

# Solutions Preparing for Total Parenteral Nutrition for Children

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*Abstract:* The article describes the methodology for the preparation of paediatric parenteral nutrition with the intention of meeting the physical needs of patients for the duration of 24 hours, and to protect the organism from the effects of starvation. The methodology involves planning, and optimal preparation of standardised solutions and basic solutions of concentrated electrolytes, which must constitute a safe product of adequate quality and efficiency.

*Key – words:* biology, paediatrics, parenteral nutrition, components, methodology of preparation of solutions, demands

## 1 Introduction

Total parenteral nutrition (TPN) [1] includes the use of all essential nutrients (macro- and micro elements) and refers to the application of hypertonic solutions of amino acids and non-protein sources of energy (carbohydrates, fats), including adequate quantities of electrolytes, vitamins, oligo-minerals and water, in order to obtain a positive nitrogen balance [2]. It is prescribed to patients which are not expected to be able to receive nutrients via the oral or enteral route for more than five days, or to patients who have previously been fed insufficiently or even malnourished.

The objective of TPN is to reduce the loss of proteins, and to protect the organism from the consequences of starvation. Thus, the physical condition of the patient is improved, the complications (be it metabolic or resulting from infections), which in turn reduces the duration of hospital care for the patients, thereby cutting costs.

## 2 Total Parenteral Nutrition

Paediatric TPN is particularly challenging. The main problem lies in the fact that there are no commercially available pre-prepared TNP solutions intended for newborn and especially prematurely born infants. This issue is addressed by preparing TNP on a regular basis and as required, wherever there is a possibility of standardised and/or individual preparation [3 – 5]. There are standard

paediatric criteria [6] regarding the prescription of daily requirements of specific TPN components, which include normal requirements, specific requirements in the event of complications, and specific requirements according to the type of disease.

Early TPN is essential with premature newborns with a low or extremely low body weight, starting from the first day of their lives; therefore the quantitative and the qualitative composition of TNP is of vital importance for them.

### 2.1 Requirements for TPN Components

The requirements for paediatric TPN components are very specific and dependant on body weight, age and the condition of the child's disease. Daily requirements for TPN are prescribed according to normal requirements, the requirements in the event of complications, and the requirements according to the type of disease.

Basic TNP ingredients are:

- amino acids,
- carbohydrates,
- fats,
- electrolytes,
- vitamins,
- trace elements (oligo-minerals),
- water.

### 2.1.1 Amino Acids (Proteins)

The requirements for amino acids among prematurely born babies and other children vary [6], which is evident in Table 1.

Table 1: Normal Requirements for Amino Acids in Paediatrics

Age	Requirements for amino acids (g/kg, BW/day)
Preemies with a low body weight	3-4
Newborns with a normal body weight	2-3
Children 1-10 years	1.0-1.2
Adolescents (boys)	0.9
Adolescents (girls)	0.8
Seriously ill children (adolescents)	1.5

In paediatrics, amino acids can be qualified as [7]:

- Essential – which the organism is unable to synthesise on its own. These are: isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan and valine. All of the above must be present in TPN solutions in correct ratios.
- Semi-essential: arginine, histidine and proline; while tyrosine, cysteine and taurine are considered essential amino acids only for preemies [3].
- Non-essential – which the organism requires in considerable amounts as the source of nitrogen, otherwise it cannot make rational use of the essential amino acids. These are: glycine, alanine, asparagine, glutamine, glutamic acid, hydroxyproline, ornithine and serine.

Today synthetically pure, crystal shapes of L-amino acids are produced, as the organism can use them without needing to transform them in order to synthesise self proteins. Correct ratio of the different amino acids is important, as a surplus or lack of one or several amino acids can lead to metabolic disorders.

When preparing TPN solutions for children, special care must be taken with regard to the following factors:

- Amino acid solutions in which amino acids are in the form of hydrochloride can provoke metabolic acidosis.
- Infusion rates. In preemies and patients suffering from liver insufficiency, a high drip rate of amino acid solutions can lead to hyperammonemia, particularly when the solutions do not include arginine.
- Adverse effects of over-dosage affect subsequent consequences of intellectual development [3].

Overdoses of amino acids in preemies, newborns and infants lead to metabolic disorders linked to hyperammonemia, acidosis and cholestasis. It has been proved that overdoses of methionine cause disorders in growth and degenerative changes in the liver, pancreas, kidneys and spleen, while phenylalanine causes a decrease in serotonin in the brain, and glutamine induces nausea and vomiting [6].

### 2.1.2 Carbohydrates

Carbohydrates are the main sources of energy. The most commonly used carbohydrate is glucose, while xylitol, sorbitol and levulose are less frequent. The energetic value of glucose is 16.8 kJ/g. US sources [8] mention dextrose, which is a monohydrate of glucose with the energetic value of 14.3 kJ/g.

### 2.1.3 Fats

Fat emulsions are TPN components. In this case, fat emulsions are not emulsions of the W/O type, but the carriers of a non-protein source of energy (i.e. of fats and of fat-soluble vitamins). Their characteristic low osmolality can be put to good use in peripheral applications.

Children who are administered TPN are often in a catabolic condition and have high energy requirements. If we provide this energy mainly with glucose, it generates an increase in carbon dioxide levels in blood (hypercapnia), and hyperglycaemia, which arises due to insulin resistance. It is therefore recommendable to meet the better part of energy requirements with fat emulsions [6].

### 2.1.4 Electrolytes

Electrolytes are sodium, potassium, magnesium, calcium, phosphate, chloride, sulphate and acetate ions. Water is the basic component of our organism and represents 70-80 per cent of body weight in children. The loss of fluids also generates the loss of electrolytes. The basic daily requirements of the organism for electrolytes and fluids are influenced by multiple factors [6]:

- increased body temperature,
- abnormal losses through the gastroenterological tract (vomiting, diarrhoea),
- increased anabolism (starvation),
- increased loss of water through damaged skin in burn patients,
- heart and kidney malfunctions,
- medical drug therapy,
- external factors (humidity, outside temperature).

Although there are general guidelines for the dosage of electrolytes in paediatrics – cf. Table 1, it

is essential to exercise frequent monitoring of the electrolyte balance.

Table 2: Daily Requirements for Electrolytes in Paediatrics

Electrolytes	Requirements (mmol/kg/day)		
	Preemies	Infants	Children
Sodium	3-5	2-5	1-2
Potassium	1-5	2-3	1-2
Calcium	1-2	1-2	0.5-1.0
Magnesium	0.6-1.0	0.6-1.0	0.5-1.0
Phosphate	1-2	1-2	0.5-1.0
Chloride	3-5	2-5	1-2

### 2.1.5 Vitamins

Fat-soluble vitamins A, D, E and K are stored in the organism. An excessive intake of these vitamins may represent potential toxicity [6]. Water-soluble vitamins are the ascorbic acid (vitamin C) and the B vitamin complex, which present no danger for toxicity, as they are excreted in the event of excess intake.

Vitamin doses are not clearly defined, but it is known that their intake is essential with long-term TPN. Commercially available vitamins come in injectable solutions. As a general rule, the daily intake of water-soluble vitamins is from 0.5 mL to 5 mL/kg BW; and from 1.0 mL to 4 mL/kg BW for fat-soluble vitamins.

### 2.1.6 Trace Elements (Oligo-elements)

Oligo-elements include zinc, copper, selenium, chromium, manganese, iron, cobalt and molybdenum. Oligo-elements present prosthetic groups of enzymes. Selenium and iodine are non-metals, while zinc, copper, chromium and manganese are metals; therefore they possess different physical and chemical properties. Cobalt, chromium, copper, iodine, manganese, molybdenum, selenium and zinc are essential elements for the upkeep of normal metabolic processes within children's organisms [6].

The recommended daily doses of oligo-elements in paediatrics [6] can be found in Table 3.

Table 3: Daily Doses of Oligo-elements in Paediatrics

Oligo-elements	Requirements ( $\mu\text{g/kg BW/day}$ )		
	Preemies	Infants	Children
Cu	30-60	20-50	20
Se	-	2-5	2
Cr	0.2	0.2	0.2
Mn	-	1	1
Fe	100-200	20-100	100

## 2.2 Demands for TPN in the Event of Complications [6]

There are four major types of complications:

- Mechanical complications, linked to the insertion of a chest tube or a catheter (pneumothorax, haemothorax, cardiac tamponades, thromboses).
- Infective complications, linked predominantly to the central vein catheter for parenteral nutrition (sepsis, local infections such as erythema, sensitivity, abscess...). Infections linked to catheters are cured with topical and systemic antibiotic treatment, or by moving or removing the catheter. Complications arise out of the different methods of parenteral nutrition.
- Metabolic.
- Nutritional.

Recommendations [6] regarding neonatal TPN in the event of complications state that the greatest danger for complication in newborn and especially in prematurely born babies lies in the loss of electrolytes and fluids.

## 2.3 Demands for TPN According to the Type of Disease

In paediatrics, indications for TPN can arise among patients who have been fed insufficiently or have even been malnourished, having lost more than 10% of their optimal body weight. The primary reasons for malnutrition among children are the quality and quantity of the nutrients. The secondary reasons are the changes of the metabolism of the nutrients. Insufficient postnatal nutrition is the cause of delayed growth and development. Indications for TPN can appear in the pre-surgery period (malnutrition), but they are more common in the event of post-surgery complications (sepsis, fistulae, gastrointestinal blockage, etc.), and in connection with certain diseases.

## 2.4 Guidelines for Determining the Nutritional Condition of Children

During hospital care, not enough attention is given to the nutrition of children, and also to the evaluation of their nutritional condition. A good nutrition has positive effects on the outcome of the treatment: wound healing is improved; the risks of infection and of post-surgery complications are reduced. The methods [8] used for determining the nutritional condition of children are:

- **Anthropometric methods:** body weight, body height, the thickness of the skin fold, shank circumference, upper arm circumference.
- **Biochemical tests: assessing the concentrations of albumin, transferrin or prealbumin in the serum.** *Albumin* is a good indicator of nutritional condition and metabolism, but only with patients who are not too affected. It does not convey reality with septic patients, as their albumins are lower also due to other reasons (e.g. a lower capacity of the liver for synthesis). *Transferrin* and *prealbumin* are somewhat better indicators, as their halving period is shorter. When there is not enough iron for absorption, transferrin values are lowered. Increasing values of prealbumin signify a positive nitrogen balance.
- **Nitrogen balance** is the most frequently used clinical method. The daily intake of proteins is measured, from which the secretion via urine is subtracted, plus another 2-4 g due to losses through the GIT and through the skin. In the condition of acute catabolism, the disintegration of tissue proteins leads to an increased loss of nitrogen in urine and, consequently, to a *negative nitrogen balance*.
- **Indirect and direct calorimetries** are two methods that enable the calculation of metabolic requirements according to the oxygen consumed, the carbon dioxide exhaled and the body temperature. These methods are fairly exact, but indirect calorimetry can only be performed if the patient is in a controlled ventilated environment. This is why direct calorimetry is more practical.
- **Skin response to antigen.** Because malnutrition usually correlates with a weakened immune condition of the patient, we can also evaluate the immune response. Although this information is not very exact as far as the nutritional condition of the patient is concerned, it is very important for the prognosis.

## 2.5 Control of TPN

The control of TPN is of vital importance in order to achieve an effective therapy with a reduced risk of complications. It includes:

- Pharmaceutical and technological control
- Clinical control
- Chemical control

The pharmaceutical and technological control includes:

- Control of the type, position, entry point and sterility of the catheter

- Selection and compounding of infusion solutions according to the appropriate clinical criteria
- Compounding of TPN solutions and considering the compatibility of the components
- Correct labelling
- Sterility of TPN solutions
- Correct storing of TPN solutions
- Correct choice of application.

Clinical control deals with the general condition of the patient that involves the symptomatology and the course of the disease, including the possible side-effects, as well as the choice of therapy.

Chemical control, performed in laboratories suited for this purpose, allows for an objective-oriented control of TPN therapy, providing information on possible complications.

## 2.6 Stability of TPN Solutions

In the administration of TPN, infusion bags of different volumes are used (150 mL to 3,000 mL). As the composition of a typical TPN solution is extremely complex, questions regarding the compatibility of its components are frequently asked, for there is a constant risk that the incompatibility might generate a series of physical and chemical interactions, leading to the instability of the system [9, 10].

The assessment of stability and compatibility of 10% and 20% fat emulsions of different manufacturers in a total parenteral nutrition solution (using optical control, microscopic examination and pH measurement) shows that all of the solutions in use remain stable within a 48 hour period at 2°C to 8°C [18].

## 2.7 Requirements for the Preparation of TPN Solutions

All TPN components are industrially manufactured sterile pharmaceutical products.

The sterility of the ingredients and of the product during the compounding process is ensured if the following is considered:

- compliance of the environment,
- compliance of the personnel,
- compliance of the critical surfaces,
- compliance of the transfer procedures,
- compliance of the duration of the transfer into an EVA bag.

The validation of the processes enables us to check all of the above parameters. The process is probed with the use of a microbiological broth, which is then incubated and analyzed to assess

microbiological contamination (validation of aseptic filling).

Workspaces must be separated from other locations and provided with filtered and sterile air under increased positive pressure, which must be higher than in the surrounding areas.

In compliance with the regulations, the access to a clean room must be preceded by three antechambers, equipped with air-locks, where the following actions are performed:

- removal of non-sterile work clothes,
- washing and disinfection of hands,
- changing into sterile (particle free) cloaks, caps, masks, gloves and footwear.

Clean rooms for the manufacture of sterile pharmaceutical products are classified into A, B, C or D degrees, depending on the required air properties. The requirements for air can be found in Table 4.

Table 4: The Degrees of Air Cleanliness for the Manufacturing of Sterile Pharmaceutical Products

Degree	Allowed number of $\leq 0.5 \mu\text{m}$ sized particles / $\text{m}^3$	Allowed number of $\leq 5 \mu\text{m}$ sized particles / $\text{m}^3$	Allowed number of microorganisms / $\text{m}^3$
A	3500	None	Less than 1
B	3500	None	5
C	350000	2000	100
D	3500000	20000	500

### 3 Preparation of Paediatric TPN solutions

Based on modern research and findings [4, 5, 22] regarding the standardisation of TPN solutions, the doctors at Splošna bolnišnica Maribor (Maribor General Hospital), in cooperation with the pharmacists, have sought to establish the foundations of standardising TPN.

TPN compounding involved the preparation of concentrated electrolyte solutions along with basic and standardised solutions. The “individualisation” was performed using all of the above solutions, while volume ratios were adapted precisely to every child’s individual needs, body weight and indications.

#### 3.1 “Individualisation” from “standardisation”

Individual dosage of paediatric TPN solutions is achieved with the intake of a certain volume of

standardised solutions, which means that with an appropriate volume of standardised solutions, one can measure out the components relative to the child patients’ needs, body weight and age. Thus, the dosage of separate components from standardised components is adapted accordingly with respect to the body weight of the individual; with the increase in body weight the requirements for fluids and energy are also increased. This type of nutrition improves the quality of living of babies, particularly preemies, especially in the beginning of their life.

Normal dosages of volume-standardised paediatric solutions amount to 150 mL per kg of body weight.

The preparation of individual paediatric TPN solutions is therefore subject to the appropriate dosage of the volume of standardised solutions, which is laid out in detail in Table 5.

Table 5: Individualisation from the standardisation of solutions with the volume of 150mL / kg BW

V (ml)	50	60	70	80	90	100	110	120
AA (g)	0.83	1.00	1.17	1.33	1.50	1.67	1.83	2.00
N (g)	0.13	0.15	0.18	0.20	0.23	0.25	0.28	0.30
GLUCO SE (g)	5.0	6.0	7.0	8.0	9.0	10.0	11.0	12.0
Na (mmol)	1.5	1.8	2.1	2.4	2.7	3.0	3.3	3.6
K (mmol)	1.0	1.2	1.4	1.6	1.8	2.0	2.2	2.4
Ca (mmol)	0.5	0.6	0.7	0.8	0.91	1.0	1.1	1.2
Mg (mmol)	0.0	0.0	0.08	0.09	0.10	0.11	0.12	0.14
PO <sub>4</sub> (mmol)	0.5	0.6	0.7	0.8	0.9	1.0	1.1	1.2
Cl (mmol)	1.5	1.8	2.1	2.4	2.7	3.0	3.3	3.6
Zn ( $\mu\text{mol}$ )	1.27	1.53	1.78	2.04	2.29	2.55	2.80	3.06
Cu ( $\mu\text{mol}$ )	0.11	0.13	0.18	0.17	0.19	0.21	0.23	0.25
Se (nmol)	8.4	10.1	11.8	13.5	15.2	16.9	18.6	20.2
Mn (nmol)	6.1	7.3	8.5	9.7	10.9	12.1	13.3	14.6
Fe ( $\mu\text{mol}$ )	1.0	1.2	1.4	1.6	1.8	2.0	2.2	2.4
I (nmol)	2.63	3.15	3.68	4.20	4.73	5.25	5.79	6.30
%	33	40	47	53	60	67	73	80

### 4 Conclusion

The concept of providing nutrition for newborn babies, especially prematurely born, involves planning and an optimised compounding of standardised solutions and concentrated electrolyte solutions, which are used to prepare individualised

solutions. The compounding of all types of paediatric TPN solutions is performed in the hospital pharmacy at Splošna bolnišnica Maribor in workspaces that ensure aseptic work conditions, in compliance with the principles of good manufacturing practice.

Children, especially preemies, demand a high liquid and energy intake due to a relatively large body surface in comparison with their body weight and growth requirements.

Because their gastrointestinal tract and the enzyme system in the liver are not yet fully developed, it is impossible to provide them with nutrients via the enteral route, which means that TPN is unavoidable. They are extremely sensitive to the slightest lack of vital total parenteral nutrition components, so the quantitative and qualitative composition of TPN is of decisive importance.

The individualisation of TPN solution preparation is performed by adjusting the quantities of standardised solutions, based on the volume and according to the age group, body weight and the child's specific needs. In this line of work, we take into consideration the requirements and recommendations of the Austrian and German Paediatric Total Parenteral Nutrition Associations, as well as the guidelines of the International & American Association of Clinical Nutritionists (IAACN) [23]. The proposed initial intake of standardised solutions on the first day of administration ranges from 60 to 70 mL/kg of BW/day, followed by a gradual increase of intake until the end of the first week (day 7) up to 150 mL/kg of BW/day (cf. Table 4).

Paediatric total parenteral nutrition (TPN) is a special challenge for the hospital pharmacist, because there are no ready-made commercially available TPN solutions, for newborns, and above all preemies. Individualised preparation is based on variable quantities of standardised solutions, which are meticulously adjusted to suit the requirements, body weight and indications of the young patient. The advantages of producing standardised TPN solutions in a hospital pharmacy do not lie solely in the possibility of a controlled therapy, but also in the practical and economical compounding of preparations, which are made according to the principles of good manufacturing practice and have a longer shelf life (3 months at -20°C; 7 days in a

refrigerator at 2°C to 8°C; 24 hours at room temperature, i.e. 25°C ± 5°C).

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