

# Parenteral Nutrition in Neonatal Intensive Care Unit (NICU), Personalized Therapy and Pharmaceutical Savings

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## Abstract

**Background:** Although breast milk remains the most adequate nutritional intake, nutritional therapy can represent a valid alternative in premature babies with very low birth weight. In this perspective, it is necessary a tailored therapy in terms of biochemical control, intake of nutrients and weight gain.

The purpose of this study was to compare personalized parenteral nutrition (PN) bag to the bag on the market from the standpoint of composition and cost.

**Methods:** A retrospective observational study was conducted in the Neonatal Intensive Care Unit (NICU) of SS. Annunziata Hospital (Calabria, Italy). We analyzed information about the flow of medical products and devices from the pharmacy to NICU, using the hospital database, between 2017 and 2019.

**Results:** Results referred to 2017 were: 1988 bags prepared, for an amount of € 79,004.00 including consumed material, nursing staff and pharmacist staff (average cost of a bag = € 39.00). In 2018: 2157 bags prepared, for an amount of € 84,665.80 including consumed material, nursing staff and pharmacist staff (average cost of a bag = € 24.16). In 2019: 1935 bags prepared, for an amount of € 90,710.61 including consumed material, nursing staff and pharmacist staff (average cost of a bag = € 41.20).

**Conclusions:** This study indicated that tailored PN can satisfy the specific needs of patients more than bags on the market, as well as leads to a reduction of costs.

## Introduction

Parenteral nutrition (PN) has become an integral part of the clinical management of premature babies with very low birth weight. The components that make up the PN formulation should be prescribed while considering the requirements of each individual infant [1]. It is reasonable to think that personalized PN solution provides the best possible result in terms of biochemical control, intake of nutrients and weight gain. Infants who at birth weigh less than 1500 g have a postnatal growth deficit in the first weeks of life. This can have significant consequences on the subsequent auxological and neurological development [2,3]. It is now clear that early feeding in the critical period plays an important role in neurodevelopment and overall long-term health outcomes [4]. Even if the mother's milk is always the first choice for the feeding of premature babies, when this is not possible, nutrition is supplied exclusively parenterally. Normally, different components of PN are prescribed while taking into account the biochemical, nutritional and physiological state of the newborn [5].

In order to provide an adequate supply of nutrients it is considered appropriate to start parenteral nutrition immediately after birth, using balanced intravenous solutions (IS). IS are used to promote a state of anabolism as soon as possible, since the nutritional needs of a very low birth weight infant are very high.

Without doubt breast milk is the first choice for all newborns, but there are specific nutritional needs for preterm infants, especially with a birth weight below 1500 g [6].

In the neonatal setting, two other clinical conditions also require the execution of a partial or total PN: extreme prematurity and severe

respiratory syndrome. Parenteral nutrition must be undertaken when access to the gastrointestinal tract is prevented for anatomical and/or functional reasons, and if this situation is presumed to be of sufficient duration that would compromise the patient's nutritional status.

In the neonatal period this occurrence is found in congenital malformation diseases such as atresia, stenosis, meconium ileus, gastroschisis, as well as in acquired intestinal pathologies (necrotizing enterocolitis, and peritonitis), both in the preoperative and postoperative phase. In these pathological situations, with a prevalently surgical nature, PN represents the only practical nutritional protection. PNs are in use in many Neonatal Intensive Care Units (NICU) around the world [7]. These formulations are commercially available as standard preparations or can be produced by the hospital Pharmacist according to the Good Preparation Standards (GPS) for the preparation of Sterile Galenic Magistral Preparations according to the Italian pharmacopoeia (FU) [8,9].

The aim of the study we are presenting here was to compare personalized PN bag to the bag on the market in terms of composition and cost, using information about annual consumption of medical

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products and devices required for tailored customized bag's preparation.

## Materials and Methods

### Materials

The materials used during our study include:

1. BD needles and connectable luer-lock syringes;
2. Sterile TNT gauzes;
3. Empty EVA bags;
4. Water;
5. Amino acids and dipeptides;
6. Glucose;
7. Lipids long, medium and short chain;
8. Electrolytes;
9. Trace elements and vitamins.

All products are acquired by regional tenders. For each product we always prefer the organic formulations, because they contain less dissociable salts, so they can give less adverse reaction and/or chemical reaction during the preparation of the bag.

### Methods

Considering that the preparation of personalized bags for Parenteral Nutrition is an integral part of galenic activities provided by the Hospital Pharmacy, according to the GPS [8], we performed a retrospective observational study in a NICU of "SS. Annunziata Hospital" (Calabria, Italy) between 2017 and 2019. All data were collected from hospital database, and encrypted prior to analysis.

Preparation of the bag is a multistep procedure that starts from the medical prescription and is finalized by the pharmacist's feasibility assessment [10,11]. In the worksheet the formula and preparation methods are described. Pharmacist and nurse-preparer are the operators involved in the neonatal PN preparation process, while a third professional figure, which can be a nurse or a nutritionist, is rotating in the process.

The operators, wearing sterile personal protective equipment (PPE), carry out all steps under a laminar flow hood disinfected with ethyl alcohol 70% solution. All products are sterile, disposable and handled in an aseptic environment. The integrity of the package, the sterility indicator and the expiry date are checked. The necessary instruments are positioned within the sterile field. The label over tailored bag shows the packaging and traceability data. All activities are subject to validated corporate procedure by the Pharmacist [12].

The hospital database records the flow of medical products and devices from the pharmacy to each hospital care unit, including NICU. It provides information about: type of product, batch number, expiry date, amount dispensed, dispensing date, and expenses. The number of daily neonatal PN preparations was taken from electronic care unit register that summed-up all worksheets. Annual expenses were calculated considering the material cost and workforce. All qualitative assessment was conducted analysing the composition of customized and available commercial products.

## Results

Our study deals primarily with comparing economic and qualitative features of a customized bag to the bag on the market. For this we collected PN preparation data over three years (2017-2019) in order to assess advantages of this process in a wide time period.

In June 2015, the Artificial Nutrition Service program commenced for the S.S. Annunziata Hospital (Calabria - Italy). The process starts from the medical prescription and is completed by the Pharmacist which elaborate the formula and the preparation methods according to the availability of the products in the Pharmacy.

In 2017, 1988 bags were prepared for PN with the following costs:

1. € 20,496.00 consumed material;
2. € 22,995.00 payment relating to nursing staff;
3. € 35,513.00 payment relating to pharmacist staff.

The average cost of a bag is € 39.00 each.

In 2018, 2157 bags were prepared for PN with the following costs:

1. € 26,157.80 consumed material;
2. € 22,995.00 payment relating to nursing staff;
3. € 35,513.00 payment relating to pharmacist staff.

The average cost of a bag is € 24.16 each.

In 2019, 1935 bags were prepared for PN with the following costs:

1. € 32,202.61 consumed material;
2. € 22,995.00 payment relating to nursing staff;
3. € 35,513.00 payment relating to pharmacist staff.

The average cost of a bag is € 41.20 each.

If we do some calculations and compare the costs of the single bag per year, with the only bag currently on the market at a cost of € 48.95, it is easy to see how there is a net saving for each single year equal to:

2017  
€ 39.00 compared to € 48.95: Savings 20.5%;

2018  
€ 24.16 compared to € 48.95: Savings 30.2%;

2019  
€ 41.20 compared to € 48.95: Savings 15.8%;

Figure 1 shows the cost of bag per year compared with bag on the market.

We have to consider the high quality level dictated by the customization of the bag to the patient's needs.

## Discussion

Last year (2019) we had a cost increase of the personalized bags, due to changes in the composition of the bags that the medical team decided to implement to further improve the results of nutritional therapies. In particular, it was decided to use medium chain triglycerides (MCT) for all preterm infants, and not just for those with specific pathologies. The use of these lipids brings several benefits to using alternative lipids such as olive/soy-based formulations or combination of lipids such as soy/MCT/olive or fish oil, compared to lipids based on soya. MCT have less inflammatory properties, are immune modulating, have higher antioxidant content, decrease risk of cholestasis and improve clinical outcomes in certain subgroups of patients. An increased supply of MCT is especially important in patients with disturbances of digestion and absorption such as disturbed bile secretion, classic coeliac disease, short bowel syndrome, inflammatory diseases of the intestines, disturbed outflow of lymph, some metabolic disease and severe food allergies. MCT have lower calorie count compared to long-chain triglycerides (LCT) (approximately 8.3 kcal/g and 9.1 kcal/g, respectively) and also higher osmolarity. This aspect should not be underestimated since it is associated with higher risk of osmotic diarrhoea. However, the hydrolysis of MCT, and the consequent absorption, are faster compared to LCT, because it does not require bile

and lipase. It has been proven that an MCT-enriched diet modulates metabolism of fats, which is manifested as a decrease in the concentration of triglycerides and cholesterol. It has been found that MCT facilitate absorption of calcium. Medium-chain triglycerides are also used in nutrition of prematurely born infants, due to the immaturity of their digestive tract and high demand for energy [13-15].

Furthermore, due to the lack of production in Italy of the only formulation containing phosphorus, the drug had to be imported from other country, with a further increase of cost.

Calcium (Ca) and phosphorus (P) are essential for various systemic functions, including bone mineralization. Hypophosphatemia was observed in preterm infants on PN with inappropriately low P intake and high amino acid dosage (refeeding-like syndrome). Adequate provision of Ca and P in paediatric parenteral nutrition solutions is necessary for skeletal growth and for the prevention of metabolic bone disease [16].

Currently, due to manufacturing problems D-Fructose-1,6-diphosphate (FDP) is the host drug in our nation (Italy). Once the supplies in the pharmacy were finished, no equivalent formulations

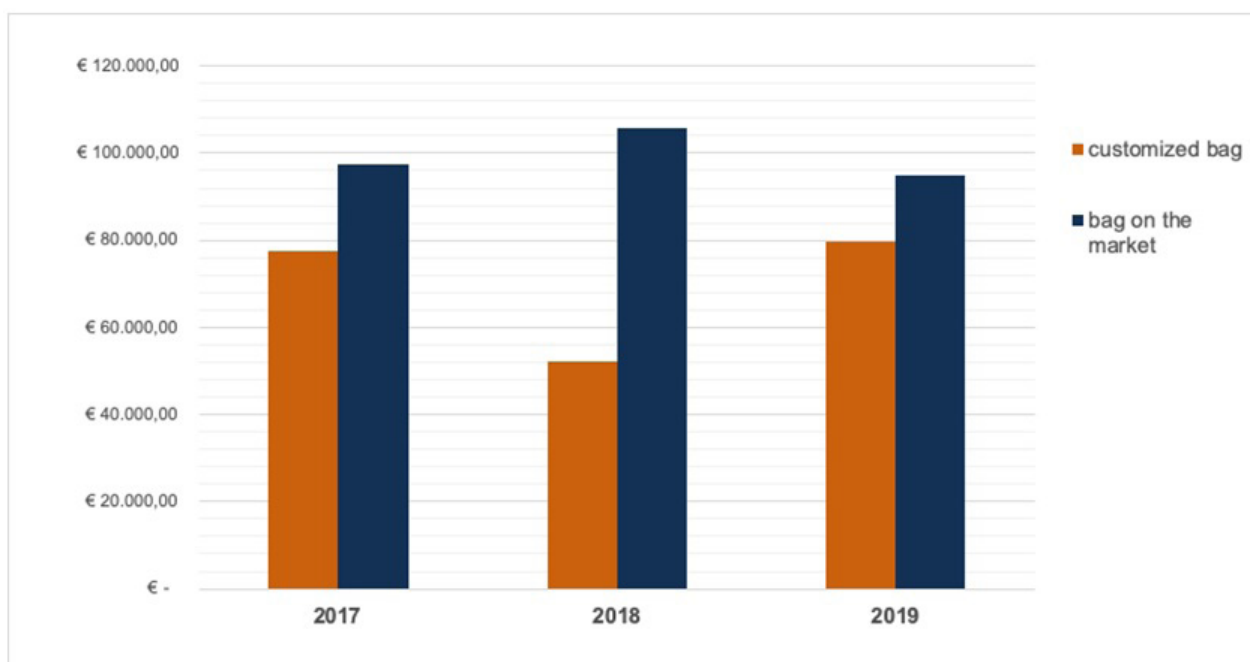


Figure 1: Cost of bag per year compared to the PN bag on the market.

	Natrium-Glycerophosphate	D-Fructose-1,6-diphosphate 0.5 g/10 ml	D-Fructose-1,6-diphosphate 5 g/50 ml	D-Fructose-1,6-diphosphate 10 g/100 ml
Phosphorus mEq/ml	1	0.21-0.235	0.44-0.47	0.44-0.47
Phosphorus mmol/ml	1	0.21-0.235	0.44-0.47	0.44-0.47
Phosphorus mg/ml	30.97	6.5-7,28	13.62-14,56	13.62-14,56
mOsm/L	2570	410	830	620
Natrium mmol/mL	2	0.3	0.6	0.44
Natrium mg/mL	45.97	6.89	13.79	10.12
pH	7.4	5.4-5.8	5.4-5.8	5.4-5.8

Table 1: Natrium-Glycerophosphate and D-Fructose-1,6-diphosphate Composition.

containing phosphorus were available on the Italian market, so the only alternative solution for the administration of phosphorus in organic form, to be used in the formulation of Total Parenteral Nutrition bags was Natrium-Glycerophosphate (Table 1).

Furthermore, as a last resort to improve the production of customized bags, it was decided to use the most appropriate devices for mixing the components and reducing the risk of accidents for operators during the preparation of the bags. We used syringes with blunt needle to reduce the risk of coring and unexpected needle sticks.

All these improvements bring us to a slight increase in the total cost of the personalized PN bags, compared to the cost reduction we observed in 2018. Despite the increase in spending due to the quality improvement of the bags, we were able to design a personalized bag that costs less than the standard bag currently on the market [17]. The calculated nutrient content of the individualized prescription was compared with the bag currently on the market and with the current ESPGHAN/ESPEN recommendations and the GPS [17,8].

To summarize, we find that over the 3 years that were included in our retrospective study we had a cost reduction of 22.16% per bag that the hospital produced, in addition to the benefits of the personalized therapy. We find this to be quite a significant achievement (Figure 2).

## Conclusion

The main advantage of the individually prescribed parenteral nutrition bag is that it is tailored to meet specific needs of preterm newborns, thus ensuring the best possible control of their nutritional and biochemical status. However, it is crucial that the personalized PN is offered using precise procedures and by qualified and well trained personnel. This will save time, reduce any prescribing errors or preparation mistakes and improve the quality of nutritional care.

The use of customized bags is indicated if the needs cannot be satisfied with the use of standard bags, an event that occurs in almost all preterm babies or newborns with specific pathologies (changes in electrolytes and serum minerals, liver complications, gallbladder complications, metabolic bone diseases, side effects of lipids, sepsis).

The only product marketed in Italy indicated for parenteral nutrition in premature infants is Numeta G13E. In our opinion this bag has several limitations. We find that the most important one is that the bag offers equal nutrient composition to all patients, not considering different needs they may have, where the needs are dependent on the weeks of gestation at birth or any pre-existing pathologies that necessitate specific nutritional adaptations. Personalized PN would overcome this limitation and help ensure adequate amounts of macro- and micro-nutrients, allowing for appropriate infant development. In addition, Numeta G13E's cost is significantly higher compared to the price of a custom bag with a medium cost reduction of 22.16% per bag.

Parenteral nutrition bag is formulated according to the specific needs of the patient. Our study shows that this can lead to a considerable reduction in costs compared to other similar PN bags on the world pharmaceutical market. It should be noted that adequate nutrition also leads to a reduction in negative health outcomes that require hospitalization, saving even more money to the healthcare sector. Our experience has also shown that a high quality service can be developed in-house and that personalized galenic products can be safely and effectively used. Provided that the cost of customization is not excessive personalization of care and therapy especially of the vulnerable paediatric population should be part of a regular clinical practice given that it offers better life expectancy.

We envision that our approach can be utilized even for treating adults with specific pathologies like phenylketonuria, liver and kidney changes or rare diseases that do not allow the use of standard bags.

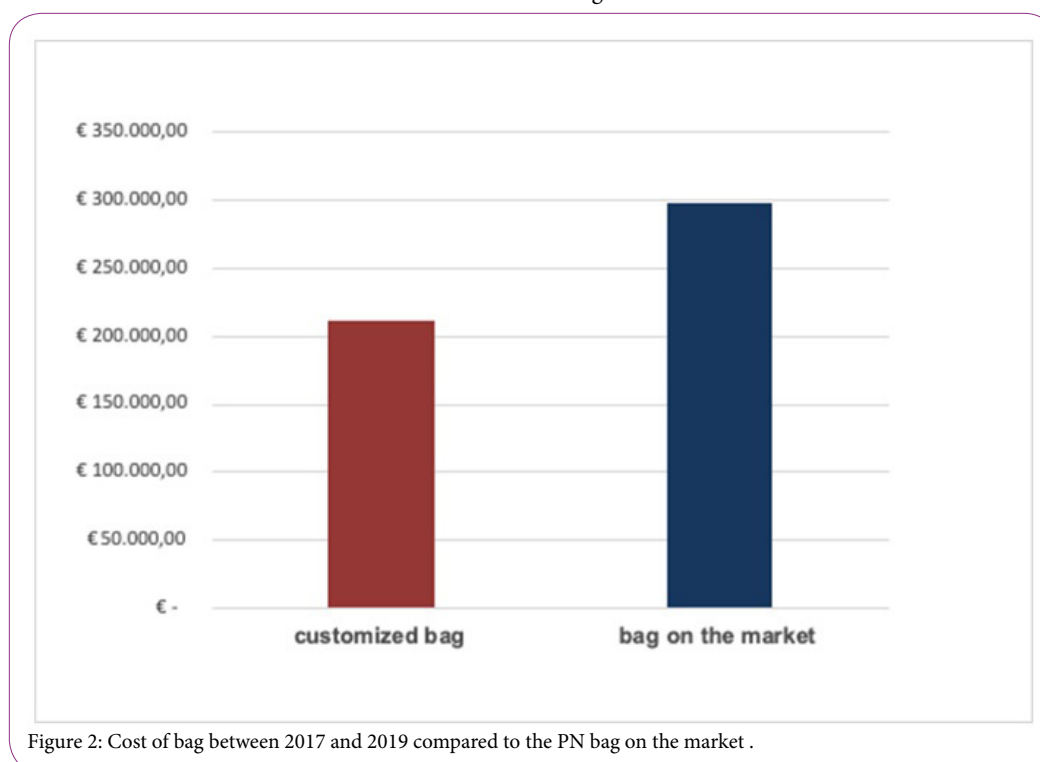


Figure 2: Cost of bag between 2017 and 2019 compared to the PN bag on the market .

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## Competing interests

The authors declare that they have no competing interests.

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