits adding them to the PN, and separate supplementation requires extra-clear fluids that are given instead of nutritionally rich PN, especially in fluid-restricted babies. The design of most standard PN formulations – that provide full nutrition at a volume of at least 150 ml/kg/day – allows little spare volume for any other additives and is problematic when smaller volumes are indicated. Bethune concluded that standard neonatal PN formulations can meet the nutritional needs of most neonates only for short periods, but if given for longer might result in inadequate nutrition with all the resultant effects on future growth and development [8]. One of the options suggested in that article was that more hospitals operate aseptic units and prepare tailored PN for neonates. However, the paper did not oppose the development of better standard commercially available PN formulations for neonates in a few specialist centers, as long as these centers allow also for next-day administration of individualized formulations [8].

### **What can go wrong? Possible problems with PN**

PN is an intravenous medication with many ingredients and additives, and as such is liable to medication errors, especially in Pediatrics, where all the calculations are also weight-based [4]. Also, the diversity and complexity of meeting the nutritional needs of children in general, and neonates specifically, turn the task of ordering PN into a difficult process for the inexperienced

clinician. An optimal PN order form, including age- and weight-specific nutrient requirements with guidelines for advancing substrates could help the clinician, improve PN prescriptions, decrease prescribing errors (although not calculation errors), and serve as an educational tool [16,17].

The stability and compatibility of PN solutions is a safety issue of great concern. The major pharmaceutical issues are the stability of lipid-injectable emulsions and the compatibility of the calcium and phosphate salts. The potentially adverse outcomes from the infusion of unstable coalesced lipid emulsions or incompatible mixtures with precipitates of calcium and phosphate can be life-threatening. The existence of a hospital nutrition support team, the use of compounding devices (the most efficient ones use automated technology), and establishing communication channels between the prescribing clinicians and the pharmacy team dedicated to PN preparation decrease these risks but do not eliminate them entirely [18-21].

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*Premature VLBW (birth weight < 1500 g) infants represent one of the largest groups of patients receiving PN*

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### **Computer-supported PN ordering – the likely solution**

From the safety point of view, information technology can handle medication and ordering of PN better than humans, based on the guidelines contained in its program [22]. Since their introduction in the 1980s [23,24], computer-assisted prescribing programs are widely used in hospitals in Europe and the United States [25]. Unlike humans, computerized ordering programs are not susceptible to fatigue or mathematical errors [4]. Puangco and co-authors [26] found that automating the process of writing and delivering PN orders saved time because it eliminated repetitive tasks and tedious calculations previously required by neonatologists, dietitians and pharmacists. Furthermore, they showed that computer ordering of PN resulted in improved nutrient content of the PN solutions (energy, protein, calcium and phosphate). This helped achieve caloric and protein goals earlier, and lower alkaline phosphatase levels – a marker of better mineral status [26]. Computer software was also able to integrate calcium and phosphorous solubility in the PN with the clinical data to improve parenteral mineral administration, which is difficult because of their relatively low solubility in the PN [27]. Such computerized nutritional software provides low cost and easy-to-use effective data of correctly calculated nutrient dosages. When data are both updated and reliable the result is better growth and better biochemical control, as evidenced in the newborn's blood samples [28]. The consensus is that we should gradually abandon paper ordering and rely solely on electronic PN ordering [17]. The more generalized, probably web-based, the better such an ordering system can be, because it will be based on wider updated knowledge and experience and not limited by regional boundaries and local practices. This in turn could lead to safer formulations as well [4]. On the other hand, we can still

individualize the PN prescription for each patient using such an electronic ordering system, thus improving biochemical control and decreasing wastage. Computer-assisted PN prescribing programs are also a valuable educational tool for the junior clinician inexperienced in clinical nutrition, and these tools facilitate the communication between the prescribing clinical team in the NICU and the pharmacy department [3].

Despite all the above, in practice the advantages of individualized computer-assisted prescriptions cannot be proved in premature infants [29]. A possible disadvantage of a computer-based prescription program is that it might encourage trivial adjustments in PN prescriptions, based on laboratory results that in clinical practice are irrelevant, in the pharmacy compounding department [3]. Beecroft et al. [3] investigated the need for individualizing PN formulations. They found that among 148 individualized PN formulations, 82% deviated from the pre-formulated computer protocol. Most of these deviations reflected the prescribers' desire to override the computer protocol and to add ingredients (glucose, sodium or phosphate). However, only 44% of the abnormal serum biochemical results (mostly low sodium or phosphate levels) prompted the prescribing physician to change the pre-formulated computer PN protocol and increase the amount of nutrients, minerals or electrolytes. Also, high serum potassium levels were usually attributed to hemolysis during sampling and did not cause the prescribing physician to decrease the pre-formulated potassium intake [3]. Based on these observations, Beecroft and associates [3] suggested that higher proportions of PN be standardized, if modified to reflect the practice pattern.

### **Standard PN formulations for neonates – possible, cheaper and safer**

Standardization reduces the chances of potential errors and is thus safer. Although not investigated, it is estimated that standardization reduces wastage and makes treatment more predictable and controllable [4]. Krohn et al. [30] evaluated the use of standard PN solutions in a pediatric intensive care unit and concluded that standard PN orders could be used in the majority of patients. They were mostly adequate and the intake of most macronutrients and electrolytes was similar to individually prescribed PN. In fact, calcium and phosphate intakes were better with standard PN compared to the individualized PN, and electrolyte imbalances occurred less frequently with the standard PN. Yeung and colleagues [31] retrospectively evaluated the difference in nutrient intake and biochemical responses in premature infants born at less than 33 weeks of gestation who received standardized versus individualized PN between days 2 and 7 of life. That study did not demonstrate any clinical advantage or improved biochemical control with individualized PN regimes. The neonates on the standardized PN received the nutrients in a fixed and proportional manner. The increase in protein was accompanied by proportional increases in the intake of glucose, electrolytes and acetate. Yeung et al. [31] found that in infants who were on standardized PN, the cumulative deficit

in protein intake by the end of the first week was 35% less than in infants on the individualized regimens. Infants on standardized PN also had higher intakes of calcium and phosphate, resulting in less commutative deficits and better bone mineralization. Since batch-produced standardized PN bags are readily available as ward stocks in the NICU, early parenteral nutrition can be initiated immediately after the delivery of a premature infant. This is the optimal way to achieve "early aggressive nutrition" and reach the goal of early regain of birth weight followed by better growth [32,33]. Commercially batch-produced standard-

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ized PN bags may also reduce the huge costs of individualized PN production [34]. Yeung and team dispute the claim that the difference between the individualized and standardized PN could have been abolished had neonatologists been made more aware of the nutritionally aggressive but more balanced protein energy PN, and prescribe accordingly. They claim that the constraint of the pharmacy PN production time and the competing demands on the clinicians' immediate attention and time are bound to result in very little time for multidisciplinary nutritional discussion. This is true for most NICUs; moreover, it is unlikely that an expert in neonatal nutrition is readily available in each hospital, which implies possible gaps in the knowledge of the physicians prescribing neonatal PN in the different NICUs. In fact, the nutrition committee of ESPGHAN (European Society of Paediatric Gastroenterology, Hepatology and Nutrition) recommends that pediatric units, and this certainly includes NICUs, should have multidisciplinary nutritional support teams to deal with the growing complexity of assessing nutritional needs and planning nutritional support for infants and children [35]. Standard PN solutions partly obviate the problem since an initial expert team can order, in advance, the most common and suitable standard PN regimes, and these regimens should be suitable for most VLBW premature infants. Commercially prepared standard PN bags reduce not only the risk of ordering errors, but also the risk of compounding errors in the hospital pharmacy that has to deal with many different PN prescriptions on a daily basis. Large-scale commercial production of standard PN bags can be further eased by using automated compounding technology that will assure better pharmaceutical control of the physicochemical stability and compatibility of PN admixtures. This can decrease the risk of potentially adverse outcomes from infusion of incompatible mixtures (e.g., precipitated calcium phosphate product) [18,21]. Large-scale commercial production of standard PN bags usually offers better aseptic manufacturing conditions than the average pharmacy hospital aseptic unit, thus decreasing the risk

NICU = neonatal intensive care unit

of PN-associated infections [8]. The need to add the parenteral multivitamins to the standard PN bag shortly before infusion [21,30] is a limitation that requires proper handling to assure aseptic conditions and avoid errors.

### The situation in Israel at present

In a recent phone survey we called all 25 NICUs in Israel, and found that 18 (72%) of them use standardized PN bags. Two-thirds of them use commercial standardized PN bags, and the rest have their standardized formulations prepared in the hospital pharmacy. The number of standardized formulations available for use in these NICUs ranges between 1 and 10, although most NICUs stated that they use 3–5 basic standardized PN formulations more frequently. The NICUs that use standardized PN formulations do so because it allows them to initiate early balanced PN with glucose and protein and reduces the need for daily prescription of PN, which requires more nutritional expertise than most residents have. These NICUs claimed that the standardized PN formulations cover 90–99% (most estimated 95%) of the clinical situations in practice, and that individualized PN prescriptions for very sick metabolically unstable newborns (estimated at one to two patients a year at the most) were rarely needed. Of note is that six of the seven NICUs that order individualized PN for their preemies on a daily basis also hold a stock of standardized PN bags for preterm infants born at night or on weekends. This allows them to start early PN nutrition.

### Recommendations for the use of standardized and individualized PN formulations

Most NICUs in Israel are small to medium in size, and do not have a readily available nutrition support team or pharmaceutical support at all times. Many clinicians, especially junior ones, have neither enough knowledge in nutrition nor the time to deal appropriately with individualized ordering. Most of the preterm VLBW infants need PN for 2–3 weeks until sufficient enteral nutrition can be established. This is considered a relatively short period for PN. Currently there are two companies in Israel that commercially manufacture standardized PN solutions for neonates. They produce a large number of standardized PN formulations, based on each hospital's current practices.

Based on European guidelines for pediatric parenteral nutrition that were recently published by ESPGHAN (European Society of Paediatric Gastroenterology, Hepatology and Nutrition) and the European Society for Clinical Nutrition and Metabolism (ESPEN) [36], we suggest that the following recommendations be adopted for the use of standardized and individualized neonatal PN formulations in Israel:

1. Standard PN solutions can be used safely in most newborn patients, including VLBW premature infants for short periods (up to 2–3 weeks).
2. A range of standard regimens to suit different clinical conditions should always be available in the NICU.
3. It is recommended that such suitable standard PN solution be started soon after the birth of a newborn infant, especially a preterm VLBW infant.
4. Adequate monitoring of the metabolic and nutritional status of the infant should be assured.
5. The appropriate standard PN regimen most suitable for the infant's condition, from the available range, should be ordered at least once daily.
6. The addition of deficient electrolytes and nutrients should be possible under appropriate aseptic conditions in the NICU or the hospital's pharmacy.
7. Individualized PN is preferred:
  - a. When nutritional needs cannot be met by the available range of standard PN formulations
  - b. In very sick and metabolically unstable newborns (such as those with abnormal fluid and electrolyte losses)
  - c. In infants requiring PN for prolonged periods (such as those with short bowel syndrome).
8. Computer-assisted prescribing of PN should become available, as this can save time, decrease prescription and compounding errors, and improve the quality of nutritional care. Such computerized programs will guide the physician to the most adequate standardized solutions and optimize the use of individualized solutions.

We suggest that the development of the required range of standardized neonatal PN formulations be on a national basis. This will enable us to gather all the knowledge and experts locally available, including neonatologists, pediatric gastroenterologists, nutritionists, nurses and pharmacists, in order to come up with the best possible formulations – nutritionally as well as pharmaceutically. We believe that such a process could result in a range of relatively low cost, readily available, commercially batch-produced, standardized neonatal PN bags. We speculate that these PN formulations could have an adequate nutritional composition that would result in satisfactory biochemical control as well as growth in VLBW infants during the different stages of their NICU course. Based on the available literature cited above, it is reasonable to assume that this process will result in increased safety, fewer formulation errors, and improved physico-chemical stability and compatibility of the PN admixtures.

Possible minor adjustments in the composition of standardized PN solutions can be achieved by:

- a. Mixing the contents of two different formulations' standardized bags in a burette by means of a Y-set [32], or
- b. Adding the required ingredients (including water) into the standardized PN bag in an aseptic dispensing facility, preferably under laminar flow in a sterile hood.

For those requiring individualized PN formulations, a web-based computerized ordering system would be most appropriate, and could be developed by the same team that will develop the standard PN formulations. The website of the Israel Neonatology Association ([www.isneonet.org.il](http://www.isneonet.org.il)) can host this computer-assisted PN prescribing engine. A next-day service of these individualized formulations from a small number of specialist manufacturing centers, which will also prepare the licensed standard neonatal PN bags, should be considered.



## Conclusion

A combination of standardized PN bags, prepared under strict standardization criteria, for most neonates, with a small number of specifically tailored individualized PN formulations for those in need for them, could reduce pharmacy workload and costs and increase safety, while maintaining the desired clinical flexibility.

**Acknowledgments.** This discussion was presented at the autumn meeting of the Israel Neonatal Association in November 2005. We thank all the neonatologists who actively participated in the discussion. We also thank Dr. Yoram Bental, chairman of the Israel Neonatal Association, for bringing this subject to discussion and supporting the ongoing work on the issues raised here. We wish to thank all the neonatologists who answered our telephone survey, gave us detailed information on the use of PN in their NICUs, and their clinical considerations regarding whether to use standardized or individualized PN and on what occasions.

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