Thesis

The Development of a Standardized and Industrialized Pediatric Parenteral Nutrition for the First Days of Life of Newborn Term and Preterm Infants and its Implementation as Standard of Care

SOMMER, Isabelle

Abstract

Parenteral nutrition (PN) can be composed of about 50 different ingredients, whereof the majority are amino acids (AA). Therefore, PN represents a complex and high-risk fabrication. Medication errors (ME) are often related to PN and may include prescription, transcription, preparation, and administration errors. As the treatment with PN is indispensable for a good cerebral and neurologic development as well as a postnatal weight gain conforming to the intrauterine growth, ME can result in growth retardation, developmental disturbances, and infections. With the aim of reducing ME potentially having an impact on vulnerable patients as well as the improvement of the security and quality of the nutritional treatment of newborn term or preterm infants, a standardized pediatric PN for the first days of life had to be implemented. A working group composed of pharmacists, clinicians, neonatologists, and industrials developed a PN solution conforming to the needs of the two implicated neonatal services. A standardized and experiential solution, as well as the ESPGHAN guidelines of 2018 haven been chosen as references. The [...]

Reference

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The Development of a Standardized and Industrialized Pediatric Parenteral Nutrition for the First Days of Life of Newborn Term and Preterm Infants and its Implementation as Standard of Care

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La Faculté des sciences, sur le préavis de Monsieur F. SADEGHIPOUR, professeur titulaire et directeur de thèse (Section des sciences pharmaceutiques, Université de Genève et Université de Lausanne, Pharmacie hospitalière, Centre hospitalier universitaire vaudois, Lausanne, Suisse), Monsieur P. BONNABRY, professeur associé et codirecteur de thèse (Section des sciences pharmaceutiques), Monsieur E. ALLEMANN, professeur ordinaire (Section des sciences pharmaceutiques), Monsieur R. PFISTER, professeur (Service de néonatologie, Hôpitaux Universitaires de Genève, Genève, Suisse) et Madame I. KRÄMER, professeure (Département de pharmacie, Universitätsmedizin de l'Université Johannes Gutenberg Mainz, Mainz, Allemagne), autorise l'impression de la présente thèse, sans exprimer d'opinion sur les propositions qui y sont énoncées.

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N.B. - La thèse doit porter la déclaration précédente et remplir les conditions énumérées dans les "Informations relatives aux thèses de doctorat à l'Université de Genève".

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Preamble

From January 2015 to December 2020, I had the opportunity to discover all aspects of an industrialized parenteral nutrition, from its conception, over its production to its application. Therefore, I worked closely together with pharmacists, pharmacy technicians, laboratory staff, industrials, neonatologists and nurses.

This manuscript embodies my doctoral thesis with the title “The Development of a Standardized and Industrialized Pediatric Parenteral Nutrition for the First Days of Life of Newborn Term and Preterm Infants and its Implementation as Standard of Care”.

I was able to accomplish this project at the department of pharmacy of the Lausanne University Hospital and at the pharmaceutical development unit of B. Braun Medical in Crissier, Switzerland. I also collaborated constantly with the neonatal unit of the department Woman-Mother-Child of the Lausanne University Hospital as well as the department of pharmacy of the Geneva University Hospital.

On the following pages of **Chapter 1**, the state of knowledge and other important aspects on the concerned patients as well as on parenteral nutrition are presented.

Chapter 2 resumes the objectives and aims of the research topic as well as the different studies and projects performed during the thesis.

All accepted and published articles on this topic are presented in **Chapter 3** and additional scientific evaluation and groundwork contributing to the outcome of this thesis are resumed in **Chapter 4**.

Moreover, to close the thesis, **Chapter 5** contains the general conclusion and perspectives for the future.

Scientific communications

Articles

Sommer I, Bouchoud L, Berger-Gryllaki M, Bonnabry P, Sadeghipour F: *Quality and Safety of Parenteral Nutrition for Newborn and Preterm Infants as an On-Ward Preparation* Eur J Hosp Pharm 2019;0:1–5; doi:10.1136/ejhpharm-2018-001788

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Sommer I, Schwebel H, Adamo V, Bonnabry P, Bouchoud L, Sadeghipour F: *Stability of N-Acetylcysteine (NAC) in Standardized Pediatric Parenteral Nutrition and Evaluation of N,N-Diacetylcystine (DAC) Formation* Nutrients 2020, 12(6), 1849; doi:10.3390/nu12061849

Oral communications

Angelstorf I, Guerreiro E: Nutrition parentérale: *Quelle méthode de production pour quelle production?* Les Journées Francophones de Nutrition, Marseille, France, December 2015

Sommer I: *Nutrition individualisée : équilibre entre contraintes techniques et intérêt clinique* Réunion annuelle commune SSMI | GSASA, St. Gallen, Switzerland, September 2017

Sommer I: *Standardisation des solutions de nutrition parentérale en pédiatrie : est-ce possible?* Nutrition clinique - journées lausannoises, Société suisse de Nutrition clinique, Lausanne, Switzerland, November 2017

Sommer I: *Nutrition pédiatrique: Formules standards versus Formules à la carte* Séminaire MAS « La préparation des médicaments parentéraux à l'hôpital », Lausanne, Switzerland, May 2017

Sommer I: *Développement d'une nutrition parentérale standardisée pour la néonatologie* Colloque PHA-PCL CHUV, Lausanne, Switzerland, March 2019

Thomann P, Sommer I, Palmero D: *Mise en place d'une nutrition parentérale standard en néonatologie* Séminaire MAS « La préparation des médicaments parentéraux à l'hôpital », Lausanne, Switzerland, June 2020

Poster presentations

Angelstorf I, Gryllaki-Berger M, Palmero D, Fischer-Fumeaux C, Sadeghipour F: *Evaluation de la qualité des fabrications de nutrition parentérale préparées dans le service de Néonatologie* GSASA congress, Zurich, Switzerland, November 2015

Angelstorf I, Gryllaki-Berger M, Palmero D, Fischer-Fumeaux C, Sadeghipour F: *Evaluation de la qualité des fabrications de nutrition parentérale préparées dans un service de néonatologie* Les Journées Francophones de Nutrition, Marseille, France, December 2015

Angelstorf I, Gryllaki-Berger M, Palmero D, Fischer-Fumeaux C, Sadeghipour F: *Evaluation of the quality of the parenteral nutrition prepared at the neonatal unit* 21st Congress of the European Association of Hospital Pharmacists, Vienna, Austria, March 2016

Angelstorf I, Rieger J, Podilsky G, Berger-Gryllaki M, Sadeghipour F: *L'osmolarité théorique est-elle réelle?* 20èmes Journées Franco-Suisses de Pharmacie Hospitalière, Bern, Switzerland, December 2016

Angelstorf I, Bouchoud L, Sadeghipour F: *Quelle est l'attitude des néonatologues et pharmaciens suisses à l'égard de la nutrition parentérale standardisée pour des enfants prématurés?* 20èmes Journées Franco-Suisses de Pharmacie Hospitalière, Bern, Switzerland, December 2016

Angelstorf I, Rieger J, Podilsky G, Berger-Gryllaki M, Bouchoud L, Sadeghipour F: *Quelle osmolarité pour la voie veineuse périphérique en néonatologie?* HopiPharm, Congrès Francophone de Pharmacie Hospitalière, Nancy, France, May 2017

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Sommer I, Bouchoud L, Bonnabry P, Sadeghipour F: *Analyse Préliminaire des Risques du Processus de Gestion des Nutritions Parentérales pour Nouveau-nés et Prématurés* GSASA congress, Fribourg, Switzerland, November 2018

Sommer I, Schwebel H, Adamo V, Bonnabry P, Bouchoud L, Sadeghipour F: *Dégradation de N-acétyle-cystéine en N,N-diacétyle-cystine dans les Nutritions Parentérales Pédiatriques* Les Journées Francophones de Nutrition, Nice, France, November 2018

Sommer I, Palmero D, Fischer Fumeaux C, Beauport L, Adamo V, Schwebel H, Bonnabry P, Bouchoud L, Sadeghipour F: *Development of a standardized pediatric parenteral nutrition for the first days of life of a term or preterm newborn* GSASA congress, virtual/Basel, Switzerland, November 2020 (swissYPG Junior Award)

Sommer I, Palmero D, Fischer Fumeaux C, Beauport L, Adamo V, Schwebel H, Bonnabry P, Bouchoud L, Sadeghipour F: *Development of a standardized pediatric parenteral nutrition for the first days of life of a term or preterm newborn* 25th Congress of the European Association of Hospital Pharmacists, virtual/Vienna, Austria, March 2021

Abbreviations

AA	Amino acid
AIO	All-in-One
ASPEN	American Society for Parenteral and Enteral Nutrition
CHUV	Centre Hospitalier Universitaire Vaudois
CPOE	Computerized physician order entry
CSPEN	Chinese Society of Parenteral and Enteral Nutrition
CVC	Central venous catheter
DAC	N,N-diacetylcystine
DCB	Double-chamber bag
EFCNI	European Foundation for the Care of Newborn Infants
ESPEN	European Society for Clinical Nutrition and Metabolism
ESPGHAN	European Society for Paediatric Gastroenterology, Hepatology and Nutrition
ESPR	European Society for Paediatric Research
EN	Enteral nutrition
FA	Fatty acid
FMEA	Failure modes and effects analysis
FMECA	Failure modes, effects and criticality analysis
GA	Gestational age
GMP	Good manufacturing practice
HUG	Hôpitaux Universitaires de Genève
ISMP	Institute for Safe Medication Practices
LAF	Laminar air flow
LBW	Low birth weight
MCT	Middle-chain triglycerides
NAC	N-acetylcysteine
NICU	Neonatal intensive care unit
Ph. Eur.	European Pharmacopoeia

PICC	Peripherally inserted central catheter
PN	Parenteral nutrition
PPN	Pediatric parenteral nutrition
PRA	Preliminary risk analysis
PUFA	Polyunsaturated fatty acid
PVA	Peripheral venous access
TCB	Triple-chamber bag
TPN	Total parenteral nutrition
VLBW	Very low birth weight
WHO	World Health Organization

Chapter 1

State of knowledge

1.1 Newborn infants

The *World Health Organization* (WHO) defines newborn infants or neonates as babies under 28 days of age [1].

Preterm infants are babies born before the completion of 37 weeks of pregnancy and are further categorized based on the gestational age (GA) [2]:

- extremely preterm <28 weeks
- very preterm 28 to 32 weeks
- moderate to late preterm 32 to 37 weeks.

Neonates born at term as well as preterm infants can additionally be classified conforming to their body weight at birth [3]:

- Threshold of viability <750 g
- Extremely low birth weight ELBW <1'000 g
- Very low birth weight VLBW ≥1'000 g and <1'500 g
- Low birth weight LBW ≥1'500 g and <2'500 g
- Normal birth weight >2'500 g
- Macrosomia >4'000 g

All newborn babies, including LBW neonates as well as normal weight infants, are at highest risk of dying within the first 28 days of life, so it is crucial to provide appropriate care which includes adequate feeding [1].

1.1.1 Neonatal care

The *European Foundation for the Care of Newborn Infants* (EFCNI) as well as the *Swiss Society of Neonatology* (SSN) define three different levels of neonatal care [4], [5]:

- Level I: Basic Neonatal Care

  A newborn nursery in a maternity hospital without on-site pediatric services. The pediatrician or the head of the maternity unit are responsible for the care of

newborns. Before discharge, every baby must be examined at least once by a pediatrician.

- Level IIA: Neonatal Special Care Unit

  Provides care for moderately ill term and preterm infants ≥34 0/7 weeks and a birth weight ≥1'500 g as well as continuous care for convalescent infants ≥32 0/7 weeks.

- Level IIB: Neonatal Intermediate Care Unit

  Provides cares for moderately ill term and preterm infants ≥32 0/7 weeks and a birth weight ≥1'250 g as well as continuous care for convalescent infants ≥30 0/7 weeks.

- Level III: Neonatal Intensive Care Unit (NICU)

  Perinatal care for a given population is organized around a tertiary perinatal center composed of a level III obstetrical unit and a level III neonatal unit, located preferably in the same building. The minimum critical mass of births/year per region (perinatal network) is 5'000 births which corresponds to the requirement for a minimum of five neonatal intensive care beds.

  In addition to the functionalities of level I and II, all critically ill newborn infants are being referred to a NICU, preferably before birth if the problem can be anticipated.

  The NICU takes care of all neonatal pathologies from birth on and at least until the end of the neonatal period (28 days after birth or completed 44 postmenstrual weeks for preterm infants).

The neonatology unit of the *Centre Hospitalier Universitaire Vaudois* (CHUV) is classified as a NICU of level III. In 2019, more than 3'200 births took place in the maternity department. In 2015, a total of 736 neonatal patients have been admitted in the NICU, whereof 50% were premature newborns. With a total of 40 beds for its' neonatal patients, the CHUV's neonatology is the biggest in Switzerland.

1.1.2 Prematurity

As discussed previously, preterm infants are neonates born before the completion of the 37th week of pregnancy. Worldwide, of the 130 million babies born every year, more than 10% are born too soon [6].

Prematurity and related complications are the main cause of child mortality before five years of age (under-5 mortality) [7].

1.1.2.1 Risks of preterm birth

In 50% of preterm births, reasons and causes of early delivery are still unknown. For the other 50%, risk factors include multiple pregnancy, health conditions in the mother and are of behavioral and psychosocial nature [6], [8]–[10].

Examples for health conditions having an influence on delivery labor are maternal diseases (e.g. high blood pressure, diabetes), infections during pregnancy, genetic predispositions, in-vitro fertilization, maternal age of <18 and >35 years and others.

Behavioral influences are for example alcohol, tobacco and/or drug consume, nutritional complications like excess or short weight, as well as intense physical exertion.

Psychosocial factors are amongst others, stress, negative-impact life events, chronic or catastrophic stress exposures and emotional conditions like anxiety and depression.

1.1.2.2 Complications of prematurity

Preterm birth is associated to a developmental immaturity, which affects a wide range of organ systems and can be differentiated in short-term and long-term outcomes [10]–[13]:

- Short-term complications:
    - Lungs and respiratory system (e.g. respiratory distress, bronchopulmonary dysplasia)

  - Gastrointestinal system (e.g. necrotizing enterocolitis)
  - Skin (e.g. hypothermia)
  - Infections and the immune system (e.g. late-onset sepsis, bacterial infections)
  - Cardiovascular system (e.g. patent ductus arteriosus)
  - Hematologic system (e.g. intraventricular hemorrhage)
  - Auditory system and hearing
  - Ophthalmic system and vision (e.g. retinopathy)
  - Central nervous system
- Long-term outcomes:
  - Neurodevelopment impairment (e.g. impaired cognitive skills, motor deficits, cerebral palsy, sensory impairment, behavioral and psychological problems)
  - Chronic health issues (e.g. chronic kidney disease, hypertension, high blood pressure)
  - Growth impairment
  - Impairment of lung function (e.g. asthma)

To prevent and reduce risks of short-term complications and long-term outcomes, initial stabilization of a preterm infant in the delivery room as well as adequate treatments in the first days, weeks and months of life of preterm infants are essential and fundamental.

1.2 Parenteral Nutrition

For patients identified for having nutritional deficiencies, an overall nutritional care plan that includes detailed nutritional assessment should be established [14]. The first choice of feeding methods is the oral route. If this is not sufficient or contraindicated, patients necessitate enteral nutrition (EN) feeding by oro- or nasogastric tubes as first artificial alternative. Only if this alternative is still not sufficient to achieve the nutritional requirements, parenteral nutrition (PN) is inevitable.

PN is the artificial, intravenous feeding of patients, bypassing the usual process of oral food intake, the gastrointestinal tube as well as the digestion.

> "The purpose of parenteral nutrition is to correct or prevent nutritional deficiencies when adequate enteral nutrition is precluded by impairment or immaturity of gastrointestinal function."[14]

Nutritional needs are defined as the amount and chemical form of a nutrient needed to support normal health, growth and development without disturbing the metabolism of other nutrients [15].

PN can be complementary to EN, therefore, enteral feeding should be introduced as soon as possible and should be privileged whenever feasible [16]–[18].

When no other route of enteral feeding is available, patients may be fed by PN exclusively. In this case patients are treated with a total PN (TPN). Patients that can receive EN, by oral route or tubing, may still need support, which is provided by the so called partial PN treatment, to complete their nutritional needs [19].

1.2.1 History of parenteral nutrition

[Vinnars 2003 [20], Dudrick 2009 [21], Nakayama 2017 [22]]

The first step towards the development of parenteral nutrition was published in 1628 by *William Harvey* who discovered the blood circulation. This discovery formed the basis for future studies on intravenous injections and infusions. In 1665, *Sir Christopher Wren*

first injected wine, ale and opiates in a dog and noticed that their injection result in the same effects as given orally. The first lipid infusion in form of olive oil was given to a dog in 1712 by *William Courten*. This abortive test showed the need for a special or modified lipid form for intravenous administration.

With the severe cholera epidemic from 1831 to 1832, an important step in the development of intravenous infusions was made. For the first time, water and salts were infused to patients by the Scottish physician *Thomas Latta*. This case demonstrated that nutritional deficiencies can be compensated by appropriate replacement solutions.

In 1873, *Edward Hodder* tested once more to intravenously administer fats in form of milk. Only two thirds of the patients survived this attempt which led to the abandoning of this idea. This and other studies confirmed the earlier observation of *Courten* in 1712 that unmodified fats could not be given to patients intravenously. Another painful and therefore unusable method was tested by *Paul Friedrich* in 1904. He tried to supply parenteral nutrients like fat, glucose and electrolytes by a subcutaneous infusion.

The Swedish scientist *Arvid Wretlind*, for his many developmental contributions to PN administration also called the “father of complete parenteral nutrition”, together with *Oscar Schuberth* developed and introduced the first nontoxic fat emulsion composed of soy-bean oil and egg yolk phospholipids, called Intralipid, in 1961.

Stanley Dudrick demonstrated in 1968 that nutrients can be safely administered over an extended period through a catheter placed in the superior vena cava. This was an important step towards the parenteral nutrition of today.

1.2.2 Composition of parenteral nutrition

[Bouchoud 2011 [23], Velaphi 2011 [24], EFCNI [25]]

The composition of PN solutions is variable conforming to patients’ needs. PN is principally composed of (Figure 1):

- Three macronutrients
  - Energy: glucose and lipids
  - Proteins: amino acids (AA)
- Three classes of micronutrients
  - Electrolytes: calcium, sodium, potassium, magnesium, phosphate and chloride
  - Vitamins
  - Trace elements
- Essential fluid intake is provided by water addition.

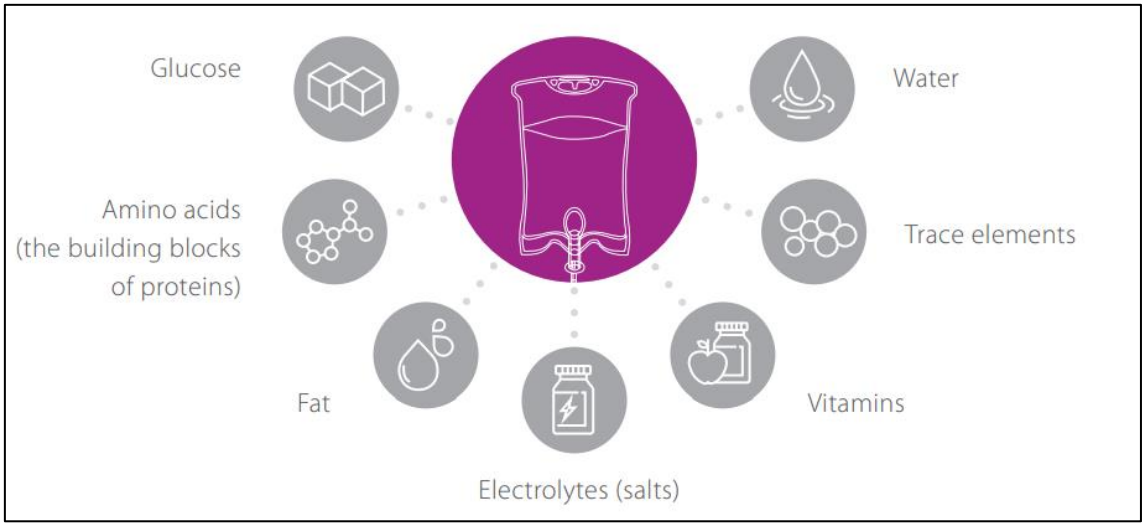


Figure 1: Composition of parenteral nutrition[i]

Two types of PN can be delivered:

- Binary PN containing water, AA, glucose, electrolytes, vitamins and trace elements
- Ternary PN containing the same ingredients as binary PN plus a lipid emulsion in one infusion bag.

[i] https://www.efcni.org/wp-content/uploads/2019/01/2018_12_03_Parenteral-nutrition_Factsheet_english_Web.pdf (accessed: August 30, 2020)

1.2.3 Individualized versus standardized parenteral nutrition

For several decades, the opinions about the question whether to individualize or standardize PN, especially for neonates, differ a lot. This debate does not only concern nutritional specialists and pharmacists on different continents or in distant countries, but also within one country. An example is Switzerland with a total of five university hospitals, where standardized PN for neonatal patients was used for several years in some university hospitals and in others, this practice was effectively refused for a long time.

For neonatal patients, it is known, that the implementation of standardized feeding guidelines reduces nutritional practice variation and facilitates postnatal growth and improved clinical outcomes [15]. Guidelines on pediatric parenteral nutrition (PPN) compiled by the *European Society for Paediatric Gastroenterology, Hepatology and Nutrition* (ESPGHAN) in collaboration with the *European Society for Clinical Nutrition and Metabolism* (ESPEN), supported by the *European Society for Paediatric Research* (ESPR) and together with the *Chinese Society of Parenteral and Enteral Nutrition* (CSPEN), also recommend to prefer the use of standardized over individualized PPN "[…] to improve patient safety (minimize procedural incidents) and optimize resource efficiency at the same time as providing clinically appropriate nutrition (meeting individual patient requirements)." [26] The corresponding guidelines established by the *American Society for Parenteral and Enteral Nutrition* (ASPEN) also "[…] address the standardization of practices surrounding PN to improve care and to limit medication errors." [27]

For adults, the feasibility of PN standardization is less difficult. This is due to the established body composition which is the challenging factor for pediatric patients (Figure 2) [28]. Additionally, for pharmaceutical companies, the development of adult PN is more interesting as the number of patients to be treated with is much higher.

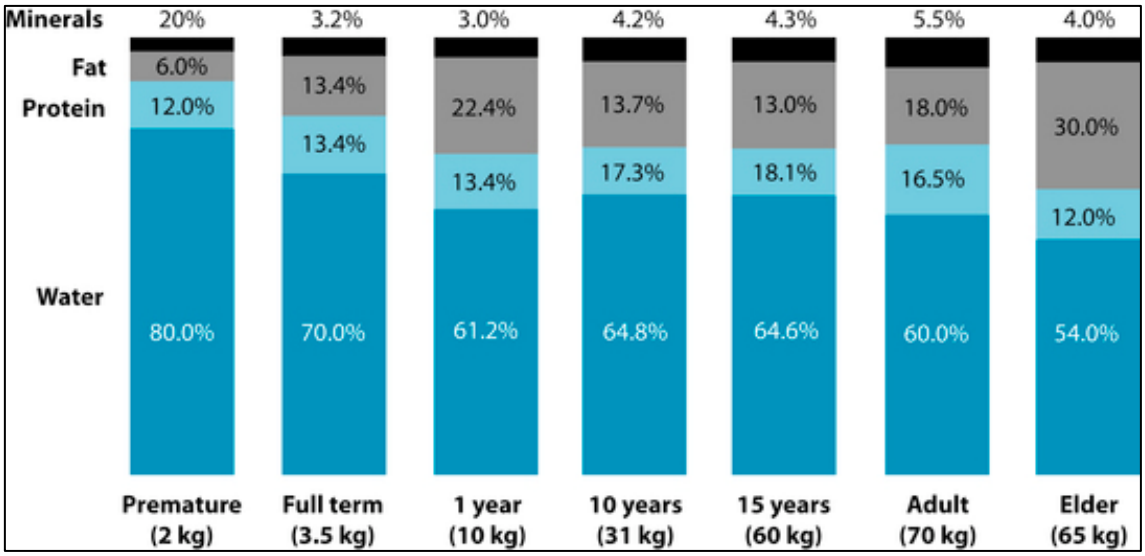


Figure 2: Changes in body composition with growth and aging[ii]

Since the introduction of the first All-in-One PN system (AIO) in 1972 by Solassol et al. [20], all kinds of standardized parenteral nutrition for adult patients have been developed by specialized pharmaceutical industries. AIO admixtures simplify parenteral nutrition usage and decrease line infection rates by reducing the contamination probability [19]. Additionally, several studies demonstrate that AIO systems provide simpler prescription, save time and reduce workload and costs as the preparation time including a physician's prescription, nurse's administration and preparation and pharmacist's PN compounding is reduced [19], [29], [30]. All these reasons lead to a routinely usage of standardized AIO PN solutions for adults as promoted by the ESPEN guidelines on parenteral nutrition [31]. Only few exceptions exist where individually compounded PN is necessary to meet nutritional requirements (e.g. severely burned patients [32]).

Companies like Baxter International, USA, Fresenius Kabi AG, Germany and B. Braun Medical AG, Germany, constantly evolved and advanced the production of standardized PN, especially for adult patients but also for children from two years of age and above.

[ii] https://clinicalgate.com/paediatrics-3/ (accessed: September 2, 2020) Adapted from Puig M, Body composition and growth. In Walker WA. Watkins JB, eds. Nutrition in pediatrics. 2nd edn. Hamilton, Ontario, BC: Decker, 1996

In Switzerland, the only commercially available PN solution for neonates is manufactured by Baxter International, USA (Numeta® Neo [33]) which is further discussed in Section 1.3.1.

Due to the constantly changing body composition of infants (Figure 2) and the resulting varying nutritional requirements [23], [24], [34]–[40], the standardization of PN is more complicated for these patients [28]. But still, the ESPGHAN/ESPEN/ESPR/CSPEN highly recommend the use of standardized over individualized PN mainly for security reasons [26].

Contrary to standardized PN, individual compounded PN provide patient-specific nutritional requirements according to energy, volume and substrate needs. This might be necessary for critically ill and metabolically unstable patients (abnormal fluid and electrolyte losses) or infants requiring PN for prolonged periods (e.g. short bowel syndrome) [26].

Individual or "à la carte" PN preparations must be compounded aseptically for intravenous administration. The best choice for this high-risk preparation is the delegation to the hospital pharmacy following current good manufacturing practice (GMP) guidelines. One of the several aims of these guidelines is to minimize the risks of particulate or microbial contamination of the product.

> "[…] The manufacture of sterile products should be carried out in clean areas, entry to which should be through airlocks for personnel and/or for equipment and materials. […] The various operations of component preparation, product preparation and filling should be carried out in separate areas within the clean area." [41], [42]

For both, standardized and individualized PN, advantages and disadvantages exist (Table 1). For each patient requiring PN treatment, an assessment of the benefit-risk balance must be performed prior to PN ordering.

Table 1: Advantages and disadvantages of standardized and individual parenteral nutrition

Standardized parenteral nutrition	**Individual parenteral nutrition**
Advantages	
Less prescribing errors	Patient-specific composition
No transcription needed	Adaptation of changing nutritional needs
Extensive quality controls	
Provision of adequate nutrition [43]	
Availability 24/7 and ready-to-use	
Less manipulation → less infections	
Long stability	
Easy storage at room temperature	
Reduced costs	
Disadvantages	
Non-consideration of changing nutritional needs	Prescription and transcription errors
Adaptation necessary if stability data available	Preparation errors
Manipulation for adaptation → risk for infection	Delivery delay
Lack of availability of industrial PN for neonatal and pediatric patients	Refrigerated storage (2-8°C)
	Short stability

It is obvious that advantages of standardized PN outbalance those of individual PN. The number of disadvantages is almost the same for both types of PN but of complete other nature. The disadvantages of standardized PN can be reduced by the development of new formulations to be made available. Those of individualized PN concern organizational aspects which are more difficult to resolve.

1.2.4 Techniques and methods of preparation

Parenteral nutrition can be prepared in different ways. In any case, the final product must be sterile and non-pyrogenic for intravenous administration. To achieve these requirements, the PN solution must either be prepared aseptically or undergo a final sterilization.

For the first method of aseptic production, the solution must be prepared under aseptic conditions following the GMP guidelines [41], [44] and in accordance with the international standard ISO 14644-1 formulated by the *International Organization for Standardization* [45]. This means that compounding must be performed in a grade A laminar air flow (LAF) hood placed in a grade B cleanroom. To achieve a sterile final product, the raw materials must be sterile as well.

The method of final sterilization can either be performed by filtration through a pore size of 0.22 µm or less or by autoclaving (heat steam sterilization). Both methods can only be performed if the products are suitable for this manipulation in terms of structural and thermal stability. If possible, autoclaving should be preferred to assure a sterile final product. Due to the final sterilization, raw materials do not necessarily have to be sterile. The preparation of products undergoing a final sterilization should be performed in a grade D and the filling should be carried out at least in a grade C environment [41].

1.2.4.1 Hospital

Aseptic products prepared in a hospital pharmacy can be realized by means of three different types of preparation depending on their field of application.

1.2.4.1.1 Formula magistralis

The *Federal Act on Medicinal Products and Medical Devices* of the *Therapeutic Products Act* of Switzerland defines a “formula magistralis” as follows:

> “Medicinal products prepared according to a doctor’s prescription by […] a hospital pharmacy, […] and for a given person or group of persons […].” [46]

Individually compounded PN belong to this category of hospital preparations. It is prepared following a medical order for one given patient. For this reason and because of the small number of preparations, the production must be performed aseptically to achieve and deliver a sterile product.

No analytical tests on the final product are mandatory for this preparation method as far as the manufacturing process has been validated [41].

1.2.4.1.2 Formula officinalis

A "formula officinalis" is defined by the *Federal Act on Medicinal Products and Medical Devices* as follows:

> "Medicinal products prepared as required or on a small industrial scale by […] a hospital pharmacy, […] conforming to a special monograph of the Pharmacopoeia or another pharmacopoeia or a formulary recognized by the Agency [*Swissmedic – Swiss Agency for Therapeutic Products*], and which are supplied to their own customers." [46]

This preparation method requires physical, chemical and/or microbial analyses corresponding to the type of product to confirm quality.

1.2.4.1.3 Formula Hospitalis

Article 9 section 2 c^{bis} and 2^{bis} of the *Therapeutic Products Act* declare that medicinal products are exempt from marketing authorization:

> "[…] for which it is proven that there is no authorized or available alternative medicinal product that is applicable and equivalent and which are manufactured in a hospital pharmacy in accordance with the hospital's own pharmaceuticals list, on a small industrial scale, and are intended for dispensing to its own customers." [46]

For the case of a standardized PN that can be given to several different patients, a batch production will be performed. This kind of production allows to prepare a higher number

of infusion bags at the same time and to be delivered to the units that distribute them to patients when needed.

In 2011, this kind of medicinal product has been defined as “formula hospitalis” [47], [48] and is unique in Switzerland. A manufacturing license to produce medicinal products must be issued to the manufacturing establishment. A production of “formula hospitalis” products on a small industrial scale can either be performed by an authorized hospital pharmacy or an industrial manufacturer.

1.2.4.2 Industry

Advantages of an industrial production are multiple. Products provided by the industry are of higher quality due to the obligation, but also the availability of facilities for the performance of extensive quality controls. Shelf life assessment is performed by multifactorial testing such as temperature, humidity and light conditions in real-time or as stress test, permitting early predication of the final stability. The aim of a long stability and easy storage conditions are the reduction of new productions and the prevention of wastage. Other interests for the hospital are the 24/7 availability of the product, the reduction of workload and resources economies.

1.2.4.2.1 Formula Hospitalis

As described in Section 1.2.4.1.3, a “formula hospitalis” can also be prepared by an industrial manufacturer without the need to apply for a marketing authorization. The important advantage contrary to a marketing authorization is that big numerical productions (limited to 3’000 packs containing a maximum of 90’000 unit doses) can be externalized from the hospital pharmacy to a contractual industrial partner without the exigence to perform clinical trials [46], [47].

A disadvantage manly for the industrial partner might be that the exemption from marketing authorization is only applicable in Switzerland and the product can therefore not be sold in other countries. If this is the objective of an industrial production, the

normal route for commercializing with marketing authorization for the final product must be taken.

1.2.4.2.2 Commercialization with marketing authorization

To obtain a marketing authorization for a medicinal product, the company applying for it must produce and show the following documents to the Agency *Swissmedic* [46]:

1. Results of physical, chemical, galenic and biological or microbiological tests (chemistry, manufacturing and control (CMC) file)
2. Results of pharmacological and toxicological tests and clinical trials, including all results from trials in specific population groups
3. Therapeutic effects and the undesirable effects
4. The labelling, the information supplied about the medicinal product, the dispensing method and method of administration,
5. An assessment of the risks and, if necessary, a plan for their systematic recording, investigation and prevention (pharmacovigilance plan)
6. The pediatric investigation plan.

For a new PN formulation, a simplified authorization procedure might be applicable since it concerns:

> "[…] medicinal products whose active substances are used in a medicinal product which […] has been authorized as a medicinal product for at least 10 years in at least one European Union (EU) or European Free Trade Association (EFTA) country and which is comparable in terms of indications, dosage and method of administration." [46]

In this case, the above-mentioned requirement numbers 1-4 must still be produced but the data for number 2 may be replaced by a compilation of equivalent scientific evidence.

Independent of the procedure to be followed, the application for a marketing authorization is time-consuming and cost intensive. The anticipated profit must outbalance the investment.

1.2.5 Stability of standardized parenteral nutrition

The difficulties in standardizing parenteral nutrition solutions are not only related to the body composition and the varying nutritional requirements of the concerned patients. The problem is furthermore to define a PN formulation, which corresponds to the current nutritional guidelines and to the physicians' practices. There are also challenging physicochemical factors influencing the stability of PN solutions. PN admixtures contain up to 50 different components, whereof the majority are AA, that may react with each other. Additionally, the step of mixing all components of the different compartments must be considered for stability and shelf life assessment.

1.2.5.1 Physical instability

The most important impairments of physical stability are the lipid or oil-in-water emulsion deterioration as well as the precipitation of particulates [49].

1.2.5.1.1 Lipid emulsion deterioration

Lipid emulsions are thermodynamically unstable and the two phases tend to separate over time [50], [51]. Favoring factors of this instability are low pH and high concentration of positively charged ions [52]. Both factors can be eliminated by separating lipids from glucose, responsible for a low pH especially after sterilization in an autoclave and electrolytes, responsible for positively charged ions [52].

Figure 3 illustrates the different ways of deterioration (creaming, flocculation, coagulation) of a lipid emulsion before the total phase separation by coalescence. The three first phases of lipid deterioration are to some extent normal emulsion aging and are reversible by agitation and therefore do not influence the quality.

To prevent this stability issue, most of the time, binary PN and separate lipids for Y-connector set administration are prepared.

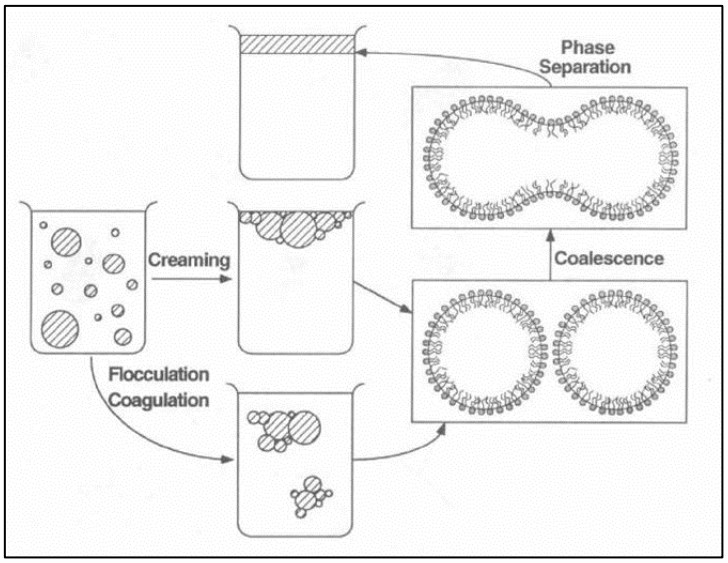


Figure 3: Lipid emulsion deterioration possibilities[iii]

1.2.5.1.2 Calcium phosphate precipitation

The well-known phenomenon of precipitation of calcium phosphate ($Ca_3(PO_4)_2$) is the most important physical incompatibility in PN. Influencing factors are the composition and concentration of AA and glucose, pH of the final solution and temperature and duration of storage. Nevertheless, the main favoring reason for precipitation is the use of inorganic salts such as calcium chloride ($CaCl_2$) and dibasic sodium phosphate (Na_2HPO_4). The resulting $Ca_3(PO_4)_2$ is insoluble and may result in catheter occlusion [53]–[55].

To prevent this precipitate formation, organic salts of calcium and phosphate should generally be used. This practice has been standard for several years because higher concentrations can be added to PN solutions to achieve patients' requirements. Examples for organic salts are calcium gluconate or calcium glubionate and sodium glucose-1-phosphate or sodium glycerophosphate [38], [53]–[57].

[iii] http://soft-matter.seas.harvard.edu/index.php/Emulsions (accessed: September 3, 2020)

1.2.5.1.3 Trace element interaction

Trace elements are known to interact with AA, for example copper and cysteine can form precipitates [50], [52]. As they are not required for every patient treated with PN, they are systematically added to the PN solution just before administration, if needed.

1.2.5.2 Chemical instability

The chemical stability is mainly influenced by AA and vitamin degradation as well as lipid peroxidation. External factors that promote this degradation are light, oxygen and temperature [52], [58]. In the case of industrial manufactured, standardized PN, the absence of oxygen as well as the choice of duration and temperature adjustment for the sterilization by autoclaving are crucial factors to avoid degradations.

1.2.5.2.1 Amino acid degradation

In contact with glucose, furnishing reducing sugar and at low pH or high temperatures, AA react beneath others to melanoidin, which is responsible for the typical yellow-brownish coloration of PN solutions. This reaction is called the Maillard reaction (Figure 4) and was first described in 1912 by the chemist *Louis Camille Maillard*. This reaction should be prevented to assure stability in both, standardized and individual PN, because their intravenous effects are not well explored yet [50], [59].

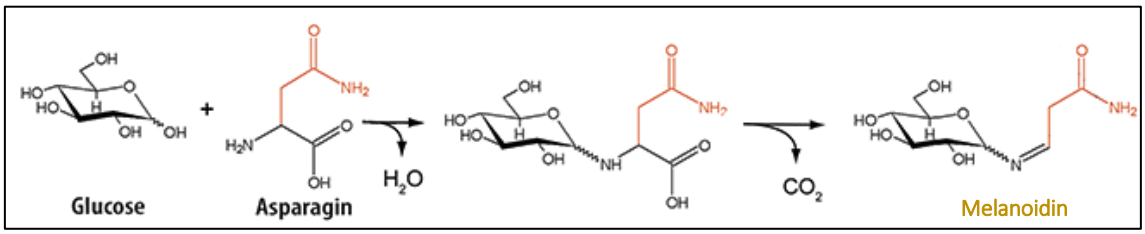


Figure 4: Maillard reaction[iv]

Additionally to the Maillard reaction, some AA are easily oxidized. One example is cysteine, which transforms to the insoluble cystine in presence of oxygen. Even the more

[iv] https://www.laborjournal.de/rubric/cooking/artikel/c_18_09.php (accessed: September 4, 2020)

stable precursor N-acetylcysteine (NAC) is oxidized to its dimer N,N-diacetylcystine (DAC). Both reactions are almost irreversible [60]–[63]. In this case, the reduction of oxygen concentration within the solution and the primary packaging for hospital compounded PN as well as within the secondary packaging for industrially produced and autoclaved PN is of high importance.

1.2.5.2.2 Lipid peroxidation

The oxidative degradation of lipid emulsions is related to light exposure and oxygen presence. The process of peroxidation passes by a free radical chain reaction mechanism in which free radicals react with non-radical molecule, producing another radical (Figure 5 [64]). When administered intravenously, these free radicals finally react with cell membrane lipids, such as retinal pigment epithelial cells or photoreceptors, resulting in cellular damage. Especially to premature infants, these radicals may be harmful [36], [65].

The phenomenon of peroxidation is particularly present in lipid emulsions with high contents of polyunsaturated fatty acid (PUFA), such as soybean oil. The vitamin E derivate α-tocopherol with the highest in vivo antioxidant effect, protects against lipid peroxidation of high parenteral PUFA supply. Another way to protect the lipid emulsion from peroxidation is the mixed administration of multivitamins containing ascorbic acid via a light protected delivery tubing, which also limits vitamin loss [36], [66], [67].

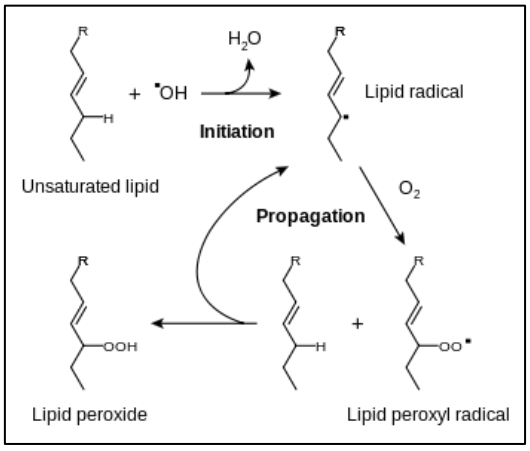


Figure 5: Mechanism of lipid peroxidation[v]

[v] https://en.wikipedia.org/wiki/Lipid_peroxidation [64] (accessed: September 22, 2020)

In summary, the most effective way to protect lipids from deterioration, as discussed in Section 1.2.5.1.1 and peroxidation, is to separate them from the other PN components, to protect them from light and to reduce the available oxygen concentration [68].

1.2.5.2.3 Vitamin degradation

The concentration of vitamins, especially ascorbic acid (vitamin C), in PN solutions decreases significantly after 48 hours at RT [69], [70]. The main reactions with vitamins are oxidation and photodegradation [40], [57]. Aseptically compounded individual PN for inpatients can be given stable up to 16 days when stored refrigerated (2-8°C) and protected from light [51], [57]. Therefore, vitamins are not integrated in the AIO admixture upon production but systematically added to the PN just before administration [50], mainly through a Y-connector set.

1.2.5.3 Stability enhancing factors

Different approaches exist to enhance the stability of PN solutions especially for an industrial production.

1.2.5.3.1 Packaging material

For several decades, multilayer bags are known to restrict oxygen permeation and increase the stability of AA and other oxygen sensitive PN components [50], [55], [71]–[73].

The aim of the primary packaging material is to reduce the oxygen permeation from the environment into the infusion bag. Therefore, gas barrier properties are necessary. When the primary packaging is overwrapped by a secondary packaging and absorbers are used to reduce residual oxygen amounts, the primary packaging material should allow oxygen dissolved in the solution to exit the infusion bag.

The secondary packaging of industrially manufactured infusion bags aims to protect them from outer mechanical impacts, but also from oxygen and moisture. Therefore, this outer layer must be impermeable for oxygen to allow oxygen absorbers (see Section 1.2.5.3.3), inserted into the secondary packaging, to maximally absorb residual oxygen

amounts of both, the solution and the headspaces of the primary and secondary packaging.

Materials and their characteristics used for the primary and secondary packaging are listed in the following Table 2 and Table 3.

Table 2: Materials and their characteristics of the primary packaging of parenteral nutrition solutions

Primary packaging material	Characteristics
Ethylene vinyl acetate (EVA) monolayer	High level of biocompatibility
Multilayer of EVA and Ethylene Vinyl Alcohol (EVOH)	High level of biocompatibility Extremely low oxygen permeability, high gas barrier properties
Polypropylene (PP) or polyethylene (PE) without plasticizers (Diethylhexylphthalat) (DEHP-free)	Good oxygen and water vapor barrier, biologically inert
V90-film, three-layer (B. Braun Medical AG, Germany)	Mechanical-resistant and liquid-impermeable
Six-layer film with EVOH	Mechanical-resistant, gas and liquid-impermeable layer

Table 3: Materials and their characteristics of the secondary packaging of parenteral nutrition infusion bags

Secondary packaging material	Characteristics
Silicon dioxide (SiO_2) foil (PP outer and inner layers and a SiO_2-coated polyethylene terephthalate (PET) middle layer)	High gas barrier

1.2.5.3.2 Multi-chamber infusion bags

To reduce degradation processes and to prevent the risk of reactions between the different components, double- and triple-chamber bags (DCB and TCB) have been developed in the past years. DCB or TCB are designed with two or three sealed compartments, respectively, that can easily be opened for mixing the components right

before administration. This development enabled the extension of shelf life of commercialized AIO PN admixtures to up to 18 months at room temperature [74], [75].

Multi-chamber bags separate the components being responsible for the short-term stability of AIO admixtures. For all multi-chamber bags, glucose and AA solutions are separated in two different compartments to prevent the well-known Maillard reaction (discussed earlier in Section 1.2.5.2.1), leading to a yellow to brownish coloration of the PN. Electrolytes are added either in the glucose [76], [77] or the AA compartment [78], depending on the development process and corresponding stability assessments of the different companies. In TCB, where lipids are included, these are always separated from the other components in their own compartment [75]. DCB without lipid emulsion have the advantage that lipids can be prepared separately from the raw solution by nurses according to the nutritional requirements of a given patient. For the case of newborn infants, lipids are not mandatory on the first day of life and the needed amounts afterwards are not uniform in this population either. Thus, the separation of lipids allows to use a DCB for a larger population of patients.

1.2.5.3.3 Limitation of oxygen

As discussed in Section 1.2.5.2, the limitation of oxygen concentrations is important to reduce the degradation of AA and vitamins as well as the peroxidation of lipid emulsions [36], [39], [40]. For this reason, the manufacturing process needs to be designed and operated with the aim to prevent residual amounts of oxygen in the solution as much as possible and within the primary and secondary packaging [73]. This can be achieved by the following steps, which can be applied separately or together to achieve the desired near absence of oxygen:

- Inertization of the solution with nitrogen
- Regulation of the filling flow rate
- Elimination of residual air containing oxygen upon the filling process
- Absorption of oxygen by means of oxygen absorbers between the primary and secondary packaging
- Corresponding packaging material as discussed before (Section 1.2.5.3.1).

Two types of oxygen absorber exist and must be chosen corresponding to the oxygen sensitivity of the product. Fast-acting absorbers (Figure 6) may be chosen for more sensitive products to oxidation because they are functional when in contact with oxygen. Others need to be activated by moist, during the sterilization process by autoclaving [79].

Additionally, an oxygen indicator (Figure 7) may be placed within the secondary packaging to indicate integrity of the product to be checked by users before administration.

Figure 6: Fast-acting oxygen absorber

Figure 7: Activated oxygen indicator

1.3 Parenteral nutrition in neonatology

As a global public health recommendation on infant feeding, the WHO promotes to exclusively breastfeed infants for the first six months of life to achieve optimal growth, development and health [80]. The advantages of breastfeeding, starting at the latest one hour after birth if possible, are a reduced risk of necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis and retinopathy of prematurity. It furthermore has a positive impact on the neuro- and immune development and also on the mother-child bond [15], [81].

Unfortunately, some medical conditions make exclusive breastfeeding, first with maternal colostrum and then with milk, more difficult. A previously discussed example are preterm infants. Especially very and extremely premature infant are at risk, as they have limited nutrient storage at birth and the sucking reflex develops at the earliest in week 32 of pregnancy [82]. This development can last until week 36 and even longer in preterm babies [83]. Therefore, these patients are enterally fed by nasogastric tubes with maternal or donor milk as first choice or formula milk if necessary [84].

Functional and anatomical immaturity of the gastrointestinal tract is one of the main reasons for feeding difficulties [85], [86]. Many studies demonstrate that inadequate and retarded postnatal nutrition is related to growth and neurodevelopmental retardation [81], [87]–[89]. Therefore, an early and aggressive nutritional treatment is indicated and necessary to allow an adequate extrauterine nutrient intake for preterm infants [87], [90]–[93].

The EFCNI states in the *European Standards of Care for Newborn Health*:

> "Parenteral nutrition is commenced on the first day after birth, usually using standard solutions, and continued until sufficient enteral feeding is established." [94]

The statement of the expert in his field *Berthold Koletzko*[vi] resumes what is explained above:

> "Early parenteral nutrition preferably starting from the first day of life is really important for very preterm and sick babies. This contributes to supporting normal growth and development and to preventing growth restriction and associated adverse effects. All neonatal units caring for preterm and sick babies need standards for providing high quality parenteral nutrition." [25]

1.3.1 Standardized pediatric parenteral nutrition

The guidelines on PPN reviewed and published in 2018 by the collaborative group of ESPGHAN/ESPEN/ESPR/CSPEN, recommend to generally use standardized PN over individualized PN for the majority of pediatric and newborn patients, including VLBW premature infants. They also recommend the use of individually compounded PN when the nutritional requirements cannot be met by the available range of standard PN solutions [26].

In Australia, the first consensus standardized neonatal PN formulations were implemented in 2012. In 2017, this Australasian consensus group reviewed the instructions, formulated new PPN solutions and developed guidelines to standardize the PN clinical practice across their facilities. For newborn term and preterm (<32 weeks GA and/or <1'500 g) infants, the six standardized PPN from 2012 have been complemented to a total of eight standardized PPN in 2017 [43], [74], [95].

Despite these recommendations and wide experiences, in Europe, there has not been formed a consensus comparable to the one form Australia and parts of Asia. Some hospitals developed their own standard solutions in collaboration with their neonatal units [23], [96]. Unfortunately, these solutions often do not correspond with the

[vi] Professor of Pediatrics, Dr. von Hauner Children's Hospital, Ludwig Maximilian University (LMU) Munich, Germany

practices of other hospitals. Therefore, in Europe, still only a few industrialized PPN are available.

For French hospitals only, Pediaven® from Fresenius Kabi France has been developed by the *Assistance publique – Hôpitaux de Paris* (APHP) to furnish a safe PPN for the first days of life [97], [98]. New formulations of Numeta® as TCB from Baxter International, USA, have been relaunched in the beginning of 2016. The solution available for premature infants, Numeta® Neo, is a complete PPN with detailed instructions to dilute or adjust the formulation to better correspond to the individual patients' needs [33]. This more concentrated, multiple-component solution and the allowed manipulation steps (dilution, adjunctions) are critical factors regarding the sterility and stability of the system. Every manipulation of the infusion bag means a risk for contamination and medication errors [99]. These reasons often lead to a usage refusal by pharmacists and/or neonatologists.

Even if standardized PN for newborn term and/or preterm infants exist, some patients may not be treated with them. Very sick and metabolically unstable patients and infants requiring PN for prolonged periods have other nutritional needs than the majority of patients treated with PN [26], [100]. For these patients, PN must be compounded individually on-wards or by the hospital pharmacy [92].

The PN preparation and analysis by hospital pharmacies under controlled conditions and by trained pharmacy staff should always be preferred to a preparation on the ward by nurses. The risk for preparation errors rises drastically and is well documented [101]–[104]. In some emergency situations, this might not be possible due to time-critical treatment decisions. The availability of a pharmacy urgency service for this kind of medication is also a limiting factor when PN is needed during the night or weekends [105].

1.3.2 Nutritional guidelines

[ESPGHAN/ESPEN/ESPR/CSPEN guidelines on pediatric parenteral nutrition [14], [26], [34]–[40], [106]–[109]]

In 2018, the long-awaited reform of the 2005s nutritional guidelines for parenterally fed pediatric patients established by the ESPGHAN/ESPEN/ESPR/CSPEN were published. The working group members selected and assessed all relevant articles related to the different topics and compared them with the previous guidelines to correct or adjust them. Based on the evidence level of included studies, experts formulated and graded recommendations.

The guidelines, including organizational aspects, treat every macro- and micronutrient for PPN separately as well as fluid requirements, venous access, home parenteral nutrition, standardized vs. individualized PN and also a wide range of safety considerations for prevention and management of complications such as central line associated bloodstream infections. They provide guidance on PN for all pediatric patients ranging from extremely premature infants up to teenagers weighing up to and over 100 kg.

For the purpose of this thesis, the following sections focus on guidelines for newborn and preterm infants only.

1.3.2.1 Macronutrients

It is important to distinguish between protein and energy intake recommendations. Recommendations for proteins aim to meet needs for lean mass accretion only, even though they may provide energy for metabolic functioning. In contrast, recommendations for energy intake include all sources of energy: proteins, lipids and carbohydrates. For these reasons, inadequate energy provision may lead to growth retardation as proteins are used as source of energy instead of source of body tissue accretion.

Energy requirements of premature neonates are at least 45-55 kcal/kg/day on the first day of life. In VLBW infants, energy intakes of 90-120 kcal/kg/day should be provided to approximate intra-uterine lean body mass accretion and growth. These recommendations aim for a weight gain in VLBW infants of 17-20 g/kg per day after the initial postnatal weight loss. Adequate protein and energy intakes from PN can significantly improve postnatal growth in very preterm infants.

The Atwater system, named after *Wilbur Olin Atwater*, is used to calculate the available and metabolizable energy of nutritional components. Following the Atwater factors, energy content of protein, carbohydrate and lipid correspond to 4, 4 and 9 kcal/g respectively. This adaption is useful in clinical practice to calculate nutritional energy intake more easily.

Fluid intake is recommended to be increased gradually in preterm and term neonates after birth (Table 4) [34]. Water is the major component of the human body at any age and is an essential carrier for nutrients and metabolites.

Table 4: Recommended parenteral fluid intake in mg/kg/d during the first days of life in neonates

Day of life	**1st day**	**2nd day**	**3rd day**	**4th day**	**5th day**
Term neonate	40-60	50-70	60-80	60-100	100-140
Preterm neonate >1500g	60-80	80-100	100-120	120-140	140-160
Preterm neonate 1000-1500g	70-90	90-110	110-130	130-150	160-180
Preterm neonate <1000g	80-100	100-120	120-140	140-160	160-180

1.3.2.1.1 Amino acids

All cells in the body contain proteins, having structural and functional tasks. Multiple AA subunits joined by peptide bonds form chains building these proteins.

Three categories of AA are differentiated (Table 5) [39]:

1. Essential or indispensable AA that must be provided in the PN
2. Non-essential AA that can be synthetized from other AA or other precursors
3. Semi-essential AA can be synthetized from other AA, but their synthesis is limited under certain circumstances.

Table 5: Essential, non-essential and semi-essential amino acids (AA)

Essential AA	**Non-essential AA**	**Semi-essential AA**
Histidine	Alanine	Arginine
Isoleucine	Aspartic Acid	Glycine
Leucine	Asparagine	Proline
Lysine	Glutamic Acid	Tyrosine
Methionine	Serine	Cysteine
Phenylalanine		Glutamine
Threonine		Taurine
Tryptophan		
Valine		

For preterm infants, the AA intake recommendations are to start supply on the first postnatal day with at least 1.5 g/kg/d to achieve an anabolic state. Afterwards, from postnatal day two onwards, AA intake should be between 2.5 g/kg/d to 3.5 g/kg/d accompanied by non-protein intakes >65 kcal/kg/d and adequate micronutrient intakes. Concerning the semi-essential AA cysteine and tyrosine, the guidelines recommend administering 50-75 mg/kg/d and at least 18 mg/kg/d, respectively.

For stable term infants, a minimum AA intake of 1.5 g/kg/d should be administered but an excess of AA intake above 3.0 g/kg/d should be avoided. The semi-essential AA tyrosine intake should be 94 mg/kg/d.

The ASPEN recommends corresponding protein intakes for preterm infants of initially 1-3 g/kg/d aiming to achieve 3-4 g/kg/d and for term infants 2.5-3 g/kg/d [110]. The maximum recommended intake of 4 g/kg/d for preterm infants is not supported by the ESPGHAN/ESPEN/ESPR/CSPEN, which prefers the use of such high AA intakes in clinical trials only.

1.3.2.1.2 Glucose

Glucose, a carbohydrate, is the main source of energy especially for brain, renal medulla and erythrocytes. In the last trimester of pregnancy, the fetus needs about 7 g/kg/d of glucose provided by the placenta. Factors influencing the metabolism of glucose and needing to be considered when prescribing PN are age, acute illness, nutritional state and the concomitant provision of other macronutrients. Glucose is the main contributor to osmolality and must therefore be paid special attention to when PN needs to be administered peripherally.

Recommended parenteral glucose supply in term and preterm newborns are shown in Table 6 [35].

Table 6: Recommended glucose intake in mg/kg/min (g/kg/d)

	ESPGHAN/ESPEN/ESPR/CSPEN 2018		**ASPEN 2019 [110]**	
	Day 1 start with	**Day 2 onwards** increase gradually over 2-3 days to	**Day 1** start with	**Day 2 onwards** increase gradually over 2-3 days to
Term neonate	2.5-5 (3.6-7.2)	5-10 (7.2-14.4) min 2.5 (3.6) max 12 (17.3)	6-8 (8.6-11.5)	10-14 (14.4-20.2) max 14-18 (20.2-25.9)
Preterm neonate	4-8 (5.8-11.5)	8-10 (11.5-14.4) min 4 (5.8) max 12 (17.3)	6-8 (8.6-11.5)	10-14 (14.4-20.2) max 14-18 (20.2-25.9)

1.3.2.1.3 Lipids

As a non-carbohydrate source of energy, intravenous lipid emulsions represent an indispensable part of PPN. In fully parenterally fed infants, the guidelines recommend

the administration of 25-50% of non-protein calories in form of lipids. They provide essential fatty acids (FA) and help with the delivery of the lipid soluble vitamins A, D, E and K. Important aspects for the efficacy and safety in neonatal patients are the rate, amount and type of lipids.

Today, all 20% intravenous lipid emulsions available for term and preterm newborns provide the recommended minimum linoleic acid (an essential FA) intake of 0.25 g/kg/day for ensuring an adequate intake of linolenic acid. Currently available lipid emulsions are composed of:

- soybean oil and olive oil
- middle-chain triglycerides (MCT) and long-chain triglycerides (LCT) from soybean oil
- MCT, soybean oil and fish oil
- MCT, olive oil and fish oil.

Fish oil contain ω-3 long-chain PUFAs, which become more and more important in the nutritional treatment of premature infants. ω-3 FA have antioxidant properties helping to prevent lipid peroxidation (Section 1.2.5.2.2) and thus, reducing oxidative stress [111].

Lipids may be given directly after premature birth and no later than on day two of life to furnish non-protein energy for the increased needs. There is not enough evidence yet to formulate a dosage recommendation, but in most randomized clinical trials or meta-analyses, 2-3 g/kg/d were used. The lipid administration container and the infusion line must be protected from light.

The ASPEN recommendation conforms to those of the ESPGHAN/ESPEN/ESPR/CSPEN and start at 0.5-1 g/kg/d of intravenous lipid emulsion for term and preterm infants to be increased gradually until 3 g/kg/d of lipids [110].

1.3.2.2 Micronutrients

The three types of micronutrients and their recommended supply to newborn term and preterm infants are described in the following sections.

1.3.2.2.1 Electrolytes

Term and especially preterm newborns generally lose up to 10% of birth weight in the first two to five postnatal days. Most of this weight loss is due to considerable insensible water losses via the immature skin followed by electrolyte disturbances.

Sodium (Na) is the principle cation and chloride (Cl) the major anion of the extracellular fluid, whereas potassium (K) represents the major intracellular cation. Cl intake should be slightly lower than the sum of Na and K intakes (Na + K - Cl = 1-2 mmol/kg/d) to avoid excessive Cl intakes and risk of iatrogenic metabolic acidosis.

All three electrolytes should be supplied when body fluid compartments are rearranged by isotonic or hypertonic contraction of the extracellular fluid compartment. This is the case in the immediate phase after birth. In any case, Na and K supply should start at the latest before the serum concentration of these electrolytes drop below recommended values.

Appropriate amounts of calcium (Ca), phosphate (PO4) and magnesium (Mg) should be provided in PPN (Table 7) to ensure optimal growth and bone mineralization [38]. To prevent severe hypophosphatemia that can result in muscle weakness, respiratory failure, cardiac dysfunction and death, the plasma phosphate concentration must be monitored. Therefore, and to reduce the risk of hypercalcemia at the same time, a molar calcium : phosphate ratio of >1 is recommended.

Due to the previously discussed stability issues, the guidelines strongly recommend the use of organic calcium and phosphate salts to prevent precipitation and to allow higher concentrations of both components.

Table 7: Recommended parenteral intake for calcium, phosphate and magnesium in mmol/kg/d (mg/kg/d)

Age	Calcium	Phosphate	Magnesium
Preterm infants during the first days of life	0.8-2.0 (32-80)	1.0-2.0 (31-62)	0.1-0.2 (2.5-5.0)
Growing premature infants	1.6-3.5 (100-140)	1.6-3.5 (77-108)	0.2-0.3 (5.0-7.5)
0-6 months including term newborns	0.8-1.5 (30-60)	0.7-1.3 (20-40)	0.1-0.2 (2.4-5)

1.3.2.2.2 Vitamins

For more than 30 years, the recommendation for vitamins is all but unchanged. Vitamins are essential for growth and development and are therefore strongly recommended for all newborn infants necessitating PN. Usually they are administered as a multivitamin mixture (e.g. Cernevit®, Baxter, Switzerland), containing lipophilic vitamins A, D, E and K and hydrophilic vitamins B and C. No optimal doses and infusion conditions have been established, as research has basically been performed on the composition of specific products. Thus, recommendations are based mainly on expert opinion.

Due to the degradation of vitamins, especially vitamin C, they should generally be protected from light exposure and be administered separately or together with the lipid emulsion.

1.3.2.2.3 Trace elements

Similar to vitamins, trace elements are usually administered as an admixture of different trace elements. These compositions (e.g. Tracutil®, B. Braun Medical, Switzerland) contain the recommended elements iron, zinc, copper, iodine, selenium, manganese, molybdenum and chromium. Trace elements participate at enzymatic and immune reactions and are essential for metabolic reactions of the organism. Generally, trace elements should only be supplemented in long-term PN.

1.3.3 Venous access

The administration of PPN can be performed by different central or peripheral venous accesses.

The peripheral venous access (PVA) should only be used for short-term PN administration [106], [112] and for products with a low osmolarity [96], [113]. The ESPGHAN/ESPEN/ESPR/CSPEN as well as the ASPEN guidelines recommend not to exceed 900 mOsm/L for a peripheral administration due to the risk of phlebitis [27], [106]. However, some publications even demonstrate a safe PN administration by PVA until 1'000 mOsm/L [112], [114]–[116].

Peripheral lines are often placed into a vein in the hand, foot or scalp and sometimes in the belly button (umbilical vessels) of babies (green points in Figure 8). The advantage of a PVA is that it can be placed without surgery, but still under sterile conditions and aseptic technique. A disadvantage is the high risk for extravasation of the solution with a subsequent inflammatory response and potential skin necrosis [113].

A central line catheter may be placed into the superior (jugular and subclavian veins) or inferior (femoral vein) vena cava (orange points in Figure 8). Two methods of central venous access are differentiated, the non-tunneled central venous catheter (CVC), also called PICC-line (peripherally inserted central catheter) and the tunneled CVC which is inserted subcutaneously. A PICC-line can often be placed without general anesthesia and has proven to be safe and effective for PN in newborns and children [113]. The guidelines recommend the use of PICC and tunneled CVC for administration of prolonged PPN during hospitalization [106].

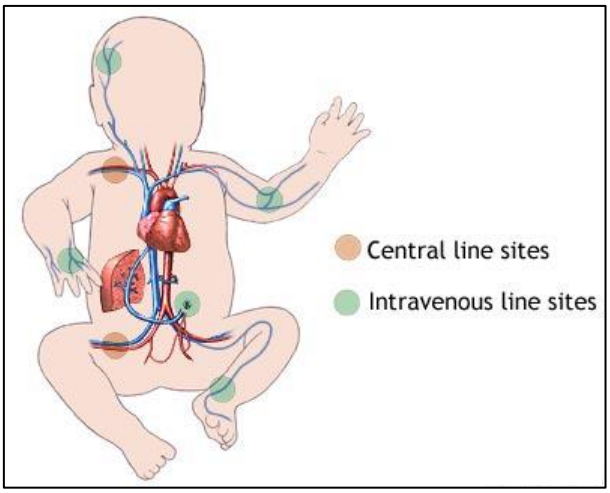


Figure 8: Venous access possibilities[vii]

Independent of the choice of venous access, the risks of contamination and related complications including infection, catheter occlusion and thromboembolism are high. Most healthcare-associated or nosocomial infections are bloodstream infections and of these, the majority is associated with the use of CVC [99]. The insertion of catheters must be realized under strict aseptic conditions by trained NICU staff only. Additionally, good catheter care and aseptic delivery of nutrients are mandatory for the prevention of catheter related infections [117]–[119].

1.3.4 Medication errors

The *National Coordinating Council of Medication Error Reporting and* Prevention (NCC MERP) defines a medication error as follows:

> "A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. […]" [120]

[vii] https://medlineplus.gov/ency/imagepages/19868.htm (accessed: August 26, 2020)

The WHO further defines medication errors as:

> "A deviation from the prescriber's handwritten or typed medication order or from the order that the prescriber has entered into the computer system. […]" [121]

Medication errors are not only related to the administration of a medication, but also to false ordering or erroneous delivery. Errors may occur in the whole process of the medical treatment of a patient. Examples for medication errors are brought together in Table 8 [121].

Table 8: Examples for medication errors

Ordering	Order communication	Drug omission	Unauthorized drugs	Extra/wrong dose or dosage form
Transcribing	Order modification	Extra/wrong dose or dosage form	Calculation error	
Compounding	Wrong preparation	Microbial contamination	Wrong dose or dosage form	Labeling/ Packaging/ Nomenclature
Dispensing	Temperature deviations	Inappropriate handling	Stability issues	
Administering	Wrong technique	Wrong infusion rate	Microbial contamination	Monitoring

The NCC MERP adopted a medication error index (Figure 9) that classifies an error according to the severity of the outcome. The aim of this index is to help healthcare professionals and institutions to report medication errors in a consistent, systematic manner [120].

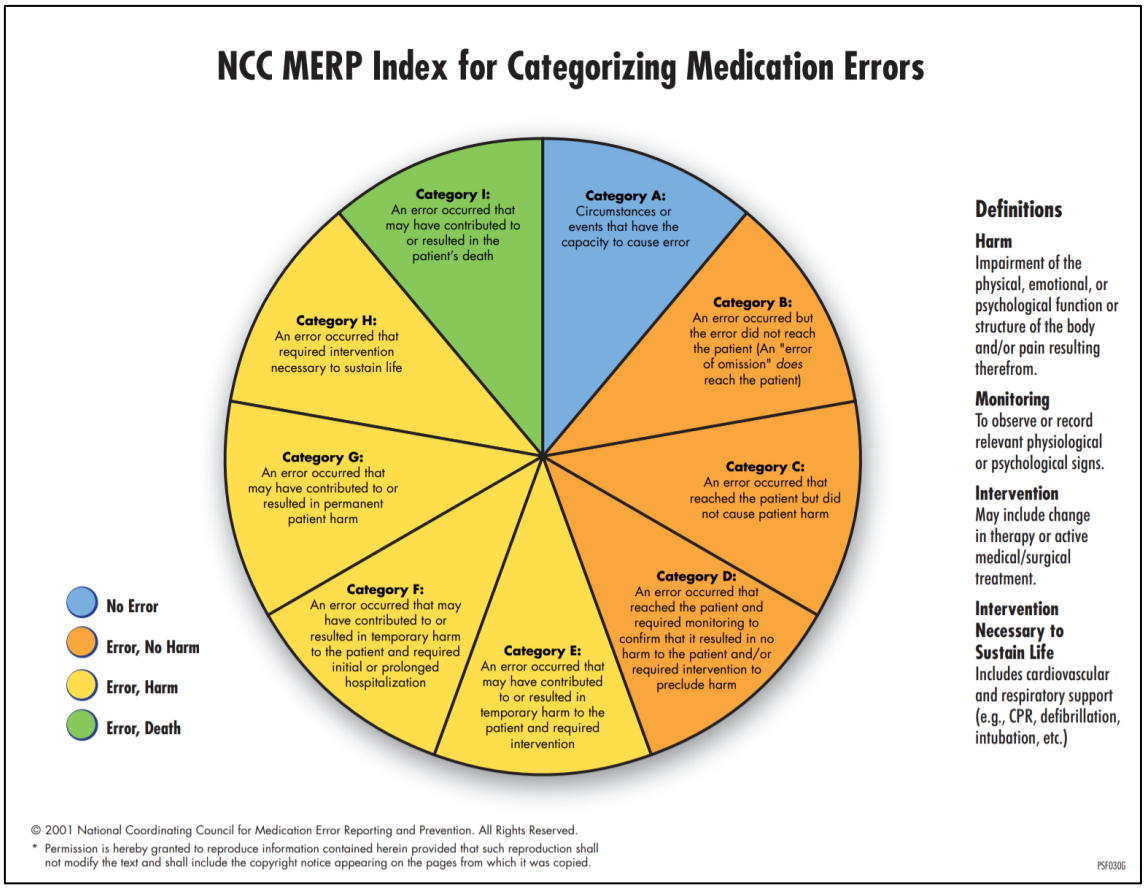


Figure 9: Index for categorizing medication errors[viii]

A major problem in the assessment of medication errors is the underreporting of these events by healthcare professionals [122]–[125]. Therefore, in the United States of America, standard taxonomy (Figure 9) as well as anonymous reporting systems are proposed by the *Institute for Safe Medication Practices* (ISMP) for recording and tracking of medication errors [120], [121], [126], [127].

Although this vulnerable, fragile patient population is at high risk of a wide range of errors, medication errors are particularly common. Several publications treat the different kinds of medication errors on neonatal or pediatric intensive care units and how to prevent or reduce them [128]–[131]. One of the most frequently cited drugs related to medication errors and defined as high-risk medication, is PN [132], [133].

[viii] https://www.nccmerp.org/sites/default/files/indexColor2001-06-12.pdf (accessed: September 15, 2020)

Different risk assessments on the high-risk process of PPN, identified prescription, preparation and administration of PN as the most critical steps within its process [125], [134]–[136].

In 1999, Kaushal et al. already identified 5.7% of medication errors with a majority of 79% of potential adverse drug events occurring during drug ordering for pediatric inpatients. The study also highlighted, that the potential adverse drug event rate was three times higher in neonates in the NICU than in a previous adult hospital study [137]. Hermanspann et al. focused on the incidence and severity of prescribing errors for pediatric inpatients. These patients are particularly vulnerable for highly individualized medical preparations like PN. An error rate of 3.9% was found for PN orders, whereof 12% could have had potential harmful consequences requiring interventions [138].

A lot of medication errors also occur during the preparation step of the medical treatment [99], [102], [139], [140]. Preparation related errors may be microbial, particulate and cross-contamination with other products or raw materials, precipitation or other drug incompatibilities as well as wrong products, dosage, dissolving or dilution of the medication [100]. The incidence of errors related to medication compounding is higher in the NICU setting than at hospitals' pharmacies [99], [101], [103], [140], [141].

Stavroudis et al. reported that almost 50% of detected medication errors were related to the administration and equipment or delivery device failures and might lead to harmful consequences [132]. Other origins of medication errors related to their administration are timing, dosage, infusion rate, missing or supplemental dose and wrong medication [142]–[145].

1.3.4.1 Prevention of medication errors

For the success of a treatment, the infants' security and the patients' outcome, it is fundamental to reduce and prevent medication errors. The ISMP identified ten key elements of the complex medication use that have an influence and impact on the safe medication application (Table 9) [146] that may help to perform a self-assessment.

Table 9: Ten key elements of medication use established by the Institute for Safe Medication Practices (ISMP)

1. Patient information	Obtaining the patient's pertinent demographic and clinical information for selecting appropriate medications, doses and routes of administration, significantly decreases preventable adverse drug events.
2. Drug information	Providing accurate and usable drug information to all concerned personnel reduces preventable adverse drug events. Drug information should be readily accessible and up to date and accurate.
3. Communication of drug information	Eliminating miscommunication and communication barriers between physicians, pharmacists and nurses, which is a common cause of medication errors.
4. Drug labeling, packaging and nomenclature	Using proper labeling and unit dose systems to avoid errors related to look-alike or sound-alike drug names, confusing drug labeling and non-distinct drug packaging.
5. Drug storage, stock, standardization and distribution	Standardizing drug concentrations and administration times and limiting the dose concentrations of available drugs.
6. Drug device acquisition, use and monitoring	Performing appropriate safety assessment of drug delivery devices as well as independent double-checks to prevent device related errors (wrong drug or drug concentration, improper infusion rate, mixing up of infusion lines).
7. Environmental factors	Preventing environmental factors that often contribute to medication errors like poor lighting, noise, interruptions and a significant workload.
8. Staff competency and education	Staff education should focus on priority topics like new and high- alert medications, medication errors occurred internally and externally, protocols, policies and procedures related to medication use.
9. Patient education	Patients must be educated by healthcare professionals about their medications, indications, doses, adverse effects, interactions and how to prevent errors.
10. Quality processes and risk management	Prevention of errors by redesigning the systems and processes that lead to those errors. Promoting the detection and correction of errors before they cause harm.

Despite these ten key elements aiming to secure the medication use process, one widely described measure to limit prescription and partly transcription errors is the implementation of a computerized physician order entry (CPOE) system [131], [137], [138], [147]–[149]. In combination with a barcode scanning, these systems help to clearly identify patients and to give dosage recommendations and error alerts for an easy, quick and secured prescription and administration process [129], [131], [150]–[153].

If such computer based systems are too cost-intensive or their implementation is too critical in terms of time, standardized, preformatted, electronic medical order forms are highly recommended [14], [27], [130], [154].

Clinical pharmacists specialized in the field of pediatrics or neonatology also help to reduce medication errors. They attend work rounds, participate at patient visits, monitor prescriptions and transcriptions and guide nurses as well as physicians in pharmaceutical questions [130], [137], [138], [153].

Another approach to reduce medication errors in terms of compounding, administration and monitoring is the standardization of procedures. This includes not only organizational aspects [14], but also the availability of ready-to-use products like standardized PN bags [26], [27], [74], [100], [139].

Last but not least, the training of implicated personnel on a constant and routinely manner plays an important role in preventing and reducing medication errors [130], [155], [156].

1.3.4.2 Risk assessments

[MEDD [157]]

The tenth key element of the ISMP medication use process is defined as “quality processes and risk management” and aims at the redesigning of systems and processes

for the prevention of errors as well as the promotion of the detection and correction of errors before they cause harm [146].

With regard to this, risk assessments should be performed and are nowadays a standard for the quality management of ISO9001 certified hospitals [158], [159]. Even for non-certified hospitals, risk analyses are an effective way to identify risks and hazards that may cause harm to patients. The primary purpose of risk assessments is to provide support for decisions about managing risks associated with those specific actions or activities [160].

For several decades, risk analyses are performed in the field of medical and pharmaceutical science for quality management purposes based on the methods applied initially in the aeronautic and military domains [161]. Different kinds of risk assessment methods exist, of which the failure modes and effects analysis (FMEA), the failure modes, effects and criticality analysis (FMECA) and the preliminary risk analysis (PRA) are the most known and applied.

1.3.4.2.1 Failure mode, effects (and criticality) analysis

In 1990, the FMEA method was first used in medical fields. The FMEA and FMECA are supposed to assess risks in a current, well established setting and to define if an action plan to secure this setting must be implemented.

The principles of the FMEA and FMECA are based on the concepts of the failure of a system (e.g. interrupt of PN infusion), the mode or effect for which the failure is observed (stopped infusion pump), the causes that led to the failure (power outage) and the effect of the failure mode (non-administration of PN).

The FMEA permits to evaluate the effects caused by a failure mode, to determine their importance for the normal functioning of the system, to evaluate the impact on security and to hierarchically organize an action plan for improvement.

The FMECA includes an evaluation of the criticality (probability and severity) of a failure. This allows to easily identify potential failures and measures to limit their effects or occurrence.

A limit of the FMEA and FMECA is that they are difficult to apply to complex systems with a huge number of potential failure modes. If too much information must be processed, these risk assessments are too time-consuming. Therefore, their application should be envisaged for well-defined parts of a system.

1.3.4.2.2 Preliminary risk analysis

The principle of the PRA is the identification of dangerous elements (e.g. products/preparations, equipment/facilities or operations) of the initially described process. For each dangerous element, one or more hazardous situations are identified, for which causes and consequences are determined. Afterwards, existing security measures of the concerned process are described. If these measures are judged as being insufficient, improvement measures must be defined.

The PRA is performed when a project is in a preliminary stage and the aim is to prevent risks during the planning of the project and to secure the new setting. It is also possible to perform a PRA on several domains of risks as far as they concern the same activity [162]. The aim of a PRA may also be to define topics needed to be further analyzed by means of a FMEA or FMECA. The advantage of a PRA is that this assessment is less time-consuming compared to the two previously discussed methods.

Chapter 2

Summary of the thesis

2.1 Introduction

Parenteral nutrition (PN) is a crucial part of the initial nutritional support provided for preterm or term neonates in critical health situations. It is indispensable for a good cerebral and neurologic development as well as a postnatal weight gain conforming to the intrauterine growth.

As PN can be composed of about 50 different ingredients, whereof the majority are amino acids (AA), its preparation is complex and at high-risk. Medication errors are often related to PN and may include prescription, transcription, preparation and administration errors. Therefore, medication errors can result in growth retardation, developmental disturbances and infections.

Worldwide, different ways of compounding PN for neonates are applied. The high-risk PN preparation steps are usually managed by the hospital's pharmacy in collaboration with the neonatal service. In some cases, the whole process, including the compounding of PN, is organized by the neonatal service. Both strategies include risks and constraints, however, the standardization of the process and the delegation of this mission to the pharmacy is strongly recommended by specialized societies [14], [27].

Only few commercialized PN are available for neonatal patients but not used routinely due to patients' varying needs of nutrients and the limited composition flexibility. Standardized PN assures an immediate and 24/7 availability of high-quality PN on wards, minimizes the risk of medication errors and improves the medical treatment and clinical outcome of the treated inpatients. These are reasons for which standardized PN, either commercialized or prepared at the hospital pharmacy, are preferably recommended, but they do not correspond to the nutritional requirements of all patients and therefore, individual PN remains indispensable.

As commercial PN adapted to a safe administration on the first days of life of premature newborns is not available, a standardized pediatric PN (PPN) for this purpose had to be developed and implemented. This PPN aims at reducing medication errors potentially

having an impact on vulnerable patients as well as the improvement of the security and quality of the nutritional treatment of newborn preterm or term infants.

2.2 Objectives

This thesis is composed of two major parts containing several projects.

The first part of this work aimed at evaluating and assessing the need for centralizing the preparation of PPN for neonatal patients at the central pharmacy of the *Centre Hospitalier Universitaire Vaudois* (CHUV) on the one hand and the need to propose standardized PN in order to offer a ready-to-use nutritional treatment on the other hand. These objectives were achieved through the following projects:

- An evaluation of the status at the CHUV was performed to investigate the security and quality of PN prepared by nurses of the neonatal intensive care unit (NICU). Microbial as well as chemical analysis were performed to test for contamination and sterility issues and for accuracy of the PN prepared on the ward. This project has been published in the *European Journal of Hospital Pharmacy* (EJHP) and is presented in Section 3.1.
- A preliminary risk analysis (PRA) was performed for the two preparation sites (on the NICU and at the pharmacy) to compare the risks related to PN compounding and to identify deficiencies to be focused on until centralization at the pharmacy is achieved and in order to better implement this intention. The execution and results of these assessments are described in an article accepted for publication (with changes) in the online journal *Dovepress – Therapeutics and Clinical Risk Management* and presented in Section 0.

The second part targeted on the development of a standardized pediatric PN (PPN) in collaboration with an industrial partner to respond to a potential need of a ready-to-use PPN with a long-lasting stability and easy storage conditions. Several projects led to the achievement of this objective and were related to the development process:

- A common PPN formulation was developed by a working group composed of pharmacists, neonatologists and industrials responding to the evaluated requirements of the two sites of application, the university hospitals of Lausanne and Geneva. The development process of the standardized PPN revealed a

considerable degradation of N-acetylcysteine (NAC), the precursor of the semi-essential AA cysteine, to the dimer N,N-diacetylcystine (DAC). This was further analyzed and evaluated and the results were published in the online journal *Nutrients* (Section 3.3). Finally, this developed standardized PPN, first prepared by the pharmacy and afterwards provided by B. Braun Medical, was introduced to the NICU of the CHUV following training of nurses and neonatologists.

- Further projects helped developing this PPN for the first days of life of newborn term and preterm infants and are resumed later in Chapter 4.
    - Two questionnaires were elaborated with the aim to gain knowledge of what is done in other Swiss hospitals. They were addressed to (1) neonatologists and (2) pharmacists working in Swiss hospitals having either a neonatal service or a drug preparing pharmacy.
    - The conformity of theoretical and real osmolarity has been assessed, as the practices for peripheral intravenous PN administration varies a lot following the literature, even though the strong ESPGHAN recommendation to limit osmolarity to 900 mOsm/L.

2.3 Pediatric parenteral nutrition at the CHUV

At the CHUV, PN is prepared partially at the central pharmacy by trained pharmacy technicians and on the neonatal ward by nurses without any involvement of the pharmacy staff. The location where the PN is prepared depends on the emergency to start or adapt nutrition, which may be urgent in critical situations like very preterm infants, (very) low birth weight ((V)LBW), metabolic disorder or critical illness.

2.3.1 Organization

During opening hours, for medically stable patients, PN is generally prepared at the pharmacy. Until early 2018, physicians manually prescribed the composition of the PN on an order sheet, which was then faxed to the production unit of the pharmacy. Since 2018, a computerized physician order entry (CPOE) system has been implemented for prescription (further discussed in Section 2.3.3.1), which is interfaced with the preparation tool of the pharmacy.

Due to the quality oriented and GMP conforming preparation process at the pharmacy, which consequently is time-consuming, nurses prepare PN on the ward for emergency situations or unstable patients rapidly needing an adjustment of nutritional supply. Furthermore, as the pharmacy does not prepare PN during the night, weekend or holiday, NICU nurses also have to prepare them for new admissions during these shifts.

Before summer of 2017, another handwritten order form was used when PN was prepared by nurses on the ward. This form served as instruction for the preparation and was used for transcription of ingredients on the label to be affixed on the prepared PN syringe or bag. Since then, an improvement of the prescription form was implemented. The new electronic prescription form is a spreadsheet (Microsoft® Excel®) including an extensive calculation base for all kinds of medication (oral, intravenous, subcutaneous, etc.) to be administered to their patients, including PN.

2.3.2 Preparation

The high-risk PN preparation steps are usually managed by the hospital's pharmacy in collaboration with the neonatal service. In some cases, the whole process, including the compounding of PN, is organized by the neonatal service. Both strategies include risks and constraints.

2.3.2.1 Pharmacy

Now, as then, PN orders are reviewed by a pharmacist, the preparation is done conforming to current good manufacturing practices (GMP) in controlled conditions (grade A horizontal LAF hoods in a cleanroom grade B) with an automated compounding system (BAXA EM 2400, Baxter Healthcare Corporation, USA) by trained and qualified pharmacy technicians as required by the applicable guidelines [41], [42], [44]. Every preparation is analyzed for quantitative determination of critical components (glucose, sodium, potassium, calcium, magnesium) to confirm composition conformity to the original medical prescription following the method described by Nussbaumer et al. [163]. Additionally, sterility testing by means of detection of endotoxins via the Limulus amebocyte lysate (LAL) method [164] is performed before pharmaceutical, GMP conforming quality release of the PN preparation and delivery for administration. This process is time-consuming, meaning that the prescription order must be placed at noon at the latest for a delivery of the individual PN until 5:00 p.m.

2.3.2.2 Neonatal intensive care unit

During the night, weekend or holiday, nurses of the NICU prepare PN for new admissions as well as for critically ill patients needing adjustments of their nutritional supply.

Nurses were preparing PN manually following handwritten medical prescriptions until autumn 2017. Since then, they are following an electronic prescription form (Microsoft® Excel® spreadsheet). The preparation is performed in a non-classified and non-qualified horizontal LAF hood placed inside the separated ward pharmacy. The transcribed labels

as well as the volume withdrawn and the raw solution of critical components like potassium (as hydrochloride or phosphate salt) are double-checked by a second nurse or a physician. For all non-critical ingredients, the preparation of PN is performed and auto controlled by a single nurse only. No analytical controls are carried out for these on-ward preparations before administration to the vulnerable patients.

2.3.2.2.1 Quality assessment

Due to the PN management described above and the fact of non-GMP conforming PN preparation on the ward, an evaluation of the physicochemical and microbiological quality of the bags prepared by nurses of the neonatal ward of the CHUV was performed.

For this purpose, samples were retrieved from on-ward prepared PN bags after their administration and were analyzed in the same way as pharmacy-prepared PN with an additional analysis for sterility according to European Pharmacopeia (Ph. Eur. 2.6.1). The obtained results were evaluated based on the specifications established by the pharmacy.

The physicochemical results showed that concentrations were below the lower limit of 90% or above the upper limit of 110% defined for compounded medicinal products in almost 30% of the analyzed PN solutions and therefore did not conform to their medical prescription.

The microbiological quality did not seem to be impacted by the preparation by nurses on the neonatal ward. However, due to the small number of analyzed samples, a reliable detection of potential contamination could not be guaranteed.

The detailed description of this quality assessment is presented in the first published article (Section 3.1).

2.3.3 Realized and future projects

With the aim and the need of continuous improvement, projects to secure the PN process have been realized and are planned to be implemented in the near future. Some

recent and future common and collaborative projects of the NICU and the pharmacy are described hereafter.

2.3.3.1 Prescription and order form

As mentioned previously, since 2017, the mode of prescription and attached order forms evolved on both sites, pharmacy and NICU.

In autumn 2017, the NICU implemented a quasi-electronic prescription tool in form of a Microsoft® Excel® spreadsheet containing an extensive calculation base for all prescribed medication including PN for their neonatal patients. This development allowed to reduce medication errors due to false calculation and illegibility. Additionally, non-nutritional supplies of glucose and/or electrolytes are considered when PN is required.

In spring 2018, the pharmacy implemented a CPOE system (Péan®, Groupe Alma, France) for managing PN prescription, preparation and dispensation. This project was realized in collaboration with neonatologists of the NICU. The CPOE system permits an easy PN prescription for physicians by showing recent ESPGHAN/ESPEN/ESPR/CSPEN recommendation ranges as well as instability issues. The pharmacists can double-check the prescription for compliance to previous ones, instabilities and feasibility. Afterwards, the PN order can be sent to the automated compounding device (BAXA EM 2400, Baxter Healthcare Corporation, USA) for production including barcode scanning for patient coherency. After pharmaceutical release following the quantitative and qualitative analyses, the PN preparation is delivered for administration. All these steps are traced in the CPOE system.

2.3.3.2 Standardization

In 2014, an internal evaluation of nutritional solutions, including simple glucose dilutions or glucose and AA admixtures, prepared by nurses on the neonatal ward was performed. This project showed that the glucose dilution used most contains 12.5% of glucose.

Therefore, the NICU requested and the pharmacy proposed the production of a 250 mL 12.5% glucose solution (G12.5%).

In December 2018, this solution was prepared aseptically as a batch production by the pharmacy ("formula hospitalis") with final heat steam sterilization and all mandatory analytical release steps. Since then, an average of 40 flasks is used monthly by the NICU.

Even though this solution is a bit more expensive than the same dilution prepared by nurses on the ward, the quality is much higher and confirmed through analytical testing for sterility and glucose concentration. The product has a 1-year stability at room temperature and is available at any time for urgent treatments with energy. This allows nurses to concentrate their time more on their patients.

2.3.3.3 Centralization

Despite the standardization of PN and to further improve the quality of individual PN, a future project is the complete takeover of PN preparations of the neonatal ward by the hospital pharmacy.

During the week there will be no modification of the actual functioning, but during weekends and holidays, the pharmacy on call service for the production unit (pharmacy technician plus pharmacist) as well as the laboratory (lab technician plus pharmacist) of the pharmacy will have to realize all PN preparations and analytical controls. This means a new organization of the urgency service of the hospital's pharmacy as well as of the NICU, meaning that additional personnel is needed, greater delays for PN delivery are expected during these shifts and higher costs for PN production are incurred.

These reasons are an incentive to keep on working on standardized PN solutions.

2.3.3.3.1 Risk assessment

Another approach to evaluate and classify the risks related to the PN preparation on the ward was the performance of a risk assessment. In prevision of the project to centralize all PN preparations at the pharmacy, a risk analysis was performed. The objectives were

to identify, evaluate and compare the risks associated with the entire management of the PN process considering the two separate preparation sites (NICU and pharmacy).

The choice was made for a preliminary risk assessment (PRA) as this method is usually used in prevision of an upcoming project and when a large and complex process needs to be analyzed. A PRA is less time-consuming than other previously described risk assessments and enables to define topics to be further focused on.

The PRA highlighted the difference in security of the PN preparation at the two sites. The results showed that seven vs. two “non-acceptable” risks were related to the preparation process at the NICU vs. at the pharmacy, respectively. A risk is already 26% less likely to occur when PN is prepared and analyzed at the pharmacy without implementing any improvement measures. The assessment emphasized the advantages of a centralized PN production, which secures the PN compounding process and increases the quality of nutritional treatment of neonatal patients.

The detailed description of this risk assessment is presented in the second article due to be published after revision and editing (Section 0).

2.4 Development process of a standardized parenteral nutrition solution

Due to the lack of standardized PPN allowing an administration directly after birth of neonatal patients, a working group composed of pharmacists, clinicians, neonatologists and industrials was set up.

The aim was to develop a standardized PPN solution conforming to the needs of the two implicated neonatal services of the university hospitals of Geneva (*Hôpitaux Universitaires de Genève* - HUG) and Lausanne (CHUV). Therefore, the first steps were to define the composition, concentrations and mode of administration of the PN resulting in a significant number of bags to be produced by the industry.

The choice fell on a moderately concentrated formulation for the first days of life of newborns needing parenteral feeding. To reach a bigger number of potential patients as well as to conform with the practices of both sites, the osmolarity was limited to 900 mOsm/L to allow a peripheral venous administration.

2.4.1 Situation and the perspectives in Switzerland

Since different practices of PN management for neonatal patients are applied worldwide, the interest in what is done in other hospitals in Switzerland grew significantly. Therefore, a national survey was performed with the aim at gaining knowledge and evaluating the actual situation and consequently approaches to the handling of PN as well as the different strategies of nutritional treatment applied in the concerned hospitals. The results are also supposed to help developing a standardized PPN that may potentially be of a nation-wide interest. A larger interest means more sold products, implies bigger batch productions and reduced related costs.

The detailed objectives, methods, results and the conclusion of this conducted national survey are described later in Section 4.1.

2.4.2 Standardized parenteral nutrition of the HUG as starting point

Several years of experience with standardized PN at the HUG allowed the working group to revert to one of these solutions developed locally by Bouchoud et al. An evaluation of PN prescriptions for their neonatal patients was performed to find the most applied PN compositions [23].

Two solutions are available for the treatment of newborn infants from birth (called "J0") up to five days of life (called "J1-4"). They are detailed in the following Table 10.

Table 10: Composition and concentrations of standardized parenteral nutrition solutions developed by Bouchoud et al. and applied at the HUG neonatal service

Formulation	**"J0" for the 1st day of life** (100 mL/kg/d)	**"J1-4" for days 2 to 5** (100 mL/kg/d)
Amino acids g/kg/d	3	3
Glucose mg/kg/min (g/kg/d)	7.5 (10.8)	7.5 (10.8)
Sodium mmol/kg/d	-	2
Potassium mmol/kg/d	-	1
Calcium mmol/kg/d	-	1.1
Phosphate mmol/kg/d	-	0.86
Heparin UI	50	50
Non-protein energy kcal/kg/d	43	43
Total energy kcal/kg/d	55	55
Osmolarity mOsm/L	950	1'000

These solutions were prepared as All-in-One (AIO) solutions in a single-chamber bag. Lipids were delivered separately in a syringe. Organic salts of electrolytes were used to increase the stability of the solution and to prevent precipitations. Due to the high osmolarity of both solutions, administration must be performed by central venous access only [165].

2.4.3 Guidelines

The revision of the ESPGHAN guidelines from 2005 was expected to be published in 2015. As this revision was finally published in summer 2018 only, this thesis, starting in 2015, was initiated with the latest version and the risk of not conforming to the new one.

2.4.3.1 Nutritional requirements

For a standardized solution aiming to be administered directly after birth and on the first days of life of newborn term and preterm infants, the PN solution "J1-4" developed at the pharmacy of the HUG corresponded well to the requirements. Nevertheless, due to the planned administration directly after delivery and the risk of hyperkalemia, potassium was completely removed from the formulation which then still corresponds to the recommendations.

Following a working group consensus, the AA supply was raised slightly as discussions on higher early AA intake up to 4 mg/kg/d potentially resulting in better cerebral development were ongoing at this time [95].

To allow a peripheral administration, the glucose concentration was reduced to conform to the osmolarity limit of 900 mOsm/L.

The use of heparin to reduce the risk of venous thromboembolism is widely discussed as there are a lot of complications related to its administration in neonates (e.g. intracranial hemorrhage). Therefore, heparin was also removed from the final formulation.

The decision was made to omit lipids from the final formulation to allow the recommended gradual increase of the amount of lipid emulsion conforming to the patients' needs during the first days of life.

2.4.3.2 Osmolarity

The ESPGHAN guidelines from 2005 served as reference for the development of the two standardized PN solutions prepared by the HUG pharmacy, which recommended the limit of 850 mOsm/L for the peripheral venous access (PVA). However, the recommended limit of osmolarity still allowing a safe PN administration by PVA was increased to 900 mOsm/L since then. Several studies even report safe peripheral administrations beyond this limit [166]. The new ESPGHAN/ESPEN/ESPR/CSPEN guidelines from 2018 finally adapted their recommendation to privilege central venous catheters (CVC) for PN solutions above 900 mOsm/L [106].

This topic was quite delicate, because it reduces the concentrations of the different PN components, especially for glucose, the main contributor for energy. Additionally, a too high osmolarity for PVA might result in venous access complications like phlebitis. In order to still allow an adequate energy intake furnished from glucose, the final formulation approaches the recommended limit for osmolarity.

Nevertheless, the interest in what kind of osmolar PN solutions are administered to neonates and whether the calculated theoretical osmolarity conforms with the analyzed real osmolarity, grew with this reflection. Therefore, the project of theoretical vs. real osmolarity described in Section 4.2 was initiated.

2.4.4 Final formulation

The final composition of the standardized PN solution developed in a collaboration of pharmacists, clinicians and neonatologists of the HUG and CHUV is presented in Table 11. An administration volume of a minimum of 150 mL has been fixed by the working group to enable the recommended fluid intake to be administered to all concerned term and preterm infants of different birth weights. It has also been defined that the glucose and electrolytes compartment will be the lower one and the AA compartment the upper one of the infusion bag. In the case that the mixing of the compartments might be forgotten, this arrangement can help to reduce the risk of a separate administration of

AA only which would then principally be used as source of energy and not as source of proteins as targeted.

Table 11: Composition of the standardized parenteral nutrition solution

Volume	**1'000 mL**
Amino acids g/L	31.4
Glucose g/L	100.1
Sodium mmol/L	20
Calcium mmol/L	11
Phosphate mmol/L	8.6
Chloride mmol/L	10
Non-protein energy kcal/L	400
Total energy kcal/L	525
Osmolarity mOsm/L	883

A detailed table of the supplied component concentrations conforming to the administration volume is shown in Appendix 1.

2.5 Industrial production

An industrial production of the developed PN solution was targeted from the beginning of this thesis. The aim of an industrial production as “formula hospitalis” was to outsource the complex and time-consuming preparation of standardized PN. At the same time, the quality and stability of the high-risk product are maximized due to extensive analytical qualitative and quantitative controls. Moreover, a terminal sterilization will be applied instead of an aseptic filling which will increase the sterility assurance level.

The industrial partner chosen for this project is B. Braun Medical who is located in Crissier, Switzerland, close to the CHUV and with whom several other subcontracts already existed. After an initial feasibility study performed by the pharmaceutical development team, B. Braun Medical Crissier accepted to perform the industrial manufacture of this new product. Internally, the project was called “HeraNeo” which stands for Hera, the goddess of women, marriage, family and childbirth as well as for Neo, the neonates for whom the solution is destinated.

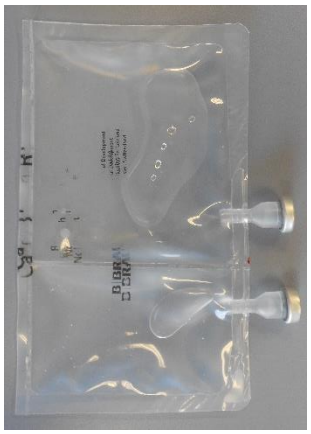
2.5.1 Packaging design

B. Braun Medical manufactures multi-chamber bags for their adult PN solutions. Thanks to this knowledge and to improve the stability as well as to increase the shelf life, a production of a double-chamber bag (DCB) has been chosen for this project. The first, upper compartment contains an AA admixture (Aminoplasmal® Paed 10%, B. Braun Medical, Germany) and the second, lower compartment is composed of glucose and electrolytes (sodium, organic calcium and organic phosphate), both conforming to the final PN formulation (Table 11).

Several tests were performed to (1) develop the best design and layout for the infusion bag (Table 12) as well as (2) achieve repeatable results for the final sterilization by heat steam. These tests resulted in an optimal filling volume of 250 mL meaning 79 mL of the

AA solution in the first and 171 mL of the glucose and electrolytes admixture in the second compartment.

Table 12: Design finding for the standardized parenteral nutrition infusion bag

Initial infusion bag design	Examples for design finding	Final infusion bag design
	 	

The material used for the primary packaging was a B. Braun Medical multilayer coextruded film. The secondary packaging with barrier properties for oxygen consisted of the high gas barrier material silicon dioxide (SiO_2) foil made of cast polypropylene (PP) outer and inner layers and a SiO_2-coated polyethylene terephthalate (PET) middle layer.

The name chosen for the final product followed the nomenclature of B. Braun Medical for their adults' PN series called Nutriflex® followed by the specialty of the concerned product. In this case, the suffix is generated by the administration of PN to neonates by PVA: Nutriflex® NeoPeri.

The label of the infusion bag was designed to indicate all mandatory information [167] as well as further information on the composition of the bag to assure a safe application of the product (Figure 10).

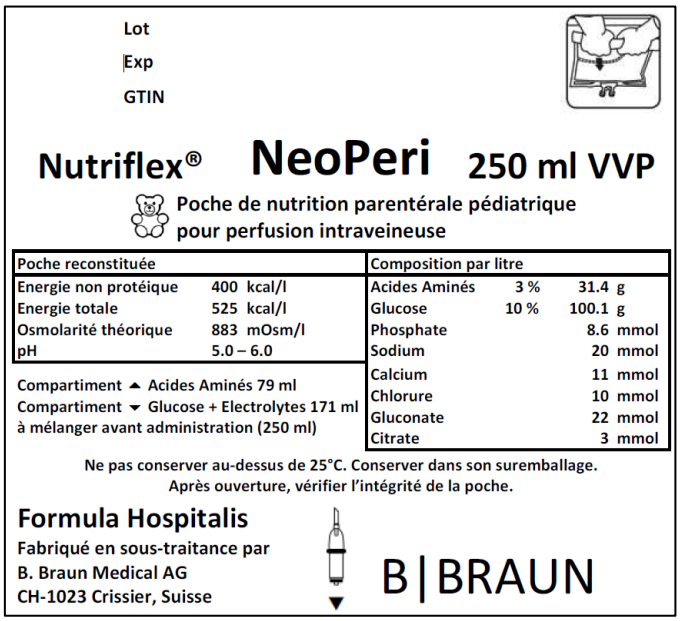


Figure 10: Label of the infusion bag

The final packaging carton was designed to contain eight Nutriflex® NeoPeri infusion bags and light protecting overwraps for each bag corresponding to the ESPGHAN/ESPEN/ESPR/CSPEN guidelines which recommend to systematically protect PPN for neonates from ambient light exposure.

2.5.2 Laboratory analyses and stability testing

Each analytical method used for quantitative and qualitative controls had to be validated previously and mandatory to conform with current GMP guidelines. For this product,

several controls in accordance with the Ph. Eur. were performed to prove quality and conformity with the predefined product specifications. These analyses were performed on all stored samples for stability testing purpose and at each timepoint. A stability of 18 to 24 months at room temperature was targeted to reduce storage constraints and limit new production cycles due to expiration. Some of these analyses have to be performed to demonstrate the conformity with the product specifications before batch release by a qualified person (Table 13).

Table 13: Analytical controls performed on stored samples for stability testing and batch release purpose (HPLC = High Performance Liquid Chromatography, Ph. Eur. = European Pharmacopeia)

Analytical control	**Test procedure**
Quantitative components analysis	Depending on component (e.g. spectrophotometry, polarimetry)
Quantitative analysis of each amino acid	HPLC
Coloration of the solution (Maillard reaction)	Ph. Eur. 2.2.2
Control of pH	Ph. Eur. 2.2.3
Detection of known degradation products (e.g. N,N-diacetylcystine)	HPLC
Clarity and degree of opalescence	Ph. Eur. 2.2.1
Detection of subvisible particles	Ph. Eur. 2.9.19
Sterility	Ph. Eur. 2.6.1
Bacterial endotoxin	Ph. Eur. 2.6.14

An in-use compatibility study with vitamins and trace elements was performed on the final product after the mixing of the two compartments aiming to confirm the safe simultaneous administration in conformity with the recommendations. Compatibility testing for adjunctions of higher concentrations of vitamins and trace elements are ongoing.

2.5.2.1 N-acetylcysteine degradation

The nutritional guidelines recommend the administration of the semi essential AA cysteine to preterm neonates due to their biochemical immaturity resulting in an inability to sufficiently synthetize endogenous cysteine. Most of the time, the soluble precursor NAC is used in PPN as it easily converts into bioavailable cysteine.

During the stability evaluation of the developed intravenous solution, raised amounts of DAC, the almost unconvertable dimer of NAC, were found.

Therefore, triggers as well as the oxidation process of NAC to DAC were investigated to evaluate possibilities of reducing DAC formation in standardized PPN.

The analysis showed that oxygen is principally delivered from the primary headspace and that DAC is exclusively delivered by NAC oxidation. The reaction of NAC to DAC is containable by limiting the oxygen concentration and therefore, the primary headspace must be minimized during manufacturing and oxygen absorbers must be added into the secondary packaging for a long-term storage.

The detailed description of this degradation investigation is presented in the third published article (Section 3.3).

2.5.3 Manufacturing process

Since merely a small batch size of ≤3'000 infusion bags is being produced, the manufacturing process is only partially automatized. The manufacturing scheme of a Nutriflex® NeoPeri bag is shown in Figure 11.

After forming of the empty infusion bags (Empty bag), labels are printed on the lower compartment by means of a thermal transfer of permanent ink (Printing). The labeled bags are afterwards equipped with ports for each of the two compartments (Port sealing). The filling process is performed semi-automatically by consecutive filling of the lower compartment with the glucose and electrolytes solution first (GL Filling) and then the upper compartment with the AA admixture (AA Filling). These filled bags are

overwrapped in a secondary packaging including two fast acting oxygen absorbers next to the port systems as well as an oxygen indicator which are to be inserted just before the sterilization process and therefore not yet on the concerned picture hereafter (Overwrapping). After the final heat steam sterilization (Sterilization), eight infusion bags are packaged in a carton including light protection overwraps for administration.

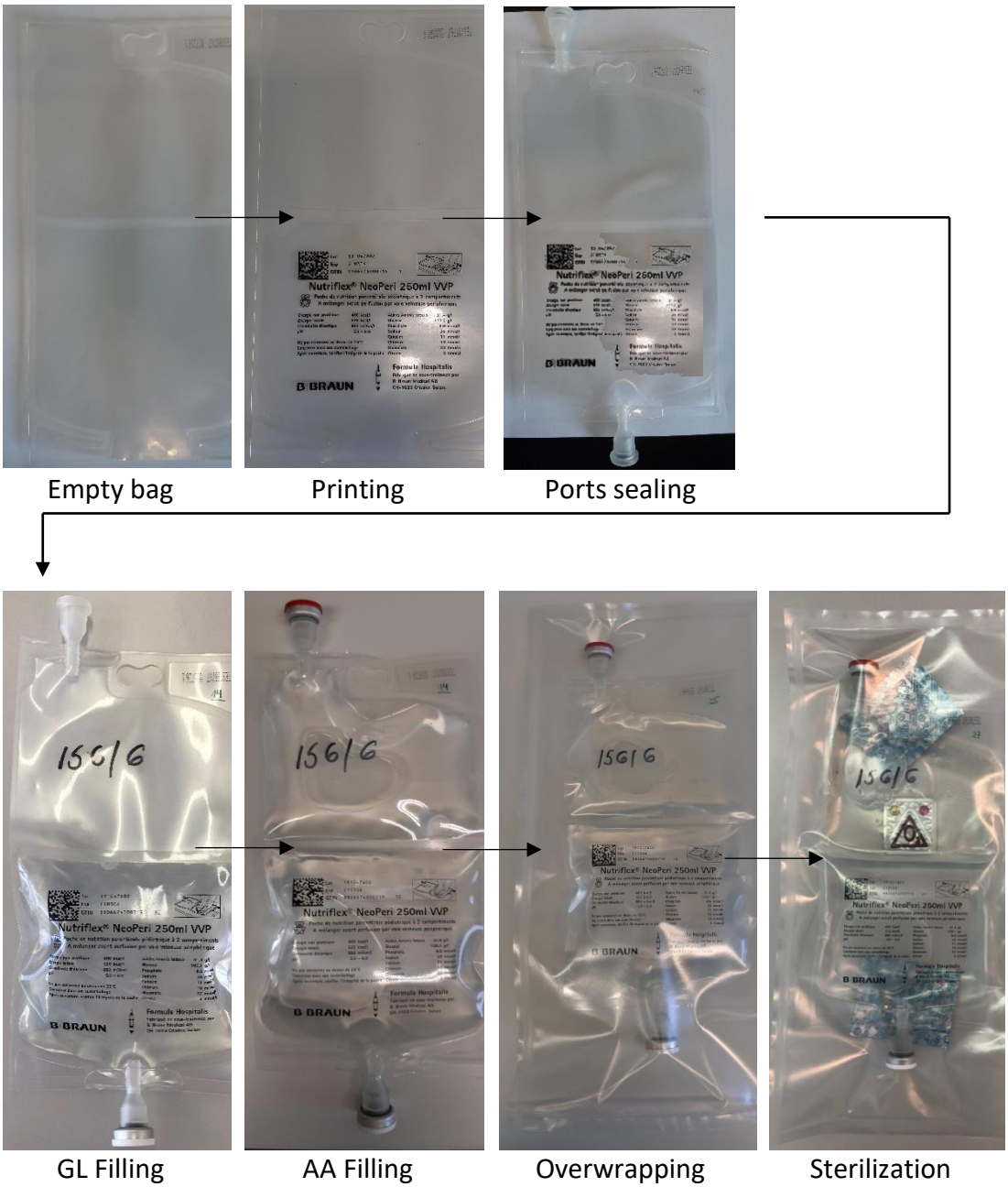


Figure 11: Manufacturing scheme of Nutriflex® NeoPeri

2.6 Implementation as a standard of care on the neonatal ward

The production of this standardized PN solution was initially realized as an aseptic "formula hospitalis" preparation with final sterilizing filtration by the pharmacy in single chamber infusion bags and a stability of 12 weeks under refrigerated conditions (2-8°C). This was a temporary solution to allow an earlier provision of a safe PN for neonatal patients awaiting the delivery of the first industrial batch.

The standardized PN solution has been implemented successfully on the neonatal ward in March 2019. Since then, an average of approximately 90 bags per month have been used. A preliminary evaluation (further discussed in Section 4.3) of the different types of PN administered to neonatal patients showed a reduction of on-ward PN preparations of nearly 80%.

2.6.1 Procedure of implementation

To prepare a good application of the first standardized PN on the neonatal ward at the CHUV, the neonatologists participating in the project since the beginning, established criteria and defined a decision tree aiming to guide all PN prescribing colleagues.

The implementation of the new product as a standard of care was accompanied by several training and information sessions for the whole neonatal site staff, including neonatologists, pediatric physicians and nurses. The product and its specifications were also presented by pharmacists during these sessions to familiarize everybody as good as possible.

The internally used electronic order form (Microsoft® Excel® spreadsheet) was adapted correspondingly to allow correct calculation of the nutritional intakes regarding all medications to be given.

A "new mindset" was and is still necessary when PN is prescribed for neonatal patients. For each neonatal patient, the benefit-risk balance must be evaluated to assure a safe PN treatment with the required nutritional needs.

2.6.2 Safety evaluation

As the neonatal ward of the CHUV never worked with standardized PN before, the physicians caring for patients by means of PN were instructed to pay special attention to adverse effects potentially related to the administration of this new solution.

When administered peripherally, the rather high osmolarity of 883 mOsm/L of the standardized PPN Nutriflex® NeoPeri might be a reason for phlebitis. Another potential complication, the extravasation of the solution, might be caused by the calcium concentration as well as a prolonged duration of PN administration by PVA.

This evaluation is still ongoing and first results will be available in December 2020, one year after starting the provision of the industrially manufactured PN solution Nutriflex® NeoPeri.

Chapter 3

Thesis articles

Article 1

QUALITY AND SAFETY OF PARENTERAL NUTRITION FOR NEWBORN AND PRETERM INFANTS AS AN ON-WARD PREPARATION

OPEN ACCESS

Quality and safety of parenteral nutrition for newborn and preterm infants as an on-ward preparation

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ABSTRACT

Background For newborn and preterm infants, standardised and individual parenteral nutrition (PN) is used. PN preparation is at risk for contamination and dosing errors. The quality of PN is crucial for infants and has a direct impact on their health status and safety.

Purpose The aim of this study is to evaluate the physicochemical and microbial quality of PN for newborn and preterm infants prepared on a neonatal ward.

Methods Sampling of various individual PN prepared by nurses on a neonatal ward was performed. Formulations included maximal four electrolytes, variable dextrose and amino acid concentrations. Depending on the sample volume, up to three quality analyses were performed: (1) test for bacterial endotoxins by kinetic-chromogenic method, (2) sterility according to the European and US Pharmacopoeia, and (3) quantification of electrolytes by capillary electrophoresis and of dextrose by ultraviolet detection after enzymatic reaction of hexokinase. The concentrations obtained were evaluated based on the US and Swiss Pharmacopoeia specifications for compounded preparations and compared to the widened pharmacy specifications.

Results The composition of 86% of the 110 analysed PN prepared by nurses on the neonatal ward corresponded to their medical prescription. 14% were out of the acceptable widened pharmacy ranges. We found no microbial contamination in the samples. All PN were free from endotoxins.

Conclusion Component concentrations of PN prepared on wards by nurses differed frequently and significantly from their medical prescription, and the deviation can be critical depending on the component and its mode of action. The sample size is too small to evaluate the microbial contamination.

INTRODUCTION

All over the world, there are different strategies of managing parenteral nutrition (PN) for newborn and preterm infants. The practices concerning the prescription, preparation, handling and administration of PN vary from one hospital to another.[1] PN standardisation increases the quality of PN and the security of the patients.[2 3] Nevertheless, there is still no common opinion on whether or not to standardise PN for neonatal patients, as individual PN can be more adapted to the patients' needs.[4]

Even though guidelines[5–7] do exist, they are not always followed by prescribers. Frequently, neonatologists define their own limits and procedures (eg, osmolarity).[8] Another reason for non-compliance to these guidelines is the clinical status (eg, unstable blood values) and medical complications (eg, venous access) of patients.[4]

PN is usually prepared at hospital pharmacies as a 'centralized preparation', but at some hospitals PN is still prepared on ward by nurses.[3] This is the case in two Swiss hospitals and in 20% of French hospitals.[9] A European survey performed in 2010 by Bouchoud *et al*[10] showed that 12% of PN are prepared on hospital wards. The requirements for the preparation area, the personnel's training and the quality control regarding intravenous medication preparation including PN vary greatly.[3] Hospital pharmacies mostly follow the current 'EU guidelines to Good Manufacturing Practice' (GMP)[11 12] and are obliged to apply the guidelines of the 'Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-Operation Scheme' (PIC/S)[13] for health system establishments, so they must produce in laminar airflow hoods in cleanrooms with validated operators. Hospital wards do not need to follow these guidelines. They are not always in possession of laminar airflow hoods to assure a clean preparation and they are not equipped and trained to realise quality controls.

Medicine preparation and administration are known to be at risk for nosocomial infection[3 4 14] as PN preparation may include more than 10 raw products and administration is mainly done by central venous access.[3 15] Following the death of three neonatal patients in the hospital of Chambéry in 2014 caused by PN contamination,[16] a national enquiry concerning paediatric PN (PPN) practices has been conducted.[9] The report (2015) included several recommendations to increase the security of these preparations. Beneath others, the IGAS (Inspection Générale des Affaires Sociales) proscribed PN preparation on hospital wards and determined the pharmaceutical responsibility for these preparations.

In 2017, the French-speaking Society for Clinical Nutrition and Metabolism started working on PN standardisation to be applied in France. They propose a limited number of standardised PPN formulations including stability data and storage conditions. Their aim is to decrease risks related to PPN practices in all French hospitals and to harmonise them.

Only few commercialised PN are available for neonatal patients but not used routinely due to patients' varying needs of nutrients and the limited composition flexibility.[15] Standardised PN assures an immediate availability on wards of analysed PN (composition, sterility), minimises the risk of prescribing errors,[17–20] and improves the medical treatment and clinical outcome of the treated inpatients.[3 21]

Check for updates

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Our hospital is one of the few hospitals in Switzerland where PPN is prepared individually on wards and at pharmacies. Our neonatology unit is composed of 40 beds, including 18 in the intensive care unit. For the preparation of injectable medication, this unit is equipped with laminar airflow hoods in a non-classified environment, but pharmaceutical aseptic preparation technique is not applied.

In 2014, more than 8500 individual PN and simple dextrose/amino acid mixtures were administered to our neonatal patients (internal project). The majority of these PN were prepared on the ward by nurses, and only 30% were prepared at the pharmacy conforming to current GMP and PIC/S guidelines.

The aim of this study is to evaluate the quality of PN for newborn and preterm infants prepared by nurses on the neonatal ward of a tertiary university hospital. Electrolytes and dextrose concentrations and microbial and endotoxin contamination are analysed in these PN.

METHODS AND MATERIALS

From July 2015 until April 2016, a sample collection of PN prepared by nurses on our neonatal ward was performed. After the PN administration to the patients for a maximum of 24 hours, the residual PN volume was withdrawn from the bag into sterile syringes using aseptic technique (mask, disinfected gloves, hairnet) under a laminar airflow hood located in a non-classified area for drug preparation on the neonatal ward. All bags and withdrawn samples were inspected for visible particles. Tests for invisible particles (e.g.: $CaPO_4$ precipitate) could not be performed due to the small sample volume.

Due to the limited residual volume of PN solution, we decided to focus on the following assays. Two or three of them were performed depending on the available volume.

1. Endotoxin analysis (<1 mL) to prove their absence by means of kinetic colouration of limulus amoebocyte lysate (LAL). The endotoxin limit being 0.5 UE/mL following the European and US Pharmacopoeia, PhEur (2.6.14) and USP <85>.
2. Sterility analysis (2× ~10 mL) in accordance with the PhEur (2.6.1) and USP <71> by incubation of ~10 mL PN solution in two different culture media for 2 weeks. The fluid thioglycolate medium was incubated at 30°C–35°C and the soybean casein digest medium at 20°C–25°C.
3. Chemical analysis (3–5 mL) to determine the quantity of PN components.[22] The concentration of each electrolyte (K^+, Na^+, Ca^{2+}, Mg^{2+}) was measured by means of a capillary electrophoresis (CE) method, and dextrose was quantified by means of an enzymatic method of hexokinase (HK) followed by ultraviolet detection. Due to the amount of analyses necessary to quantify all amino acids, their concentrations were not determined. The obtained results were compared with the medical prescription of the concerned PN.

All collected samples were stored in a fridge for a minimum of time (maximum of 60 hours) before being analysed in order to maintain the contamination status of the withdrawn solution as bacterial growth is limited at 2°C–8°C.

For the endotoxin analysis, we used the Endosafe nexgen-MCS system. Endosafe cartridges containing chromogenic LAL reagent measure colour intensity directly related to the endotoxin concentration in a sample. For economic reasons, equal volumes (<1 mL) of up to three samples were diluted 1:20 with sterile water and vortexed for being analysed once. A positive control furnished by the manufacturer was analysed in parallel to each sample run.

Table 1 Characteristics of capillary electrophoresis

Capillary	BGB (USA), TSP-050375, uncoated fused silica, 64.5 cm, 50 µm ID
Conductivity of buffer	Approximately 20 µA
Temperature of cassette	25°C
Temperature of sample	25°C
Tampon	100 mM Tris-acetate pH 4.5/acetonitrile (80: 20, V/V)
Voltage	30 kV
Injection	40 mbar × 10 s
Duration of analysis	5 min

For the sterility testing, a maximum of 10 mL of the PN sample (≤10% of the medium solution) was injected in each medium solution of 100 mL. The samples were incubated for 2 weeks at 30°C–35°C in the fluid thioglycolate medium and at 20°C–25°C in the soybean casein digest medium. For each sampling a negative control was performed by injecting 10 mL of an intravenous 5% dextrose solution withdrawn aseptically from a new and disinfected vial. After incubation, the solution was inspected for turbidity. The method was validated by imitating a PN preparation of the neonatal ward, mixing the possible components in usual concentrations. This PN solution (10 mL for each test) was inoculated aseptically with a maximum of 100 colony forming units for each of the following species of micro-organisms in accordance with the PhEur (2.6.1) and USP <71>. For the composition analysis approximately 5–10 mL was necessary. Each sample was analysed once. Conforming to the method of Nussbaumer *et al*, the samples were diluted in distilled water to obtain a final concentration between 1 and 4 mM for K^+ and Na^+ and between 0.5 and 2 mM for Ca^{2+} and Mg^{2+}.[22] Addition of 500 µL of LiCl 50 mM as internal standard to the PN solution and dilution ad 20 mL with sterile water for injection. This mixture (500 µL) is analysed by means of a CE, with the characteristics described in table 1. The chloride salts of K^+, Na^+, Ca^{2+} and Mg^{2+} are identified by their retention time (T_r) in the capillary. The results are calculated as follows: ratio=(area cation/T_r cation) / (area Li^+/T_r Li^+).

The quantification of the different cations is done by Excel. A comparator solution is prepared containing all four electrolytes. The determination of dextrose concentration was performed by means of spectrometry using the enzymatic method of HK.[23] An aliquot of each sample calculated from the medically prescribed concentration of dextrose in the PN is diluted ad 100 mL of water for analyses to contain an anhydrous dextrose concentration of 0.5 mg/mL. Of this dilution, 200 µL is mixed with 1.8 mL of HK reagent (e.g.: Gluco-Quant, Roche). The vortexed mixture must react during 4 min before determining the dextrose concentration by using a spectrophotometer (e.g.: Cary 50) at 340 nm. Three other solutions are prepared and analysed for method validation purpose: a furnished standard and an internal laboratory solution at 0.5 mg/mL anhydrous dextrose and a non-coloured solution (water). Each of these solutions is mixed with the HK reagent for a 4 min reaction.

The results of the concentration analyses were expressed in percentages. The mean concentration values and their SD were calculated based on the pooled results of all analyses of each component.

The specifications for PN conformity were justified following the concentration limits of a minimum of 90% and a maximum of 110% for compounded preparations[24] defined by the USP[25] and the Helvetian Pharmacopoeia (PhHelv).[26]

Table 2 Conformity specifications

Component	K^+	Na^+	Ca^{2+}	Mg^{2+}	Dextrose
Pharmacopoeia concentration limits for compounded preparations (%)	90–110	90–110	90–110	90–110	90–110
Internal acceptable concentration limits of pharmacy (%)	85–110	85–115	81–120	81–120	85–120

Internal acceptable concentration ranges have been introduced for the analysed PN components by the pharmacy's laboratory based on the variable influences on the results, like preparation and analysis inaccuracy. The mode of action, potential risk factor and impact of the different components on the clinical outcome of the treated patients were also taken into account. The specifications for PN acceptability were justified following these widened concentration limits. A comparison of the conformity specifications is shown in table 2.

RESULTS

Within 10 months, a total of 127 samples were collected.

Endotoxin testing with a limit of 0.5 UE/mL was performed on all retrieved samples and showed no positive result. All 127 PN prepared by nurses on the neonatal ward were free of endotoxins.

Sterility testing showed no microbial contamination in both media solutions for all 92 analysed PN.

The composition analyses (K^+, Na^+, Ca^{2+}, Mg^{2+}, dextrose) were performed on 110 PN bags, which contained one to five analysed components. Only few PN contained all electrolytes, as the treated patients either were born recently and the blood values were not available yet, or they just needed intravenous hydration to complete the enteral feeding. The quantification of electrolytes represented 118 analyses and dextrose concentration was measured 110 times. None of the analysed PN contained additional or missing prescribed components.

The medical prescription of each component equates to 100% and represents the theoretical value. The measured concentrations are expressed in percentage and represent the real value. The mean real value and the SD of the obtained results were calculated. The number of analyses performed for each component, their concentration range, mean concentration, SD and the median concentration are shown in table 3.

Following the USP and PhHelv concentration limits (90%–110%) for compounded preparations, 48 (21.1%) component analyses representing 37 (33.6%) prepared PN did not conform to their medical prescription, as shown in table 4.

Following the widened concentration limits established by our hospital's pharmacy, 18 (7.9%) component analyses representing 15 (13.6%) of the 110 tested PN were not acceptable for administration from a pharmaceutical point of view. These PN would not have been dispensed by the pharmacy for administration due to the risk of overdose or underdosage.

Table 3 Component analyses and results

Component	Parental nutrition analysed (n)	Range measured (%)	Mean value (%)	±SD (%)	Median value (%)
K^+	34	75–113	97.2	±8.0	97.0
Na^+	14	83–119	99.4	±11.7	97.5
Ca^{2+}	66	58–164	97.5	±13.7	99.0
Mg^{2+}	4	92–102	95.8	±4.5	94.5
Dextrose	110	60–137	96.3	±8.6	97.5

Table 4 Concentration limits and conformity

Component	Pharmacopoeia concentration limits (%)	Preparations out of pharmacopoeia limits, n/n_{tot} (%)	Pharmacy concentration limits (%)	Preparations out of pharmacy limits, n/n_{tot} (%)
K^+	90–110	6/34 (17.6)	85–110	4/34 (11.8)
Na^+	90–110	7/14 (50.0)	85–115	2/14 (14.3)
Ca^{2+}	90–110	20/66 (30.3)	81–120	4/66 (6.1)
Mg^{2+}	90–110	0/4 (0)	81–120	0/4 (0)
Dextrose	90–110	15/110 (13.6)	85–120	8/110 (7.3)

DISCUSSION

The chemical analysis of PN prepared on the neonatal ward by nurses revealed a lack of quality of these preparations for high-risk patients. The quality issue concerned the preparation accuracy, which has a direct impact on the concentration and dosage of the different prescribed PN components. Almost 14% of the 110 tested PN would not have been delivered from the pharmacy to the site for administration because of non-conformity following the widened internal concentration limits. With more than 6000 PN prepared by nurses on the ward in 2014, 14% equate to the administration of more than 840 non-conforming PN bags. Concentrations of the two mostly used components (Ca^{2+}, dextrose) reached from 58% to 164% of the medically prescribed dosage. This confirms the issue of prescription and preparation errors mentioned by Krzyzaniak and Bajorek[17] and Hermanspann *et al*[19]. In comparison, in 2015, only 5 PN out of 2646 prepared at the pharmacy did not pass the chemical analyses of the components and had to be prepared a second time.

Fortunately, the results of the analyses on microbial and endotoxin contamination were negative. No PN contamination was found, which is described as one of the major risks of PN preparations in the publications of Puntis[15] and White[3]. However, as shown by Stucki *et al*,[27] microbial contamination in intravenous medication prepared on wards occurs in around 0.2%. Therefore, our sample size of 92 analysed PN as well as the volume analysed are too small to show contamination. Stucki *et al*'s work confirms the need for a minimum of 500 analyses to detect at least one contaminated preparation. Beneath the 6000 PN prepared by nurses on the ward in 2014, 12 (0.2%) might have been contaminated. To control the cleanroom environment for aseptic preparations, at every working session, the pharmacy performs microbial settle plates and glove prints on culture media plates, which are not done on the ward. In 2015, 14 out of 771 (1.8%) settle plates and 21 out of 1578 (1.3%) glove prints were contaminated. Only with knowledge of non-conformities corrective actions can be undertaken throughout the yearly qualification of each operator by preparing PN with culture media.

As shown in our project, up to 14% of PN prepared on the ward do not conform to their medical prescription and result in an inappropriate treatment of patients. This percentage is probably even more important when analysing all PN preparations realised on the ward. These concentration deviations might be harmful for the patient depending on the component and its mode of action. Concentrations of dextrose, which is the major source of energy and essential for neonatal inpatients, out of the target values may lead to hypoglycaemia or hyperglycaemia and a diminished or exceeded metabolism of amino acids. Calcium is the most abundant electrolyte in human bodies. Most of it

is directly incorporated in skeletal bones. Magnesium is also important for the development of the skeletal bones. In a long term, a deficit of calcium and magnesium may lead to rickets, fractures, bone mineralisation troubles and reduction of growth. Hypokalaemia or hyperkalaemia and hyponatraemia and hypernatraemia may lead to heart rhythm disturbances as potassium and sodium maintain the resting potential of the nerve, muscles and heart cells. A study performed in Western Europe by Bouchoud *et al*[10] in 2007 showed that 12% of PPN are prepared by nurses on the ward without being analysed for composition before administration. This signifies that approximately 2% of all administered PN to paediatric patients may lead to adverse events.

A weakness of our study is the small sample size due to organisational difficulties. Resulting from the relatively high stress level on our neonatal ward, nurses did not always remember to keep the used PN for sampling and hence often discarded them. An alternative to collecting more samples could have been visiting the other, second Swiss hospital where PN is prepared on the neonatal ward, which was a logistical problem due to the necessary sample storage in a fridge before testing.

The recommendations of the American Society of Parenteral and Enteral Nutrition (ASPEN) are already encouraging a standardised process for PN management, but to keep the flexibility to treat patients individually when necessary.[7] These recommendations should be taken as starting point to unify knowledge and experiences to harmonise PN management in hospitals treating newborn and preterm infants. In France, after the death of three neonatal patients in 2014 as a result of contaminated PN, the inspection authority IGAS prohibited all PN preparations by nurses on the hospitals' wards. Additionally, they delegated all responsibility concerning PN preparation exclusively to pharmacists. The approach of the IGAS to centralise PN preparation in hospital pharmacies and to propose national standardised PN formulations is rigid but offers several advantages in quality and organisational questions, and especially increases the security of the patients.

Our project's results suggest two interesting future research projects. One could be a cause identification of the described composition deviations. The reasons for this issue observed in our research were multiple. They included errors in prescription transcription, calculation, dilution, raw material, label preparation and so on. The percentage of these different errors was not evaluated in our study because of a missing traceability of the different steps and the focus on the quality of PN. Another could be an impact evaluation of the administration of non-conforming PN on the treated infants. If performed prospectively, this might cause an ethical problem due to its potential harmfulness to the patients. In our study, the sampling was performed retrospectively and therefore did neither raise ethical concerns nor put patients knowingly at risk.

CONCLUSION

The management of PN preparation for newborn and preterm infants still varies in the entire world, but also within one country.[1 3] The results of this work show that there is a lack of quality of PN preparations when prepared on the ward by nurses. Additionally, these quality issues—component identity and concentration, and microbial and endotoxin contamination—cannot be identified on the ward due to the absence of facilities. Our study emphasises the recommendations published by ASPEN, IGAS and other associations. The preparation of individual PN needs to be centralised at hospital pharmacies where they are produced in cleanrooms in ISO 5 hoods. Standardised PN solutions need to be taken into consideration as they increase quality and security.

The current methods applied on neonatal wards represent major risk factors for the clinical status of patients.[3 4 15] The centralisation and standardisation of PN preparation for newborn and especially preterm infants increase the quality of delivered PN and the security of patients, and reduce errors related to prescription, preparation and administration. These points can only be guaranteed by means of a routinely performed quality control of the PN before administration to vulnerable patients.

What this paper adds

What is already known on this subject

- There is complexity in parenteral nutrition (PN) preparation.
- Neonatal patients are at risk for infections and malnutrition; therefore, the quality of PN preparation is crucial for these patients and has a direct impact on their health status and safety.
- Microbial and chemical quality of PN prepared on wards are not controlled or documented.

What this study adds

- PN prepared on wards by nurses does not conform to their medical prescription.
- On wards, PN is prepared under non-aseptic conditions.

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Article 2

PARENTERAL NUTRITION POCESS MANAGEMENT FOR NEWBORN AND PRETERM INFANTS – A PRELIMINARY RISK ANALYSIS

Therapeutics and Clinical Risk Management

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ORIGINAL RESEARCH

Parenteral Nutrition Process Management for Newborn and Preterm Infants – A Preliminary Risk Analysis

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Background: There are variable practices in the management of the parenteral nutrition (PN) process in hospitals having a neonatal intensive care unit (NICU). In our hospital, PN is prepared partially on the neonatal ward by nurses but also at the central pharmacy by trained pharmacy technicians. A previous study showed a concentration non-conformity of 34% of on-ward PN preparations potentially resulting in under- or overfeeding of the patients.

Objective: The objectives were to perform preliminary risk analyses (PRA) in preparation for our hospital's transition to universal central pharmacy PN compounding.

Methods: A working group including pharmacists, neonatologists, nurses, and pharmacy technicians performed two PRA. The risks of 9 management steps of the PN process were identified, evaluated, and quoted. A comparison of the number of risks and their criticality index (CI) was conducted.

Results: A total of 36 and 39 risks were identified for PN preparation in the NICU and the pharmacy, respectively. For the NICU, ten risks (28%) had an "acceptable" CI, 15 risks (42%) were "under control" and eleven (31%) were defined as "non-acceptable". For the pharmacy, 14 risks (36%) had an "acceptable" CI, 19 risks (49%) were "under control" and six (15%) were defined as "non-acceptable". Risks directly related to the preparation process, including the steps preparation hood, PN preparation and analytical quality control, represented a cumulated CI of 145 for eleven NICU-risks vs 108 for twelve pharmacy risks (−26%). The implementation of immediate improvement measures, eg, an electronic prescription form, reduces the total CI by 5.7% and 2.2% for the NICU and the pharmacy, respectively.

Conclusion: This PRA highlighted the safety differences between PN preparation in the NICU vs the pharmacy at our institution, and facilitated our moving forward with a process change that should improve the care of our neonatal patients. Nevertheless, long-term improvement measures have to be implemented to further reduce risks related to the PN management process.

Keywords: parenteral nutrition, drug compounding, risk assessment, standardization, neonatology, preterm infants

Introduction

Parenteral nutrition is a crucial part of the initial nutritional support provided for critical preterm or term neonates. Worldwide, different ways of compounding parenteral nutrition (PN) for neonates are applied.[1,2] High-risk PN preparation steps are usually managed by the hospital's pharmacy in collaboration with the neonatal service. In some cases, the whole process, including the compounding of

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PN, is organized by the neonatal service. Both strategies include risks and constraints.

In our hospital, PN is either prepared at the central pharmacy by trained pharmacy technicians or on the neonatal ward by nurses without any involvement of the pharmacy staff. The place where PN is prepared depends on the physician's evaluation concerning the emergency to start or adapt nutrition, which may be urgent in critical situations like very preterm infants, (very) low birth weight, metabolic disorder, or critical illness.

In 2015, the Inspection générale des affaires sociales (IGAS) of France published the report of a nationwide survey on PN treatment.[3] This survey was performed following the death of five babies in the hospital of Chambery, France in 2012 caused by the administration of contaminated PN. The IGAS came to the decision to totally prohibit on-ward preparations for PN treatment and to delegate the whole responsibility to pharmacists. Due to this report and the different PN preparation practices at our hospital, our interest was directed on the situation of safety of PN treatment at our site.

As PN preparation is known to be one of the most critical steps within its management[4] and a major risk factor for healthcare-associated infections in neonates,[2] its centralization at the pharmacy is recommended.[5] The planned centralization at our site will include the take-over of PN compounding still performed on-ward during the week (Monday to Friday) in a first step and during weekends by the pharmacy emergency service in a second step.

ISO9001 certified, the hospital pharmacy has a quality management system to assure pharmaceutical services. Conforming to the guidelines Q9[6] of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) as well as GMP[7] of the European Commission's EudraLex on quality risk management, a risk assessment of this hybrid model was performed.

This study aims to compare the management processes of the two PN preparing sites (NICU and pharmacy) by means of a preliminary risk analysis (PRA) and describes our center's evaluation of the risks and benefits associated with transitioning towards universal pharmacy PN preparation for our NICU.

Methods and Materials

Process Description

At our university hospital, PN containing glucose and amino acids with or without electrolytes was prepared at the hospital pharmacy as well as on the ward of the NICU.

During opening hours, for medically stable patients, PN is generally prepared at our hospital pharmacy. The process being time consuming, meaning that the prescription order must be placed at noon at the latest for a delivery of the individual PN at 5:00 pm, nurses have to prepare PN on the ward for emergency situations or unstable patients. Furthermore, as the pharmacy does not prepare PN during the night, weekend or holiday, NICU nurses have also to prepare them for new admissions during these shifts.

The neonatal ward also wished for maintaining the flexibility and knowledge of preparing PN on-ward when a preparation at the pharmacy is too time-critical.

At our hospital, no data is available for infections related to contaminated PN or electrolyte disturbances related to under- or over-concentrated PN. This lack of data is due to the unusual process of analyzing PN treatment as root cause for these cases. What is known, is that 34% of PN prepared on the ward is likely to not conform to the medical prescription in a range from 90% to 110%.[8]

Pharmacy

At the moment of this study, each prescription was written manually on a PN order form which was edited and validated by neonatologists and pharmacists. This form – only used for PN preparation at the pharmacy – was faxed to the pharmacy where technicians transcribed the PN order in a validated Excel sheet interfaced with the compounding automate BAXA EM 2400.[9] Before the PN preparation, each prescription was double-checked and validated by a pharmacist.

The pharmacy, qualified by the national authority Swissmedic, followed Ph. Helv. GMP guidelines and was therefore working with a GMP class A Horizontal Laminar Airflow Hood (HLAH), placed in a GMP class B cleanroom, operating with trained and qualified personnel.[10] The high-risk PN preparation was completed by means of an automate (BAXA EM 2400) and analytical controls for quantitative determination of critical components (glucose, Na^+, K^+, Ca^{2+}, Mg^{2+}) were performed on each final product before pharmaceutical release of the PN preparation.[11,12]

Neonatal Intensive Care Unit

When PN was prepared by nurses on the ward, another order form was used than the validated one for the pharmacy. This form served as instruction for the preparation as well as for transcription of ingredients on the label to be

affixed on the prepared PN syringe or bag. New nurses were trained by reference nurses for PN treatment on the handling, preparation and administration of PN. No regular requalification was mandatory.

PN was prepared manually by nurses following the handwritten medical prescription in a non-classified and non-qualified HLAH placed inside the NICU pharmacy. The transcribed labels as well as the volume withdrawn and raw solution of critical components like potassium (as hydrochloride or phosphate salt) were double-checked by a second nurse or physician. For all non-critical ingredients, the preparation of PN was performed and auto controlled by a single nurse only. No analytical controls were carried out for these on-ward preparations before administration to the vulnerable patients.

Even with a huge staff of nurses, PN preparation represented a time-consuming task and reduced the time for patients' care.

Preliminary Risk Analysis

Since several years, risk analyses are performed in the field of pharmaceutical science for quality management purposes based on the methods applied initially in the aeronautic and military domains.[13] Different kinds of risk assessment methods exist, of which the failure modes and effects analysis (FMEA), the failure modes, effects, and criticality analysis (FMECA), and the preliminary risk analysis (PRA) are the most known and applied.[14] The FMEA and FMECA are supposed to assess risks in a current, well-established setting and to define if an action plan to secure this setting must be implemented.[15] The PRA is performed where a project is planned and the aim is to prevent risks when carrying out the project and to secure the new setting.[16] It is also possible to perform a PRA on several domains of risks as far as they concern the same activity.[17]

As the project of centralization of PN compounding at the pharmacy is planned, the PRA method was chosen to analyze existing and potential future risks associated to the whole PN management process from prescription based on patients' laboratory values until administration of the individual PN. To define the urgency for centralizing and the need of an action plan awaiting the completion of this project, the PRA was performed for the two PN preparing sites to compare the risk levels. Results of this risk assessment will help to better conduct and legitimate the project and to implement the planned measures.[18]

Composition of the Working Group

The working group of nine participants comprised the chief pharmacist, the clinical pharmacist for the neonatology department, the responsible pharmacist for PN preparation, a pharmacy technician, a PhD student (pharmacist) moderating the PRA, the neonatologist responsible for PN, the chief nurse of neonatology department, the chief nurse of the unit, and a clinical nurse.

Definition of the PN Management Process Steps

Following a brainstorming with all members of the working group during the first meeting, nine principal topics have been defined to describe the different steps of the PN process:

1. Medical prescription
2. Transcription of medical prescription
3. Primary material
4. Preparation hood
5. PN preparation
6. Analytical quality control
7. PN administration
8. Documentation and traceability
9. Laboratory values

All nine process steps were discussed separately and one after the other to identify all possible risks related to the tasks composing the concerned process step.

Risk Quotation

All identified risks were quoted separately by consensus of all working group members during the second meeting. This was done once for the risks identified for the neonatal department and once for the pharmacy.

The assessment of each risk was performed by identifying the level of severity (S) as shown in Table 1 and the level of probability (P) as shown in Table 2.[17] The effects of severity levels as well as the frequency of probability levels have been defined in advance of the PRA by the working group following internal examples (eg, previous risk assessments) and experiences.

The evaluation of all risks was done by consensus regarding clinical and pharmaceutical aspects of each risk independent on its nature.

Risk Evaluation

The criticality index (CI) of each risk was calculated by multiplying the quoted severity and probability. The acceptability of risks was defined using the Pareto

Table 1 Level of Severity (S)

Quotation	Severity	Effect
1	Minor	Negligible effect on PN quality and patient's safety
2	Significant	Impact on PN quality but not on patient's safety
3	Major	Impact on PN quality and on patient's safety
4	Critical	Reversible impact on patient
5	Catastrophic	Irreversible impact on patient

Table 2 Level of Probability (P)

Quotation	Probability	Frequency
1	Extremely improbable	1x every 5 years
2	Very rare	1x per year
3	Rare	4x per year, every 3 months
4	Probable	1x per month, every month
5	Very probable	1x per week or more

principle or 80/20 rule,[19] meaning that about 20% of most critical risks will need to be focused on to reach the most positive outcome of the whole assessment. Therefore, as shown in Table 3, risks with a CI of 1–6 (green) were defined as "acceptable", CI of 7–14 (yellow) were risks classified as "under control", and "non-acceptable" risks had a CI of 15–25 (red).

Following this risk assessment for the two preparation sites, the third meeting served to focus on all "non-acceptable" risks of CI $\geq$ 15. For some of these risks, planned measures for improvement already existed. In this instance, a second assessment was performed exactly like the first one including the calculation of a hypothetical CI. The aim still being the identification of residual risks and the need of a corrective and preventive action plan (CAPA plan). For the remaining risks without an already planned improvement project, measures were proposed but the corresponding risks were not quoted again.

Results

1st PRA

In total, 75 risks have been identified, 36 of which were for the whole PN management process at the NICU and 39 risks at the pharmacy.

The number of risks identified for the two preparation sites are listed in Table 4. Several risks were the same for the two sites but sometimes differed in calculated criticality. Risks in common were for example related to the medical prescription what has to be done for both scenarios and what presents the same risks for the final product and the patient. An example for risks not in common are related to the PN preparation as this step is quite different between the two sites.

The CI distribution of all identified risks is shown in the following Table 5.

Comparison of Main Process Differences

The PN management steps that significantly differ between the NICU and the pharmacy include steps n° 4. Preparation hood, n° 5. PN preparation and n° 6. Analytical quality control, for which the differences of CI are shown in Table 6.

Focused Risks

The working group focused on all "non-acceptable" risks (CI = 15–25) following the Pareto principle. Therefore, the attention was brought to 11 vs 6 risks for the NICU and

Table 3 Criticality Index (CI) and Level of Acceptability (Green: "Acceptable"; Yellow: "Under Control"; Red: "Non-Acceptable")

Probability (1–5)					
Very probable	5	10	15	20	25
Probable	4	8	12	16	20
Rare	3	6	9	12	15
Very rare	2	4	6	8	10
Extremely improbable	1	2	3	4	5
	Minor	Significant	Major	Critical	Catastrophic
					Severity (1–5)

Table 4 Number of Risks for Each of the 9 Management Steps for Parenteral Nutrition

Management Step	Neonatal Unit	In Common	Pharmacy
1. Medical prescription	7	7	7
2. Transcription of medical prescription	2	2	3
3. Primary material	5	5	5
4. Preparation hood	2	1	1
5. PN preparation	8	5	9
6. Analytical quality control	1	0	2
7. PN administration	8	8	9
8. Documentation and traceability	2	2	2
9. Laboratory values	1	1	1
Total of risks	36	31	39

Table 5 Distribution of Criticality Index (CI) of Identified Risks

Criticality Index CI	Risk Acceptability	Neonatal Unit	Pharmacy
1–6 (green)	Acceptable	10 (28%)	14 (36%)
7–14 (yellow)	Under control	15 (42%)	19 (49%)
15–25 (red)	Non-acceptable	11 (31%)	6 (15%)
Total of risks		36	39
Cumulated CI		386	360
Mean CI		10.7	9.2
Median CI		11	8

the pharmacy, respectively. Two of the 17 focused risks were identified as equal for both preparation sites (risks related to PN administration), meaning that 15 different risks of CI $\geq$ 15 were further discussed (Table 7).

2nd PRA

Table 7 details the risks the working group focused on to define measures to reduce their criticality. The hypothetic risk assessment was also performed on these risks following a brainstorming and an evaluation of the potential influence of the planned and immediately possible measures as detailed hereafter.

Medical Prescription

An improvement measure from the NICU planned to be implemented shortly after the second PRA was a prescription form (Excel sheet) including an extensive calculation base for all kinds of medication (oral, intravenous, subcutaneous, etc.) to be administered to their patients including PN. This quasi-electronic prescription form is the evolution of a preformatted medical order sheet that has been introduced previously for medication prescription except for PN.[20] It represents an important step towards a complete electronic prescription, a so-called computerized provider order entry (CPOE) system. This measure hypothetically allows to reduce three risks related to the prescription step as shown in Table 8.

PN Preparation

Another improvement measure within the preparation step that hypothetically allows to reduce the CI for risk 5.5. "Non-respect of procedures and auto-control" is the revision and

Table 6 Comparison of Criticality Index (CI) Sums of Differing Management Process Steps

Management Step	Criticality Index Neonatal Unit	Criticality Index Pharmacy
4. Preparation hood	20 for 2 risks	5 for 1 risk
5. PN Preparation	110 for 8 risks	79 for 9 risks
6. Analytical quality control	15 for 1 risk	24 for 2 risks
Cumulated CI	145	108
Total of risks	11	12
Mean CI	13.2	9
Median CI	15	9

Table 7 Details of "Non-Acceptable" Risks with Criticality Index (CI) of 15 and Higher for the Neonatal Unit (NICU) and the Pharmacy (PHA)

Management Step	Risk Cause	Consequence	Risk for NICU or PHA
1. Medical prescription	1. False patient identity	False prescription/dose	PHA
	2. Copied prescription	False prescription/dose	PHA
	3. Prescription environment	False prescription/delay	NICU
	4. Calculation error due to manual prescription	False dose	NICU
4. Preparation hood	1. Non-respect of hygienic procedures	Contamination (bacteria, germs)	NICU
5. PN preparation	1. False labeling	False product, false dose	PHA
	2. Defective facilities (automatic compounding)	Manual preparation	PHA
	3. Preparation environment	Low quality and delay of final product	NICU
	4. False assembling (infusion line, filter, pump)	Contamination, leakage, underfeeding	NICU
	5. Non-respect of procedures, auto-control	False final product (composition, dose)	NICU
	6. Imprecisions, inattention	False dose	NICU
	7. Manual preparation	False dose	NICU
6. Analytical quality control	1. Nonexistence of analytical facilities	Lack of control, false dose	NICU
7. PN administration	1. False infusion rate	Over- or underfeeding	Both
	2. Non-respect of hygienic procedures	Contamination (bacteria, germs)	Both
Total of risks/cumulated CI		Neonatal Unit Pharmacy	11 risks/CI=187 6 risks/CI=102

Table 8 Hypothetical Reduction of Criticality Index (CI) After Implementation of Planned Improvement Measures for the Pharmacy (PHARM) and the Neonatal Intensive Care Unit (NICU)

Risk	Improvement Measure	Criticality Index Reduction	Reason for Improvement
Risk 1.2. "Copied prescription"	Informatic prescription form	20 → 12 (PHARM)	Prescription can be compared more easily to previous ones
Risk 1.3. "Prescription environment"	Informatic prescription form	15 → 9 (NICU)	Calculation will be performed automatically, and prescription ranges help to optimally compose PN
Risk 1.4. "Calculation error due to manual prescription"	Informatic prescription form	20 → 12 (NICU)	Calculation will be performed automatically
Risk 5.5. "Non-respect of procedures and auto-control"	Standard operating procedures	16 → 12 (NICU)	
Risk 7.1. "False infusion rate"	Sensitizing on importance of infusion rate	16 → 12 (NICU)	

application of standard operating procedures (SOP) for the PN preparation on-ward as well as new notices and information for the auto- and double-control.

PN Administration

Finally, the risk 7.1. "False infusion rate" of the administration step might be reduced by sensitizing the nurses to the importance of the correctness of the infusion rate adjustment and to fulfill the requested double-control.

For the NICU, the second PRA reduced the number of "non-acceptable" risks from 11 to 7 and their cumulated CI from 187 to 165.

For the pharmacy, the number of "non-acceptable" risks were reduced from 6 to 5 and the cumulated CI for these risks sank from 102 to 94.

With these short-term improvements, the total CI can be reduced from 386 to 364 (−5.7%) and from 360 to 352 (−2.2%) for the NICU and the pharmacy, respectively.

Long-Term Improvement Measures

Despite the above described as immediately possible and planned improvement measures, the working group defined long-term measures to improve the 15 risks rated with a CI of 15 and higher prior to the centralization of PN preparation at the pharmacy.

In total, six different measures are supposed to have a positive impact on 14 of the 15 risks. Only one risk (6.1.) will probably remain unchanged (CI = 15) as no measure for improvement is envisaged, because the NICU will not be able to perform analytical quality controls on-ward.

Hereafter, the six proposed improvement measures are described:

Computerized Provider Order Entry (CPOE) System

A CPOE system including calculation base and recommendation ranges, interfaced with an automated preparation tool will permit to secure the prescription step and to improve all related risks (1.1.-1.4.). The risk "false labeling" which is related to the preparation step (5.1.) will also be reduced by generating labels automatically and scanning the barcode of these labels to start production.

Training and Standardized Protocols

During our PRA, the working group identified that training and standardized protocols will have an impact on the risks 4.1., 5.4., and 5.5. These measures, already in place for the PN process, need to be revised and harmonized.

High-Visibility Vest

The high-visibility vest, to be worn on the NICU during preparation and administration of PN, might reduce risks related to these two PN management steps (5.3., 5.6. and 7.2.). This will allow neonatal staff handling PN to be easily identifiable and to not be disturbed when wearing this vest.

Standardized Nutritional Solutions

Standardized nutritional solutions like standard glucose dilutions or standardized PN infusion bags will drastically reduce the risk related to the PN preparation on the ward (5.7.).

Backup Preparation Tool

The risk related to defective facilities for automated compounding at the pharmacy (5.2.) will be minimized by acquisition of a backup preparation tool (BAXA EM 2400).

New Infusion Pumps

New infusion pumps precisely programmable and clearly showing the infusion rate will have a huge impact on this risk related to the administration step (7.1.).

Discussion

Even though several risk assessments have been performed on the parenteral nutrition (PN) processes,[15,16,21–24] the novelty of our work is the comparison in risks of two sites within the same hospital that are involved in the process of PN for neonatal patients.

The preliminary risk analyses (PRA) performed on the management process of PN for the neonatal intensive care unit (NICU) and the pharmacy showed that most of the risks are related to the medical prescription, the PN preparation and the PN administration. Corresponding statements were recently reported by Palmero et al for our NICU.[25] The AMELIORE study conducted by Boulé et al identified the same process steps as principal sources of risks by performing a failure mode, effect, and criticality analysis (FMECA).[26] Our results also correlate with those of Villafranca et al who conducted a failure mode and effects analysis (FMEA) on the neonatal PN process from the perspective of the hospital's pharmacy.[27]

Bonnabry et al were the first to perform a FMECA on PN order and compounding to compare the handwritten prescription with a computerized provider order entry (CPOE) system as well as the manual with the semi-automatic compounding technique.[15] They repeated their risk assessment on the CPOE system some years later to generally improve the high-risk prescription process of all kinds of medications including PN.[22] In our study, the implementation of a CPOE system including patient data, nutritional recommendations (ESPGHAN/ESPEN/ESPR guidelines), calculation base and error alerts as well as an interface with the automated preparation tool (BAXA EM 2400)[9] will be the most important measure to improve several identified risks.

The NICU who plans to implement a quasi-electronic prescription form (Excel sheet), is already aware of some deficiencies within their process and is facing them actively while awaiting the centralization of PN preparation at the pharmacy. A real CPOE system for PN prescription will be a common tool for NICU and pharmacy and is known to improve the prescription and transcription process.[28]

Another study described that PN preparation error rates at pharmacies decreased from 37% to 22% when the process was partly automated. Most of these errors included wrong dose (>3%) of components of PN solution or observed omission.[4] We also showed in a previous article that 34% of PN prepared manually by nurses on the ward did not conform to their medical prescription (Pharmacopoeia concentration limits for compounded preparations: 90–110%) and concentration of ingredients ranged from 58% to 164% based on their target value (=100%).[8]

Following our assessments, measures to standardize the PN preparation process were proposed to face these risks as recommended by the American Society for Parenteral and Enteral Nutrition ASPEN.[29] As immediate action until the complete take-over of compounding at the pharmacy, standardized PN preparation protocols for the NICU must be reviewed and applied.

At the same time, a standard ready-to-use PN solution is in development to furnish immediate nutritional treatment for newborn term and preterm infants as recommended by the ESPGHAN guidelines[30] and practiced all over France.[31] The supply with a standardized PN solution for neonatal patients offers a safe, high-quality, and ready-to-use alternative to individually compounded PN and therefore reduces the number of PN needing to be prepared under unsafe conditions.

PN administration safety can principally be influenced by the neonatal caregivers by the simple measure of patient-focused (high-visibility vest) control of correspondence of medication and medical prescription, infusion bag assembly and pump data entry following standard administration procedures as suggested in the ASPEN guidelines. They also recommend to "purchase infusion pumps with capacity to reduce errors due to incorrect programming" which was contemplated at the moment of our risk assessments.[32]

Most of the risks quoted with a criticality index (CI) of 15 and higher ("non-acceptable") potentially resulted either in microbial contamination of the product or in a false dose of the different components meaning under- or overfeeding of the patient. The consequences of false doses can be eliminated by analyzing the composition (glucose, Na^+, K^+, Ca^{2+}, Mg^{2+}) of the compounded PN before administration as already performed on PN prepared by the pharmacy.[33,34] Potential contamination might also be analyzed by means of endotoxin testing on pharmacy compounded PN.

Our risk assessments show that the whole process is slightly safer when the pharmacy is involved in the management of parenteral nutrition for patients treated on the neonatal ward (total CI of 386 for the NICU vs 360 for the pharmacy). For the whole process, 36 vs 39 risks have been identified for the NICU and the pharmacy, respectively. The number of risks being higher for the pharmacy can be explained by the multiple steps and interventions on PN before, during and after its preparation process including control of the medical prescription by pharmacists as well as the analytical quality of the final product. The compliance to GMP guidelines being mandatory for the pharmacy but not for the NICU is another reason for the difference in number of risks and their quotation.

When having a look at the management process steps that are independent between the two sites, a clear difference in safety can be observed. The steps concerned are the preparation hood, PN preparation and analytical quality control. The CI of the two sites differ from 145 to 108 for the NICU and the pharmacy, respectively. This means a risk is 26% less likely to occur for the vulnerable patients when PN is prepared at the pharmacy in controlled conditions (class A hood in cleanroom class B) with an automated compounding system by trained pharmacy technicians and with analytical quality controls to prove conformity of the PN preparation with the prescription.

Risks concerning the steps of primary material, documentation and traceability, and laboratory values are more or less the same for both sites, but do not necessarily have the same occurrence (probability) or the same impact on the system or the patients (severity). All these risks were quoted with a CI <15 and therefore not considered as critical but as "acceptable" or risks "under control". They have not been further discussed.

The residual high-quoted risks, like hygienic issues causing contamination of the final product or of the infusion line and the venous access, might persist even after centralization of PN preparation. These kinds of risks are well known and are difficult to avoid completely,[35] but measures to control and minimize their probability are in place (NICU: training of site personnel; pharmacy: in process contamination control, annual control of aseptic working technique, endotoxin testing).

Our study showed the need of standardized computer assisted procedures for the PN management process to secure these high-risk products for vulnerable patients. This standardization is independent of the place of PN preparation. When PN needs to be prepared by nurses on the ward due to an emergency, this PRA demonstrated that the patients are not unnecessarily at risk. Thus the PN preparation at the pharmacy should be preferred as there are more measures in place to guarantee the conformity of PN preparation to its medical prescription as well as the microbial quality.

Still, procedures of both sites (NICU and pharmacy) must be improved to further secure the whole multiple-step PN management process whilst awaiting the centralization of PN preparation at the pharmacy.

All risk assessments are mainly limited by their subjectivity of defining and judging risks related to well-known processes. Therefore, the working group is supposed to represent a wide spectrum of professions and, in consequence, should be sufficiently large. Professionals not knowing the process add important inputs to describe and evaluate possible risks. The lack of this input causes a small limitation of our study since all working group members who participated in our PRAs knew the processes because they work with PN routinely. Nonetheless, the expertise of the working group was of great value to the study.

Another limitation of our study is that we did not distinguish risks where one or the other service does not have influence on, as for example the PN administration which can be influenced by the NICU-staff only. This fact lead to a sort of mix-up of the CI of the two PN preparing sites.

Conclusion

Our PRA demonstrated a potential reduction of 26% in the risk of PN preparation errors when all PN are prepared centrally at the pharmacy, compared to the existing hybrid model of NICU and pharmacy preparation when focusing on the main differing steps (preparation hood, PN preparation, analytical quality control). Although we considered NICU preparation as beneficial for offering a rapid and adequately safe PN preparation process, the potential safety improvements we identified in our PRA outweigh these benefits for this vulnerable population. All working group members as well as the heads of the concerned departments (NICU and pharmacy) agreed that this hybrid model is no longer the state of the art and must be revised rapidly.

Ethics Statements

No review or approval was required for this research by an institutional review board or ethics committee as no intervention on humans was performed and no patient data was analyzed and examined.

Disclosure

The authors report no conflicts of interest in this work.

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Article 3

STABILITY OF N-ACETYLCYSTEINE (NAC) IN STANDARDIZED PEDIATRIC PARENTERAL NUTRITION AND EVALUATION OF N,N-DIACETYLCYSTINE (DAC) FORMATION

nutrients

MDPI

Article

Stability of *N*-Acetylcysteine (NAC) in Standardized Pediatric Parenteral Nutrition and Evaluation of *N*,*N*-Diacetylcystine (DAC) Formation

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Abstract: The ESPGHAN/ESPEN/ESPR-Guidelines on pediatric parenteral nutrition (PPN) recommend the administration of the semiessential amino acid (AA) cysteine to preterm neonates due to their biochemical immaturity resulting in an inability to sufficiently synthetize endogenous cysteine. The soluble precursor *N*-acetylcysteine (NAC) is easily converted into bioavailable cysteine. Its dimer *N*,*N*-diacetylcystine (DAC) is almost unconvertable to cysteine when given intravenously resulting in a diminished bioavailability of cysteine. This study aims to understand the triggers and oxidation process of NAC to DAC to evaluate possibilities of reducing DAC formation in standardized PPN. Therefore, different air volumes (21% O_2) were injected into the AA compartment of a standardized dual-chamber PPN. O_2 concentrations were measured in the AA solution and the headspaces of the primary and secondary packaging. NAC and DAC concentrations were analyzed simultaneously. The analysis showed that O_2 is principally delivered from the primary headspace. NAC oxidation exclusively delivers DAC, depending on the O_2 amount in the solution and the headspaces. The reaction of NAC to DAC being containable by limiting the O_2 concentration, the primary headspace must be minimized during manufacturing, and oxygen absorbers must be added into the secondary packaging for a long-term storage of semipermeable containers.

Keywords: parenteral nutrition; pediatrics; amino acids; cysteine; *N*-acetylcysteine; *N*,*N*-diacetylcystine

1. Introduction

The new ESPGHAN/ESPEN/ESPR Guidelines on pediatric parenteral nutrition (PPN) published in 2018 state "Standard parenteral nutrition (PN) solutions should generally be used over individualized PN solutions in the majority of pediatric and newborn patients, including very low birth weight (VLBW) premature infants" [1] (p. 2). Beneath other recommendations concerning the constitution of standardized and individual PPN, these guidelines, as well as the previous ones from 2005, recommend the administration of bioavailable cysteine to preterm neonates [2].

Normally, in healthy adults and infants as well as term newborns, cysteine is synthetized from the essential amino acid (AA) methionine, which serves as donor of sulfur (S-donor), and the

nonessential AA serine, which serves as donor of carbon fragments (C-donor). The recommendation for supplementation of cysteine is given due to the biochemical and metabolic immaturity of the premature patients resulting in an inability to sufficiently synthetize endogenous cysteine [3]. Therefore, the so-called semiessential or conditionally essential AA cysteine becomes an essential one [2,4].

Cysteine, having a good solubility, can be administrated intravenously as its hydrochloride salt (cysteine-HCl). The problem is its short stability in solution. Consequently, it should be added to the PPN at the end of administration [2]. Nevertheless, some pharmaceutical companies use cysteine-HCl for their pediatric AA solutions, such as Primene® 10% and Numeta® Neo (Baxter International, Deerfield, IL, USA) or TrophAmine® 10% (B. Braun Medical Inc., Bethlehem, PA, USA), containing 1.89 g/L, 1.13 g/L, and 0.16 g/L of cysteine, respectively. The cysteine concentrations contained in the products of Baxter are quite higher than the recommendations of the ESPGHAN/ESPEN/ESPR Guidelines.

Much more stable in solution but sparingly soluble is the oxidized form cystine, which is composed of two molecules of cysteine. Due to its poor solubility, it is unusable for PPN [2].

A soluble precursor is *N*-acetylcysteine (NAC), the acetylated form of cysteine [5]. In vivo, it is easily converted into bioavailable cysteine after catalysis by an acylase [6,7]. Therefore, cysteine is commonly supplemented by means of administration of a PPN for preterm infants containing an amino acids (AA) mixture including 0.7 g/L of NAC (equivalent to 0.52 g/L of cysteine) (Aminoven® Infant 10%, Fresenius Kabi AG, Germany; Aminoplasmal® Paed 10%, B. Braun Medical AG, Germany; Aminopaed® 10%, Baxter International, Deerfield, IL, USA).

Unfortunately, the bioavailability of NAC is only 50% [8]. "The 2006 Cochrane analysis indicated that Plasma levels of cysteine were significantly increased by cysteine supplementation but not by *N*-acetylcysteine supplementation." [3] (p. 3).

Another disadvantage of the precursor NAC is that it reacts in the presence of oxygen (O_2) during the sterilization process and upon storage to its dimer *N*,*N*-diacetylcystine (DAC). DAC is soluble and more stable in PPN solution than NAC. However, it is converted 30 times slower into cysteine when given intravenously than after oral administration where DAC is reduced by cystine-reductase during its passage through the small intestine [6].

Safety, pharmacology, and toxicology studies on DAC in animals revealed no findings that would prevent further clinical evaluation of DAC in animals or humans [9,10]. No other publication treated the topic of DAC safety and/or toxicity.

In order to conform to the ESPGHAN/ESPEN/ESPR recommendation for the use of standardized PPN [1], a working group of pharmacists, neonatologists, and an industrial partner was established. This collaboration aims to develop a standardized PPN as a dual-chamber infusion bag for newborn and preterm infants. Today, such PPN are mostly compounded individually from several sterile raw solutions (AA, glucose, and different electrolytes) in single-chamber containers representing a preparation at risk with short stability. Only a few standardized PPN exist for newborn and especially for preterm infants, like Numeta® Neo (Baxter International, Bethlehem, PA, USA) or Pediaven® AP-HP (Fresenius Kabi AG, Bad Homburg, Germany) for the French market only. However, these formulations do not always conform to therapeutic protocols of all hospitals. Therefore, this standardized PPN represents an alternative solution for nutritional care for newborn and premature infants with a high product quality, long stability, and easy storage conditions.

The development process of this new standardized PPN includes, amongst others, stability testing of all components (AA, glucose, and electrolytes) during storage in the final packaging where analysis of the different AA components showed an increasing presence of DAC, the degradation product of NAC. In conclusion, a decreasing concentration of NAC can also be observed, meaning a diminished availability of cysteine for the treatment of the concerned patients.

Due to the fact that no safety and toxicity issues are reported for DAC, the degradation limit for active ingredients of 10% was fixed for the product specification, meaning a maximum of 10% of NAC may be lost through oxidation to DAC.

For these reasons, the aim of this study was to find and understand triggers of the chemical reaction of NAC to DAC in PPN to reduce and limit its formation.

2. Materials and Methods

For a long-term stability of the final product, a 250 mL dual-chamber infusion bag was used to separate amino acids from glucose and electrolytes to avoid the Maillard reaction of AA in presence of glucose [11]. The material used for the primary packaging was a B. Braun multilayer coextruded film with barrier properties for oxygen. The secondary packaging consisted of the high gas barrier material silicon dioxide SiOx foil made of cast polypropylene outer and inner layers and a SiOx-coated polyethylene terephthalate middle layer.

The AA compartments of 16 dual-chamber infusion bags were filled with 79 mL of oxygen-saturated AA solution (Aminoplasmal® Paed 10%, B. Braun Medical AG, Melsungen, Germany). As analyses are focused on the AA compartment, the glucose and electrolyte compartments were filled with 171 mL of water for injection. The filling volumes of the dual-chamber infusion bag corresponded to the developed final product, meaning 79 mL of AA solution and 171 mL of a mixture containing glucose and electrolytes. By means of a syringe, residual air from the filling process was withdrawn from the 16 compartments of AA. Afterwards, exact volumes of air (21% of O_2) were reinjected. The amounts of O_2 added in the primary headspace (HS1) of the AA compartments were 2 mL = 18.7 µmol (n = 6 infusion bags), 8 mL = 75.0 µmol (n = 8 infusion bags), and 16 mL = 150.0 µmol (n = 2 infusion bags). Before the terminal sterilization process ($F_0 \geq 15$ min, 121 °C), all bags were packaged in the secondary packaging without or with two fast-acting oxygen absorbers SS-500BXMBC with air absorption capacity greater than 500 mL from Mitsubishi ($n_{2mL} = 3$, $n_{8mL} = 4$, and $n_{16mL} = 1$ for each packaging configuration). Most of the headspace volume being cumulated at the port systems, the first oxygen absorber was placed next to the AA port system and the second one next to the port system of the glucose and electrolyte compartment as shown in Figure 1.

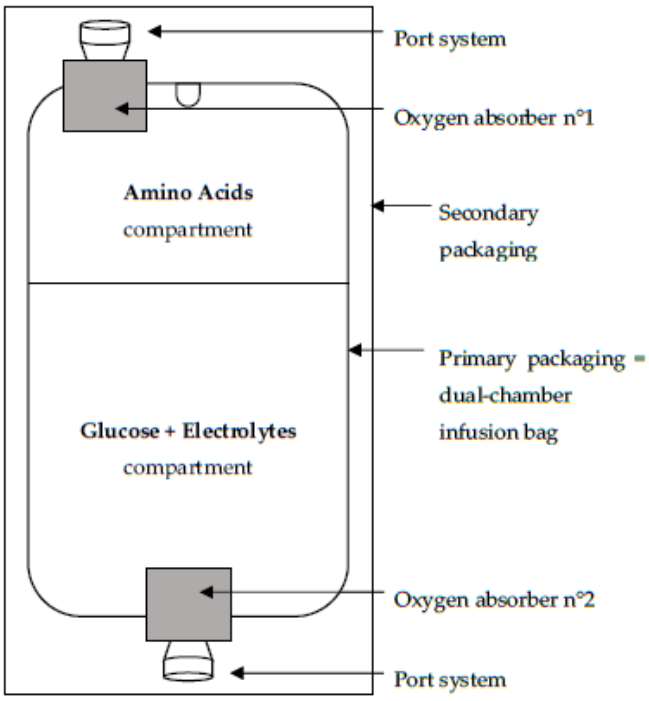

Figure 1. Schematic representation of the packaged dual-chamber infusion bag.

The NAC and DAC concentrations were measured by high performance liquid chromatography (HPLC) based on the method described in the European Pharmacopeia [7] and validated by B. Braun Medical for their AA solution Aminoplasmal® Paed 10%.

A variance analysis was determined in accordance with ISO 5725 from three series of six analyses by varying operating conditions (day, analyst, and instrument). The analyses were performed using a homogeneous amino acid mixture sample spiked at around 15 mg/L of DAC in the analytical solution.

The intermediate precision variance, corresponding to the sum of repeatability variance and intergroup variance, was calculated with NeoLiCy® software, version 2.1. Expressed as relative standard deviation, the value of intermediate precision was expected to be <5%.

The same is applicable for the standard deviation of the beta expectation tolerance interval when using the same set of values. According to ISO 21748, this value can be associated to the standard measurement uncertainty. With the experimental design, the number of degrees of freedom (ν) was calculated using the Welch–Satterthwaite approximation.

This validated method was carried out with an Atlantis™ dC_{18} column (4.6 mm × 150 mm, 3 µm). A solution of ammonium formate at 5 mM was used as mobile phase, the flow rate was fixed at 0.7 mL/min and the oven temperature was set to 40 °C. Precisely, 5 µL of the prepared sample solution was injected. Detection was performed by a UV-detector at 210 nm wavelength. All 16 packaged infusion bags were stored at room temperature and protected from light. For each configuration—without or with two oxygen absorbers—8 bags were tested (n_{2mL} = 3, n_{8mL} = 4, and n_{16mL} = 1). The NAC and DAC concentrations as well as the O_2 amount were analyzed once at each of the seven time points on day 0–before and right after injection of air and at 2.5 h, on days 7, 13, 46, and 95.

Fifteen concentration analyses of the abovementioned bags were randomly chosen to perform a mass balance analysis for NAC and DAC aiming to show any other source of DAC formation or any other degradation product of NAC. Minimum one of each bag configuration concerning storage time (7, 13, or 46 days), air volume (2, 8, and 16 mL), and presence of oxygen absorber (with or without) were chosen to represent all possibilities of final product conception. The results were illustrated as molar percentage of the initial NAC amount present in the AA solution.

For the HPLC analyses, five NAC standard solutions of different concentrations (75, 90, 100, 110, and 120 mg/L) and one reference solution of 100 mg/L were prepared from a stock solution of 1000 mg/L. Five DAC standard solutions (8, 20, 30, 45, and 60 mg/L) and one reference solution of 30 mg/L were prepared from a stock solution of 100 mg/L. Each of these standard solutions were measured twice for the concentration determination of the component to be analyzed (NAC or DAC).

The O_2 concentration was measured by means of an optic fiber probe (type NTH-PSt7, PreSens) to be inserted with a needle or an optic patch sensor (type SP-PSt8-YAU, PreSens) attached to the inner surface of the primary and secondary packaging. Data were captured and converted using the oxygen-meter Microx 4 from PreSens. The O_2 concentration was measured in the headspace of the secondary packaging, the headspace of the AA compartment, and directly in the AA solution. This analysis was performed once on all 16 infusion bags and at each of the seven time points (on day 0–before and right after injection and at 2.5 h, on days 7, 13, 46, and 95). The focus was put on the development of O_2 and DAC concentrations within the HS1 and the solution. Data including error bars were presented in graphs for the different configurations.

The O_2 consumption was calculated as a ratio of the O_2 and DAC concentrations throughout the storage duration. The correlation of DAC formation from NAC was evaluated by comparing the concentrations along the test duration.

3. Results

The validation of the HPLC method was conform to the fixed specifications. Considering the preparation factor of the method (dilution 2:1), the precision of the method is characterized for levels of DAC at about 0.030 g/L in the AA solution. The Welch–Satterthwaite approximation was 2.84, which gives a coverage factor of 3.4 (Student *t* quantile for ν with 95% of confidence). With this coverage factor, the expended uncertainty can be assumed to be 14.6%.

The concentration analysis performed for NAC and DAC showed that DAC is exclusively delivered by oxidation of NAC. At the same time, this finding also implies that NAC only degrades to DAC and no other side products. The corresponding mass balance resulted in 100% ± 1% for all different storage and manipulation configurations as shown in Figure 2.

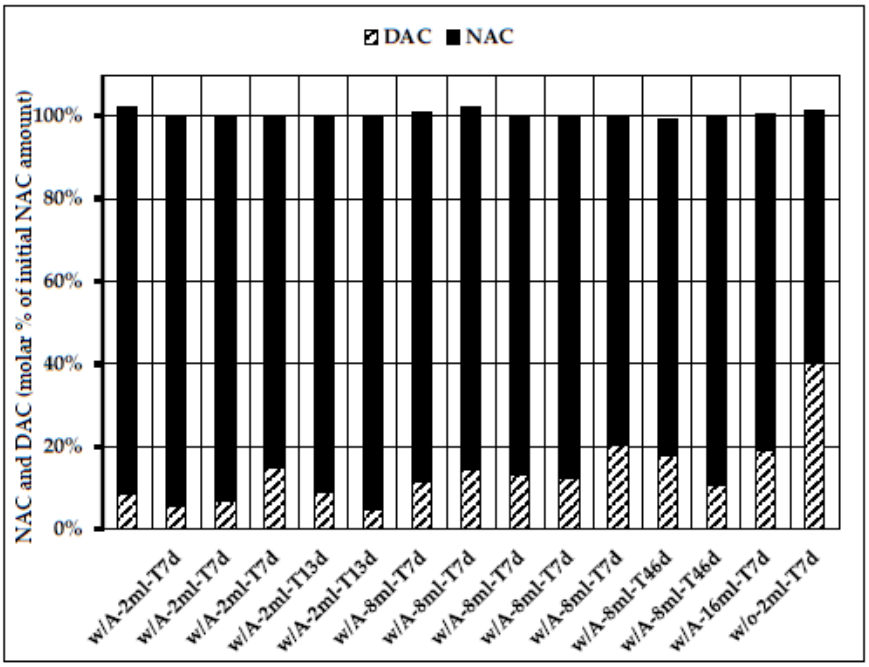

Figure 2. Mass balance for *N*-acetylcysteine (NAC) consumption and *N*,*N*-diacetylcystine (DAC) formation for different storage and manipulation configurations (w/A = with oxygen absorber, w/o = without oxygen absorber, XmL = air volume (21% O_2), and TYd = days of storage duration).

Additionally, as shown in Figure 3, DAC formation was directly correlated to the O_2 consumption (R^2 = 0.9972) and the slope value obtained indicated that 1 molecule of O_2 forms 1.2 molecules of DAC.

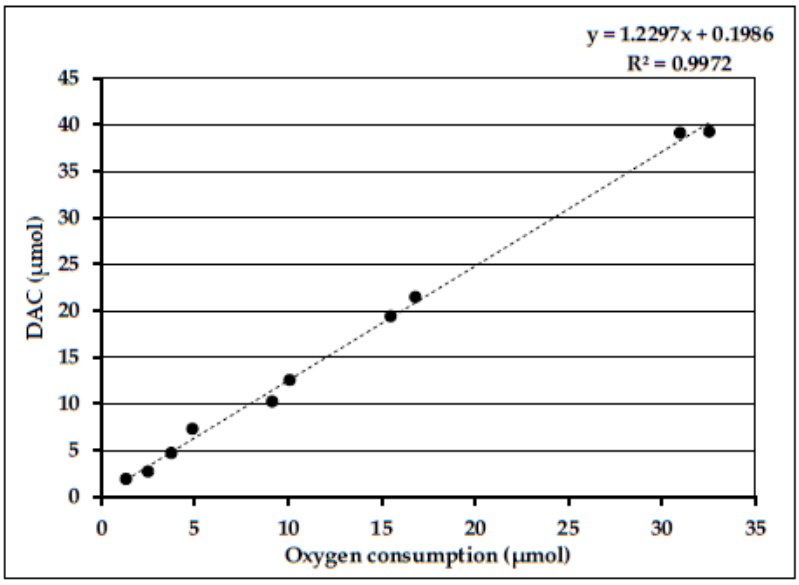

Figure 3. *N*,*N*-diacetylcystine (DAC) formation in correlation with oxygen consumption.

The analysis also showed that HS1 represents the most important contributor of O_2 available for the chemical reaction of NAC to DAC. Logically, the higher the volume of HS1, the higher its O_2 amount. Contrary to this result, the available O_2 amount within the solution remains unchanged

(22.2 µmol) because of a dynamic equilibrium between HS1 and solution. The total available O_2 amount depending on different HS1 volumes are illustrated in Figure 4.

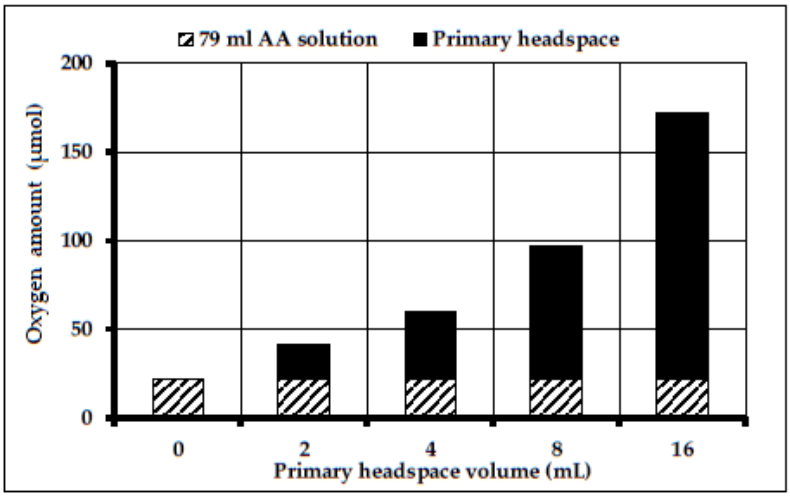

Figure 4. Total oxygen amount within the filled amino acid (AA) compartment depending on the primary headspace (HS1) volume.

In the absence of oxygen absorbers in the secondary packaging, the headspaces of the primary (HS1) and secondary packaging (HS2) are saturated with O_2 (~21%). Therefore, the oxidation of NAC to DAC takes place without limit and the DAC concentration raises constantly during the study duration. Due to the dynamic equilibrium between solution and HS1, even after 95 days of storage duration, there is still enough O_2 available for the formation of DAC from NAC, meaning that this reaction will last until exhaustion of DAC or O_2. Figure 5 shows that the O_2 concentrations do not decrease significantly during storage (light symbols) even though DAC concentration raises constantly amongst time (solid symbols). No difference in DAC formation quantity or velocity was observed between the different air volumes (2, 8, and 16 mL) within HS1 (three superposed DAC concentration curves). Error bars are too small to be visible. There was no need to perform other statistical comparison.

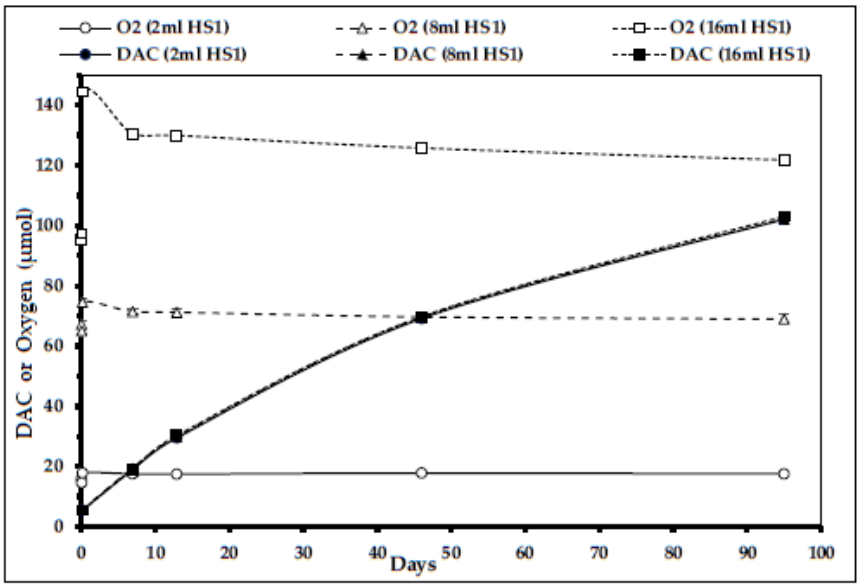

Figure 5. *N*,*N*-diacetylcystine (DAC) concentration depending on primary headspace (HS1) volume in the absence of oxygen absorbers (n_{2mL} = 3, n_{8mL} = 4, and n_{16mL} = 1) (curves for DAC (2 mL HS1), DAC (8 mL HS1), and DAC (16 mL HS1) are superposed).

The results of the same analysis performed in the presence of two oxygen absorbers showed a considerable decrease of O_2 concentration (30% in 2.5 h) within the primary packaging headspace (HS1) of the AA compartment, which limits DAC formation considerably (Figure 6). Error bars were present for every curve except for the 16 mL HS1 as only one bag was analyzed. The precision of results was acceptable, error bars never overlapped, so no other statistical testing was performed.

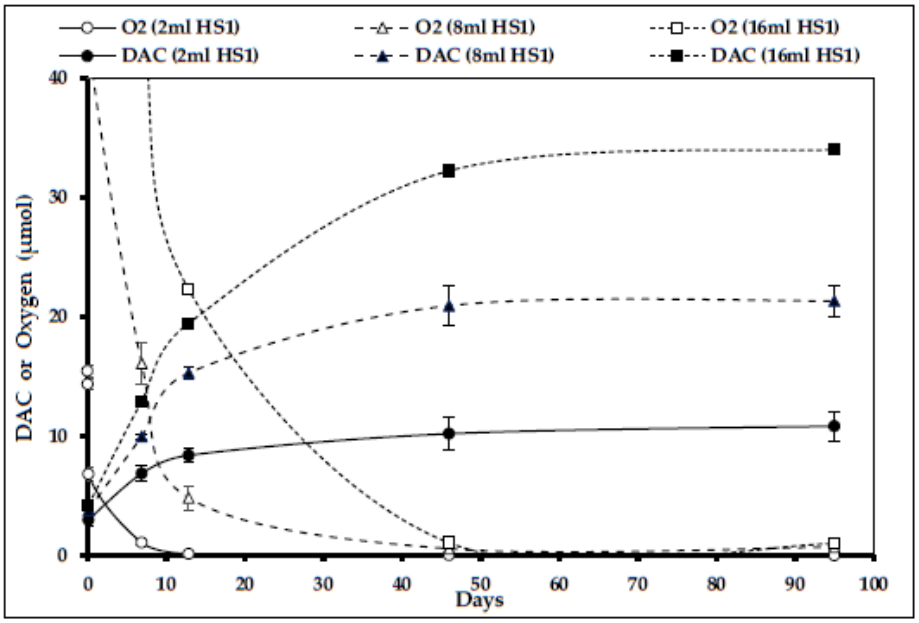

Figure 6. *N*,*N*-diacetylcystine (DAC) concentration depending on primary headspace (HS1) volume in the presence of oxygen absorbers (n_{2mL} = 3, n_{8mL} = 4, and n_{16mL} = 1).

The data showed that once all available O_2 molecules reacted with NAC, no further DAC was formed. The higher the initial O_2 concentration, the longer it took to reach the DAC plateau.

With one oxygen absorber having an oxygen absorption capacity of 500 mL, the O_2 concentration reduction after 24 h was 38 ± 3% (95% confidence intervals 31; 45%) and 42 ± 5% (95% confidence intervals 35; 49%) for dual-chamber infusion bags packaged with one and two oxygen absorbers, respectively (Figure 7). No difference was observed between the dual-chamber infusion bags packaged with one or two oxygen absorbers, $p = 0.28$.

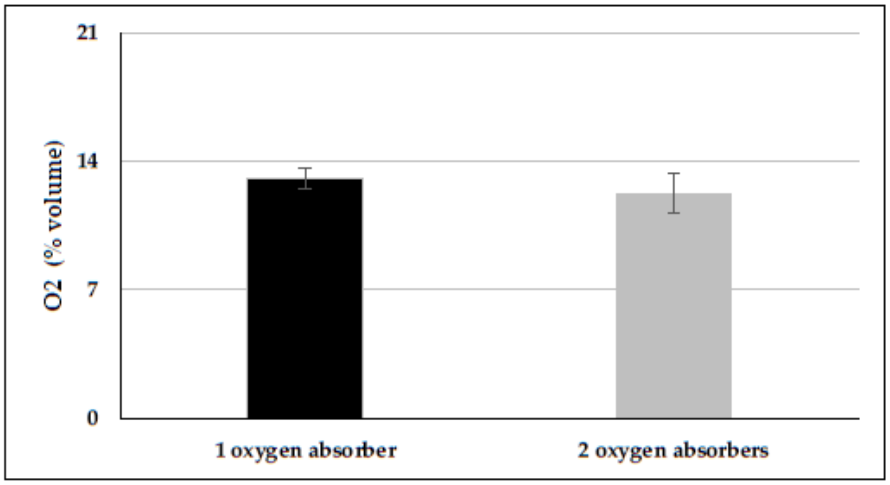

Figure 7. Residual oxygen amount within the primary headspace HS1 after 24 h, starting at 21% of oxygen.

4. Discussion

The ESPGHAN/ESPEN/ESPR Guidelines on pediatric parenteral nutrition (PPN) published in 2018 recommend the use of standardized PN for pediatric patients including newborn and very low birth weight premature (VLBW) infants instead of individual PPN [1]. This recommendation considers individual compounded PN to be high-risk preparations due to its high amount of different ingredients and the accompanying multiple manipulation steps. The ESPGHAN/ESPEN/ESPR Guidelines also recommend the administration of the semiessential amino acid cysteine [2,4] to newborn and preterm infants, but they do not mention the best source to be used (cysteine-HCl or *N*-acetylcysteine) [2,3]. Due to its good solubility and stability in PPN and its ability to be easily transformed into cysteine [6,8], most amino acid mixtures for pediatric patients contain *N*-acetylcysteine (NAC) although its bioavailability is of only 50% [3].

It is known that NAC is oxidized to its dimer *N*,*N*-diacetylcystine (DAC) [6,7]. When given orally, this reaction is easily reversible as DAC is reduced to NAC and further to cysteine during its passage through the small intestine. This is the missing step when NAC is administered intravenously [6,8]. Therefore, oxidized NAC stays unavailable for cysteine delivery in PPN.

The problem with the degradation product DAC in PPN seems to be quite a new one. No publication was found despite the study of Böhler from 1988 [6] treating the product DAC in parenteral nutrition. As DAC is tested in mice for oral treatment of atherosclerosis, for instance, there is no evidence of toxicity or nonsecurity of DAC in animals [9], but this has never been subject to research in humans.

The development process of a standardized PPN in a dual-chamber infusion bag for the first days of life of a newborn and/or premature infant revealed the problem of oxidation of NAC to DAC, which has never been described as having any toxicological consequences on the treated patients [10]. Nevertheless, profound examinations of this chemical reaction have been conducted.

The results of this study show that DAC is exclusively generated from NAC in presence of oxygen (O_2). The mass balance of NAC and DAC concentrations being 100% excluded the formation of other degradation products of NAC. These facts lead to the conclusion that the focus on available O_2 is the most important point to limit this reaction.

We also demonstrated that the headspace of the primary packaging of the dual-chamber infusion bag is the most important source of O_2. Therefore, this volume of potential O_2 donor needs to be reduced to a minimum. A headspace volume of 2–8 mL for the AA compartment volume of 79 mL seems to be the most adapted and feasible way to limit the oxidation of NAC to DAC. Additionally, one oxygen absorber must be placed in the secondary packaging next to the port system of the AA compartment, where most of the air is cumulated. This helps to maximally reduce the O_2 concentration within the primary headspace and the AA solution. Indeed, our bags have a multilayer coextruded film which is still little permeable for oxygen. A second oxygen absorber may be placed next to the port system of the glucose and electrolyte compartment to help reduce the O_2 concentration within this compartment as well.

For standardized parenteral nutrition solutions as well as for individual compounded PN, the total amount of O_2 present in the system should generally be kept at a minimum level to prevent any possible oxidation. Our study's results suggest two interesting future research projects. First, finding of the definition of an acceptable limit for the transformation of NAC to DAC, knowing that the available concentration of the semiessential amino acid cysteine reduces at the same time. It is not known whether the recommended concentration of cysteine for PPN published by the ESPGHAN/ESPEN/ESPR Guidelines [2] takes this reaction into account. Second, carrying out a retrospective pharmacovigilance study to evaluate the impact of this chemical reaction, its resulting diminished bioavailability of cysteine, as well as the presence of DAC in the newborn and preterm infants.

5. Conclusions

There is no official recommendation of which source to use for the supplementation of cysteine in standardized or individual pediatric parenteral nutrition for newborns including very low birth weight preterm infants. The main precursor of cysteine used is *N*-acetylcysteine. It is soluble in PPN solutions, but easily oxidized to its dimer *N,N*-diacetylcystine in the presence of oxygen. To limit this reaction and the resulting diminished bioavailability of cysteine in PPN solutions, the concentration of oxygen needs to be reduced to a minimum in the primary headspace of the amino acid solution compartment of a dual-chamber infusion bag. This can be achieved by limiting the headspace volume in the amino acid compartment and by adding performant oxygen absorbers into the secondary packaging.

For our developed standardized PPN, based on the results obtained, we decided to reduce the air volume of the primary headspaces to a minimum (<8 mL) during the semi-automated filling process. To reduce the residual oxygen amount in the system and the resulting *N,N*-diacetylcystine formation, the filled dual-chamber infusion bag is packaged as soon as possible in the secondary packaging including two oxygen absorbers placed next to the port systems of the two compartments (Figure 1). Fast-acting oxygen absorbers that do not need to be activated by means of sterilization are used so that the absorption of oxygen can start directly after the packaging process. An indicator of integrity of the secondary packaging is also included for proof of sterility and functionality of the absorbers.

Author Contributions: Conceptualization, H.S.; data curation, H.S.; formal analysis, I.S. and H.S.; investigation, I.S.; methodology, I.S. and H.S.; project administration, V.A. and F.S.; resources, V.A.; supervision, V.A., L.B., and F.S.; validation, V.A., L.B., and F.S.; visualization, I.S. and H.S.; writing–original draft, I.S.; writing—review and editing, P.B., L.B., and F.S. All authors have read and agreed to the published version of the manuscript.

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Chapter 4

Scientific evaluation and groundwork

4.1 National survey

In 2016, two questionnaires in French and German accompanied by a cover letter (Appendix 2) were developed and addressed via SurveyMonkey® to neonatologists and pharmacists working in Swiss hospitals having either a neonatal service or a drug preparing pharmacy. The survey was conducted during four months from March to June.

The hospitals were chosen by means of the 2016 members list of the Swiss Society of Neonatology (SSN). The neonatal ward and the pharmacy of the CHUV hospital were included in the survey. In total, 19 neonatologists and 16 pharmacists of 19 different hospitals in Switzerland were contacted. Amongst the 19 contacted hospitals there were five Swiss university hospitals (Basel, Bern, Geneva, Lausanne, Zurich), as well as eight cantonal hospitals (Aarau, Baden, Grisons, Fribourg, Lucerne, Munsterlingen, St. Gallen, Winterthur) and six regional or pediatric hospitals (Biel, Morges, Neuchâtel, Sion and St. Gallen, Zurich).

The questionnaire addressed to neonatologists (Appendix 3) concerned inter alia the number, composition and administration type (venous access) of PN given to newborn term and preterm infants, the number of beds available for neonatal patients, the neonatologists' opinions regarding the standardization of PN and their willingness to change habits in case of availability of standard PN for their neonatal patients.

The pharmacists' questionnaire (Appendix 4) treated the points of how (manually, automatically) PN is prepared, stored and transported as well as the quantity and the type of PN (binary, ternary) prepared and also the quality controls performed on each preparation.

A descriptive analysis was performed of the data and answers received.

4.1.1 Answers to the questionnaires

The survey showed that there are variable strategies for prescription, preparation, conservation, transportation, analysis and administration of PN within Switzerland.

A total of 28 (80 %) of the 35 sent questionnaires were returned. From the 17 out of 19 different hospitals that participated at the survey, 14 responses were obtained for each, neonatologists (74 %) and pharmacists (88 %).

The 14 responding neonatal wards comprise a total of 276 beds, ranging from five to 40, for newborn term and preterm infants. Within the year preceding this national survey, more than 15'000 PN have been administered to neonatal patients conforming to the partial information given by neonatologists. In four hospitals, no neonatal patients are treated with PN and therefore no responses were obtained for evaluation from those neonatologists and pharmacists.

Five hospitals are only administering standardized PN to their neonatal patients, six neonatologists indicated that they use exclusively individual ones and two centers work with both types of PN.

Every hospital has its own directives concerning the venous line used for PN administration. The use of peripheral and central venous access amounts to 48% and 52% respectively.

The 14 responding pharmacies prepared a total of over 23'000 PN within the year preceding this survey. Four of them indicated that they prepare binary PN (glucose/AA/electrolytes without lipids), only one pharmacy is preparing exclusively ternary PN (glucose/AA/electrolytes/lipids included) and four others prepare both types, binary and ternary PN. Five hospital pharmacies do not prepare PN at all.

The organization, including PN compounding, quality control and storage, depends on the quantity of PN prepared. In seven pharmacies, standardized PN are prepared with a stability varying from eight days to six months at refrigerated conditions (2-8°C). One pharmacy stores its standardized PN for maximally three months in a freezer (-18°C). Six out of nine pharmacies prepare PN on demand on the day of administration, except for weekends, with a stability of three to eight days under refrigerated conditions (2-8°C).

Only two of the nine responding pharmacies already work with a CPOE system. All others still use manual prescription sent by fax. The methods to control prescriptions and to

translate them into preparation worksheets are different at all nine pharmacies. Some use commercial programs, some use customized programs and most of them use individually preformatted Microsoft® Excel® spreadsheets that are most commonly validated by means of double check. Two pharmacies do not have any program and therefore double check the computation of the ingredients.

Three hospital pharmacies prepare their PN manually, four use an automated compounding device and two are using both systems depending on the kind of PN to be prepared.

Quality controls of PN are not part of the routine. Those who use an automated compounding device have a gravimetric control during and at the end of the production. The composition of the prepared PN is controlled in four pharmacies. Microbiological tests are already performed in six pharmacies, but endotoxins are tested in only one of them. It can be observed that the quality aspect is getting more and more important and those who do not have controls yet are planning to install them shortly.

The survey treated the question of whether the neonatologists and pharmacists are interested in a commercially available standardized PN for neonatal patients. The reply was mostly positive as well as the willingness to change their habits related to PN treatment and administration in consequence.

4.1.2 Conclusion for an industrial production

Since the participation in the survey was quite high, the general interest in this topic is recognizable. The answers to the questionnaires demonstrate that pharmacists as well as neonatologists would appreciate well-formulated, standardized pediatric PN solutions for neonatal patients. The availability of commercial PN allows to reduce practice disparities, recommendation discrepancies, nutritional diversities and especially medication errors related to PN treatment.

Most of the survey's participants are interested in standardized PN and are willing to change habits and applied practices to secure their processes.

For the thesis and the industrial partner, this knowledge was encouraging and significant because it demonstrated a huge interest in this domain and a potential nation-wide success of a product to be developed.

4.2 Theoretical vs. real osmolarity

This topic was examined when the interdisciplinary working group was deciding on the limit of osmolarity to be chosen for the final PN formulation. The question was whether it is possible to rely on the theoretical osmolarity for PN to decide on what kind of venous access to use for administration. Therefore, a conformity evaluation of the calculated theoretical and the analyzed real osmolarity was performed on PN administered to neonatal patients of the CHUV.

For this evaluation, PN prepared at the pharmacy was considered. Samples retained for the analytical controls for release have been used. The theoretical osmolarity was calculated conforming to the PN composition and compared to the real osmolarity resulting from analyses for osmolality (mOsm/kg) and relative density (g/cm^3).

The result was that six out of eight PN samples with a theoretical osmolarity of <900 mOsm/L had a real osmolarity above this limit. The mean deviation of real to theoretical osmolarity was of +23% with a standard deviation of ±14 %. This can be explained by the fact that each raw material also has a higher osmolarity than indicated in the product information.

In conclusion, this experiment demonstrated that even if the recommendation is adhered to, the real osmolarity can be drastically higher. It is never known exactly what concentration of osmotic active molecules are actually given despite the solution being analyzed for osmolarity. Therefore, the limit of 900 mOsm/L for the calculated theoretical osmolarity should be strictly adhered to, because even PN with a lower theoretical osmolarity can effectively reach this limit for the analyzed real osmolarity. On a positive note, PN close to this limit having been administered through peripheral veins did not result in more complications.

4.3 Use of nutritional solutions

A monitoring of the use of the different types of nutritional solutions was performed just before and right after the introduction of the developed standardized PN in March 2019. The aim was to directly compare the impact of the introduction of this PN solution and the attitude of prescribing physicians towards the standard.

The month before the standardized PN was provided from the pharmacy to the neonatal ward, all PN prescriptions were consulted and the different types of PN preparations administered to inpatients were recorded for 28 days. Three types of PN preparations were available at this time: PN prepared by nurses on the ward, PN prepared at the pharmacy and a standardized 12.5% glucose dilution delivered by the pharmacy.

The same procedure was conducted right after the introduction of the standard in March 2019 for a total of 16 days. Additionally to the three types of nutritional solutions, the standard PN solution was available.

The results presented in Table 14 show a significant decrease of almost 80% of PN preparations performed by nurses on the neonatal ward (red values) and of more than 70% of the 12.5% glucose dilution, but no change of the number of PN prepared by the pharmacy (orange values). Nearly 50% of all nutritional administrations were performed with the developed standardized PN after its introduction (green value).

Table 14: Comparison of the use of nutritional solutions before and after the introduction of the standardized parenteral nutrition (No. = number, PN = parenteral nutrition, Pt = patient, G12.5% = 12.5% glucose dilution, NICU = neonatal intensive care unit, PHA = pharmacy, STD = standardized)

	Before introduction (28 days)				**After introduction (16 days)**			
	No. PN	**%**	**No. Pt**	**PN/Pt**	**No. PN**	**%**	**No. Pt**	**PN/Pt**
G12.5%	25	21.0	18	1.4	7	6.7	5	1.4
PN NICU	59	**49.6**	24	2.5	13	**12.4**	8	1.9
PN PHA	35	**29.4**	7	5.0	33	**31.4**	8	4.1
PN STD					52	**49.5**	20	2.6
Total	**119**		**49**	**2.4**	**105**		**40**	**2.6**

The neonatal patients to whom the standard PN was administered were born at a large scale of gestational age (GA), from 29 up to 42 weeks of pregnancy.

In conclusion, the introduction of the standardized PN solution on the neonatal ward fulfilled its purpose of reducing the number of PN preparations performed by nurses on the neonatal ward under non-GMP conforming conditions and without analytical controls to confirm their composition and the absence of endotoxins.

Chapter 5

General conclusion

Perspectives

5.1 General conclusion

Parenteral nutrition (PN) is a crucial part of the initial nutritional support provided for newborn term or preterm infants in critical health situations. It is mandatory for a good cerebral and neurologic development as well as for a postnatal weight gain conforming to the intrauterine growth.

The composition and the preparation of PN is complex and at high risk. Related medication errors include prescription, transcription, preparation and administration errors, consequently resulting in growth retardation, developmental disturbances and infections.

Only few commercialized pediatric PN (PPN) are available for neonatal patients and are not used routinely due to patients' varying needs of nutrients and the limited composition flexibility. Standardized PN assures an immediate and 24/7 availability of high-quality products on wards, minimizes the risk of medication errors and improves the medical treatment and clinical outcome of the treated inpatients. It also decreases the number of individual infusion bags needed to be prepared by nurses on the neonatal ward or in urgency situations.

With the aim of reducing medication errors by the improvement of the security and quality of the nutritional treatment of newborn term and preterm infants, a standardized PPN for the first days of life has been developed in collaboration with the industry and implemented at the *Centre Hospitalier Universitaire Vaudois* (CHUV). This opens the prospect of a future registration of this product at Swiss or even European level.

The first part of this thesis aimed at evaluating and assessing the need for centralizing the preparation of PN for neonatal patients at the central pharmacy on the one hand and the need to propose standardized PN in order to offer a ready-to-use nutritional treatment on the other hand. These objectives were achieved through the following projects:

- An evaluation of the status at the CHUV was performed to investigate the security and quality of PN prepared by nurses on the neonatal ward. Microbial as well as chemical analyses were performed to test for contamination and sterility issues as well as the accuracy of the prepared PN.
- A preliminary risk analysis (PRA) was conducted for the two preparation sites to compare the risks related to the whole PN process, to identify deficiencies to be focused on and to improve the preparation of the project to centralize all PN preparations at the pharmacy.

The second part targeted the development of a standardized PPN in collaboration with an industrial partner to respond to the need of a ready-to-use PPN with a long-term stability and practical storage conditions. Several projects lead to the achievement of this objective and were related to the development process:

- Two questionnaires addressed to neonatologists and pharmacists were elaborated aiming to gain knowledge about the state of the art in other Swiss hospitals.
- A new formulation of PPN was developed by a working group composed of pharmacists, neonatologists and industrials, responding to the estimated requirements of the two sites of application, the university hospitals in Lausanne (CHUV) and Geneva (HUG).
- The development process of the standardized PPN revealed a considerable degradation of N-acetylcysteine (NAC), the precursor of the semi-essential AA cysteine, to its dimer N,N-diacetylcystine (DAC). This was further analyzed and evaluated. In order to counter this problem, oxygen absorbers were inserted into the industrial secondary packaging to maximally absorb residual oxygen amounts and consequently reduce the oxidation of NAC and its degradation to DAC.

The results of all these projects and this thesis in its entirety are more than satisfying so far. The implementation of the standardized PN on the neonatal ward of the CHUV experienced an overall acceptance shown by a constant use of this nutritional treatment

for more than one and a half year. The centralization of all PN preparations at the pharmacy is ongoing and supposed to be realized in the beginning of 2021. Depending on the increase of PN preparations to be performed by the pharmacy from this moment on, new personnel and further standardized PN need to be acquired.

Even if the process of developing such a high-quality product takes long, it is worth the time, effort and energy put into it. The most vulnerable hospitalized patients will benefit enormously from an improved and secured nutritional treatment.

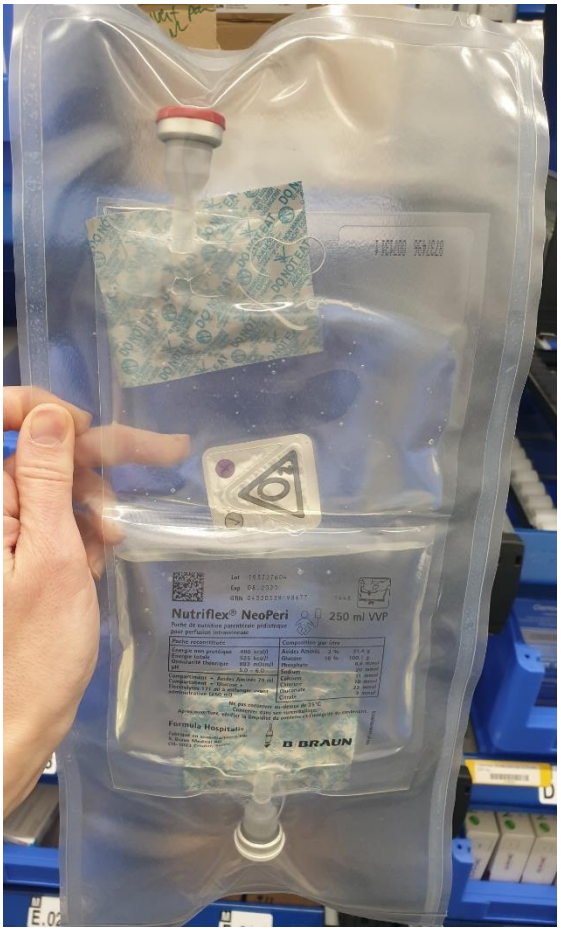

Figure 12: Nutriflex® NeoPeri infusion bag

Figure 13: Nutriflex® NeoPeri outer carton including eight infusion bags

Figure 14: Nutriflex® NeoPeri cartons

5.2 Perspectives

The multidisciplinary collaboration of pharmacists, clinicians, neonatologists and industrials opened numerous perspectives of future projects helping to further secure the high-risk management process of PN treatment.

5.2.1 Collaboration between pharmacy and neonatology

Concerning PN management, the collaboration between the production unit of the pharmacy and the neonatology of the CHUV has never been this fruitful before the initiation of this thesis.

As a high-quality nutritional treatment of neonatal patients is crucial for their development, growth and clinical outcome, this collaboration is of highest interest for all involved parties including the neonatal patients and their parents. Therefore, this bond should be strengthened further by constantly improving the PN process from prescription to preparation and administration.

5.2.1.1 Satisfaction questionnaire

After a certain period of use of the standardized PN, a satisfaction questionnaire is planned and going to be addressed to neonatologists and nurses of the neonatal ward to gain knowledge about their experiences with and remarks on the developed standardized PPN. As a next step, the general use and handling of the double-chamber bag (DCB) as well as indications of its administration is going to be recorded.

This information will be helpful to define if regular training might be necessary to present the advantages of standardized PN or if there are practical barriers for a higher utilization of this PPN that need to be eliminated.

5.2.1.2 Further standardized solutions

The above-mentioned questionnaire might also be helpful for a development of further types of standardized PN for neonatal patients.

The standardized PN developed within the scope of this thesis is hopefully only the beginning of a set of standardized PN to be used for neonatal and pediatric patients. Nutriflex® NeoPeri is supposed to be administered directly after birth and the first days of life only, therefore, a complementary ensuing standardized PN is needed to raise the nutritional supply for increased requirements.

This development will potentially need less time than the presented one as the whole industrial development with and by B. Braun Medical has already been realized and can be adapted for future PN DCB.

5.2.2 Centralization

The centralization of all PN preparations for neonatal and other pediatric patients at the central pharmacy of the hospital is strongly recommended in literature and the applicable nutritional guidelines. Therefore, this project of centralization has been in discussion for several years already. For a long time, the neonatology of the CHUV was not convinced of the purpose of this project as it was preferred to keep the liberty to quickly produce PN when it was considered necessary by a physician.

By means of the quality assessment performed as first project of this thesis, the lack of quality in terms of composition conformity was demonstrated. The second project, the preliminary risk assessment, also highlighted the higher risk for vulnerable patients when PN is prepared on the ward and not at the pharmacy.

These reasons as well as the 24/7 availability of a ready-to-use high-quality PN helped to convince the department and hence centralization of the PN preparation is starting in the beginning of 2021.

5.2.3 Financial impact

The whole project has been put on hold for approximately one year due to financial discussions and the initial refusal by the financial department of the CHUV due to a too high increase of costs related to neonatal PN. Therefore, a request for proposal to other GMP-manufacturing suppliers had to be performed, which resulted in only one positive proposal coming from B. Braun Medical.

For this reason, an evaluation of the actual financial impact of the implementation of a standardized PN solution needs to be performed including all aspects related to PN treatment (prescription, preparation, administration). At the same time, the care time for patients gained by nurses who do not need to prepare PN any more as well as the time gained at prescription by neonatologists, need to be evaluated and allocated in a financial value.

5.2.4 Clinical research and marketing authorization

An additional objective of the development of an industrialized “formula hospitalis” solution was a nation-wide provision of the standardized PN for the first days of life without needing to perform long-lasting clinical trials. If this can be achieved, the second step towards a marketing authorization is the performance of clinical trials to proof the safety and efficacy of the developed PN.

Clinical trials may also demonstrate that standardized PN given to term and preterm infants directly after birth result in a better nutritional treatment and clinical outcome as well as in a significant reduction of medication errors related to PN prescription, preparation and administration.

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Figures and Tables

Figures

Tables

Appendices

Appendix 1 – Component concentrations conforming to administration volumes

Volume Nutriflex NeoPeri [mL]	40	50	60	70	80
Amino acids [g/kg/d]	1,3	1,6	1,9	2,2	2,5
Glucose [mg/kg/min]	2,8	3,5	4,2	4,9	5,6
Sodium [mmol/kg/d]	0,8	1,0	1,2	1,4	1,6
Calcium [mmol/kg/d]	0,4	0,6	0,7	0,8	0,9
Phosphate [mmol/kg/d]	0,3	0,4	0,5	0,6	0,7
Chloride [mmol/kg/d]	0,4	0,5	0,6	0,7	0,8
Energy [kcal/kg/d]	21,0	26,3	31,5	36,8	42,0

Volume Nutriflex NeoPeri [mL]	90	100	110	120	130
Amino acids [g/kg/d]	2,8	3,1	3,5	3,8	4,1
Glucose [mg/kg/min]	6,3	7,0	7,6	8,3	9,0
Sodium [mmol/kg/d]	1,8	2,0	2,2	2,4	2,6
Calcium [mmol/kg/d]	1,0	1,1	1,2	1,3	1,4
Phosphate [mmol/kg/d]	0,8	0,9	0,9	1,0	1,1
Chloride [mmol/kg/d]	0,9	1,0	1,1	1,2	1,3
Energy [kcal/kg/d]	47,3	52,5	57,8	63,0	68,3

Volume Nutriflex NeoPeri [mL]	140	150	160	170	180
Amino acids [g/kg/d]	4,4	4,7	5,0	5,3	5,7
Glucose [mg/kg/min]	9,7	10,4	11,1	11,8	12,5
Sodium [mmol/kg/d]	2,8	3,0	3,2	3,4	3,6
Calcium [mmol/kg/d]	1,5	1,7	1,8	1,9	2,0
Phosphate [mmol/kg/d]	1,2	1,3	1,4	1,5	1,5
Chloride [mmol/kg/d]	1,4	1,5	1,6	1,7	1,8
Energy [kcal/kg/d]	73,5	78,8	84,0	89,3	94,5

Appendix 2 – Cover letter accompanying the questionnaires

Bonjour,

Dans le cadre de ma thèse à la Pharmacie du CHUV à Lausanne, nous sommes en train d'élaborer une **formule standard d'une nutrition parentérale pour l'administration en voie veineuse périphérique (VVP)** (voir annexe).
Ce questionnaire est destiné aux néonatologues et pharmaciens et sert à connaître les pratiques d'autres hôpitaux et l'intérêt pour une telle formule au niveau de la suisse.

La formule a été élaborée d'une équipe se composant des pharmaciens et néonatologues des hôpitaux universitaires de Lausanne (CHUV) et Genève (HUG) et des industriels pharmaceutiques.
Le but de la formule en question est de pouvoir mettre à disposition une nutrition parentérale pour VVP tout de suite après la naissance d'un enfant prématuré.
Cette nutrition parentérale standardisée permettra de:

- diminuer le temps d'attente de l'alimentation du prématuré
- diminuer le risque d'erreur lors d'une fabrication dans l'unité des soins
- diminuer le stress de trouver la bonne formule dans un court délai
- diminuer le nombre de préparations à faire en urgence par la pharmacie
- augmenter la qualité et la sécurité de l'administration d'une nutrition parentérale
- augmenter la traçabilité de ce qui a été donné aux prématurés.

Je me permets de vous demander de remplir le questionnaire en ligne ou de transférer ce mail à la personne qui sait répondre au mieux aux questions posées. Répondre à ce questionnaire vous prendra environ 5 à 10 minutes.

Je vous remercie d'avance pour votre disponibilité et votre collaboration et je reste à votre disposition pour toute question.

Je vous souhaite une très bonne journée.
Avec mes meilleures salutations,
Isabelle Angelstorf

Appendix 3 – Questionnaire for neonatologists

Service de néonatologie

a. Votre service se compose de combien de lit pour enfants prématurés ?
   .....

b. Administrez-vous des nutritions parentérales ?
   ☐ Oui ☐Non
   Si oui, combien de poches de nutrition parentérale sont administré par an ?
   .....

c. Utilisez-vous des nutritions parentérales standardisées ?
   ☐ Oui ☐Non
   Si oui, lesquelles ? .....
   .....
   .....

d. Utilisez-vous des nutritions parentérales « à la carte » ?
   ☐ Oui ☐Non
   Si oui, qui fabrique les poches pour votre service ? .....
   .....
   .....

e. Quelles voies d'administration utilisez-vous et en quelle proportion (%) ?
   ☐ VVP ..... ☐VVC .....

f. Pensez-vous que vos poches sont standardisable ?
   ☐ Oui ☐ Non
   Si oui, dans quel ordre de grandeur ? .....
   .....
   .....

g. Seriez-vous intéressé par une nutrition parentérale standardisée pour la voie veineuse périphérique commercialisée ?
   ☐ Oui ☐Non
   Commentaire : .....
   .....
   .....

h. Seriez-vous ouvert à changer vos pratiques si une telle formule sera disponible sur le marché ? .....
   .....
   .....

i. Si vous êtes intéressé par cette formule, quelle serait votre consommation approximative par an ? .....

Appendix 4 – Questionnaire for pharmacists

Service de pharmacie

a. Préparez-vous des poches de nutrition parentérale dans votre service ?
☐ Oui ☐Non ☐Sous-traitance : .....
Si oui, de quel type ? ☐Standardisées ☐« à la carte »
Commentaire : .....
.....
.....

b. Quels types de solutions préparez-vous ?
☐ Binaires (Glucose + AA + Electrolytes) ☐Ternaire (Binaires + Lipides)

c. Quand fabriquez-vous les poches de nutrition parentérale les jours de la semaine ?
☐ La veille ☐Le jour même

d. Quand fabriquez-vous les poches de nutrition parentérale en fin de semaine ?
☐ Le vendredi ☐Au jour le jour (garde de weekend)

e. Combien de poches fabriquez-vous par an ? .....

f. Comment recevez-vous les prescriptions ?
☐Manuellement (fax) ☐ Logiciel de prescription : .....
Commentaire : .....
.....
.....

g. Travaillez-vous avec un logiciel pour les calculs et la fabrication des poches de nutrition parentérale ?
Non ☐ Oui : ☐ Calculs ☐Fabrication ☐Les deux

h. Quelle méthode de fabrication utilisez-vous?
☐Manuelle ☐Automate : .....

i. Quelle stabilité et sous quelles conditions donnez-vous aux poches fabriquées à la pharmacie ? .....
.....
.....

j. Comment transportez-vous les poches vers les unités de soins et sous quelles conditions ?
☐ Chaîne du froid ☐ Transport dédié ☐ Transport par unité de soins
.....
.....

k. Effectuez-vous des contrôles analytiques sur vos poches ?
☐ Non ☐Oui : ☐Composition ☐Microbiologie ☐Endotoxine
Commentaire : .....
.....
.....